Sample Size Selection

Role of Regulators, USP, and ASTM

Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Acting Director
Office of Generic Drugs
CDER, FDA

Why Test?

- Assessment of Quality
- Verification of Quality
- End-Product Testing
  - Rejection of out-of-spec lots
- In-process Testing
  - In lieu of end-product testing
  - As part of in-process QC system

Two Types of Quality

- The suitability of either a drug substance or drug product for its intended use.
  - *ICH Q6A Specifications Guideline*

- The state of having an acceptably low risk of failing to achieve the desired clinical attributes.
  - *J. Woodcock, M.D.*
    - *Amer. Pharm. Rev. (November–December 2004)*

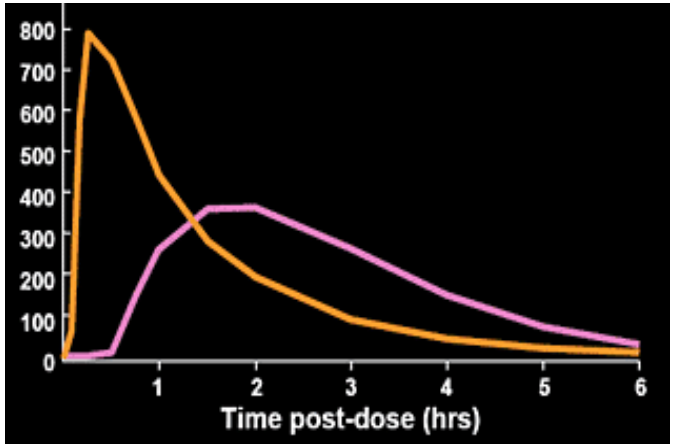
"Desired State"

- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes

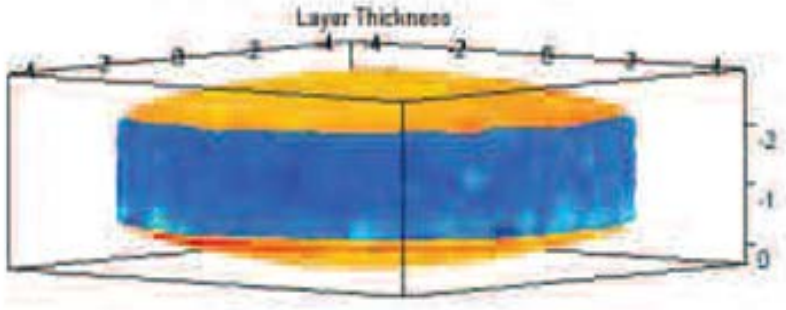
Two Types of Quality

- Product design



http://www.medscape.org/viewarticle/540104_4

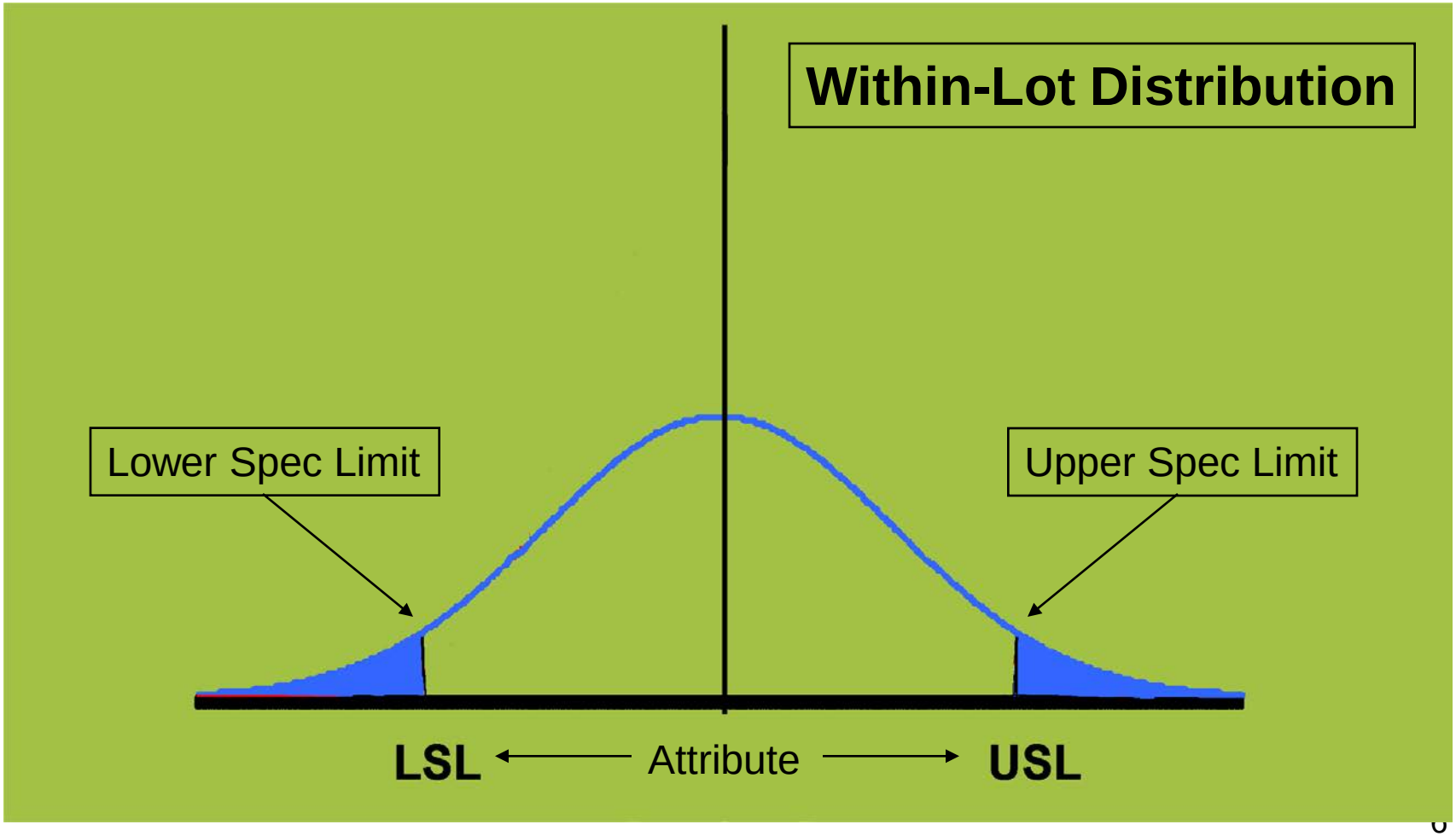
Tablet Coating Design



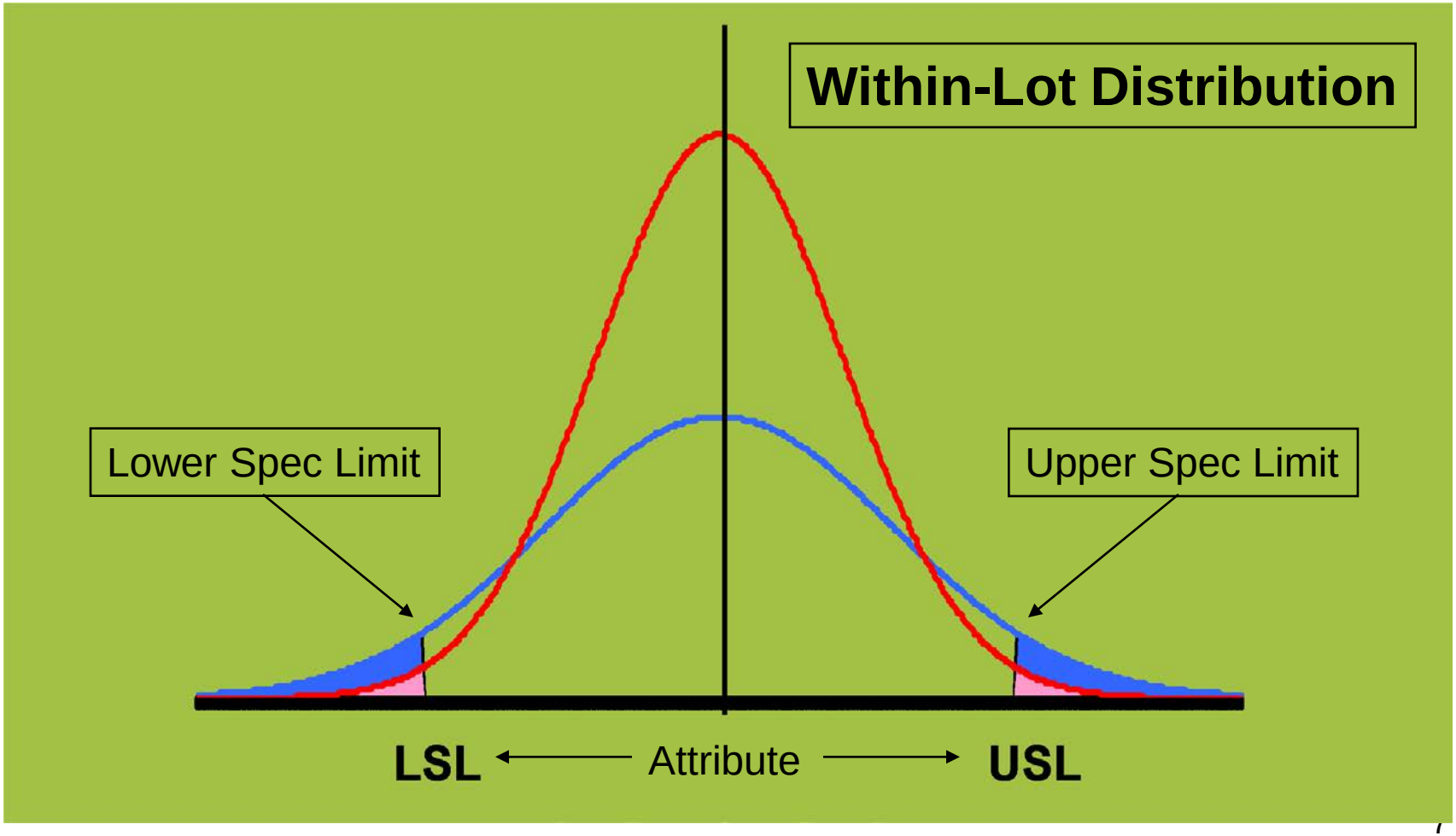
From: *Pharmaceutical Formulation & Quality*
TABLET COATINGS: Tune into Terahertz
L Ho, KC Gordon, T Rades, & P Taday

- Specifications define the design.

Batch/Lot Quality



Batch/Lot Quality



Numbers of tablets out-of-spec

Spec range = 75-125%
batch size = 1,000,000 tablets

	Mean		
Sigma	95%	100%	105%
6%	430	30	430
7%	2150	360	2150
7.8%	5232	1350	5232

Dr. Janet Woodcock, April 9, 2002

Sample Size and Confidence

- Calculating Sample Size (ASTM: E122 - 09)
- Demonstrating Confidence in Complying with an Acceptance Procedure (ASTM: E2709-10)
- Confidence in Attribute Sampling (ASTM E2334-09

FDA , USP, ASTM

- Each is involved in setting standards associated with product quality.

Regulators Role

- Reviewer, Inspector, Compliance Officer

- Set and enforce regulatory standards for:
  - Product quality (lot release & shelf life)
  - Quality control
  - Manufacturing control

Reviewer's Role

- Ensure that product design is consistent with product's performance requirements
- Ensure that process design is capable of producing product that meets specifications
- Assess the process controls and the level of confidence that units in a batch will meet specifications

Inspector's Role

- Assess the ability of the manufacturer to appropriately manufacture the product in accordance with cGMPs and the parameters in the marketing application.
  - Maintaining control
    - Routine sampling
  - Adequately responding to and investigating deviations
    - Enhanced sampling – adequate for intended purpose?

Compliance Officer's Role

- Work with the Reviewer to ensure that the sampling plans to be approved are compliant with cGMPs
- Work closely and coordinate with ORA Headquarters and Field Units on the review of inspectional observations (483) and Establishment Inspection Report (EIR) to determine what (if any) regulatory action is necessary to achieve compliance with cGMPs.

Regulation on Selection of "Units"

- 21 CFR 211.165(d)
  - "…adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release"

USP's Role

- Standards Mandated by Law
  - USP/NF referenced in 21 U.S.C. 351
- Market Standards

Adulteration & the USP

A drug may be considered adulterated :

"If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium,…"

FDCA 501(b)

USP General Notices 34th Revision

- "At times, compendial standards take on the character of statistical procedures, with multiple units involved…… 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 necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia."

USP General Notices 34th Revision

- "The manufacturer's specifications, and good manufacturing practices generally (including, e.g., Quality by Design initiatives) are developed and followed to ensure that the article will comply with compendial standards until its expiration date"
- "Frequency of testing and sampling are left to the preferences or direction of those performing compliance testing, and other users of USP-NF, including manufacturers, buyers, or regulatory authorities."

Consensus Standards Orgs. (e.g., ASTM)

- Congress: National Technology Transfer and Advancement Act (NTTAA); 1995
- Office of Management and Budget (OMB): Circular A-119; 1998 (original in 1993)
- http://standards.gov/standards_gov/index.cfm

Consensus Standards Orgs. (e.g., ASTM)

- OMB Circular A-119
  - "…this Circular directs agencies to use **voluntary consensus standards** in lieu of government-unique standards except where inconsistent with law or otherwise impractical."

"Use voluntary consensus standards"

- "To determine whether established regulatory limits or targets have been met"
  - "Test methods"
  - "Sampling procedures"
  - "Protocols"

ASTM Standards for Sampling / Statistics

E105 - 10:	**Probability Sampling Of Materials**
E122 - 09:	**Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process**
E141 - 10:	**Acceptance of Evidence Based on the Results of Probability Sampling**
E178 - 08:	**Dealing With Outlying Observations**
E2709 - 10:	**Demonstrating Confidence in Complying with Acceptance Procedures**
E2587 - 10 :	**Statistical Process Control**
E2334 – 09:	**Confidence in Attribute Sampling**
E2281 – 10:	**Process Capability**

CSO's and FDA's authority

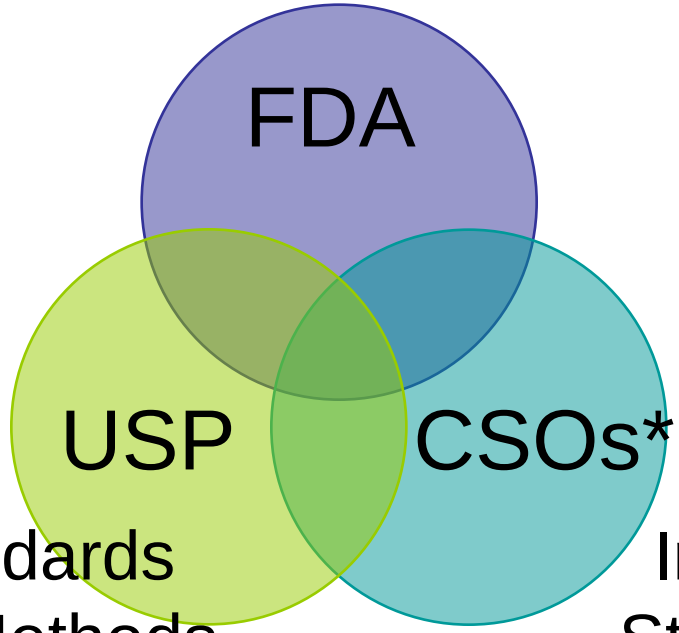
- "This policy does not preempt or restrict agencies' authorities and responsibilities to make regulatory decisions authorized by statute."
- These include
  - "Determining the level of acceptable risk"
  - "Setting the level of protection"
  - "Balancing risk, cost and availability of technology in establishing regulatory standards."

FDA , USP, ASTM

- Each is involved in setting standards for product quality.
- FDA – Regulatory standards
  - Product design & quality control
- USP – Market stds. & standard methods
- CSOs (e.g., ASTM) – Industry standards
  - Standard Methods

FDA, USP, ASTM

Regulatory Standards



Market Standards
& Standard Methods

Industry
Standards

*e.g., ASTM

Acknowledgements

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