IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

SR #3. Data Variance, Central Tendency, and Measurement Calculations (Continued)

By 
Alan M Golden

Feb 24, 2022 8:00 am EST

Peer Reviewed

Statistics Roundtable (SR) is an IVT feature that provides readers an opportunity to discuss information about statistics and demonstrate the application of statistics to pharmaceutical problems. The use of statistics is fundamental in regulated industries; the statistical basis for decision-making is an expectation. Any effort to increase the understanding and application of statistics in daily work life will be useful to readers.

The potential scope of SR content is extensive; statistics applications in validation and QA activities are numerous. Our goal in SR is to provide basic understanding of statistics concepts specific to pharmaceutical applications. We will discuss statistics concepts in validation and QA in simple language, and then demonstrate their use in example problems. Readers have opined their preference for case studies describing practical applications of theory; we intend to emphasize representative problem applications.

Comments from readers are needed to help us fulfill our objective for this column. SR will be most successful when validation, quality, and statistics communities participate in this endeavor. Suggestions for future discussion topics are invited. Readers are also asked to contribute manuscripts for publication – please share your successful experiences with others. Please contact column coordinator Jeremy Ebersole via the comments section below with questions, suggestions, or topics for discussion.

INTRODUCTION

This paper continues discussion of basic statistical concepts that are useful in validation studies. The previous paper (1) explored the definition of statistics, why statistics are important in validation, and the regulatory requirements for statistics in our processes. We discussed the concept and measurement of variance and data distribution and the relationship of variance to validation. We looked at ways to measure variance, and when different types of measurements are appropriate. Here we will continue that discussion with additional concepts and methods.

COEFFICIENT OF VARIATION

The Coefficient of Variation (%CV) combines the mean and the standard deviation of a data set to give a measure of how big the variation is relative to the quantity being measured. It is calculated by diving the standard deviation by the mean and multiplying by 100 to get a percent.

$$\%CV = \left(\frac{SD}{\bar{X}}\right) 100$$

The %CV is useful in measuring variation in data whose mean and standard deviation tend to vary together. Examples could include variation in sampling is greater for when sampling larger surfaces than smaller surfaces or variation is greater for larger tanks than smaller tanks. In these cases, %CV allows cross population comparisons of variance in populations with different means. If the mean and SD don't vary together, %CV is much less useful. As you divide by the mean, %CV becomes very large at the low end of the measurement scale as the variance tends to be less at lower values across a range. While numerically correct, it can give the impression of an inflated variation in the data set. If the mean and standard deviation do not vary together, reporting the SD and mean individually could give a clearer picture of the data set.

PROCESS CAPABILITY

Now that we have seen how to measure variability in our system, how do we use it in validation? How do we know if the variance in our process or test method is low enough to give us good product or tell us reliable test results? This is where the concept of process capability is relevant.

We have seen how we could calculate probable ranges for data in a normal distribution with known mean and SD. For quality assurance, we need to match those probable ranges with the ranges allowed by in process ranges, test method allowed variance, or customer specifications. The indices for measuring the goodness of this match areCp andCpk.

Cp is the measure that compares the actual process spread with the allowable process spread.

$$\text{Cp} = \frac{\text{Allowable Process Spread}}{\text{Actual Process Spread}}$$

$$\text{Cp} = \frac{\text{USL} - \text{LSL}}{6\ \text{SD}}$$

- USL and LSL are the upper and lower specifications for the product or process
- 6 SD (6 sigma) gives you 99.73% degree of compliance
- $\pm$ 3.0 SD on either side of the mean
- The larger the Cp, the greater the potential of the process to produce product within specification limits or the test method to be capable of detecting defects.

The following figures illustrate capable and non-capable processes.

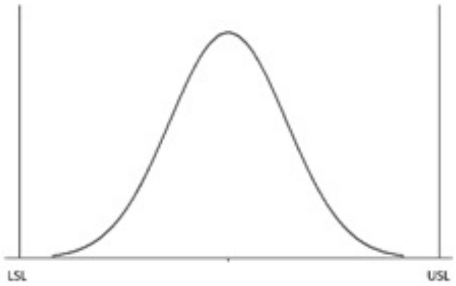

Figure A. This figure illustrates a process with a Cp > 1. The process spread in within the process limits. This process is capable of producing product or test results with very few defects.

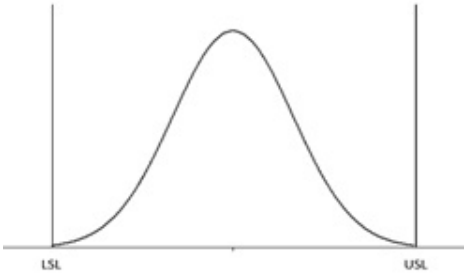

Figure B. Figure B illustrates a process with a Cp = 1. The process spread is exactly at the process limits. If the process is perfectly centered, the process or method will produce 0.3% defectives.

Figure C. This illustrates a process with a Cp < 1. The process spread is greater than the tolerance. This process or method could produce an unacceptable level of defects.

The determination of an acceptable Cp for your process is based on the needs of the process and the level of risk associated with a defect. A through risk analysis should always be performed to determine what level of process spread or variance is acceptable. And of course, you have to know the allowable process spread. Another way to look at Cp is to use it to determine the maximum variance your process or test method can tolerate and still be capable. This just requires a simple algebraic rearrangement of the formula.

$$Cp = \frac{USL - LSL}{6\,SD} \rightarrow SD = \frac{USL - LSL}{6\,Cp}$$

You plug in the value of Cp that you want your process to have, and you can calculate the maximum SD that your process or test method can have during validation. If the measured variance during validation is less than or equal to the target SD, the validation passes. The following table lists some common industry standards for Cp (Montgomery (2004).

Table 1

Situation	**Recommended minimum process capability for two-sided specifications**	**Recommended minimum process capability for one-sided specificati**
Existing process	1.33	1.25
New process	1.50	1.45
Safety or critical parameter for existing process	1.50	1.45
Safety or critical parameter for new process	1.67	1.60
Six Sigma quality process	2.00	2.00

Process capability can also be used to predict the number of defects per million opportunities (DPMO). This is expressed using a probability density function (PDF). The PDF is used to specify the probability of adata point falling within a particular range of values by looking at the area under the distribution. The PDF can be expressed by the following equation:

$$\Phi(\sigma) = \frac{1}{\sqrt{2\pi}} \int_{-\sigma}^{\sigma} e^{-t^2/2}\, dt$$

Using the PDF, the following table illustrates the process yield and DPMO for a range of Cp(k) values:

Table 2

Cpk	**Sigma level (?)**	**Area under the Probability Density Function**	**Process yield**	**DPMO**
0.33	1	0.682689492	68.27%	317311
0.67	2	0.954499736	95.45%	45500

1	3	0.997300204	99.73%	2700
1.33	4	0.999936658	99.99%	63
1.67	5	0.999999427	100.00%	1
2	6	0.999999998	100.00%	0.002

As is apparent, trying to optimize a process to increase Cpk > 2 may have limited value in terms of effort and expense.

Cp does not account for “off aim” performance in a process. If the process mean is not centered within the process limits, the index Cpk can be used. The “k” indicates the degree off center the process is. Cpk is calculated by using the spread between the process mean and the nearest specification limit to the mean.

$$\text{Cpk} = \min\left\{\frac{\text{USL} - \bar{\text{X}}}{3\ \text{SD}}, \frac{\bar{\text{X}} - \text{LSL}}{3\ \text{SD}}\right\}$$

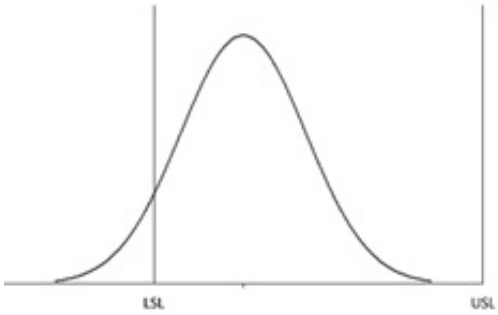

Figure D. This is an illustration of off-center performance. The Cp calculation could give a good result, but the Cpk calculation would show this is not acceptable performance. Off-center performance is not always a bad situation. If the Cpk calculation shows that the process spread is still within the specification limits, the process would still perform capably.

It is possible to calculate k to determine how far off center the process is. All you need is the preferred target for the process -- normally the center of the process limits. It is then possible to calculate k as follows:

$$\text{k} = \frac{|\text{Target} - \bar{\text{x}}|}{\left(\frac{\text{USL} - \text{LSL}}{2}\right)}$$

$$\text{Cpk} = \text{Cp}(1 - \text{k})$$

$$\text{k} * 100 = \%\ \text{Off Center}$$

This is a very useful measurement to make during development. It can allow the development team to make adjustments in manufacturing to center the process or reevaluation of the process limits if possible.

If your process limits are a one-sided spec, you can still calculate a Cp value to determine capability. The formulas look similar to the Cpk calculation in that they only use one half of the curve. The formula you use depends on if you have an upper specification or a lower specification. You only multiply the SD by 3, as you are only looking at the variance spread on the side of the curve nearest to the specification limit. See Figure E.

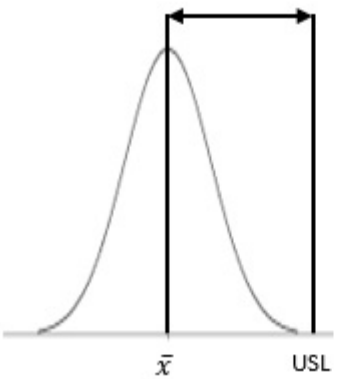

Figure E

$$\text{Cp(U)} = \frac{\text{USL} - \bar{\text{X}}}{3\ \text{SD}}$$

$$\text{Cp(L)} = \frac{\bar{\text{X}} - \text{LSL}}{3\ \text{SD}}$$

SUMMARY

In validation, the primary concern is with variance and the measurement and control of variance. To restate, variance is the natural tendency of a system to “wobble” a bit, so that the same action taken at different times, with different people, with different samples, in different locations, and with different equipment will give different results. Using statistics, we can determine if this natural wobble is the result of common cause variation or special cause variation and if the amount of variation inherent in the system exceeds the tolerances of our product or process. The most common reason of validation failures is a lack of understanding of the process variance prior to validation. A thorough characterization is required prior to validation to ensure all sources of variance are understood and controlled if needed. If the variance in the process is greater than what is tolerable, than either variance has to be reduced or specifications have to be adjusted. Failure to show a capable process will result in an unacceptable level of process or product failures during production. The proper use and application of basic statistics allows the window into our process, so appropriate determinations and decisions can be made. Also, the proper use of statistics allow proof that our processes and test methods meet their intended use.
The next paper in the series will discuss acceptance sampling and its application to validation, and the differences between validation and lot acceptance sampling.

REFERENCES

1. Berger, R. W., Benbow, D. W., Elementary, A. K., Walker, H.F. (2007) The Certified Quality Engineer Handbook, Second Edition. Milwaukee, Wisconsin: ASQ Quality Press
2. Boyles, R., (1991)."The Taguchi Capability Index.".*Journal of Quality Technology*. 23(1).Milwaukee, Wisconsin:American Society for Quality Control.
3. David, Stirzaker (2007). Elementary probability. Boston, Mass. Cambridge University Press
4. Ghasemi, A.,Zahediasl, S., (2012) Normality Tests for Statistical Analysis: A Guide for Non-Statisticians. Int J Endocrinol Metab. 10(2): 486–489. Accessed on line January 30, 2019, at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3693611/
5. Grubbs, F. E. (February 1969). "Procedures for detecting outlying observations in samples". Technometrics. 11 (1): 1–21.
6. Montgomery, D., (2004).Introduction to Statistical Quality Control.New York, New York: John Wiley & Sons, Inc.
7. Process Capability (Cp, Cpk) and Process Performance (Pp, Ppk) – What Is the Difference? https://www.isixsigma.com/tools-templates/capability-indices-process-capability/process-capability-cp-cpk-and-process-performance-pp-ppk-what-difference/ (accessed on Jan 22, 2019)
8. Razali, Nornadiah; Wah, Yap Bee (2011)."Power comparisons of Shapiro–Wilk, Kolmogorov–Smirnov, Lilliefors and Anderson–Darling tests." Journal of Statistical Modeling and Analytics. 2 (1): 21–33.
9. Thode, H. (2002). Testing for Normality. New York: Marcel Dekker, Inc.
