# Establishing Target Fills for Semisolid and Liquid Dosage Forms

**Pramote Cholayudth**

COMSTOCK

**To meet the requirements of the *USP* ⟨755⟩ Minimum Fill and ⟨698⟩ Deliverable Volume tests, target fill levels greater than 100% must be established. This article proposes a criterion for establishing an appropriate target fill level such that a sample will have a 95% probability of passing these *USP* tests at 95% confidence.**

**Pramote Cholayudth** is the managing director of the Professional Conference Center in Bangkok, Thailand, and a validation consultant to Biolab Co., Ltd, 625 Lane 7A, Bangpoo Industrial Estate, Samutprakarn, 10280 Thailand, cpramote2000@yahoo.com.

Meeting the *USP* requirements for minimum fill and deliverable volume is a serious concern in pharmaceutical production. Filling operations must be controlled throughout the filling cycle to ensure that the sampled filled products will meet quality control specifications based on the *USP* ⟨755⟩ Minimum Fill or ⟨698⟩ Deliverable Volume tests. The common acceptance criterion of the two *USP* tests is that the average content of all samples tested must not be less than 100% of the labeled amount. Such a requirement will lead to a filling volume target greater than 100% of the labeled amount. This article proposes a criterion for establishing an appropriate target fill such that a sample will have a 95% probability of passing these *USP* tests at 95% confidence, *i.e.*, that the established target fill will guarantee with 95% confidence that 95 out of 100 samples will pass the *USP* tests.

## The *USP* ⟨755⟩ Minimum Fill test

The *USP* ⟨755⟩ Minimum Fill test applies to liquids, semisolids, and solids such as creams, gels, jellies, lotions, ointments, pastes, powders, and aerosols, including pressurized and nonpressurized topical sprays that are packaged in containers in which the labeled amount is not more than 150 g or 150 mL (1).

According to the test, the acceptance criteria for units with a labeled amount ≤60 g or mL/unit are as follows:

**Stage 1.** For a test of 10 units:

- The average content of 10 units must not be less than 100% of the labeled amount.
- None of the units tested may contain less than 90% of the labeled amount.

If the average content is less than 100% of the labeled amount or if not more than 1 unit contains less than 90% of the labeled amount, proceed to stage 2. Fail if the average content is less than 100% of the labeled amount or if more than 1 unit contains less than 90% of the labeled amount.

**Stage 2.** Following a test of 20 additional units:

- The average of 30 units must not be less than 100% of the labeled amount.
- Not more than 1 unit may contain less than 90% of the labeled amount.

Otherwise, fail.

The acceptance criteria for units with a labeled amount >60

and ⩽150 g or mL per unit are as follows:

**Stage 1.** For a test of 10 units:

- The average content of 10 units must not be less than 100% of the labeled amount.
- No unit may contain less than 95% of the labeled amount.

If the average content is less than 100% of the labeled amount or if not more than 1 unit contains less than 95% of the labeled amount, proceed to stage 2. Fail if the average content is less than 100% of the labeled amount or if more than 1 unit contain less than 95% of the labeled amount.

**Stage 2.** Following a test of 20 more units:

- The average content of 30 units must not be less than 100% of the labeled amount.
- Not more than 1 unit may contain less than 95% of the labeled amount.

Otherwise, fail.

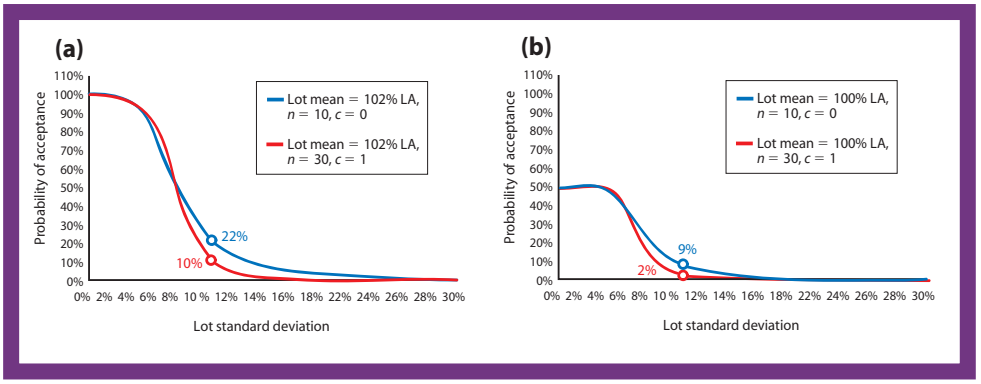



**Figure 1:** Operating characteristic curves for a *USP* Minimum Fill sampling plan (⩽60 g or mL per unit). LA = labeled amount.

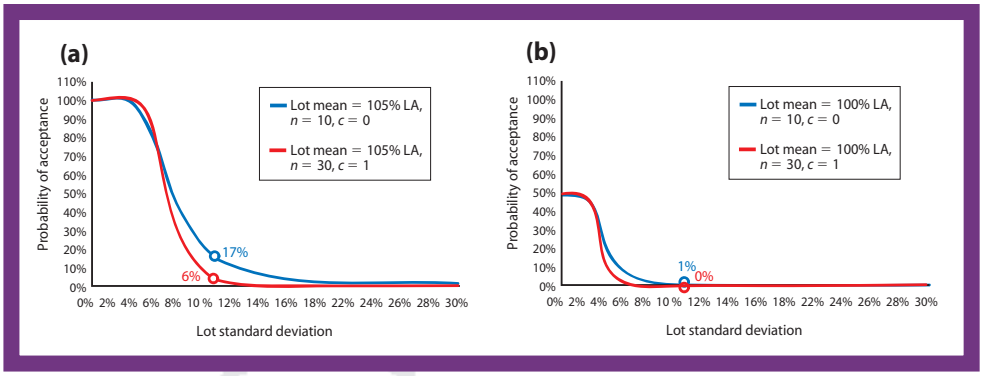



**Figure 2:** Operating characteristic curves for *USP* Minimum Fill sampling plan (>60 and ⩽150 g or mL per unit). LA = labeled amount.

## The *USP* ⟨698⟩ Deliverable Volume test

The USP ⟨698⟩ Deliverable Volume test establishes the volume requirement for oral liquids. The test is designed to ensure that oral solutions and suspensions will, when transferred from their original containers, deliver the labeled volume of the product. The test applies to products labeled to contain ⩽250 mL, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon the addition of a designated volume of a specific diluent.

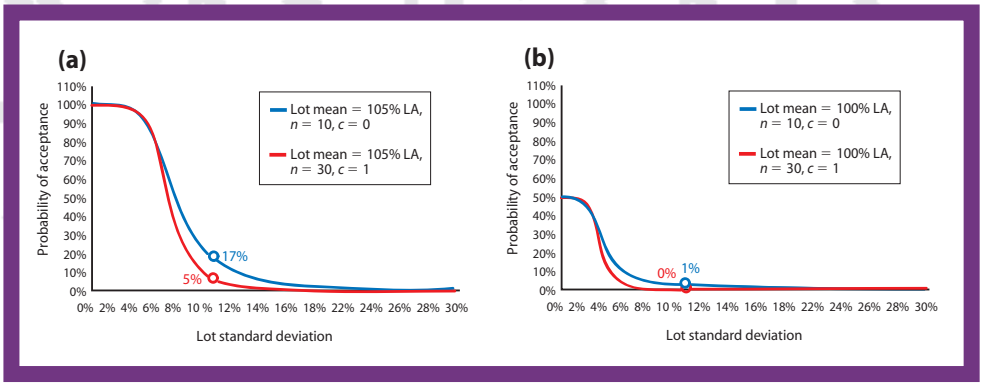



**Figure 3:** Operating characteristic curves for the *USP* Deliverable Volume sampling plan (⩽250 mL per unit). LA = labeled amount.

The acceptance criteria for the deliverable volume test are as follows:

**Stage 1.** For a test of 10 units:

- The average content of 10 units must not be less than 100% of the labeled amount.
- No unit may contain less than 95% of the labeled amount.
- For single-unit containers, no unit may contain more than 110% of the labeled amount.

If the average content is less than 100% of the labeled amount or if not more than 1 unit contains less than 95% of the labeled amount, proceed to stage 2. Fail if the average content is less than 100% or if more than 1 unit contain less than 95% of the labeled amount.

**Stage 2.** Following a test of 20 additional units:

- The average content of 30 units must not be less than 100% of the labeled amount.
- Not more than 1 unit may contain less than 95% and no unit may contain less than 90% of the labeled amount.
- For single-unit containers, not more than 1 unit may contain more than 110% but more than 115% of the labeled amount.

Otherwise, fail.

## Sample size

Some firms establish release specifications for minimum fill and deliverable volume using sample sizes different from those established in the *USP* tests. A common sample size is 20 units.

Even if the sample size is larger than what is stated in the *USP*, however, the acceptance criteria do not change. For example, the average content of 20 units tested must not be less than 100% the labeled amount, and so on.

## Sampling plan views of the two tests

Any quality parameter is subject to its variability, *i.e.*, its standard deviation (SD). Therefore, it may be useful to illustrate a sampling plan curve, known as the *operating characteristic* (OC) *curve*, for the sampling plans for the minimum fill and deliverable volume tests (see Figures 1, 2, and 3).

In Figures 1, 2, and 3, it can be seen that the probability of acceptance ($p_a$) is based on the likelihood that the sample averages (from stages 1 or 2 of the test) will be not less than 100% of the labeled amount at varying lot SD or sigma ($\sigma$) values. The $p_a$ also is based on the lot average (mean), *i.e.*, a higher lot mean will have a higher probability of acceptance than will a lower lot mean. For example, for a lot SD of ⩽4%, a lot mean of 102% of the labeled amount has a much higher probability of acceptance ($p_a$ = 100%) than a lot mean of 100% does ($p_a$ = 50%).

## Establishing the target fill for products required to pass the *USP* Minimum Fill test

A target fill value should be established that will guarantee with 95% confidence that 95 out of 100 samples will pass the *USP* Minimum Fill test. Because the common acceptance criterion of the Minimum Fill and Deliverable Volume tests is that the average is not less than 100% the labeled amount, the distribution of the sample mean will be used to determine the target fill level. For example, let us suppose that $\sigma$ for the minimum fill test data is known. By statistical rule, $\sigma$ for distribution of the sample mean or standard error of the mean ($\sigma_{\bar{x}}$) is equal to $\sigma/\sqrt{n}$, in which $n$ is the sample size (10 or 30). Figure 4 shows the distributions for individual and average (sample mean) values for a sample size of 10. The distribution curve for the averages is reillustrated in Figure 5, in which the mean is the target fill. This target is greater than 100% of the labeled amount. The next key step is to determine the location of the target fill level.

It can be seen in Figure 5 that the average values below 100% of the labeled amount are classified as defects. Thus, the percentage area below 100% of the labeled amount is determined to be the defect rate. This area can be calculated in Microsoft Excel by a trial and error method using the following equations:

$$\text{Conf.} = 1 - \text{BINOMDIST}(5,100,0.10225,\text{TRUE}) = 95.00\%$$

$$Z = \text{NORMSINV}(0.10225) = -1.26884$$

Using these equations, this area is determined to be 0.10225 or 10.225%, such that 95 of 100 samples will have an average not less than 100% of the labeled amount at 95% confidence. Because the defect rate is 10.225%, if we test many sets of samples, in which each set comprises 100 samples of 10 units, the numbers of failed tests, ranging from 2 through 20, will have the binomial distribution shown in Figures 6 and 7.

The location of the sample mean at 100% of the labeled amount shown in Figure 5 may be transformed (normalized) into a $Z$ score using the following equation in Microsoft Excel:

$$Z = \text{NORMSDIST}(0.10225) = -1.26884.$$

This implies that if

$$(L - T)/(\sigma_{\bar{x}}) = -1.26884$$

then

$$T = L + 1.26884\ \ \sigma_{\bar{x}} \qquad [1]$$

$$T = L + 1.26884\ \ \sigma/\sqrt{n} \qquad [2]$$

$$T = L + 0.4\sigma \text{ (for QC sample size } n = 10) \qquad [3]$$

$$T = L + 0.28\sigma \text{ (for QC sample size } n = 20) \qquad [4]$$

in which $T$ is the target fill value in g or mL, $L$ is the labeled

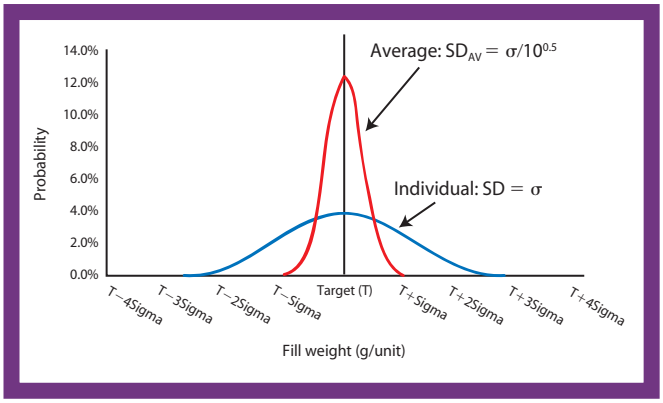



**Figure 4:** Distribution curves for individuals and averages ($n$ = 10).

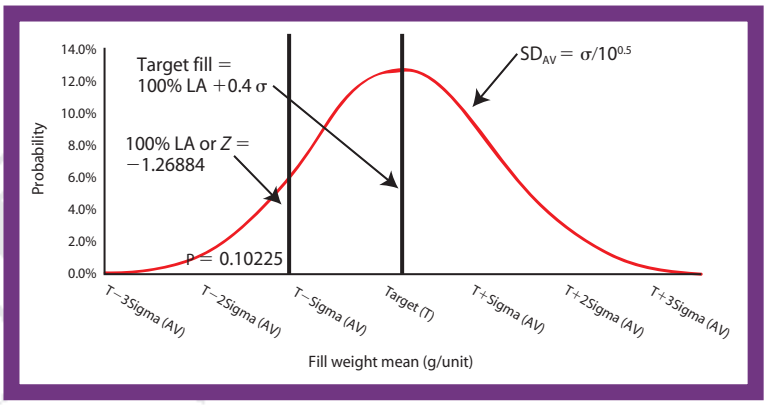



**Figure 5:** Distribution curve for averages ($n$ = 10). LA = labeled amount.

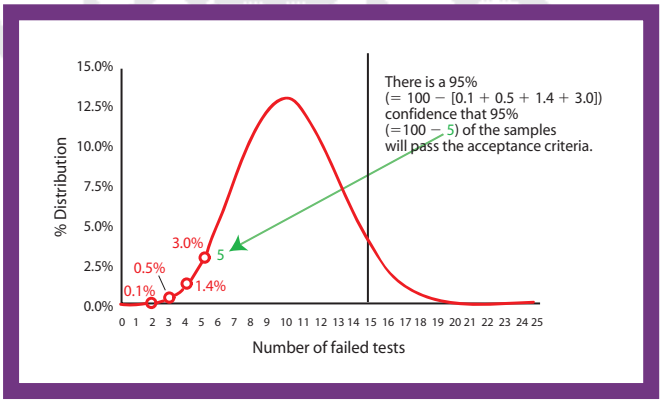



**Figure 6:** Binomial distribution curve.

amount (*i.e.*, 100% of the labeled amount) in g or mL, $\sigma_{\bar{x}}$ is the lot sigma for mean distribution (standard error of the mean), and σ is the lot sigma.

Equations 1 and 2 are the general equations for target fill. Equations 3 and 4 are used for sample sizes of 10 and 20 units, respectively.

## How to obtain the lot sigma

Samples of 10 or 20 units may be randomly taken throughout the filling cycle to form a large composite sample of at least 200 units. The computed SD is estimated to be the lot sigma. A case study was conducted to establish the target fill for a cream product in a 5-g tube. Fourteen samples of 20 filled tubes were taken randomly throughout the filling cycle to form a composite sample of 280 tubes. The computed SD (*i.e.*, the lot sigma) was 0.068 g. The average tare weight of an empty tube was 2.37 g and the sample size was 20. The check-weighing for in-process control was done on individual gross weights (net plus tare weight) from samples of 20 units taken every 30 min (in advanced facilities, automatic check-weighers often are used). To calculate the target fill value ($T$), the following equations were used:

$$T = \mathrm{L} + 0.28\sigma$$

$$T = (5 + 2.37) + (0.28 \times 0.068) = 7.39 \text{ g/tube}$$

The control limits for in-process control charts were determined on the basis of the actual distribution of the available data, as follows:

$$\text{upper action limit} = T + 2.5\sigma = 7.56 \text{ g/tube}$$

$$\text{upper warning limit} = T + 1.5\sigma = 7.49 \text{ g/tube}$$

$$\text{lower warning limit} = T - 1.5\sigma = 7.29 \text{ g/tube}$$

$$\text{lower action limit} = T - 2.5\sigma = 7.22 \text{ g/tube.}$$

## Data determination results

The results of the application of the equations are seen in Table I. In all cases, the probability between $\pm Z = 1.0$ was computed in Microsoft Excel using the following equation:

$$P = \mathrm{NORMSDIST}(1) - \mathrm{NORMSDIST}(-1)$$

$$= 0.6827 = 68\% \text{ (rounded).}$$

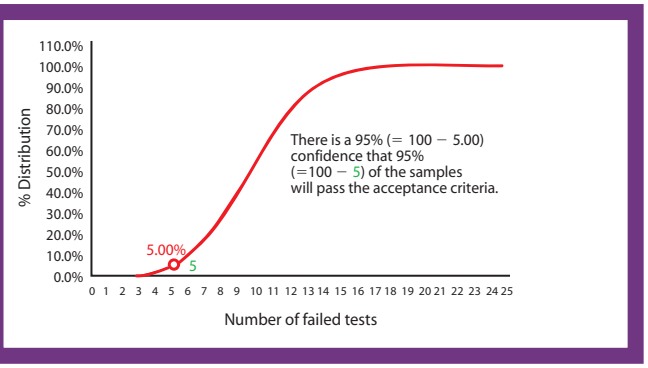



**Figure 7:** Cumulative binomial distribution.

**Table I: Data distribution using the equations.**

| Actual distribution | | Normal distribution | |
|---|---|---|---|
| Range (mean ∓$Z\sigma$) | Distribution (%) | Range (∓$Z$) | Distribution (%) |
| Mean ∓1.0σ | ~71 | ∓1.0 | ~68 |
| Mean ∓1.5σ | ~90 | ∓1.5 | ~87 |
| Mean ∓2.0σ | ~96 | ∓2.0 | ~95 |
| Mean ∓2.5σ | ~99 | ∓2.5 | ~99 |

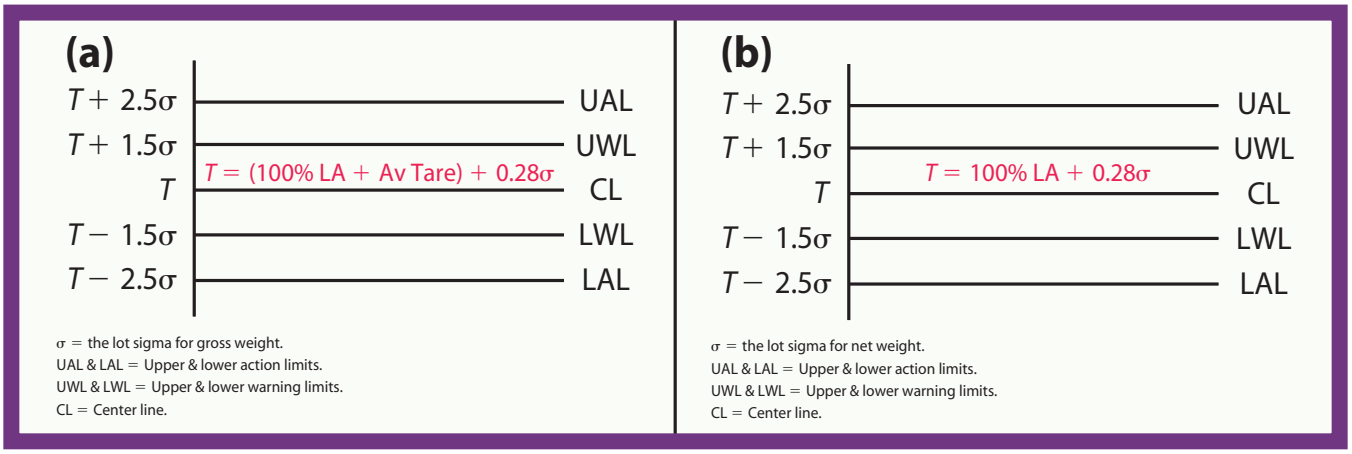
The data distribution was determined by tabulating the data (280 values) from minimum to maximum. For example, to calculate the ±1.0σ distribution, the number of values between the upper and lower limits (average ± 1.0σ) were counted and computed to be ~71%. We used ±1.5 and ±2.5σ to tighten the warning and action limits, respectively. However, conventional control chart limits (*i.e.*, ±2 and ±3σ) can be used as well.

Because the lot sigma is known (by estimation), one can find the probability that one tube will be below 90% of the labeled amount (in this case, the $Z$ score), by making the following calculations:

$$Z = (90 - 100) \times 5 / (100 \times 0.068) = -7.35$$

The probability at $Z_{-7.35}$ is 0.00. Therefore, the probability that the contents of one tube will be below 90% of the labeled amount is 0.00%.

The target fill and control chart limits for thes gross weights




**Figures 8(a) and (b):** Schematic in-process control chart for a cream's individual weight. LA = labeled amount.

are practical for use with tubes with good tare-weight uniformity. For tubes with poor tare-weight uniformity, the target fill and the control chart limits for net weight may be used and established in the same way, as follows:

$$T = L + 0.28\sigma$$

$$T = 5 + 0.28 \times 0.068 = 5.02 \text{ g/tube}$$

The net weights may be obtained by preweighing and temporarily marking the tubes before feeding the filling machine. Once those tubes are filled, the net weights are obtained.

## Establishing the target fill for products required to meet the *USP* Deliverable Volume test

The overall procedure and acceptance criteria for establishing the target fill levels to meet the *USP* Deliverable Volume test are the same as those for meeting the *USP* Minimum Fill test. Because the acceptance criteria for the sample average are the same as the criteria for the sample average for the Minimum Fill test (*i.e.,* not less than 100% of the labeled amount), the target fill of labeled volume plus 0.28σ ($L + 0.28\sigma$) also is applied to a quality control sample of 20 units (see Figures 9 and 10).

The lot sigma for deliverable volume may be estimated from the SD of sample data of individually measured volumes of at least 30 units. The lot sigma is then estimated using $c_4$, which is the control chart or statistical process control factor used to convert the sample SD to lot sigma by dividing the sample SD by c4, as follows (see Table II):

Lot $\sigma = SD/c_4$.

In practice, it may not be accurate enough to measure volumes in calibrated cylinders. An alternative method is to weigh them on a balance and convert the weight to volume using the correct density value.

With either of these two methods of checking the individual weights and volumes (individual chart), it may take a long time to record the results. Another approach is to use the average (X-bar) and range (R) charts, in which the sample averages and ranges are recorded.

To construct the X-bar chart, the center line (*i.e.,* the target fill level) is established using equations 1 or 2, described previously:

$$T = L + 1.26884\ \sigma_{\bar{x}} \quad [1]$$

$$T = L + 1.26884\ \sigma/\sqrt{n} \quad [2]$$

In theory, the two equations should be interchangeable if only one of $\sigma_{\bar{x}}$ or $\sigma/\sqrt{n}$ is known. A study of a 30-g cream product was conducted to compare the values of $\sigma_{\bar{x}}$ and $\sigma/\sqrt{n}$. In the study, 54 samples of 20 tubes were taken throughout the filling cycle. Each sample data (gross weight) was computed for average $(\bar{X})$ and SD. All the averages were calculated for SD for sample means $(SD_{\bar{x}})$ and directly estimated to $\sigma_{\bar{x}}(SD_{\bar{x}} = \sigma_{\bar{x}} = 0.109 \text{ g})$ because of the large number (54) of samples. The SDs of all sample were averaged $(\overline{SD} = 0.066$ g) and estimated to the lot sigma using $c_4$ ($\sigma = \overline{SD}/c_4 = 0.066 / 0.9869 = 0.067$ g, then $\sigma/\sqrt{n} = 0.067 / \sqrt{20} = 0.015$ g).

According to Nash, "…what is possible in other industries is not always achievable in pharmaceutical processes." This statement is confirmed by our study results. We have seen that the $\sigma_{\bar{x}}$ of 0.109 g and the $\sigma/\sqrt{n}$ of 0.015 g are greatly different. Therefore, it was determined that the equation "$L + 1.26884\ \sigma_{\bar{x}}$" should be used to calculate the target fill. Using this equation, the actual standard error of the mean, 0.109 g, is used.

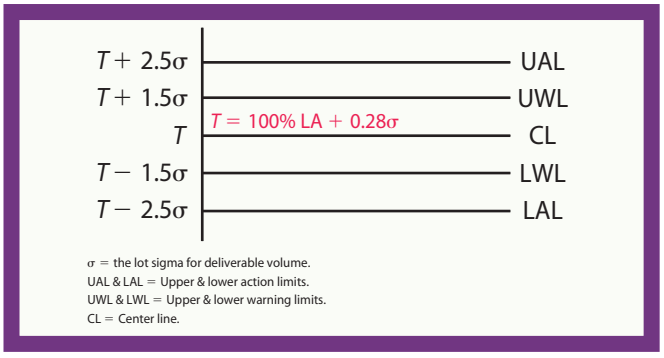



**Figure 9:** Schematic in-process control chart for an oral liquid's individual volume. LA = labeled amount.

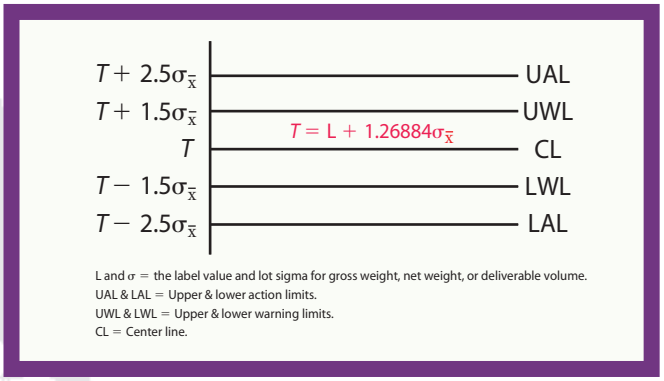



**Figure 10:** Schematic in-process control chart for a sample average.

**Table II. Statistical process control factors.**

| *n* | $c_4$ | $d_2$ | $d_3$ | $D_1$ | $D_2$ | $D_3$ | $D_4$ |
|---|---|---|---|---|---|---|---|
| 5 | 0.9401 | 2.326 | 0.8641 | 0 | 4.9183 | 0 | 2.1145 |
| 10 | 0.9727 | 3.078 | 0.7971 | 0.6867 | 5.4693 | 0.2231 | 1.7769 |
| 15 | 0.9823 | 3.472 | 0.7562 | 1.2034 | 5.7406 | 0.3466 | 1.6534 |
| 20 | 0.9869 | 3.735 | 0.7287 | 1.5489 | 5.9211 | 0.4147 | 1.5853 |
| 25 | 0.9896 | 3.931 | 0.7084 | 1.8058 | 6.0562 | 0.4594 | 1.5406 |
| 30 | 0.9914 | 4.086 | 0.6926 | 2.0082 | 6.1638 | 0.4915 | 1.5085 |

## Summary

Both the *USP* ⟨755⟩ Minimum Fill and ⟨698⟩ Deliverable Volume tests require that the average content of quality control samples be not less than 100% of the labeled amount. To meet these requirements, overfilling is necessary to meet target fill levels requirements.

During regular operations, the filling process is regularly controlled to keep the lot average content close to the target fill amount. By using the proposed equations, the lot average will provide a 95% probability of passing the quality control spec-

ifications (*i.e.,* that the average content is not less than 100% of the labeled amount) at 95% confidence. Using these equations to establish an appropriate target fill level will help prevent excessive overfill and improve product yield.

The probability that the samples will not meet the other specifications of these *USP* tests (*i.e.,* that no unit may contain less than 90% of the labeled amount) can also be computed using these equations and should be very low. In the case study in which these equations were applied, this probability was zero.

The equation "$L + 1.27\ \sigma_{\bar{x}}$" (rounded), is probably the most practical and thus is recommended for use. In this expression, $L$ represents the net content in weight or volume, or an equivalent such as gross weight. Standard values for lot sigma and the actual standard error of the mean for a product may be obtained from the averages of at least three production lots.

To calculate in-process controls using an individual (X) chart, the following definitions may be used:

Target fill ($T$) or center line (CL):
$$L + 1.27\ \sigma_{\bar{x}}$$

Warning limits: $T \pm 1.5\ \sigma$

Action limits: $T \pm 2.5\ \sigma$

To calculate in-process controls using X-bar and R charts, the following equations may be used:

X-bar chart:

Target fill (T) or center line (CL):
$$L + 1.27\ \sigma_{\bar{x}}$$

Warning limits: $T \pm 1.5\ \sigma_{\bar{x}}$

Action limits: $T \pm 2.5\ \sigma_{\bar{x}}$

R chart:

Upper control limit $= D_4\,\bar{R}$

Center line $= \bar{R}$

Lower control limit $= D_3\,\bar{R}$



## References


1. United States Pharmacopeia, "⟨755⟩ Minimum Fill," *USP 27–NF 22* (United States Pharmacopeial Convention, Rockville, MD, 2004), p. 2325.
2. United States Pharmacopeia, "⟨698⟩ Deliverable Volume," *USP 27–NF 22* (United States Pharmacopeial Convention, Rockville, MD, 2004), p. 2300.
3. D.C. Montgomery, *Introduction to Statistical Quality Control* (John Wiley & Sons, New York, NY, 2d ed., 1991), pp. 201–250.
4. S. Bolton, *Pharmaceutical Statistics: Practical and Clinical Applications* (Marcel Dekker, Inc., New York, NY, 3d ed., 1997), pp. 62–98.
5. American Society for Quality Statistics Division, *Glossary and Tables for Statistical Quality Control* (ASQ Quality Press, Milwaukee, WI, 3d ed., 1996), pp. 158–159.
6. R.A. Nash, "Understanding the Process Capability Index Concept," *J. Valid. Technol.* **4** (3), 202–204 (1998). **PT**