Understanding Variation Can Improve Your Supply Chain

Fernando Portes, MEng/MPS/MBA/PMP/CQE
Principal and Owner, Best Project Management
Affiliate Professor, Stevens Institute of Technology

About the Author

Fernando Portes, MEng/MPS/MBA/PMP/CQE, Principal and Owner, Best Project Management (www.bestpjm.com) is an experienced project /program manager, engineer, and educator, who has written several managerial and technical publications (http://www.bestpjm.com/our-staff.html). He is listed in Who is Who in Science and Engineering, in Who is Who in the US, and in Who is Who in the World. He has taught at the graduate and undergraduate levels in three universities, and is currently rated as one of the best project management professors at the Howe School of Stevens Institute of Technology, where he developed the pharmaceutical project management class, which he has taught to several Fortune 500 organizations since 2005. He can be reached at portes@bestpjm.com.

(this presentation can be downloaded from: http://www.bestpjm.com/our-staff.html)

The Facts

- A pharmaceutical organization had frequent release failures of its top selling product.

- Had set up a fairly common stability limit*, which triggered investigations when an stability point differed by more than 5% from its previous measurement.

**. Identification of Out of Trend Stability Results. A Review of the Potential Regulatory Issue and Various Approaches. PhRMA CMC Statistics and Stability Expert Teams. Pharmaceutical Technology. April 2003.*

The Problems

Frequent release and stability failures which resulted in:

- Several supply chain interruptions, which complicated relationships with customers.
- Inconclusive stability failure investigations, all of which consumed funds, time, and organizational resources.
- Lost of several million dollars in the profits that this product was supposed to generate.

The Reaction

The Supply Chain Vice President:

- Assembled a cross-disciplinary team with the relevant functional departments.
- Hired a consultant (Fernando Portes) to manage this project, and to provide quality engineering* skills to the organization.

**. Quality engineering is the science of understanding and controlling variation.*

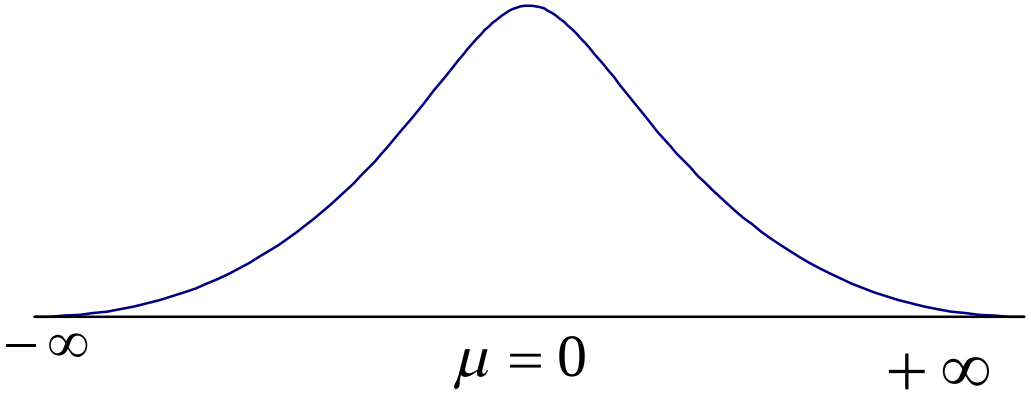
Reason to Like Theories

"Experience without theory teaches nothing. In fact, experience cannot be even recorded unless there is some theory, however crude, that leads to a hypothesis and to a system by which to catalog observations"

Source: Mind and the World Order. Clarence Lewis. 1956, Page 195. Quoted in Out of the Crisis. Edward Deming. 1991. Page 317.

Variation Fundamentals

Normal Distribution



$$f(x) = \frac{1}{\sqrt{2\pi}} e^{\frac{-x^2}{2}}$$

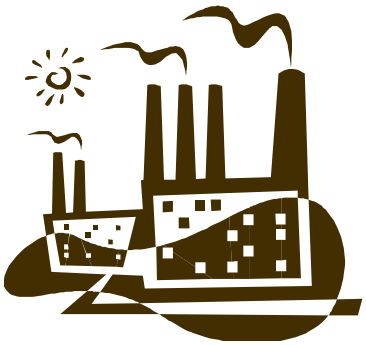
$\mu \pm \sigma$	68% of the population
$\mu \pm 2\sigma$	95% of the population
$\mu \pm 3\sigma$	99% of the population

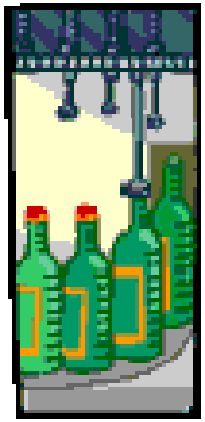
To account for means different than 0 and standard deviations different than 1, the distribution is normalized by:

$$Z = \frac{Xi - \mu}{\sigma}$$

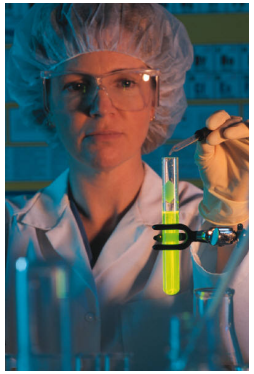
Variation in a Pharma Supply Chain

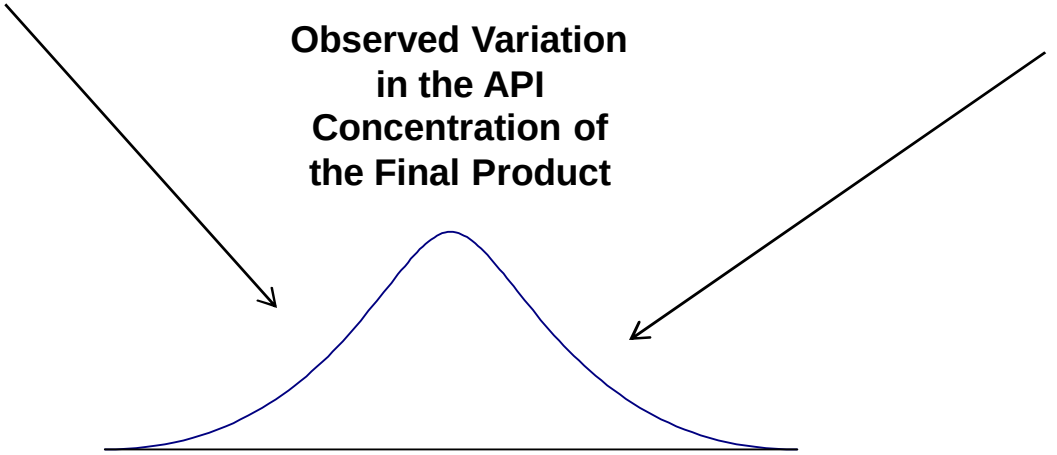
Manufacturing Processes





API Testing

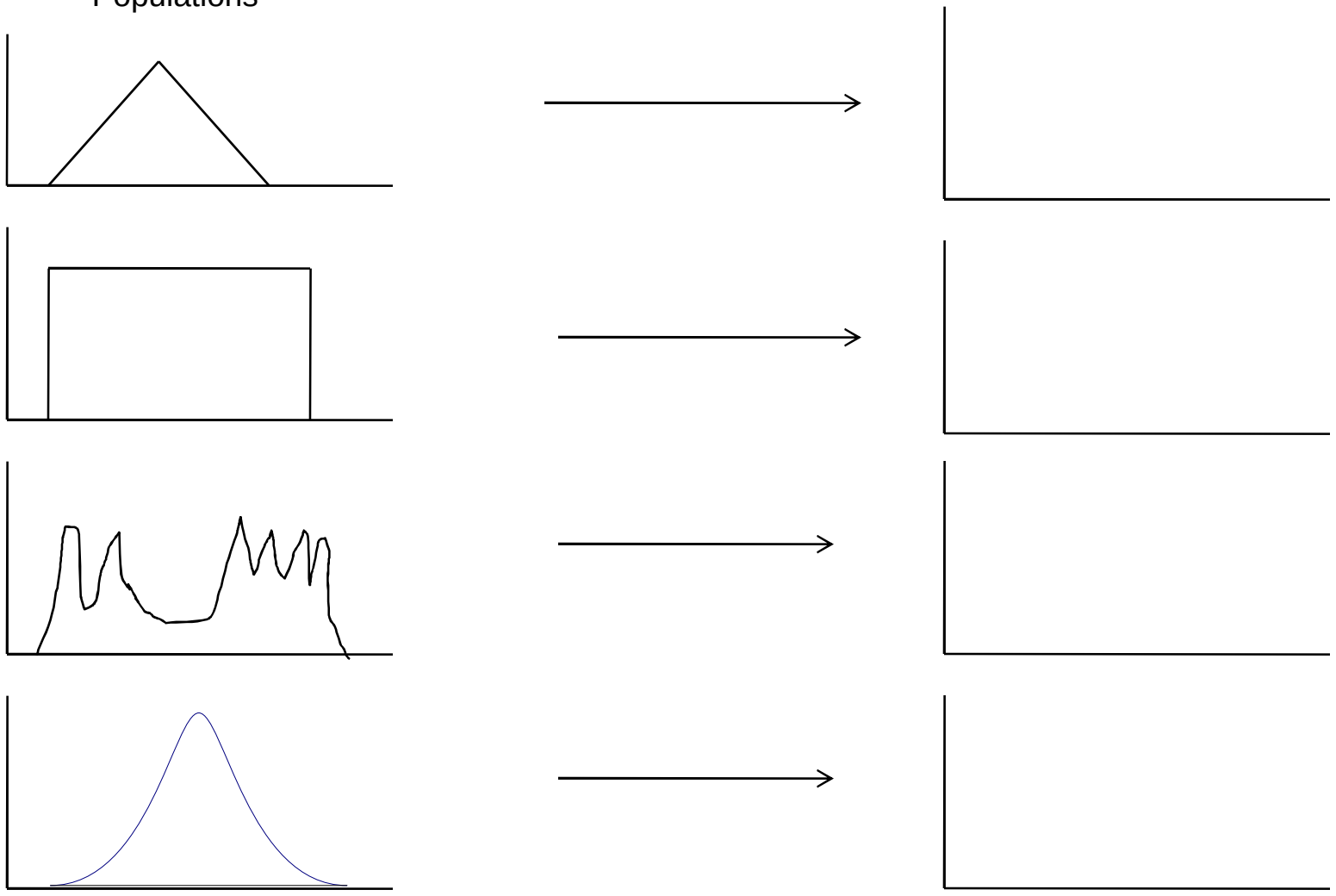




Why the Normal Distribution?

Populations

Distributions of the Averages of Samples Taken from the Populations



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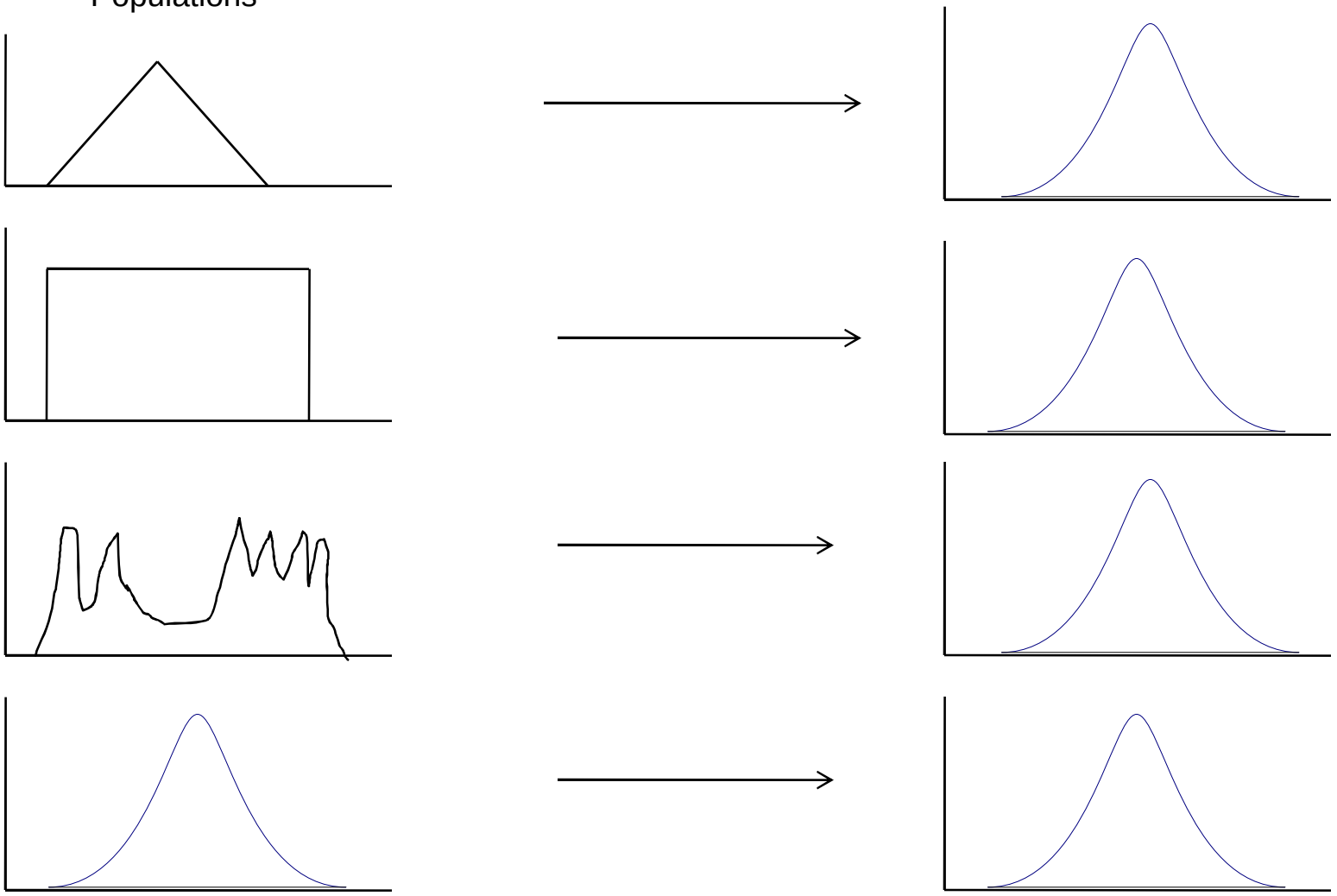
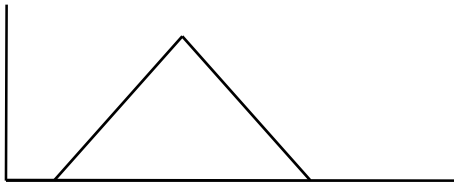
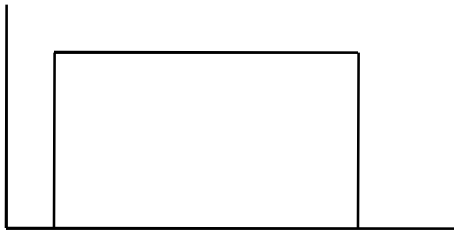
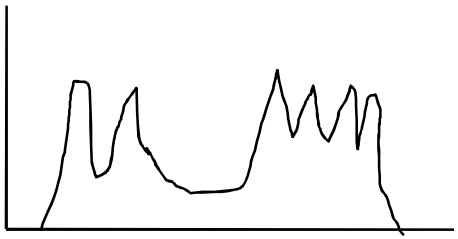


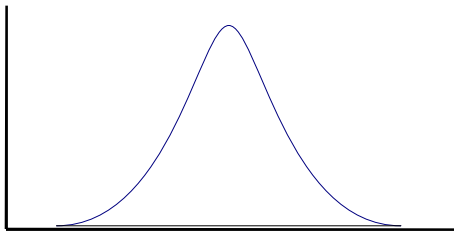
The Central Limit Theorem

Populations

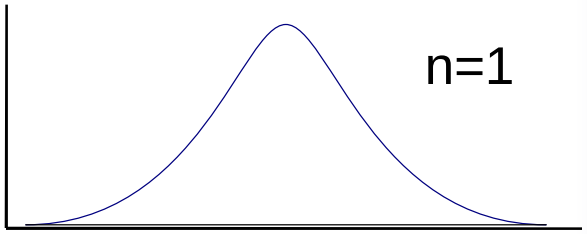




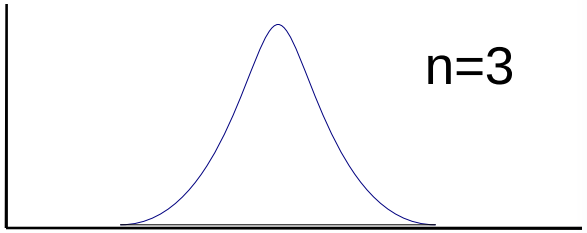


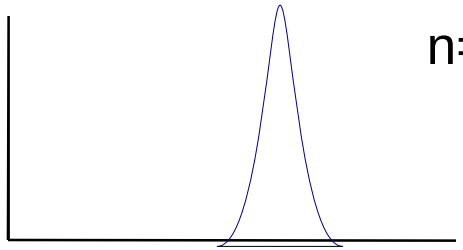


Distributions of the Averages of Samples Taken from the Populations



$$S_{\overline{X}} = \frac{\sigma_{population}}{\sqrt{n}}$$





The Math of Variation

Total Variation:

$$\sigma^2_{observed} = \sigma^2_{process} + \sigma^2_{assay}$$

$$\sigma^2_{assay} = \sigma^2_{repeatability} + \sigma^2_{reproducibility}$$

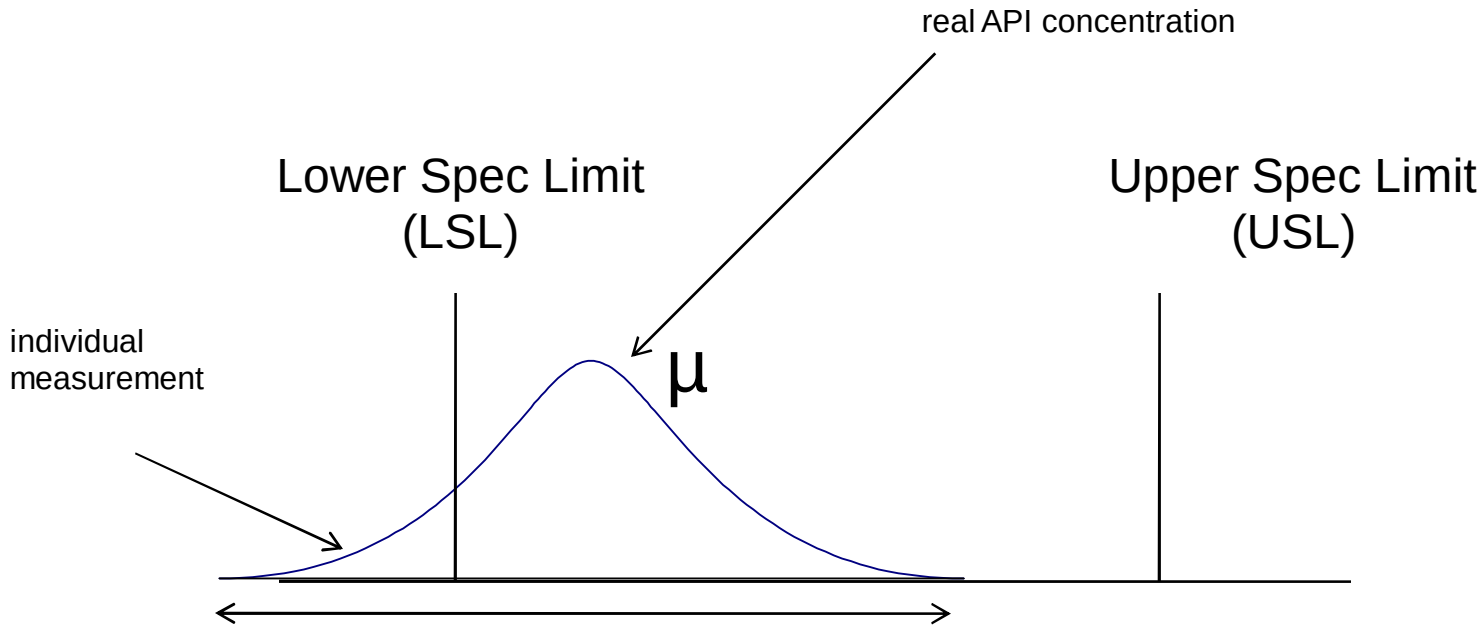
$\sigma^2_{repeatability}$ Precision: the variance obtained when the same assay is performed by the same analyst, in the same equipment, during consecutive measurements, during the same day.

$\sigma^2_{reproducibility}$ Variation between different analysts performing the same assay, in the same equipment, at different days.

Measurement Error and Specs

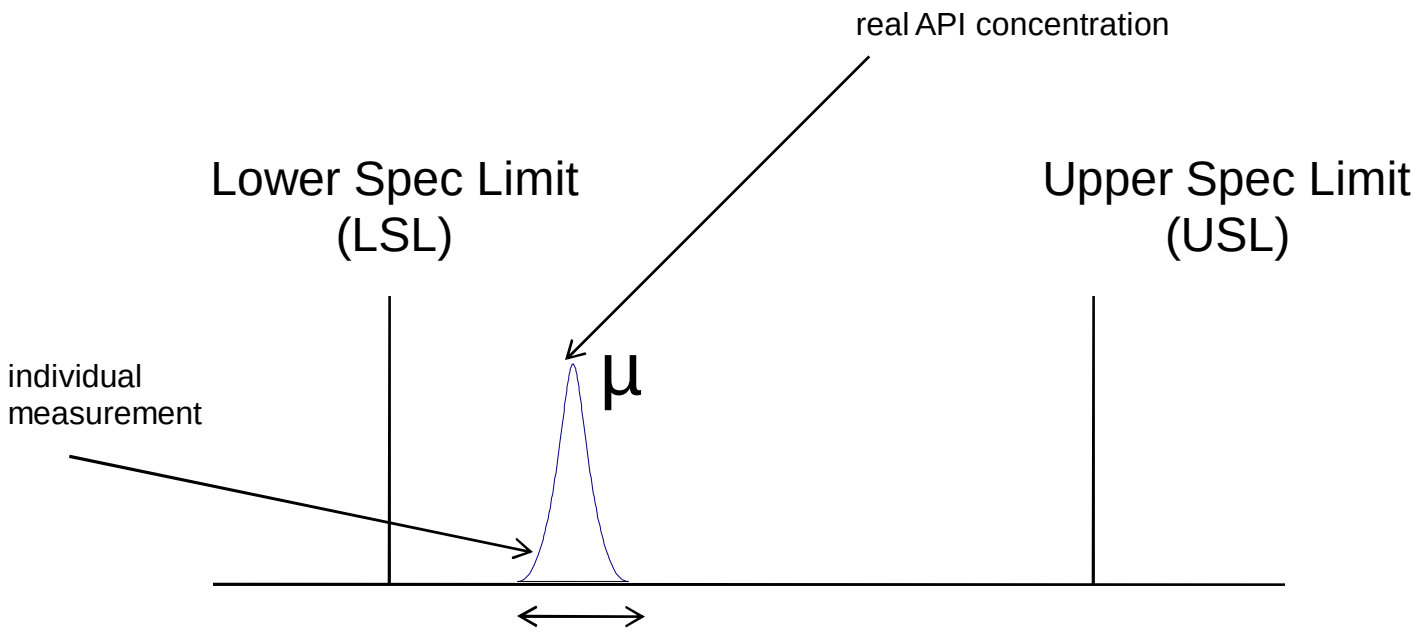
The Measurement Error is six times σ_{assay} and should be less than 10% of the spec range.

Measurement Error Being > 10% of the Spec Range: Can Reject Good Product



Measurement Error and Specs

Measurement Error Being < 10% of the Spec Range: <u>Will Make Better Conclusions on What is Really Happening in the Process</u>



Measurement Error and Specs

The measurement error can be reduced by increasing the sample size (Central Limit Theorem):

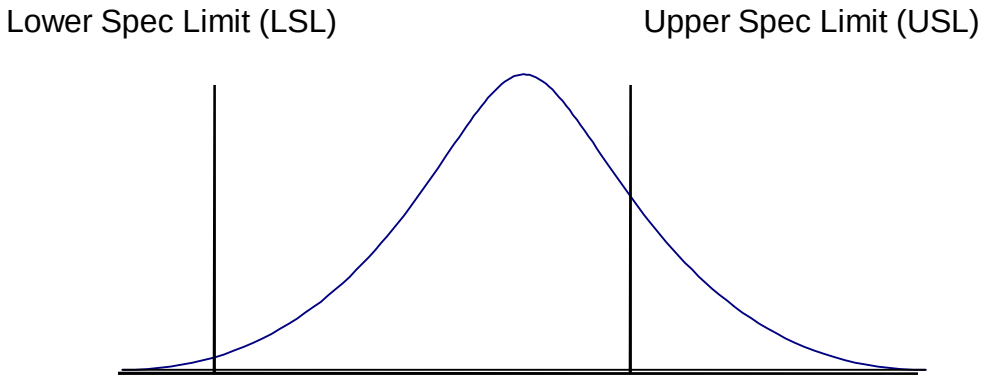
$$\sigma_{assay} = \frac{\sigma_{measurement}}{\sqrt{n}}$$

Also, $$\frac{\sigma_{assay}}{\sigma_{observed}} \leq 10\%$$

Process Capability (Cpk)

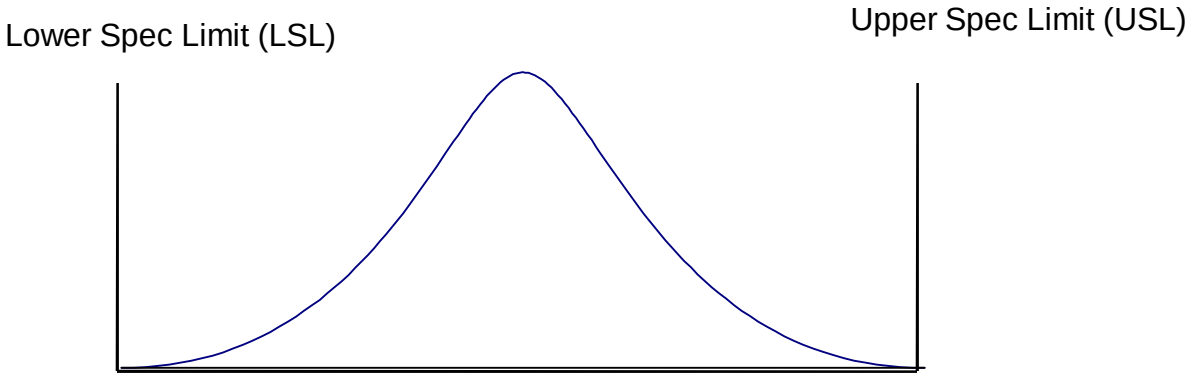
$$C_{pk} = \min\left[\frac{USL - mean}{3\sigma} or \frac{mean - LSL}{3\sigma}\right]$$

Cpk < 1: Out of Spec Products

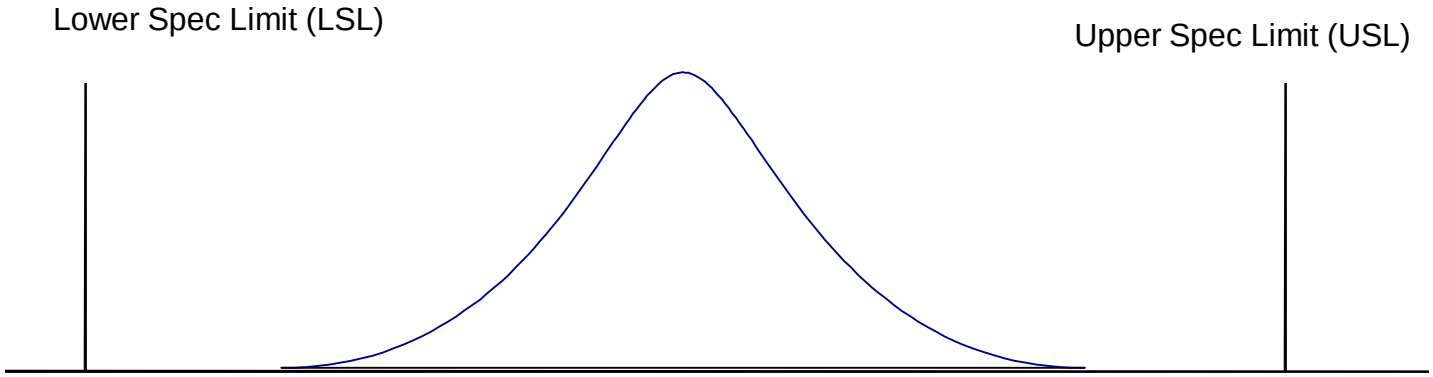


Process Capability (Cpk)

Cpk = 1: Barely Making It



Cpk > 1: Preferred



Solving the Release Failures

- Release data from approximately 30 lots was collected to calculate the process averages and the observed variabilities (total variation).

- This product has several actives. One Cpk per active was calculated.

- Several of the Cpks were below 1.

Solving the Release Failures: Increase the Cpks

- To increase a Cpk one could increase the spec range, or one could reduce the observed variance.

- The first option is cheaper and faster, if there are scientific reasons to support it.

- With the approval of the Medical Affairs department of this organization, the specification ranges were increased to +/- four standard deviations from the process averages.

- This increased the Cpks to 1.33.

Solving the Release Failures: Increase the Cpks

•Increasing Cpks through reduction in the observed variability is far more complicated, lengthy, and expensive.

• It involves reducing the variance of the process and/or reducing the variance of the assay, which might require process and/or assay development.

•Alternatively, per the Central Value Theorem, one can reduce the variance of the assay by increasing the sample size.

Solving the Release Failures: What to Do with the Failed Lots?

- Increasing an spec range is a prior approval change, and required months of waiting for the FDA to render a decision.

- Only one sample per assay used to be tested to release the product.

- Variability analysis shows that **seven** additional independent samples per active needed to be tested to meet the requirement that six times the assay standard deviation (measurement error) should span less than 10% of the specification range.

Solving the Release Failures: What to Do with the Failed Lots?

- Those additional tests were performed those samples **and the failing results** were used instead as estimators of the true concentrations of the actives in those lots.

- All new averages felt within the old specification limits and the initially failing lots were released based on a solid scientific base.

Were FDA Guidelines Violated by Releasing the Initially Failing Lots?

•Where it is proven that the assays variabilities are significant, it is statistically defendable to release a batch based on an average falling within the specification limits, even if some measurements that were included in the calculation of those average fall outside the specifications.

Source: Fernando Portes (see slide # 13).

•If you wish further assurance in addition to the speaker, see: *Identification of Out of Specification Results. Alex M. Hoinowski, Sol Motola, Richard J. Davis, James V. McArdle. Pharmaceutical Technology. January 2002.*

Were FDA Guidelines Violated by Releasing the Initially Failing Lots?

"If the samples can be assumed to be homogeneous (i.e., an individual sample preparation designed to be homogeneous), using averages can provide a more accurate result. In the case of microbiological assays, the USP prefers the averages because of the innate variability of the biological test system".

Source: Investigating Out of Specification Spec Results for Pharmaceutical Production. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). September 1988.

How About the Barr* Decision?

The Barr decision was not violated because:

-There was a limit at which retest stopped (seven additional samples).

-There was a clear decision on what to do before the retests: release the lots if averages fall within the old specifications. Reject the lots if those averages fall outside those ranges.

*. *USA Versus Barr Laboratories, Civil Action Number 92-1744. February, 1993.*

Are you Really Really Really Sure?

-Analysis of variance (ANOVA) and t-test analysis were used to gain additional confidence in this decision by using three independent statistical tests to prove by three different methods that there were no statistically meaningful differences between the lots with all passing results, and the lots in which some of the results had fallen outside the old specification limits.

-Conclusion: Yes, I am really (assay variability), really (ANOVA), really (t-test) sure that those batches can be released based on solid scientific facts.

Solving the Problem of Stability Failures

-Stability limits have to be calculated on a case-by-case basis, based on each situation and set of data*.

-This organization had set up a fairly common stability alerts limits when an stability result differed in more than 5% from a previous value. This is not statistically defendable**, and it triggered automatic investigations, which were all inconclusive.

-The calculation of the assay variability with data from the assay validation reports demonstrated that this 5% limit did not make sense because the assay variations of several of the actives were much higher than 5%.

-The elimination of this 5% limit saved thousands of dollars in retests and investigations.

**. Identification of Out of Trend Stability Results. Part II. PhRMA CMC Statistics and Stability Expert Teams. Pharmaceutical Technology. October 2005.*

***. Identification of Out of Trend Stability Results. A Review of the Potential Regulatory Issue and Various Approaches. PhRMA CMC Statistics and Stability Expert Teams. Pharmaceutical Technology. April 2003.*

Conclusion

All organizations (Pharmaceutical, Medical Device, Biotech, Chemical, Mining, Metals, etc) can improve the reliability and robustness of their supply chains by understanding and improving the variabilities associated with those chains. Quality Engineering fundamentals can help in this understanding.