An Invitation to the Applied Stats Interest Group

By Jason J. Orloff

Agenda

- Before the Math – The Morality
- Conceiving of the USP as a standard, not a sampling plan.
- 2011 PV Guidance - Why is the important stuff always in the footnotes?
  - ASTM E2281-03
  - ASTM E2709-09
  - ASTM E2500-07
    - Maintenance of Specifications – A Tale of 2 Strategies
- Golden Balls

Everything should be made as simple as possible,
but no simpler.
~ A. Einstein

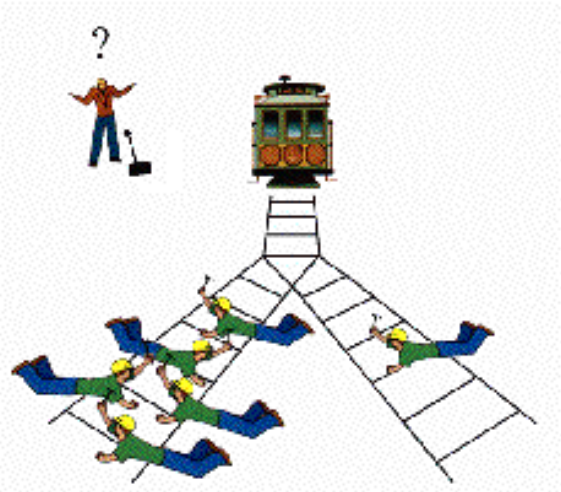
BEFORE THE MATH – THE MORALITY

RadioLab Episode 91508-Morality

Quality Assurance

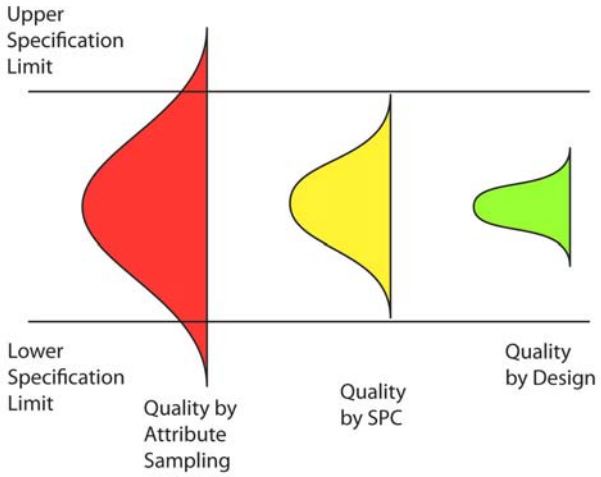
Joshua D. Greene, author of "Moral Tribes", < http://www.wjh.harvard.edu/~jgreene/ >

Operations



Joshua D. Greene, author of "Moral Tribes", < http://www.wjh.harvard.edu/~jgreene/ >

Inner Chimp versus the Accountant?



The Moral of the Story?

- If morality is the result of competing systems arriving at different conclusions and duking it out, then is this an answer to the dilemma of balancing our responsibility to the patient to do no harm weighed against a manufacturer's mandate of the greatest good for the greatest number?
- Could statistical levers and arbitrary numbers undermine QA's inner chimp?

USP AS A STANDARD, NOT A SAMPLING PLAN

Decisions and the USP

At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. First-party (manufacturer), second-party (buyer), or third-party (regulator) compliance testing may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies.

~ USP 32 *General Notices and Requirements, 3.10*

2011 PV Guidance

WHY IS THE IMPORTANT STUFF ALWAYS IN THE FOOTNOTES?

2011 PV Guidance, p 14, Footnote 18

Some references that may be useful include the following: ASTM E2281-03 "Standard Practice for Process and Measurement Capability Indices," ASTM E2500-07 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment," and ASTM E2709-09 "Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure." This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.

ASTM E2709-09

ASTM E2709-09 “Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.”

1. Scope

1.1 This practice provides a general methodology for evaluating single-stage or multiple-stage lot acceptance procedures which involve a quality characteristic measured on a numerical scale. This methodology computes, at a prescribed confidence level, a lower bound on the probability of passing a lot acceptance procedure, using estimates of the parameters of the distribution of test results from the lot.

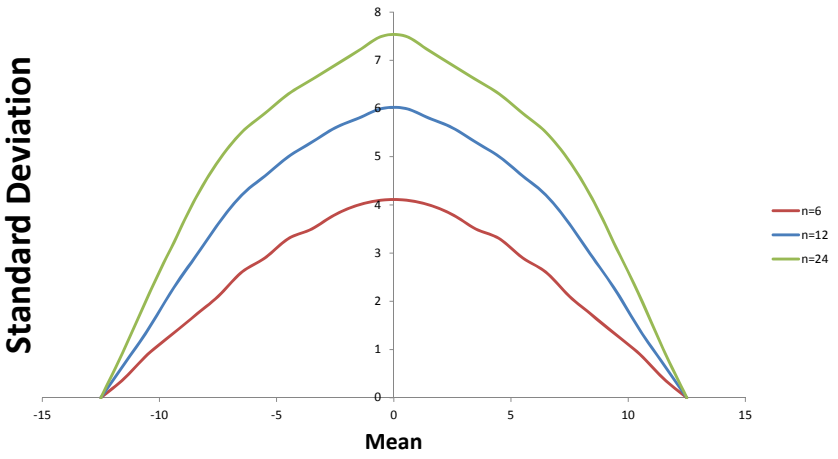
1.2 For a prescribed lower probability bound, the methodology can also generate an acceptance limit table, which defines a set of test method outcomes (for example, sample averages and standard deviations) that would pass the multiple-stage procedure at a prescribed confidence level.

1.3 This approach may be used for demonstrating compliance with in-process, validation, or lot-release specifications.

1.4 The system of units for this practice is not specified.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

ASTM 2709



ASTM E2500-07

ASTM E2500-07 "…Specification, Design, and Verification of …Manufacturing

4. Summary of Guide

4.1 This guide describes a risk-based and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety.

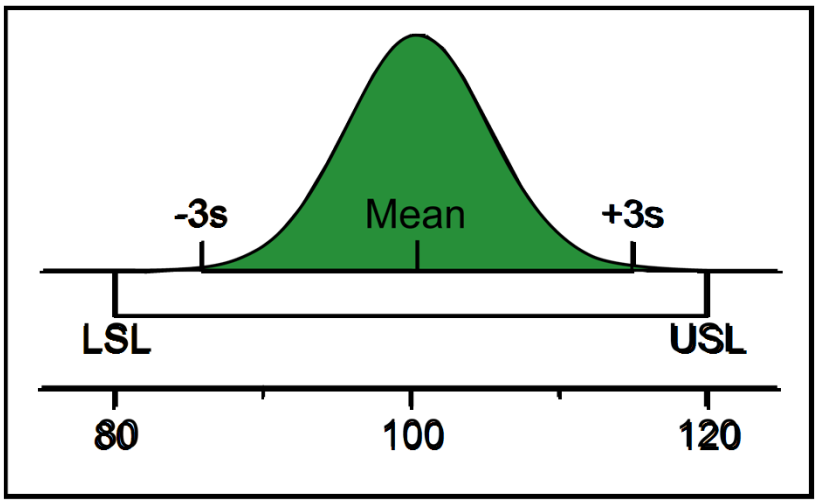
4.2 This guide describes a systematic, efficient, and effective way of ensuring that manufacturing systems and equipment are fit for intended use, and that risk to product quality, and consequently to patient safety, are effectively managed to the extent that these are affected by such systems and equipment.

4.3 The overall objective is to provide manufacturing capability to support defined and controlled processes that can consistently produce product meeting defined quality requirements.

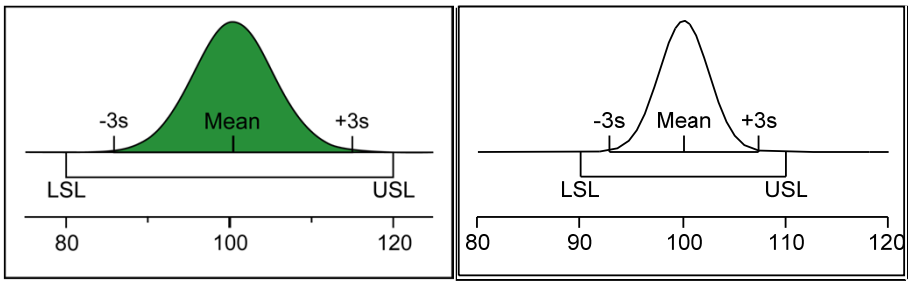
4.4 The approach described within this guide also supports continuous process capability improvements and enables innovation such as the implementation of Process Analytical Technology (PAT).

TWO APPROACHES TO MANAGING VARIABILITY – CONFORMANCE WITH SHRINKING SPECS

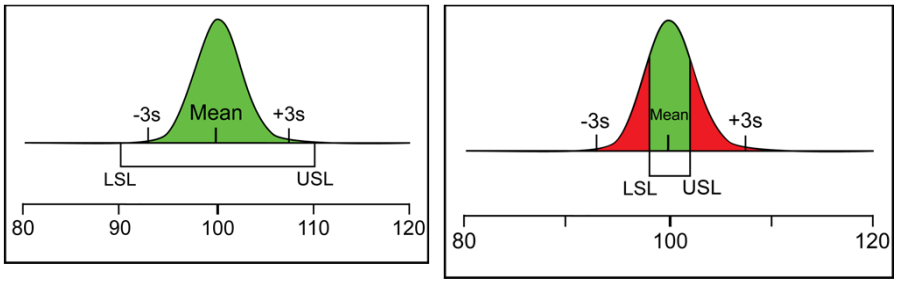
A Tale of Two Specs - Shrinking



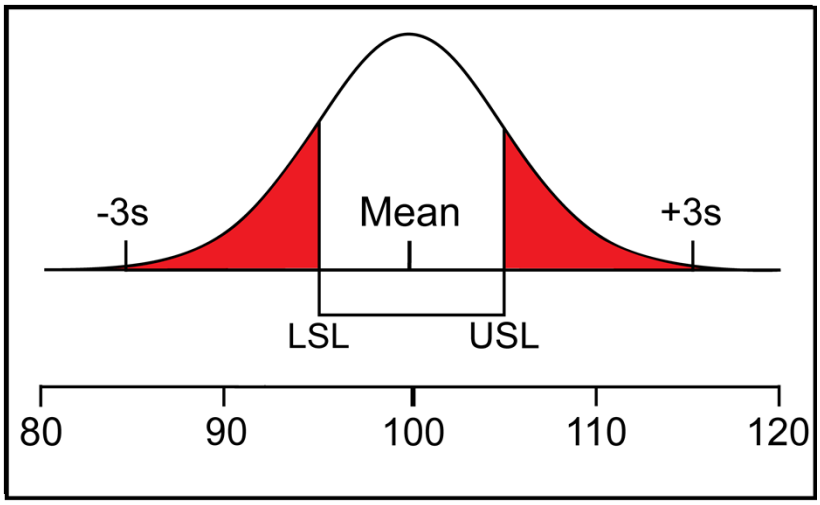
Development



External Review



A Tale of Two Specs - Shrinking



A Tale of Two Specifications - Summary

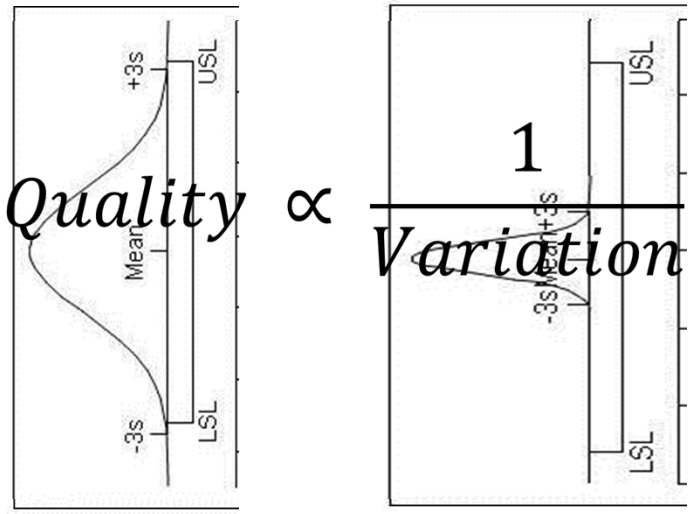
Changing specs to reflect the process capability:

- undermines continuous improvement,
- drives up the costs of health care,
- decreases the volume available to patients,

and artificially inflates *risk to the patient*.

TWO APPROACHES TO MANAGING VARIABILITY – PERFORMANCE

[q]uality is the Inverse of Variation

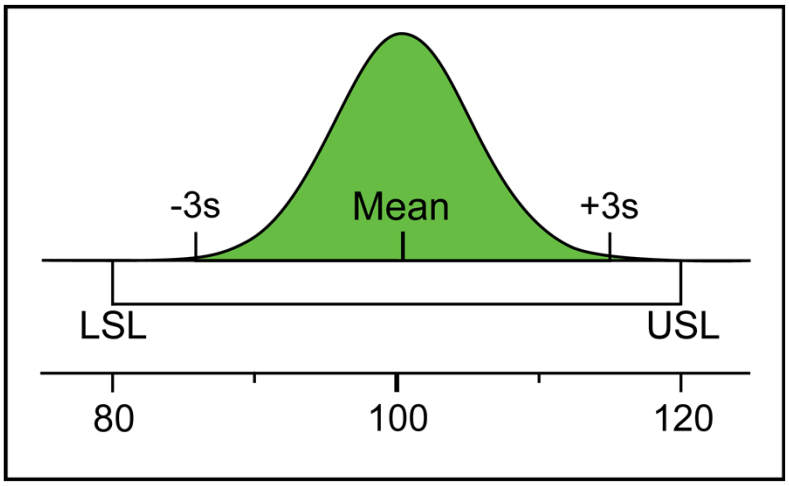


Guidance: Investigating OOS Test Results for Pharmaceutical Production

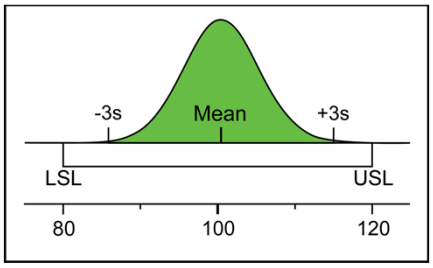
[6] Although the subject of this document is OOS results, much of the guidance may be useful for examining results that are out of trend.

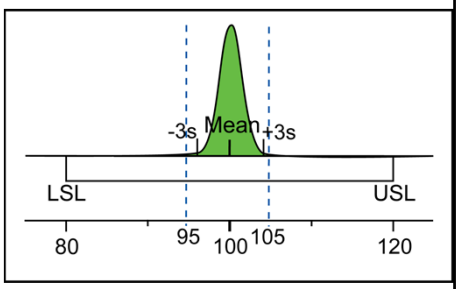
~ p 3

A Tale of Two Specs - Performance



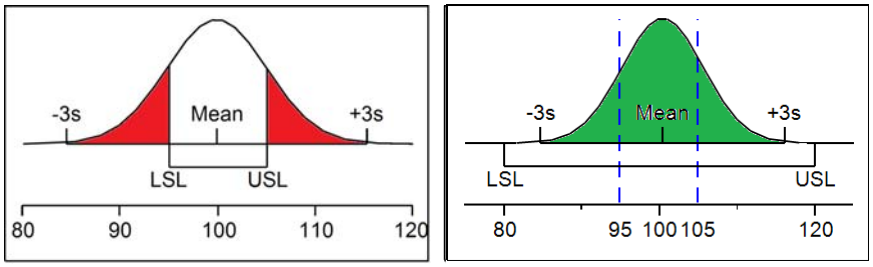
Development





OOS Range Bounds Design Space

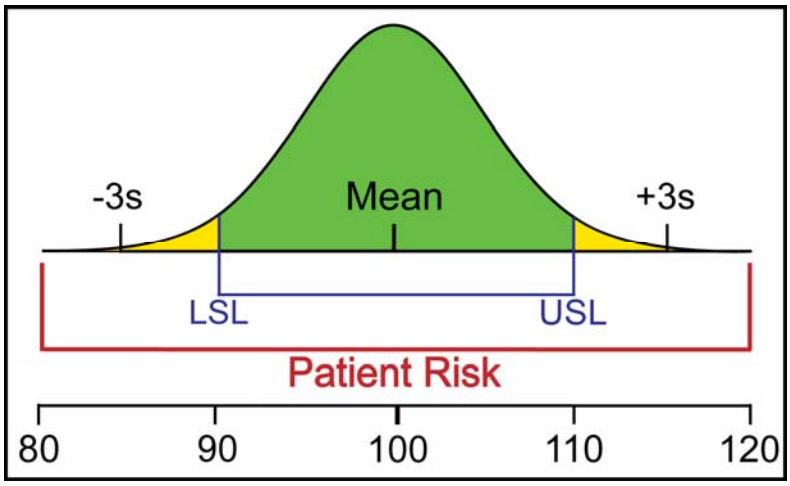
Shrinking Specifications **Performance Challenges**



A Tale of Two Specifications - Summary

We need to decouple Performance (e.g. process capability…) from protecting the patient with Conformance to specifications.

Update You Risk Assessment



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2011 PV Guidance

…This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.

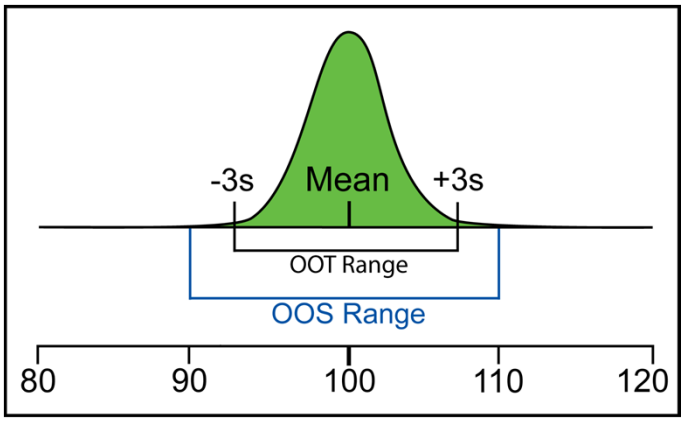
ASTM E2281-03

ASTM E2281-03 “Standard Practice for Process and Measurement Capability Indices”

1. Scope

1.1 This practice provides guidance for the use of capability indices for evaluating process capability and performance. Process capability indices compare the variability of a process quality measure against product specifications or tolerances and assume the process is in a state of statistical control. Process performance indices are useful in situations when the process is not in a state of statistical control.

CQA Capability (OOS/OOT)



$$Critical\ Quality\ Attribute\ Capability\ = \frac{Variability\ Allowed\ by\ Specs}{Variability\ of\ the\ Process}$$

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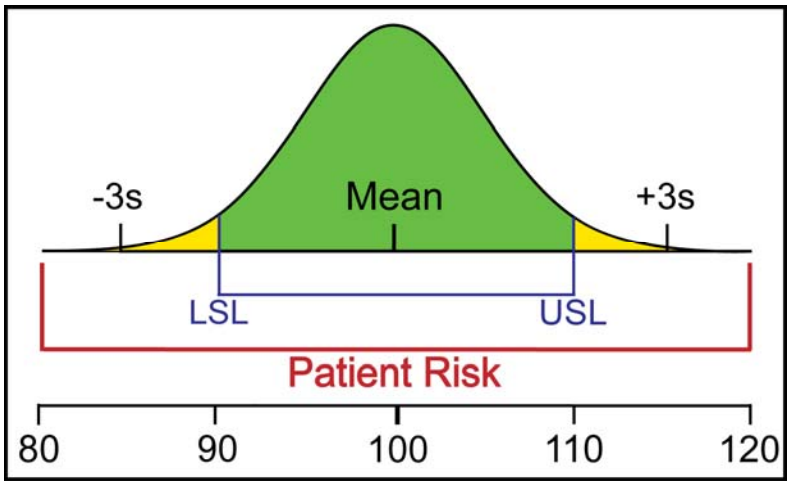
Title VII Sec. 705, Risk-based Inspection Frequency

"This section requires FDA to replace the previous two-year drug inspectional frequency requirement with a risk-based inspection schedule for domestic and foreign drug facilities. Inspection criteria include the establishment's compliance history and the inherent risk of the drug being manufactured..."

~ **FDASIA Title VII Overview**
<www.FDA.gov>

Update You Risk Assessment



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GOLDEN BALLS

TQM, PAT, QbD…

Is Pharmaceutical Compliance A Trail of Dashed Hopes & Broken Promises?

If pharmaceutical manufacturing is, as the economists say, in a mutually interdependent relationship then FDA is playing the correct gambit.

GOLDEN BALLS

GOLDEN BALLS