# STATISTICAL TECHNIQUES

## FDA INDUSTRY CONFERENCE
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# Disclaimer

# Objectives

- Discuss the CFR requirements for statistical techniques, with an emphasis on sampling plans
- Review basic concepts and methods to describe data
- Review integration of risk in sampling plans
- Discuss concepts such as attributes sampling, acceptance quality limit, and lot tolerance percent defective
- Review examples of inspectional observations related to procedures, sampling plans or methods

# QSR Requirements

**§820.250(a) Procedures**

Manufacturer shall establish/maintain procedures to establish, control & verify acceptability of:

- Process capability
- Product characteristics

**§820.250(b) Sampling Plans**

- Sampling plans shall be written and based on a valid statistical rationale
- Establish/maintain procedures to:
  - Ensure sampling methods are adequate
  - Ensure sampling plans are reviewed when changes occur

# QSR Requirements

**§820.100(a)(1) CAPA**

Employ appropriate statistical methodology (where necessary) to detect recurring quality problems.

**§820.200(b) Servicing**

Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with **820.100**.

# Basic Concepts

- **Statistics**
  - A collection of techniques ***used to make decisions*** about a population based on information taken from a sample

- **Descriptive Statistics**
  - Provides information about data
    - Central tendency or location (e.g., mean, median)
    - Variation or dispersion (e.g., standard deviation, variance, range)
    - Shape of a set of data (e.g., bell-shaped)

# Basic Concepts

**Standard deviation** – measures amount of variation or dispersion of a set of values.

- **Low** standard deviation: values tend to be close to the mean (expected value)]

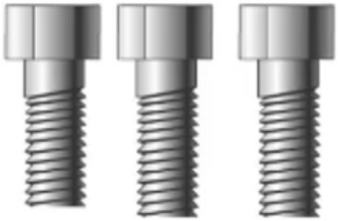
- **High** standard deviation - values are spread out over a wider range.

Manufacturer B claims that the screws they manufacture are the same as the ones manufactured by Manufacturer A and provides the following comparison data (length) of three screws:

Manufacturer A: 1.95 “, 2.03”, 2.02” (Mean = 2.00)

Manufacturer B: 1.70”, 1.80”, 2.50” (Mean = 2.00)

**Manufacturer A**



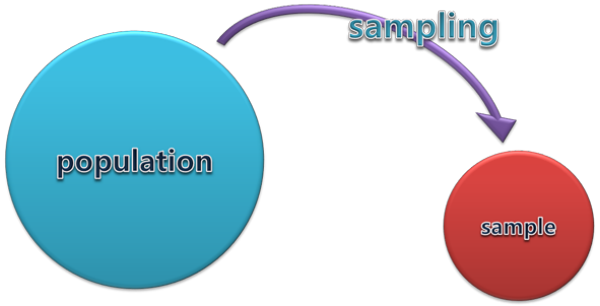

**Standard deviation = 0.04**

**Manufacturer B**


**Standard deviation = 0.44**

# SAMPLING

- ✓ Sampling Procedures
- ✓ Acceptance Sampling
- ✓ Attributes Sampling
- ✓ Variables sampling



# QSR Requirements

- §820.250 (b)
  - Sampling plans shall be written and based on a valid statistical rationale.
  - Establish/maintain procedures to ensure sampling methods are adequate and sampling plans are reviewed when changes occur.

# Sampling Procedures

- Procedures should address:
  - ✓Sampling plans (specifying sample sizes and acceptance criteria)
    - Statistical rationale
  - ✓Characteristics to be inspected/measured
    - Critical to quality
  - ✓How samples will be selected and taken
    - Representative samples are critical to making valid inference about the population

# Sampling Procedures

- Procedures should address *(Continued)*
  - ✓Who will do the sampling (roles and responsibilities)
  - ✓How to handle nonconforming products
  - ✓Applicability to operations; for example:
    - Design verification and validation
    - Process validation
    - Incoming, In-process and final inspection
  - ✓Standards and tools (e.g., ANSI sampling tables)

# Acceptance Sampling

- A method of inspecting samples of a lot
- Decisions to accept or reject the lot
- Should reject all “bad” lots while accepting all “good” lots
- Sampling plan is critical for consumer protection

# Attributes Sampling

**Attributes Sampling –**

Inspection where the unit of product is classified simply as conforming or nonconforming, **or** the number of nonconformities in the unit of products is counted (ANSI Z1.4).

# Attributes Sampling

## Acceptance Quality Limit (AQL)

- "quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling" *(ANSI Z1.4)*

- Expression of nonconformance refers to the percent of nonconforming units or number of nonconformities per hundred units

$$\text{Percent nonconforming} = \frac{\text{Number nonconforming}}{\text{Number of units inspected}} \times 100$$

$$\text{Nonconformities per hundred units} = \frac{\text{Number of nonconformities}}{\text{Number of units inspected}} \times 100$$

# Attributes Sampling

## Lot Tolerance Percent Defective (LTPD)

- unacceptable quality level with a 90% probability of rejection

- lots at or above the LTPD are routinely rejected

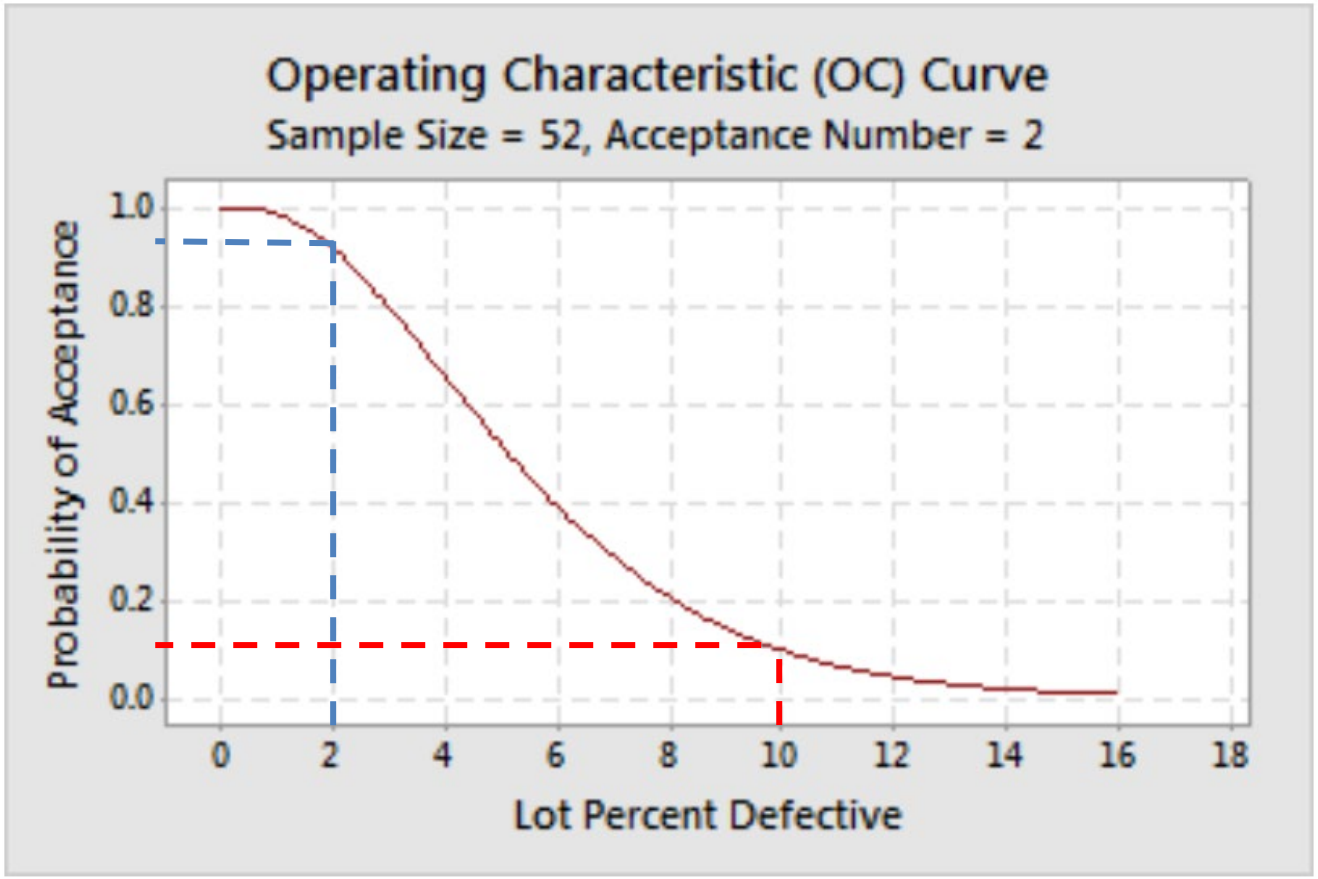
# Attributes Sampling

**Operating Characteristic Curve** (OC Curve

- Shows the relationship between the percentage of defectives, and the probability of accepting those lots
- Describes the discriminatory power of an acceptance plan
- Firms should use the OC curve to choose the appropriate sampling plan

# Attributes Sampling

## OC Curve (AQL =2; Sample Size = 52)

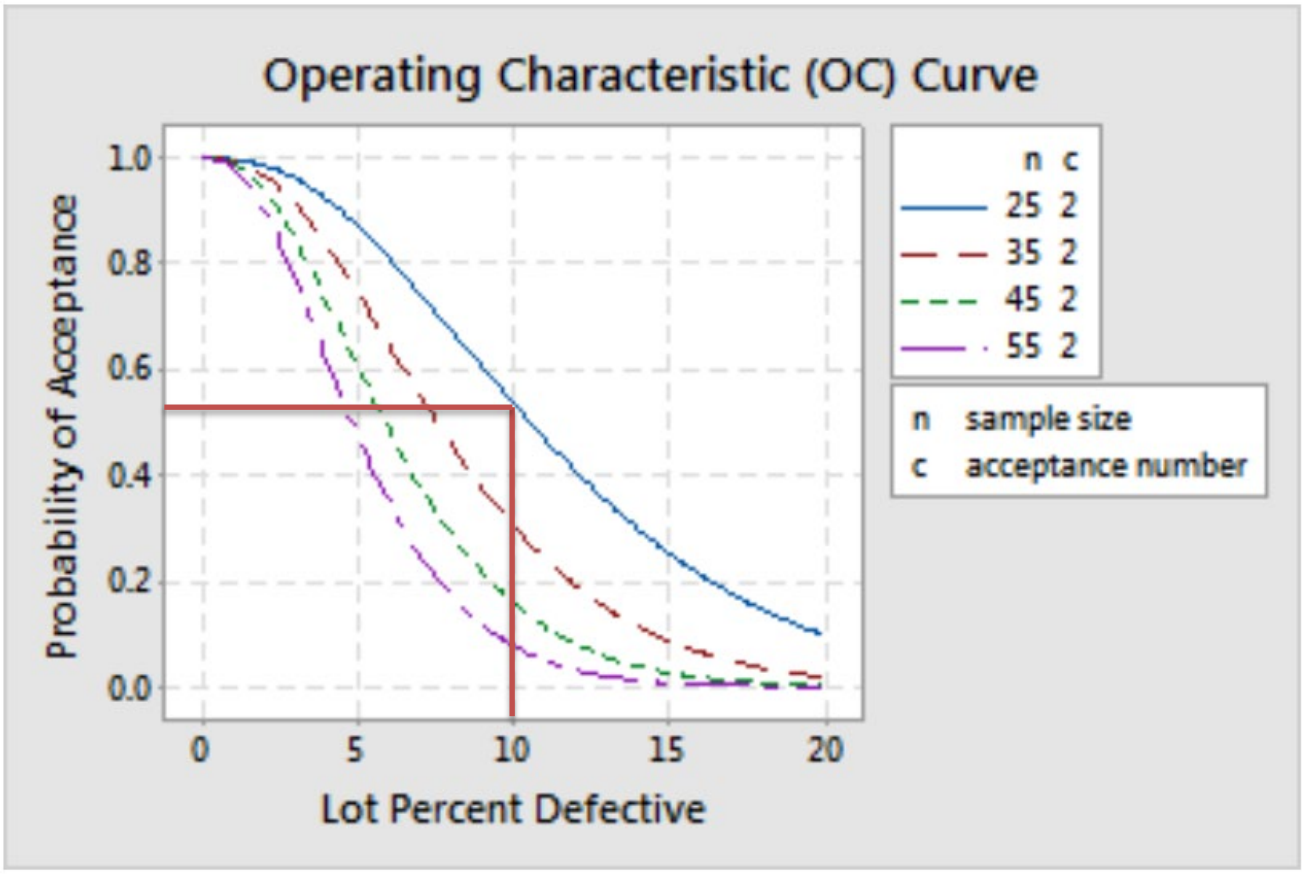



**AQL = 2**

**LTPD = 10**

# Attributes Sampling

## OC Curve



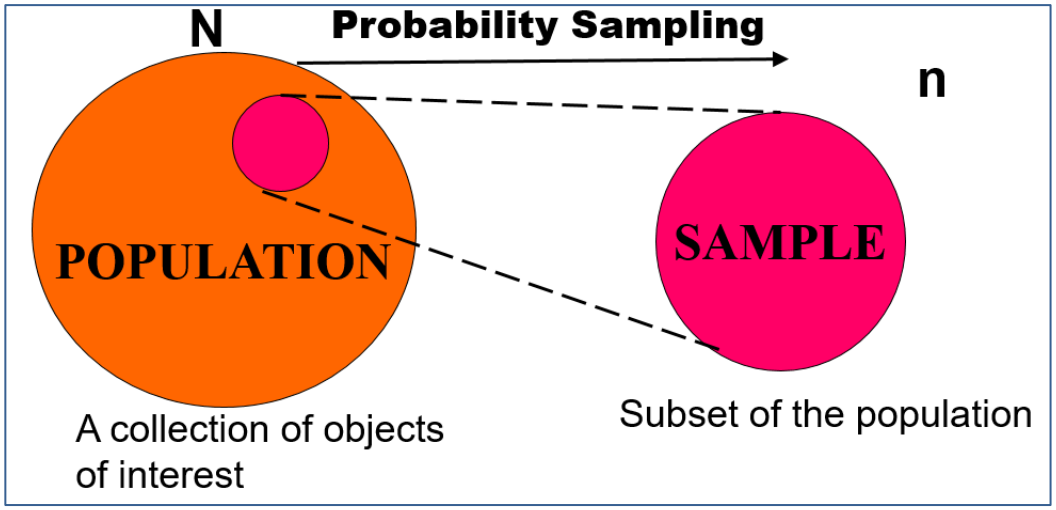

**AQL = 2**

# Variables Sampling

**Variables Sampling -**

Applies to a single quality characteristic which can be measured on a continuous scale.

# Variables Sampling




**Parameter** (measurement describing a characteristic of a population)

**Statistic** (measurement describing a characteristic of a sample)

| | Parameter | Statistic |
|---|---|---|
| Size | N | n |
| Mean | $\mu$ | $\bar{x}$ |
| Standard Deviation | $\sigma$ | s |
| Variance | $\sigma^2$ | $s^2$ |

# Variables Sampling

## Central Limit Theorem

Given a random sample ($X_1$, $X_2$, … $X_n$) from some population with mean ($\mu$) and variance ($\sigma^2$), for large n, the sampling distribution of the mean approaches a normal distribution with mean ($\mu$) and variance ($\sigma^2/n$)

## In other words…

When a random sample is taken from a population, the mean of the sample means will tend to be normal.

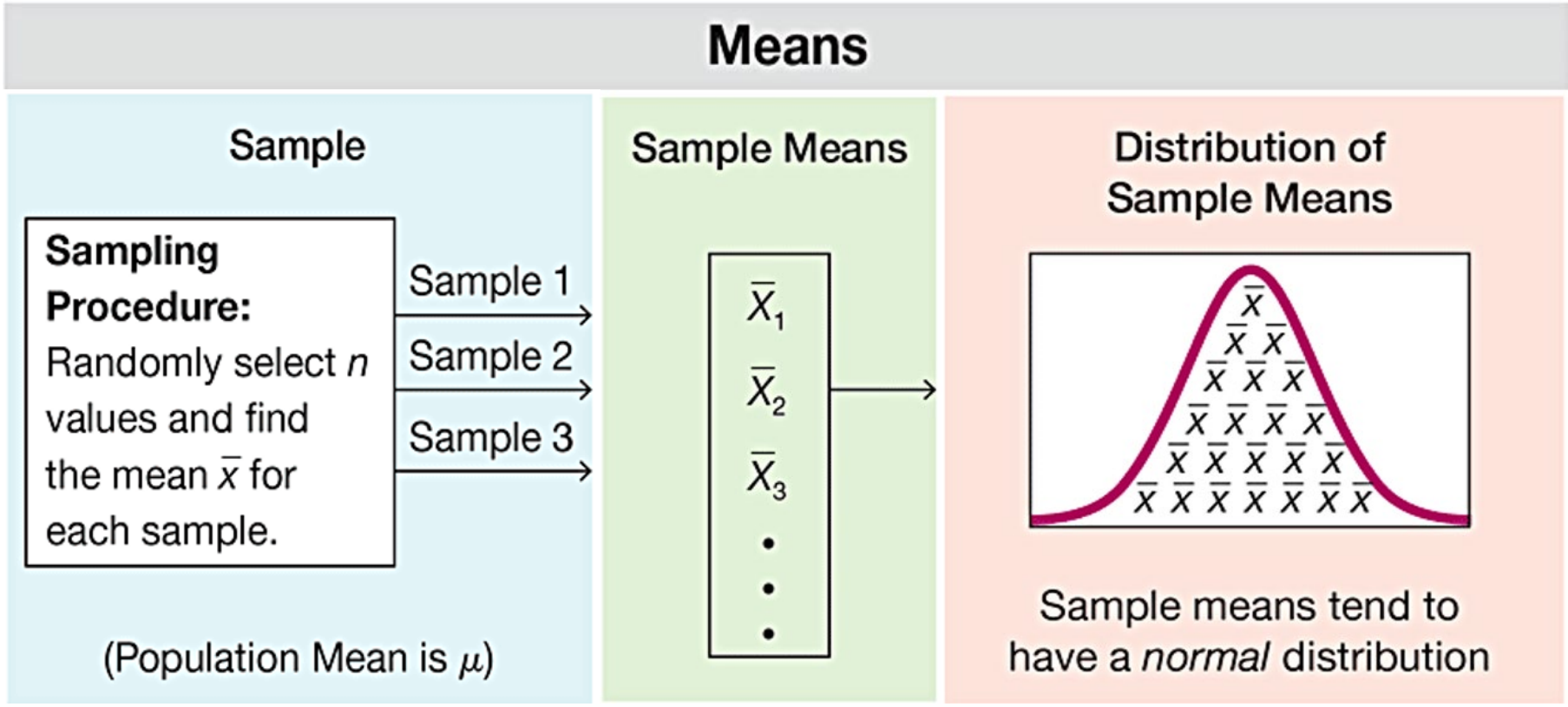
# Variables Sampling

## Central Limit Theorem

- Applies even if the population is not normal
- Sampling distribution will approach a normal distribution as the sample size increases
- If the population distribution is not normal, the sample size has to be large enough
- Statisticians consider a sample size of 30 or more to be sufficiently large.

# Variables Sampling

## Sampling distribution

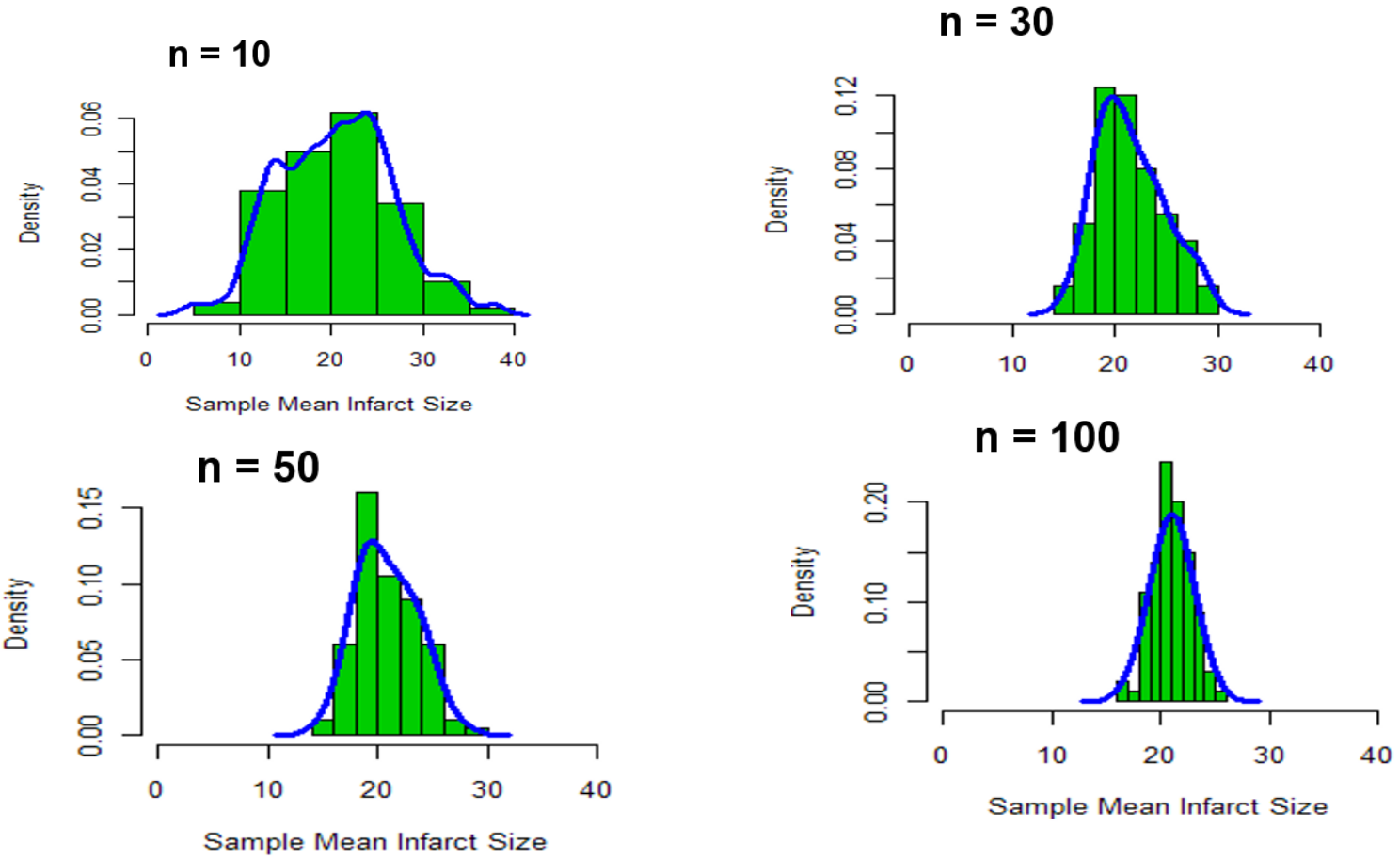





*Pearson, Essentials of Statistics, Sixth Edition, Mario F. Triola*

# Variables Sampling

- Sampling distribution will approach a normal distribution as the sample size increases




Charts taken from a presentation by Dr. Vandana Mukhi (CDRH)

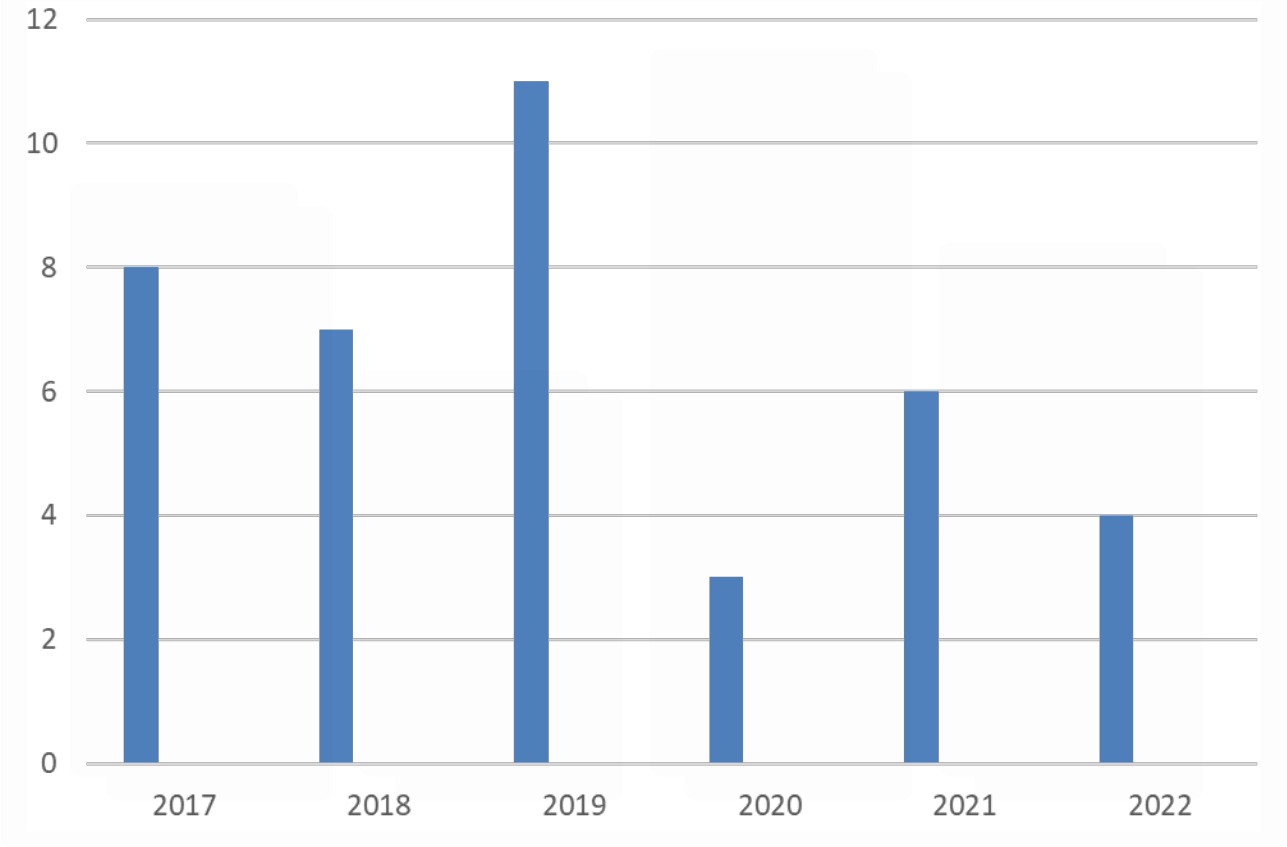
# Variables Sampling

## Sample Size –

- When the distribution of the population is **not normal or unknown**,
  - a minimum of 30 samples is needed (based on the central limit theorem)
- Sample size can be calculated using:
  - Estimated standard deviation of the samples (based on historical data)
  - Margin of error allowed
  - Confidence level (based on allowable risk)
- Sample size could be based on an industry standard

# FDA 483 Observation - 820.250(a)

**Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been [adequately] established.**



# Example of FDA 483 Observation

**Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.**

Specifically, insufficient statistical assessments were in place for establishing, controlling, and verifying process capability and product characteristics.

A. Your firm provided no rationale for the acceptability of your sampling plan at lot release based on the risk associated with releasing defective product. The AQL (Acceptable Quality Limits) sampling plan and associated Lot Tolerance Percent Defective (LTPD %) is not commensurate with the product risk based on intended use and design inputs of the product.

B. Your firm does not currently distinguish the failure modes of rejected components/units that are collected in reject bins on the manufacturing assembly line. In addition, your firm does not currently track or trend the rejects from the assembly manufacturing line and there are no action limits associated with the number or type of rejects.

# Example of FDA 483 Observation

**Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.**

Specifically, insufficient statistical assessments were in place for establishing, controlling, and verifying process capability and product characteristics.

C. Your firm failed to routinely evaluate ongoing state of control of the equipment and process. For example,

1. The capability and suitability of equipment to produce conforming units was not assessed. Specifically, process capability evaluations did not reflect inherent capability of the process equipment to produce conforming units. Instead, you only calculated process capability after a large number of defects were inspected out of the batch.
2. Your firm failed to adequately analyze data to determine process points in which excessive variation occurred and defective units were produced.
3. Your firm lacked sufficient ongoing trending of numerous in-process attributes that are critical to the quality of the finished product. For example, there was insufficient ongoing trending to periodically assess (e.g., process trending reports, Annual Review) process performance to promptly detect atypical variability that may affect product quality.

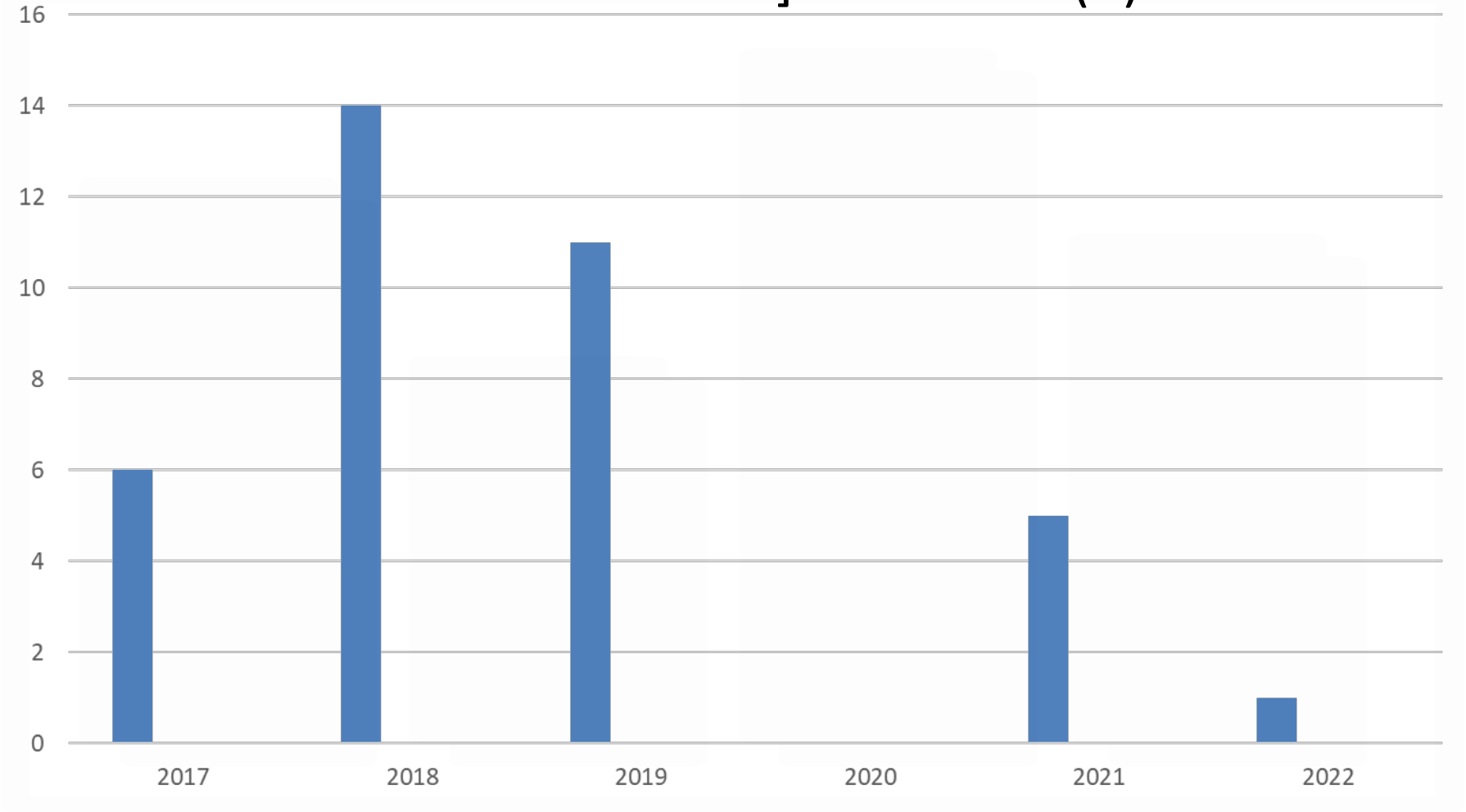
# Example of FDA 483 Observation

**Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.**

Specifically, the XX sub-assembly production procedure provides instruction for the sub-assembly that occurs at your firm. The XX is a device used during laparoscopy. Page 2 of the sub-assembly procedure instructs the inspector to "randomly check some units of every bag." This step does not provide a valid statistical technique for verifying product acceptability.

# FDA 483 Observation

Sampling plans are not [written] [based on valid statistical rationale]. - 820.250(b)



# Example of FDA 483 Observation

**Sampling plans are not written and based on valid statistical rationale.**

Specifically, for XX, your firm manufactured approximately 200,000 XX for lot number XX. XX data was obtained using the incorrect sample sizes, which were signed as QC passing. According to your Sampling Procedure, Rev C, effective XX/XX/XX, the MIL-STD-105E standard is being used with an AQL level of 0.025% and specified that XX data should be obtained using the sample size of 5 specified in "Special Inspection Level" S-1. However, your firm failed to use the proper table and sample size specified in your procedure.

Your firm accepted this sampling size and released these products for distribution.

# Example of FDA 483 Observation

**Sampling plans are not written and based on valid statistical rationale.**

Specifically, your firm did not base the sampling plan for the "XX," PR-XXX-000 and PR-XXX-001 on valid statistical rationale.

PR-XXX-000 required a total of 160 units; PR-XXX-001 required 171 samples of X and 179 bottles of X bottles. It is unknown how these sample numbers were selected and why the sample numbers were revised between the two protocols.

# Example of FDA 483 Observation

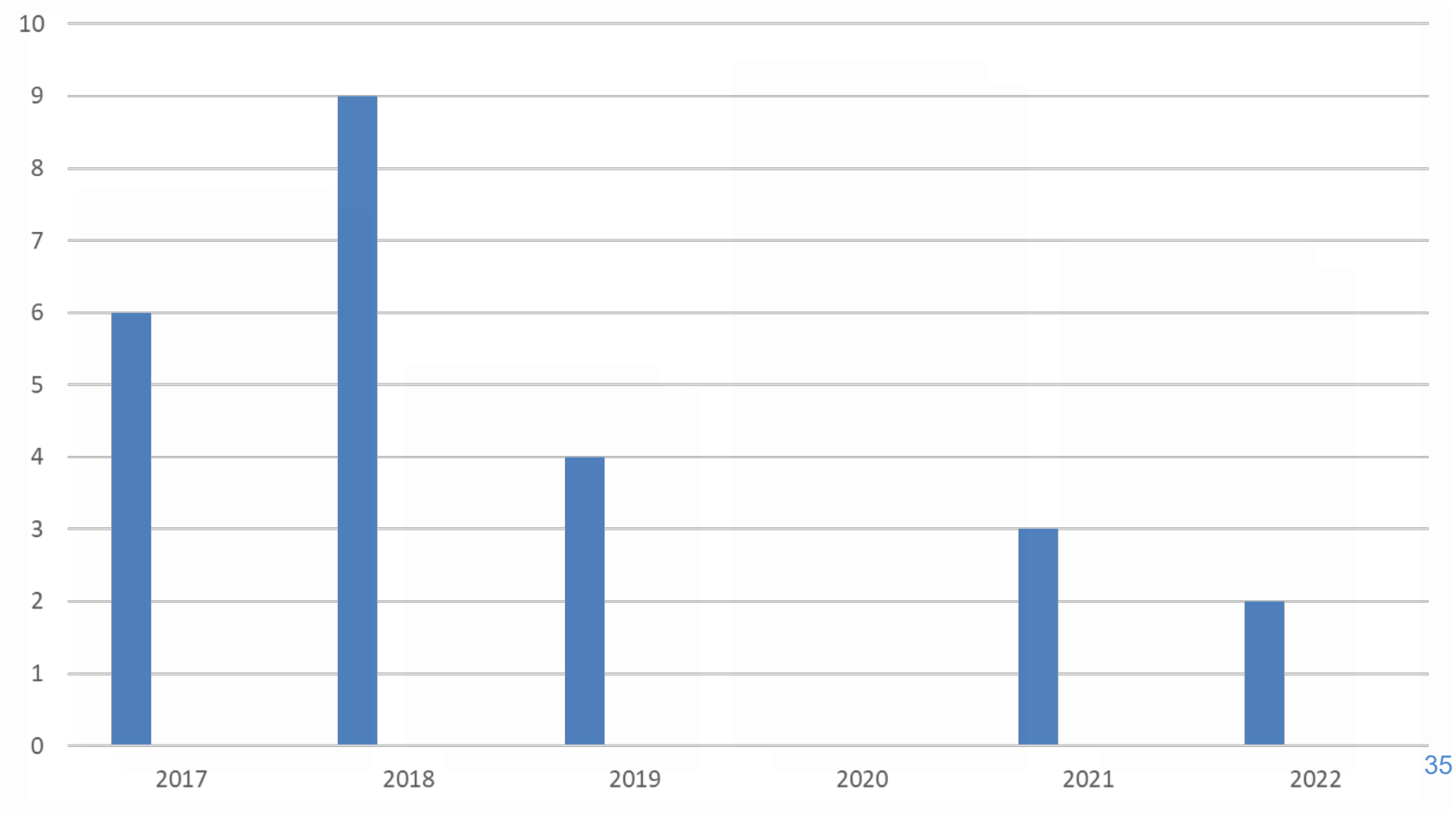
**Sampling plans are not based on valid statistical rationale.**

Specifically, there is no documented evidence to substantiate that sample sizes employed as part of shelf-life study protocols were based on a valid statistical rationale.

As per protocol "PRXX Protocol for Shelf-Life Testing (5 year, 6 year, 7, year, and 8 year Real Time and Accelerated Aging) of XX Products Packaged in XX", a population of samples tested for resulting device density was representative of only 3 device units at each given time point to be tested. There is no documented evidence to justify that the sample size was based on a valid statistical rationale.

# FDA 483 Observation

Procedures to ensure sampling methods are adequate for their intended use have not been [adequately] established. - 820.250(b)



# Example of FDA 483 Observation

**Procedures to ensure sampling methods are adequate for their intended use have not been adequately established.**

Specifically,
A. During design verification of X (document X; report approved xx/xx/xxxx), your firm tested the viscosity of two groups of four X after eight hours of simulated use. Statistical rationale for this sampling plan was not documented.

B. During the OQ phase of your firm's X process validation (document X; report approved xx/xx/xxxx), your firm tested ten (10) X for viscosity and water weight percentage at each process limit. Statistical rationale for this sampling plan was not documented.

# Example of FDA 483 Observation

**Procedures to ensure sampling methods are adequate for their intended use have not been established.**

Specifically, the requirement for incoming inspection of the X require 4 X from each bag of 9600 to have a X test performed. However, there is no statistical basis for this number or reference to a valid sampling plan to justify the reliability of amount sampled.

# Example of FDA 483 Observation

**Procedures to ensure sampling methods are adequate for their intended use have not been adequately established.**

Specifically,
a. Your firm changed/increased the sample size used for X testing of the raw material lots of X several times and did not document the statistical rationale for the acceptance sampling plan chosen, in accordance to your procedures X. The "heightened" X testing of the incoming X was in response to SCAR X and complaints.

b. On xx/xx/xxxx, you used a sample size of "Double Normal per RMQAS" (160/20) to perform the first article inspection of X, and combined 4 different incoming batches into one inspection lot to use for this sampling inspection.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