Uniformity of Dosage Units, Part 1: Acceptance Value

Pramote Cholayudth

The concept of acceptance value must be redefined to remove bias and more closely reflect quality targets. This paper describes how this can be done.

In methods currently used to ensure the uniformity of dosage units (UDU) (1), the test acceptance value (AV) is based on the following formula: $AV = |M - \bar{x}| + ks$, where M is reference value, $\bar{x}$ is sample mean, k is acceptability constant, and s is sample standard deviation.

Despite its widespread use, this method can result in bias and may allow batches of inferior quality to be released. The bias can result in fluctuated conclusions, especially when guidance established by the American Society for Testing and Materials' (ASTM) E2810 standard guide (2) is followed. Studies have found lack of correlation between AV and probability (ASTM E2810) computed using validation data. In addition, AV, as it is typically computed, is also inconsistent with lot coverage (3). This inconsistency is caused by the conditional determination criteria that are used to determine the reference value (M).

In order to remove bias from the AV limit, the definition of M must be adjusted. One way to do this is by replacing it with the process target (T). Appropriate derivation using statistical techniques can result in an unbiased formula with increased discriminative power to generate a new AV distribution. Using this approach, the higher power would be indicated by one AV limit for each sample size, for example, as well as one limit for each target, and limitation of "T-Xbar" values, effectively preventing the release of inferior quality batches.

Critical AV values (at locations with 95% or 99% coverage) can be determined after simulation studies and complete construction of the distributions, so that new and unbiased AV limits can be established. This article will briefly describe how to do this.

The test acceptance criteria for current (UDU) (1) are summarized as follows, where AV = acceptance value, M = reference value, s = standard deviation, $\bar{x}$ = content uniformity data mean, x_{min} = minimum, and x_{max} = maximum of 30 units:

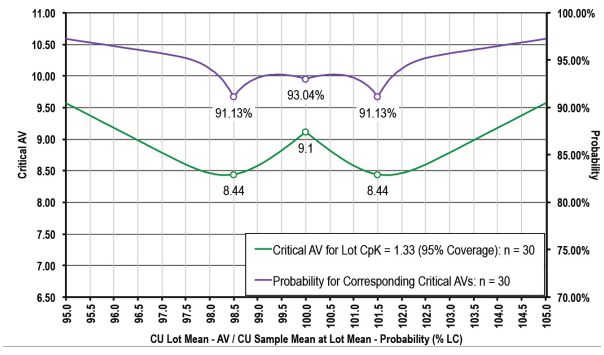
- Stage 1: assay 10 units. Pass if $AV = |M - \bar{x}| + 2.4s \leq 15$ criteria are met.
- Stage 2: assay 20 additional units. Pass if $AV = |M - \bar{x}| + 2s \leq 15$ criteria are met, provided that $x_{min} \geq 0.75M$ and $x_{max} \leq 1.25M$ criteria are also met.

The determination criteria for reference value (M) are subject to the target value (T), which may be not more than 101.5% of the label claim (LC) (where M may be $\bar{x}$, 98.5 or 101.5% LC) or more than 101.5% LC (where M may be $\bar{x}$, 98.5 or T% LC). See *United States Pharmacopeia* (*USP*) (1) for more detail.

Pramote Cholayudth is validation consultant to Biolab Co., Ltd. in Thailand. He is a guest speaker on process validation to industrial pharmaceutical scientists organized by local regulatory authorities. He is the founder and manager of PM Consult and can be contacted via cpramote2000@yahoo.com.

Submitted: June 12, 2018
Accepted: July 20, 2018

Figure 1: The relationship among critical acceptance values (AVs), probability, and mean value for content uniformity (CU) (validation sample size $n = 30$).



A previous study (4, 5, 6) suggests that AV values are not always consistent with reliability, so they cannot fully guarantee that the batches being tested meet UDU. According to part three of that study (6), the definition of the AV formula, $AV = |M - \bar{x}| + ks$, where AV is acceptance value, M is reference value, $\bar{x}$ is sample mean, s is sample standard deviation, and k is acceptability constant, is the root cause of the bias since it is associated with the biased determination criteria. For example, the previous formula forces M for any samples with means less than 98.5% or more than 101.5% LC to be 98.5 or 101.5% LC, respectively (when the target is not more than 101.5% LC).

The following (see **Figure 1**) is a relevant example of errors (6). **Figure 1** illustrates lack of correlation between AV and probability graphs (according to ASTM E2810) due to its non-linearity. The probability pitfalls at 98.5% and 101.5% LC mean locations illustrate how the formula influences the AV parameter's reliability.

Use of the working AV limits (6) (e.g., not more than [NMT] 12.5 for $n = 10$) still has a limitation (i.e., its validity exists only when sample mean values are those other than 98.5% or 101.5% LC). For 91.13% probability, as shown in the figure, there is 90% assurance (a 90% joint confidence interval) that at least 91.13% of all samples tested for content uniformity will pass the *USP* test.

The new concept of acceptance value (AV)

To remove the discriminative power bias and subsequently fix the method currently used to establish AV limits, the definition of M needs to be adjusted through directly using the process target (T). In order for the formula to be unbiased and more discriminative, it must divide by the square root of sample size n (i.e., in the same manner used to determine the standard error of the mean, $\sigma/\sqrt{n}$) so that it is a function of sample size. Taking this approach, the current formula (**Equation 1**)

$$AV = |M - \bar{x}| + ks \qquad \text{[Eq. 1]}$$

would become the following expression (**Equation 2**),

$$AV = |T - \bar{x}| / \sqrt{n} + ks \qquad \text{[Eq. 2]}$$

Simulation studies must be run, however, to confirm the validity of this hypothesis.

An appendix to part one of the study mentioned previously (4), describes the statistical methods that are used, which include deriving the probability density function (pdf) formula involved. Since the overall approach will be exactly the same as that used in the previous study (4), it may be sufficient to compare current AV numbers with derivations using the new AV formula derivation. This comparison is shown in **Table I**. When using the Microsoft Excel formula (**Equation 3**):

Probability (P) = CHISQ.DIST(x,n - 1,TRUE) [Eq. 3]

where, for practical use, chi variable χ^2 is now replaced by x variable. In **Table I** and **Equation 3**,

- χ^2 is the Chi-square variable (it is a numerical variable equivalent to each of the AV data on the x-axis)

Table I: Current vs. new acceptance value (AV) formulas and how they're derived.

Current acceptance value	New acceptance value
• To create the new formula, the reference value M in the current formula is replaced with the target value, T. To make the formula discriminative, it needs to be divisible by the square root of the sample size n, in the same manner as the expression for the standard error of the mean, $\sigma/\sqrt{n}$.	
Current AV formula: $AV = \lvert M - \bar{x} \rvert + ks$	New AV formula: $AV = \lvert T - \bar{x} \rvert / \sqrt{n} + ks$
• To create the probability density function (pdf) using chi square statistics (4), the average value $\lvert M - \bar{x} \rvert$ in the current chi square formula must be replaced with the average value $\lvert T - \bar{x} \rvert / \sqrt{n}$ (where $\lvert T - \bar{x} \rvert = 0.94748$ in cell "G2" in **Table II**). The only difference is the average values. This is why the approach remains the same.	
Current χ^2 formula: $\chi^2 = \frac{(\mu/\sigma)^2 + 1}{1/\left\{\left(\frac{n-1}{k^2\mu^2}\right)\left(AV - \lvert M - \bar{x} \rvert\right)^2\right\} + 1/n}$	New χ^2 formula: $\chi^2 = \frac{(\mu/\sigma)^2 + 1}{1/\left\{\left(\frac{n-1}{k^2\mu^2}\right)\left(AV - \lvert T - \bar{x} \rvert/\sqrt{n}\right)^2\right\} + 1/n}$
For more detail, see reference 4.	In Excel format, see cell "G4" in **Table II**.
• From the χ^2 formula: To generate the probability density using the corresponding chi square function in MS Excel, the same formula must be used for both current and new, i.e. Probability (P) = CHISQ.DIST(χ^2,n-1,TRUE) or CHISQ.DIST(x,n-1,TRUE) see **Equation 3** above. See also cell "G5" in **Table II**.	

ALL FIGURES ARE COURTESY OF THE AUTHOR.

Table II: New acceptance value (AV) vs. probability data (n = 10) (Microsoft Excel spreadsheet). ABS is the absolute function in Microsoft Excel.

	A	B	C	D	E	F	G	H	I
1	**Descriptions**			n	Mean	Sigma	(T-Xbar) av.	Lot CpK	K
2				10	100.00	3.75	0.94748	1.33	2.40
3	New AV data (x-axis)			6.00	6.25	6.50	6.75	7.00	7.25
4	Chi square variable			3.61	3.94	4.28	4.63	4.99	5.37
5	Probability density (cumulative)			6.50%	8.45%	10.76%	13.44%	16.50%	19.92%
6	Probability density (y-axis)			1.78%	2.13%	2.50%	2.87%	3.24%	3.59%
7	G2 = 0.94748 (the average of all IT-Xbarl values generated from the simulation study *N* = 900,000)								
8	H2 = MIN(115-E2,E2-85)/(3 * F2) = 1.33333								
9	G3 = F3 + 0.25 = 6.75, H3 = G3+0.25, I3 = H3 + 0.25, and so on								
10	G4 = (($E$2/$F$2)^2 + 1)/((1/((($D$2 - 1)/(($I$2*$E$2)^2))*((G3-$G$2/$D$2^0.5)^2)))+(1/$D$2)) = 4.63								
11	G5 = CHISQ.DIST(G4,$D$2 - 1,TRUE) = 13.44%								
12	G6 = ABS(H5 - F5)/2 = 2.87% (probability density at AV = 6.75)								

- *n* is sample size
- *n-1* is n-1 degrees of freedom
- μ is process mean (mu)
- σ is process standard deviation (sigma)
- *AV* is acceptance value (on x-axis)
- *M* is reference value
- *T* is target value
- $\bar{x}$ is sample mean
- *k* is acceptability constant
- $|M - \bar{x}|$ is absolute value between reference value (*M*) and sample

Figure 2: New acceptance value (AV) distributions: Lot Mean and Target = 100% LC (n = 10).

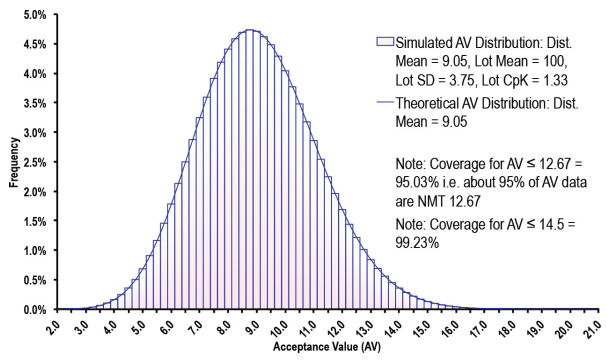


Figure 3: New acceptance value (AV) distributions: Lot Mean and Target = 105% LC (n = 10).

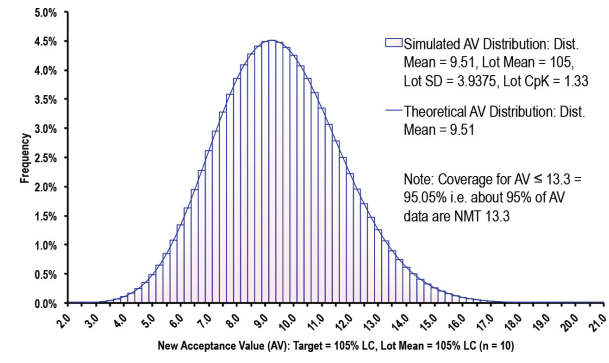


Table III: Microsoft Excel spreadsheet for normal data simulation and acceptance value (AV) calculation. ABS is the absolute function in Microsoft Excel.

	A	B	C	D	E	F	G	H	I
1	Data #	Mean	100.00	Sigma	3.75	n	10	k	2.4
2	1	100.76	103.93	103.46	101.53	102.06	98.84	105.63	96.12
3	2	103.19	100.84	97.24	99.83	103.43	102.71	102.77	100.96
…	…	…	…	…	…	…	…	…	…
10	9	103.72	103.77	107.05	96.16	104.06	97.25	95.63	100.59
11	10	102.75	101.24	92.45	95.16	103.77	99.74	101.27	108.42
12	Mean	101.28	100.54	99.61	99.09	101.10	101.72	98.97	100.42
13	SD	2.80	2.87	5.42	3.18	3.10	2.84	4.08	4.62
14	AV	7.13	7.07	13.14	7.92	7.78	7.36	10.13	11.22
15	ABS	1.28	0.54	0.39	0.91	1.10	1.72	1.03	0.42
16	Lot Mean	100.34	Lot SD	3.67	Lot CpK	1.33	ABS avg.	0.92200	N = 90
17	Each simulated normal data cell (B2 through I11) = NORM.INV(RAND(),$C$1,$E$1)								
18	B12 = AVERAGE(B2:B11)					B16 = AVERAGE(B12:I12) = 100.34			
19	B13 = STDEV(B2:B11)					D16 = STDEVP(B2:I11) = 3.67			
20	B14 =ABS($C$1-B12)/($G$1^0.5)+$I$1*B13					F16 = MIN(115-B16,B16-85)/(3*D16) = 1.33			
21	B15 =ABS($C$1-B12)					H16 = AVERAGE(B15:I15) = 0.92200			
22						I16 = "N = "&COUNT(B2:I11)&"" = N = 90			

mean ($\bar{x}$) and $\overline{|M-\bar{x}|}$ is the average of all $|M-\bar{x}|$ data in simulation

- $|T-\bar{x}|$ is absolute value between target value (T) and sample mean ($\bar{x}$) and $\overline{|T-\bar{x}|}$ is the average of all $|T-\bar{x}|$ data in simulation
- P is probability density (%) (on y-axis)
- CHISQ.DIST is the MS Excel function that will return the chi square (χ^2 or x) distribution (%)
- TRUE is the cumulative distribution

Construction of theoretical AV distribution (n = 10)

According to part one of the previous study (4), the minimum process capability index, CpK, i.e., Lot CpK at 1.33 (using mean = 100 and sigma = 3.75) is used as a benchmark and the baseline for working AV acceptance limits. The same baseline is also applied in this study.

An Excel function (**Equation 3**) is used to compute the probability density (% frequency), when the spreadsheet in **Table II** is keyed with parameters such as n = 10, mean = 100, and sigma = 3.75. In **Table II**, within thick-line border, if the new AV = 6.75 (x-axis), then the chi-square variable = 4.63, and the cumulative probability density will be 13.44%, while the non-cumulative probability density will be 2.87%.

The data in x-axis and y-axis rows, rows three and six in **Table II**, can be plotted into AV distributions as required. However, this table is only intended as an example to demonstrate how the method works. The actual working spreadsheet table must be customized so that the population size (N) is large enough for implementation.

Table IV: Managed acceptance value (AV) data prior to construction of AV distribution. ABS is the absolute function in Microsoft Excel.

	A	B	C	D	E	F	G	H	I
1	New AV data (x-axis)			6.00	6.25	6.50	6.75	7.00	7.25
2	Cumulative frequency			6.50%	8.45%	10.76%	13.44%	16.50%	19.92%
3	Non-cumulative frequency (y-axis)			1.78%	2.13%	2.50%	2.87%	3.24%	3.59%
4	G2 = COUNTIF($B$14:$I$14,"<="&G1)/COUNT($B$14:$I$14) = 13.44%								
5	G3 = ABS(H2-F2)/2 = 2.87%								
6	Note: The cumulative and non-cumulative data (two decimals) may look the same as the theoretical values. In fact, they are different at decimal points three or four. In simulation studies run by the author, N = 900,000 (n = 10), so 90,000 AV data are available.								

Figure 4: Critical new acceptance value (AV) (95% coverage) and content uniformity (CU) lot means (with target 100% LC) relationship (n = 10, 30, and 70).

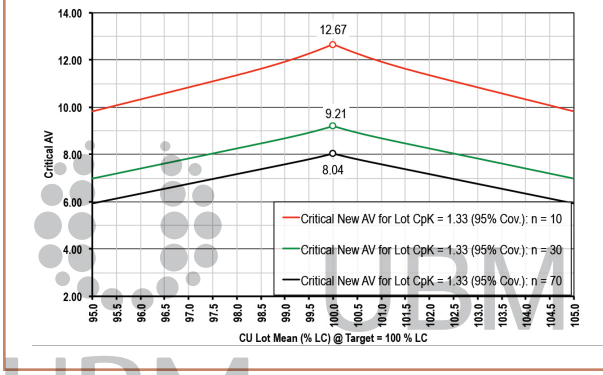
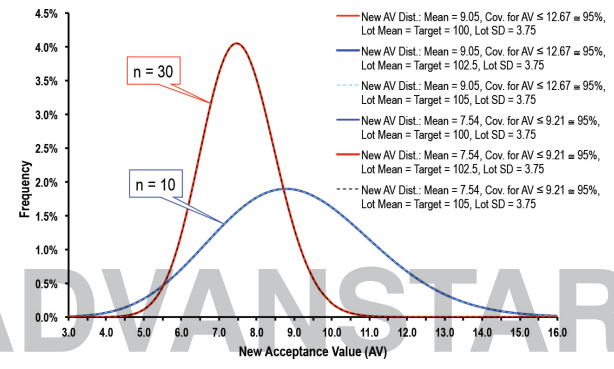


Figure 5: New acceptance value (AV) distributions for three different targets (100, 102.5, and 105% LC): n = 10 and 30.



In simulation studies conducted by the author, N is up to 900,000 (6 sheets x 150,000 elements of data/sheet). More detail can be seen in Table I in part one in the previous study (4). The solid line distribution curve (theoretical) in **Figure 2** (or **Figure 3**, n = 10) is the example for the implemented cases.

Construction of simulation AV distribution (n = 10)

When a simulation for sample size n = 10 is planned, the first step is to simulate (i.e., generate) a pool of normal data using the spreadsheet in **Table III**, where it is keyed with parameters such as mean = 100, sigma= 3.75, n = 10 and k = 2.4. The computed AV results are then rearranged in an ascending manner (from minimum to maximum) on a separate spreadsheet (**Table IV**) so that % frequency (probability density) is managed (i.e., distributed). The data in x-axis and y-axis rows, rows one and three in **Table IV**, can be plotted into AV distribution as required. Also note that **Table III** containing 90 data (N = 90) is intended for example only while the simulation conducted by the author comprises N = 900,000 (6 sheets x 150,000 data/sheet). The working spreadsheet is to be customized so that N is large enough for implementation. More detail can be seen in **Table I** of part one in the previous study (4).

See also the simulated distribution curve (bar) in **Figure 2** (or in **Figure 3**, n = 10, lot mean = 105% LC) as the implemented case. **Figures 2** and **3** will provide the evidence that the simulation tests conducted are successful because the simulated data properly fit to the theoretical solid-line distributions. It also strongly suggests that the pdf formulae (theory) introduced in this article are valid.

Understanding the new acceptance value

All AVs discussed above are associated with those lots having targets and lot means at 100% LC. Another case involves lots with a variety of means, including 100% LC (the target is still 100% LC) where the AV limits (critical AVs) dedicated to individual lot means can be computed and illustrated in **Figure 4**. The author has run simulation studies to obtain these values, using Microsoft's Excel program (.xlsm, not .xlsx). Since one never knows the exact lot means, the corresponding AV limits cannot be specified. One way around this problem is to use the representative acceptance limits based on those critical AVs at lot mean location equal to the target of 100% LC, such as 12.67 (n = 10), 9.21 (n = 30), and 8.04 (n = 70), as illustrated in **Figure 4** where lot CpK is fixed at 1.33. The alternative is based on an assumption that lot means and sample means are at about 100% LC most of the time if the target is 100% LC. Note that, according to statistical textbooks (7), the acceptability or tolerance constants (k), at 90% confidence interval and 90% coverage, for n = 10 and 30 are 2.53 and 2.03, respectively. Using these two constants, the critical AV values would be 13.34 (n = 10) and 9.34 (n = 30). When determining the formula $AV = |T - \bar{x}| / \sqrt{n} + ks$, if T

Figure 6: Critical new acceptance value (AV) (95% coverage) and content uniformity (CU) lot means (with target 105% LC) relationship (n = 10, 30, and 70).

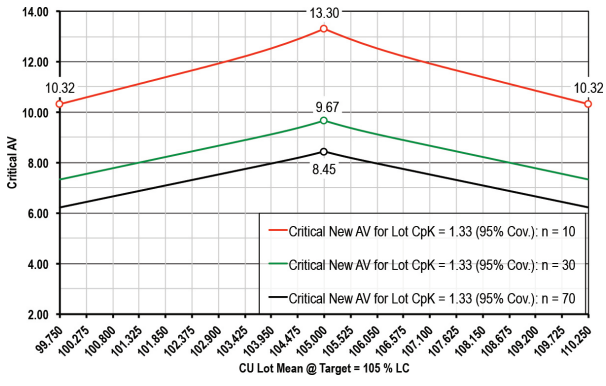


Figure 7: Standard acceptance value (AV) distributions.

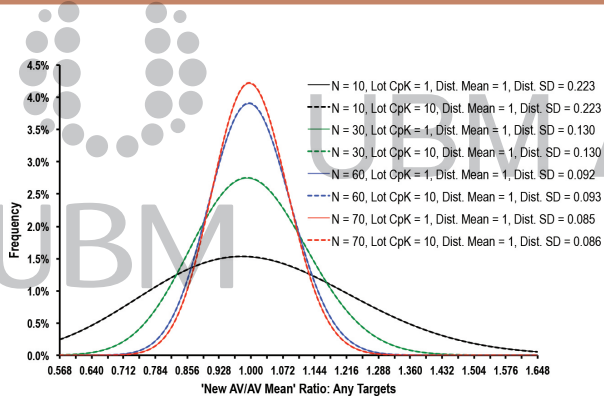
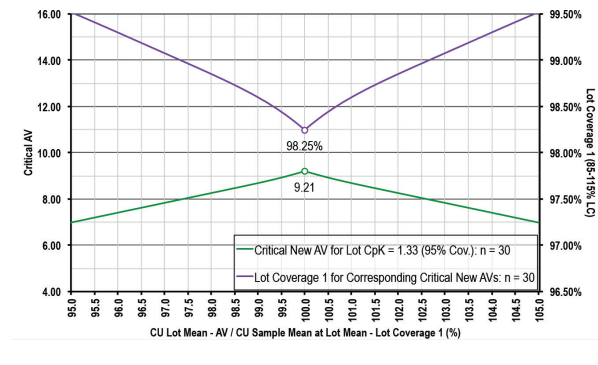


Figure 8: Critical new acceptance values (AVs) and Lot Coverage 1 relationship (n = 30)



increases, $\bar{x}$ will increase accordingly, so the absolute value will remain nearly the same.

If process targets other than 100% LC are planned, the same AV limits may be employed. For example, if a target of 100, 102.5, or 105% LC is required, the AV limit (n = 10) used is 12.67. This is confirmed by **Figure 5**, which illustrates AV distributions (n = 10 and 30) from lots with different targets (100, 102.5, and 105% LC) where the three distributions for each sample size are practically identical. This implies that AV limits established for the target of 100% LC are also applicable to any other targets, provided that lot standard deviations (SDs) are the same (3.75 in the figure). **Figure 6**, the special case of **Figure 4**, will fully illustrate how the AV limits for a target of 105% LC are proportional to those of 100% LC (e.g., 13.30) (**Figure 6**) is equal to 12.67 x (105/100) (**Figure 4**). This is the case with fixed lot CpK (1.33) with different lot means and SDs.

Figure 7 illustrates standard AV distributions for n = 10, 30, 60, and 70. This implies that this particular characteristic still exists as it does in the AVs (4, 5, 6). Standard AV distribution may be defined as: when individual AV data are divided by its distribution mean, the new distributions of 'AV/Mean' ratio data—from significantly different lot CpKs (one vs. 10 in **Figure 7**)—will be practically identical to each other with their means equal to one (1.00).

Such a typical characteristic can be applied such that AV control chart constants can be established, i.e., upper and lower control limits (UCL and LCL) can be computed using such factors. For calculation example: if n = 10 (in the figure), the UCL factor will be 1 + 3x0.223 = 1.669 and the LCL factor will be 0.331. The control chart ranges using these factors will be more narrow (stringent) than those computed using the conventional principle "mean±3SD" directly from the original AV data (5), so results will be at least three times more accurate than those using the conventional approach. Since the factors relevant to the new AVs are nearly equal to those of the current ones (e.g., for n = 10, UCL and LCL factors = 1.71 and 0.29, respectively), the new chart ranges will also be three times better than those derived using the conventional approach.

In addition to the AV charts, in-house limits may be computed for use in the future, i.e., UCL and LCL will become the upper and lower limits for the in-house specifications.

In comparison with the current AV behavior, **Figure 8** illustrates that there is an obvious correlation between the new AV parameter and Lot Coverage 1 (i.e., the resulting graph shows a sample size-based linearity [not exactly straight line] of the plotted data).

Establishing the new AV acceptance criteria limits

Determination of the critical AV values at 95% coverage, as illustrated in **Figures 2**, **3**, **4**, and **6**, is the basic approach to establishing the corresponding acceptance limits. Such AV limits are summarized in **Table V**. They are applied to

Table V: New acceptance value (AV) acceptance criteria limits.

Sample sizes (n)		Acceptability constant (k)	AV limits (L)		AV average limits	Application (AV average limits)
QC data (routine batches)					Cumulative QC data (routine batches)	
10		2.4	12.7	14.5	9.1	Continued process verification (CPV).
30		2.0	9.2	10.0	7.5	
Validation data (validation batches)					Cumulative validation data (validation batches)	
Sampling Plan A (≥ 70 units)	30	2.0	9.2		7.5	Process validation summary review.
	70	1.87	8.0		7.0	
Sampling Plan B (≥ 140 units)	60	1.89	8.2		7.1	
	140	1.79	7.4		6.7	

Note 1: Use $AV = |T - \bar{x}| / \sqrt{n} + ks \le L(T/100)$. If n = 10 and the target is 102.5% LC, $AV = |102.5 - \bar{x}| / \sqrt{10} + 2.4s \le 13$ where the acceptance limit is 12.7 x (102.5/100) = 13.0. Subsequently, the AV average limit is 9.1 x (102.5/100) = 9.3.

Note 2: Meeting the AV limits will provide the information that at least 98.25% (**Figure 8**) of the lot will fall within 85–115% LC where the target is 100% LC. If the target is 102.5% LC, it implies that at least 98.25% of the lot will fall within 87.125–117.875% LC. Performing the calculation, 87.125 is 85 x (102.5/100).

Note 3: Meeting the AV average limits will summarize that the Lot CpK, on average, is not less than 1.33, which is the conventional process benchmark for establishing these particular new AV acceptance criteria limits.

Note 4: These "default" limits (99% coverage; **Figure 2**) may be used as quality control limits in continued process verification (CPV) batches.

Table VI: New (proposed) and current acceptance value (AV) acceptance criteria (*n* = 10 and 30). USP is *United States Pharmacopeia*.

Stage #	New acceptance criteria (proposed)	Current acceptance criteria
1	Assay 10 units ($n = 10$). Pass if $AV = |T - \bar{x}| / \sqrt{10} + 2.4s \le L(T/100)$ and $|T - \bar{x}| \le 6.0$ are met ($L_{n=10}$ is 12.7 or 14.5).	Assay 10 units ($n = 10$). Pass if $AV = |M - \bar{x}| + 2.4s \le 15$ criterion is met.
2	Assay 20 additional units ($n = 30$). Pass if $AV = |T - \bar{x}| / \sqrt{30} + 2s \le L(T/100)$, $|T - \bar{x}| \le 4.0$, $x_{min} \ge 0.75T$, and $x_{max} \le 1.25T$ are met ($L_{n=30}$ is 9.2 or 10.0).	Assay 20 additional units ($n = 30$). Pass if $AV = |M - \bar{x}| + 2s \le 15$, $x_{min} \ge 0.75M$ and $x_{max} \le 1.25M$ criteria are met.
–	*T* may be 100 (nominal), 102.5, or 105% LC. For other sample sizes, refer to **Table V**.	*M* is determined according to USP (as earlier described).

Application: The new acceptance criteria are applied to both *Weight Variation* (CU) and *Content Uniformity* (CU).

Note: One of the causes of "Fail" in each stage of the new method may be identified using the expression $|T - \bar{x}| \le (15/\sqrt{n} + 1.25)$, i.e., $|T - \bar{x}| \le 6.0$ and $|T - \bar{x}| \le 4.0$ in stage one and two, respectively.

all processes with targets not less than 100% LC. AV and AV average limits must be computed following the calculation examples in **Table V**. AV average limit requirements are implemented when several batches produced are evaluated (e.g., in continued process verification or process validation batches). The successful average results show that Lot CpK is, on average, not less than 1.33. **Table VI** introduces the two-stage acceptance criteria for UDU using the new AV limits.

Discussion

Justification of sample mean ($\bar{x}$) values is important and assumes that the natural ranges for the mean data are known. In theory, for sample size *n* the acceptance range is $15/\sqrt{n}$. However, the working ranges about the target must account for some process errors. For example, suppose that the following justification criteria are given:

- Individual range: ±15% about the lot mean (justification: "15" is commonly used, i.e., derived from 115% - 100% or 100% - 85% [- is minus]).
- Sample mean range: $\pm 15/\sqrt{n}$% about the lot mean (justification: this criterion is in the same manner as standard error of the mean $\sigma/\sqrt{n}$).
- Lot mean range (process error): ±1.25% about the target (justification: process error may be not more than 10% of the individual range 15, 1.25% or 8.33% of 15 is determined adequate).

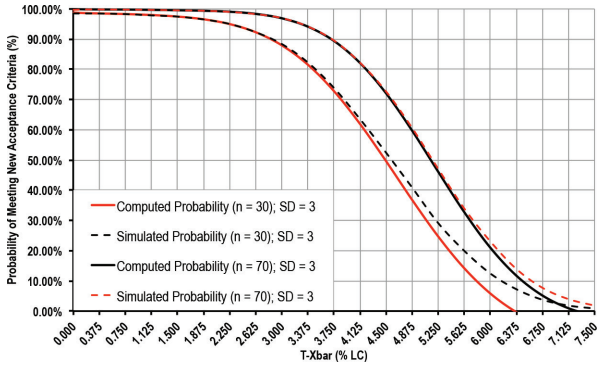
The working mean range will, therefore, be not more than $\pm(15/\sqrt{n} + 1.25)$ about the target, i.e., $|T - \bar{x}| \le (15/\sqrt{n} + 1.25)$. In summary using this particular expression, the CU working mean ranges for $n = 10$, 30, 60, 70, and 140 will be ±6, ±4, ±3.2, ±3, and ±2.5% about the target, respectively, where the target may be 100%, 102.5%, 105% LC or other. See also the calculation examples regarding "T-Xbar" in **Table VII**.

Table VII: Comparison between new and current methods.

Example #	New acceptance criteria (proposed)		Current acceptance criteria
Example 1: both pass on first.	Stage 1: LML = 95, UML = 110, T = 102.5, Xbar = 102, SD = 4.6, n = 10 (M = 102)		
	$AV = \lvert 102.5 - 102 \rvert / \sqrt{10} + 2.4 \times 4.6 = 11.20 (< 13.0)$		$AV = \lvert 102 - 102 \rvert + 2.4 \times 4.6 = 11.04 (< 15)$
	T-Xbar = 0.5 (< 6)	Conclusion: pass.	Conclusion: pass.
Example 2: fail-fail/fail-pass.	Stage 1: LML = 90, UML = 110, T = 100, Xbar = 107, SD = 4.6, n = 10 (M = 101.5)		
	$AV = \lvert 100 - 107 \rvert / \sqrt{10} + 2.4 \times 4.6 = 13.25 (> 12.7)$		$AV = \lvert 101.5 - 107 \rvert + 2.4 \times 4.6 = 16.54 (> 15)$
	T-Xbar = 7 (> 6)	Conclusion: fail.	Conclusion: fail.
	Stage 2: LML = 90, UML = 110, T = 100, Xbar = 106.5, SD = 4.6, n = 30 (M = 101.5), minimum = 78, maximum = 118.2.		
	$AV = \lvert 100 - 106.5 \rvert / \sqrt{30} + 2 \times 4.6 = 10.39 (> 9.2)$		$AV = \lvert 101.5 - 106.5 \rvert + 2 \times 4.6 = 14.2 (< 15)$
	MnAV = 75.00, MxAV = 125.00		MnAV = 76.125, MxAV = 126.875
	T-Xbar = 6.5 (> 4)	Conclusion: fail.	Conclusion: pass.
Example 3: both fail-fail.	Stage 1: LML = 90, UML = 110, T = 100, Xbar = 107, SD = 4.6, n = 10 (M = 101.5)		
	$AV = \lvert 100 - 107 \rvert / \sqrt{10} + 2.4 \times 4.6 = 13.25 (> 12.7)$		$AV = \lvert 101.5 - 107 \rvert + 2.4 \times 4.6 = 16.54 (> 15)$
	T-Xbar = 7 (> 6)	Conclusion: fail.	Conclusion: fail.
	Stage 2: LML = 90, UML = 110, T = 100, Xbar = 106.5, SD = 5.2, n = 30 (M = 101.5), minimum = 94.7, maximum = 127.1.		
	$AV = \lvert 100 - 106.5 \rvert / \sqrt{30} + 2 \times 5.2 = 11.59 (> 9.2)$		$AV = \lvert 101.5 - 106.5 \rvert + 2 \times 5.2 = 15.4 (> 15)$
	MnAV = 75.00, MxAV = 125.00		MnAV = 76.125, MxAV = 126.875
	T-Xbar = 6.5 (> 4)	Conclusion: fail.	Conclusion: fail.

LML & UML = Lower & upper monograph limits; MnAV & MxAV = Minimum & maximum allowed values.

Figure 9: Operating characteristic (OC) curves for probability of meeting new acceptance value (AV) acceptance criteria (n = 30 and 70).



Using an acceptance threshold of 95 or 99% coverage point is statistically justified. The higher coverage value, at 99% appears to be more practical, however. Such default limits (99%), i.e., 14.5 (n = 10) and 10.0 (n = 30), can be used as quality control (QC) limits in initial batches such as continued process verification (CPV) batches. In routine batches (after successful CPV batches), the 95% coverage working limits, i.e., 12.7 (n = 10) and 9.2 (n = 30), can be used.

After using either default limits (99%) or working limits (95%), the cumulative AV data must be evaluated and included in the annual product review (APR), and, in the future, may be computed for use as in-house limits (for quality assurance) in place of the two limits.

Note: The terms "default limit," "QC limit," or "working limit" are used in this study, rather than using the terms "official limit" or "specification limit," because this new AV concept has not yet been recognized by pharmacopeia.

Calculation examples

Using the data from the calculation examples provided on the *USP* web page (*USP–NF* General Chapter <905> "Uniformity of Dosage Units") (1), the new and current methods are compared in **Table VII**. Note that the new method is more discriminative as demonstrated in example two, where the "T-Xbar" data also exceed the acceptance ranges (±6 and ±4 for n = 10 and 30 respectively). In the table, the working formulae are $AV = \lvert T - \bar{x} \rvert / \sqrt{10} + 2.4s \le 12.7(T/100)$ and $AV = \lvert T - \bar{x} \rvert / \sqrt{30} + 2s \le 9.2(T/100)$.

If default limits are employed in the table, the results will be the same (e.g., failure results in example two). This implies that the discriminative power of the 99% coverage limits is also attainable.

Another case involves actual lots of 50-mg tolperisone tablets, where the CU average and SD data are 93.11% and 3.68% LC, respectively (n = 10, target = 100% LC). The computed current and new AVs are 14.22 (not more than 15, i.e., pass) and 11.01 (not more than 12.7), respectively. Although the product passes

the new AV limit, the T-Xbar value (6.89) exceeds the limit of not more than 6, so it ultimately fails to pass the overall acceptance criteria in stage one (i.e., discrimination already occurs in stage one). Testing in stage two is required.

Operating characteristic (OC) curves

Illustrated in **Figure 9** is the simulated operating characteristic (OC) curves for probability of meeting new AV acceptance criteria, with $L_{n=10} = 14.5$ and $L_{n=30} = 10.0$, using validation sampling plan A ($n \geq 70$), i.e., validation testing plan $n = 30$ and 70 (10,000 simulation trials for each of probability points on T-Xbar axis). In the figure, the probability dedicated to sample SDs fixed at 3% LC is demonstrated. One can see that the probability will gradually decrease over the increasing T-Xbar values. In other words, the sample means closer to the target will have the higher probability. Detail on the OC curves, relevant to validation sampling plans A and B and their discrimination, will be discussed in part two of this article.

Conclusion

The simulation test results for the new AV parameter and its corresponding distributions are successful (**Figure 2**) even for targets other than 100% LC (**Figure 3**). The concept of formula design (with square root of sample size n) and acceptance thresholds (95% and 99% coverage points) is statistically natural. The requirements for discrimination properties are also fulfilled, such as sample size-based (discriminate between different sample sizes, i.e., one limit for one sample size) and target-based (discriminate between different targets, i.e., one limit for each target) acceptance limits. The "T-Xbar" limit (i.e., $|T - \bar{x}| \leq (15/\sqrt{n} + 1.25)$) is also part of building the discriminative power as illustrated in **Figure 9**. Upon using the new acceptance criteria and *USP* data (**Table VII**), it is proven to be more discriminative than the current one.

From a quality assurance point of view, the lifecycle approach to implementing the new AV concept through using AV limits (for individual batch release) together with AV average limits (for AV data evaluation at least in CPV) is recommended.

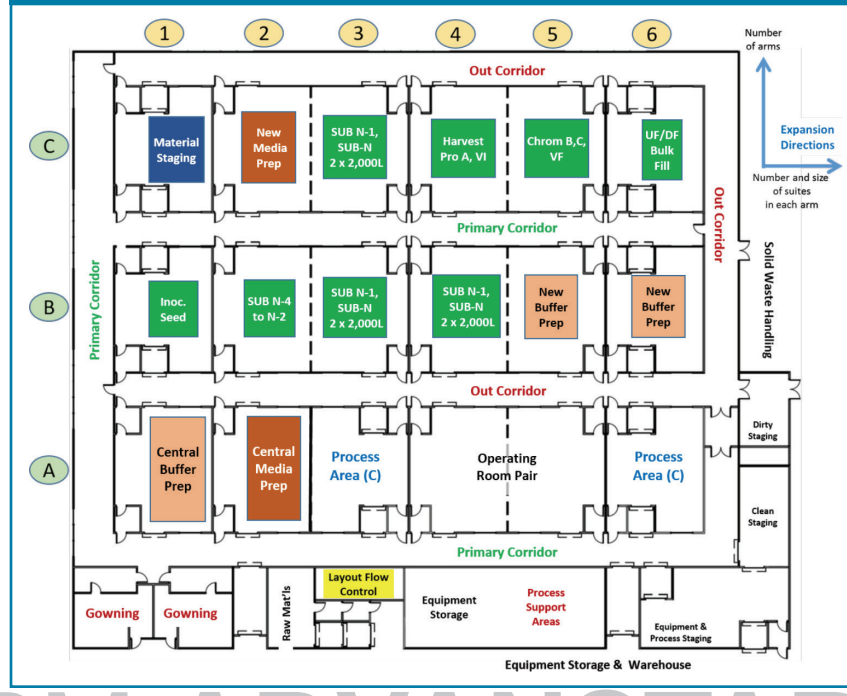
The typical characteristic of the new AV parameter is also associated with what we called "standard AV distributions" (**Figure 7**) (5), where the AV chart factors can be established in the same way as traditional factors such as B3 and B4 in S charts or D3 and D4 in R charts. AV charts may be used for AV data trend analysis in APR.

Contin. on page 45

If operated at capacity, the facility shown in **Figure 3** would have a very high utilization rate and an annual capacity of approximately 1.5 Mtons/year (6 grams/L, 42+weeks/year, 50% purification yield). Yet, if the campaign is shortened or the process removed, the same facility without modification can be returned to running small- or medium-sized processes for other products.

If Arms B and C are replicated either in the initial design or by an expansion at the top of **Figure 3** as Arms D and E, the plant's capacity can be further increased by an additional 1.5 Mtons/year. Very large-scale production of one or more products can be achieved by building multi-purpose facilities with numerous arms configured like Arms B and C. If sustained long term demand for the product is established, the large-scale process in Arms B and C can be easily transferred to a similarly designed multi-purpose facility for long-term operation and the launch facility returned to developing new processes and products.

Figure 3: One possible logical operating unit (LOU) arrangement for the large-scale, 6 x 2000-L monoclonal antibody (mAb) process. Support LOUs are added as needed.



Conclusion

Regulatory agencies continue to do much to expedite the approval of important new therapies. The biopharmaceutical industry must match these regulatory initiatives by creating a new class of manufacturing facilities capable of taking manufacturing off the critical path of launching and supplying products. Manufacturing these complex products over their entire lifecycle requires immediate access to available and qualified manufacturing facilities that can be adapted to produce a wide variety of products when they are needed using a wide range of processes. These facilities, using modern single-use systems in movable equipment within appropriately controlled multi-functional cleanrooms, are capable of quickly adapting to overcome the industry's manufacturing challenges. Processes and products will come and go, but the facility that can readily adapt to the different processes remains essentially the same. Only existing, operationally ready facilities flexible enough to manufacture whatever is required with minimal or no modifications can rapidly and efficiently fulfill the industry's future manufacturing challenges.

References

1. S.L. Nightinggale, J.M. Prasher, and S. Simonson, *Emerging Infectious Diseases* online, 13 (7) 1046. DOI: 10.3201/eid1307.061188.
2. M. F. Witcher and H. Silver, *Pharm.Tech.* 42 (9) 34, 38-41 (2018).
3. FDA, *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (Procedural)* (CDER/CBER, May 2014). **PT**

PEER-REVIEWED — *contin. from page 39*

In short, the new method for calculating AV is natural (i.e., it requires no intervention into calculations), valid (i.e., has already been confirmed by successful simulation test results), and discriminative (i.e., it offers a way to guarantee that only conforming batches are released into the market). The method can also be useful for setting trend analysis tools with regard to AV chart factors and AV in-house limits.

References

1. *USP* General Chapter <905>, "Uniformity of Dosage Units" (US Pharmacopeial Convention, Rockville, MD, 2014).
2. ASTM, "Standard Number E2810—11: Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units," October 2011.
3. J. S. Bergum, *ISPE Pharmaceutical Engineering* 35 (6) 68–79 (2015).
4. P. Cholayudth, *Pharmaceutical Technology* 40 (12) 34-43 (2016).
5. P. Cholayudth, *Pharmaceutical Technology* 41 (8) 30-39 (2017).
6. P. Cholayudth, *Pharmaceutical Technology* 42 (5) 34-44 (2018).
7. D.C. Montgomery, *Introduction to Statistical Quality Control* (John Wiley & Sons, New York, 2nd Ed., 1991). **PT**