Sample Size Rationale For Medical Device Package Validation

Andrew Bevil
Engineering Services Manager
WESTPAK

Steven Walfish
President
Statistical Outsourcing Services

Dec 2017

Agenda

- Introduction / Definitions
- Calculators
- Solution Case Studies
- Statistics Overview
- Sampling Error
- Sample Size for Individual Values
- Attribute Sampling Plans
- References

WESTPAK EXCELLENCE IN TESTING

Introduction

- There are important considerations to be made when determining sample sizes for specific applications.
- This presentation will offer examples of statistically-based solutions from actual customer inquiries submitted to a package testing laboratory.
- Sample size determination is an important step to be executed prior to packaging study implementation and should help to ensure that the information obtained will be useful for decision making.

WESTPAK
EXCELLENCE IN TESTING

Introduction

- Sample Size Calculators
  - Qualitative (Attribute)
  - Quantitative (Risk Level)

- www.westpak.com/page/resources/calculator
  - Sample Size for Comparing Means
  - Sample Size for Attributes when C = 0
  - Sample Size for Individuals

WESTPAK® EXCELLENCE IN TESTING

Definitions – Qualitative Testing

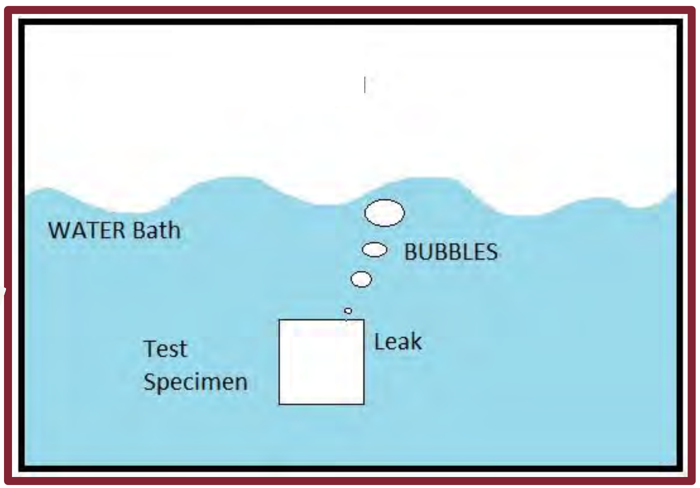
- Qualitative Testing
  - Test to identify whether a particular failure is present, but does not give an indication of how much is present.
  - Data that can be observed but not measured.

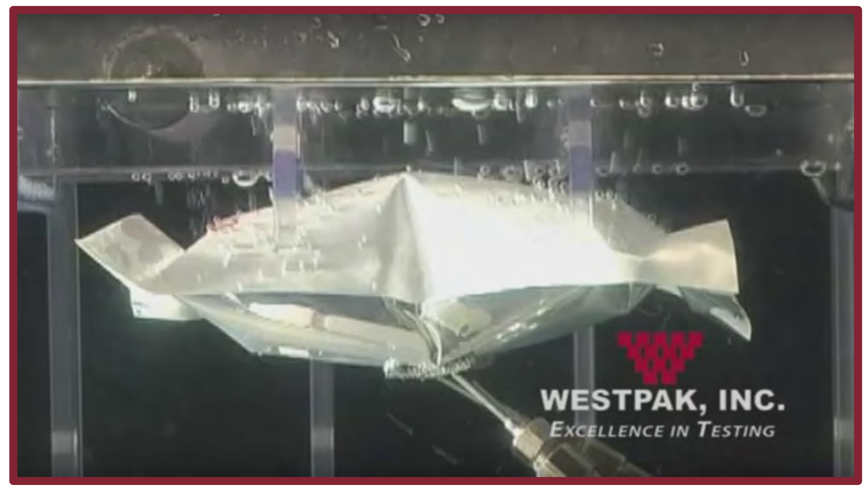
- Examples
  - Visual inspection
  - Gross leak testing
  - Vacuum leaks
  - Dye penetration
  - Scuff testing
  - Material testing

WESTPAK
EXCELLENCE IN TESTING

Definitions – Qualitative Testing (cont'd.)

- Qualitative Testing
  - Examples
    - Gross Leak Testing (ASTM F2096)
      - Identify the presence of gross leaks





[YouTube: Gross Leak Testing per ASTM F2096]

WESTPAK
EXCELLENCE IN TESTING

Definitions – Qualitative Testing (cont'd.)

- Qualitative Testing
  - Examples
    - Dye Penetration Testing (ASTM F1929 and F3039)
      - Identify the presence of channel leaks

[YouTube: Dye Penetration Testing per ASTM F1929]

WESTPAK
EXCELLENCE IN TESTING

Definitions – Qualitative Testing (cont'd.)

- Quantitative Testing
  - Test to identify whether a particular criteria is present.
  - Data that can be measured.

- Examples
  - Seal strength testing
  - Burst testing
  - Compression testing
  - Tensile testing
  - Tape adhesion testing

WESTPAK
EXCELLENCE IN TESTING

Definitions – Quantitative Testing

- Quantitative Testing
  - Examples
    - Seal Strength Testing (ASTM F88)
      - Determine Peel Separation Force
        - » Collect Mean, Standard Deviation, Max, Min

[YouTube: Seal Testing per ASTM F88]

WESTPAK
EXCELLENCE IN TESTING

Definitions – Quantitative Testing (cont'd.)

- Quantitative Testing
  - Examples
    - Burst Testing (ASTM F2054)
      - Determine Burst Force
        - » Collect Mean, Standard Deviation, Max, Min

[YouTube: Burst Testing per ASTM F2054]

WESTPAK® EXCELLENCE IN TESTING

Solution Case Study #1

- Dye Penetration Testing (Qualitative)
  - Defects and leaks in the seal area are observed by the test operator as an accept/reject criteria; zero defects are allowed.
    - For 95% confidence and 90% reliability, a samples size of 29 samples to be dye tested would be necessary.

WESTPAK EXCELLENCE IN TESTING

[YouTube: Dye Penetration Testing per ASTM F1929]

Solution Case Study #1 (cont'd.)

- Seal strength testing (Quantitative)
  - The peel test measures the peak force required to separate a pouch seal.
  - The mean peel strength for a new pouch seal needs to be a minimum of 4N to ensure a sterile barrier.
  - The risk is determined to be major requiring a confidence level of 95% with a reliability of 90%.
  - Data from the packaging qualification showed that the standard deviation was 0.5N with a mean of 4.5N.

Question: What is the sample size for the package validation study to show that the mean peel strength is a minimum of 4N?

Solution Case Study #1 (cont'd.)

- Seal strength testing (Quantitative)
  - The approach would be as follows:
    - One-Sided or Two-Sided: 1
    - Type I Error: 95%
    - Type II Error: 90%
    - Standard Deviation of Sample: 0.5
    - Difference to be Detected: 0.5

YouTube: Seal Strength Testing per ASTM F88

Answer: A sample consisting of 9 peel strength tests would be needed to have 95% confidence that if the true mean peel strength was less than 4N it would be detected 90% of the time.

WESTPAK
EXCELLENCE IN TESTING

Solution Case Study #2

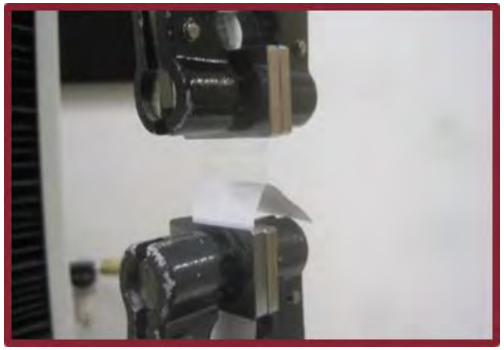
- Commonly seen Sample Size quantities

  Gross leak testing – 59 samples

  - Qualitative

  Seal strength testing – 30 samples

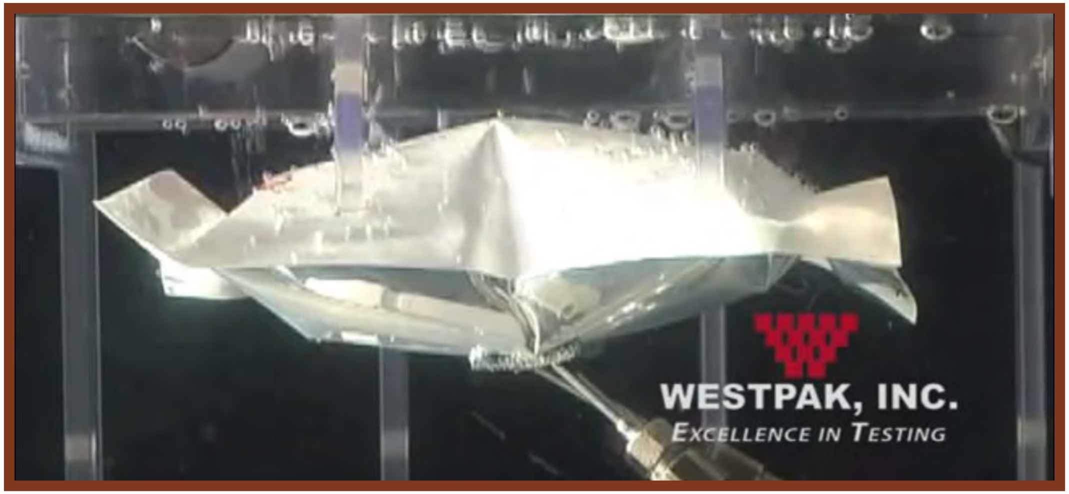
  - Quantitative



WESTPAK® EXCELLENCE IN TESTING

Solution Case Study #2 (cont'd.)

- Gross leak testing – 59 samples
  - 95% confidence and 95% reliability

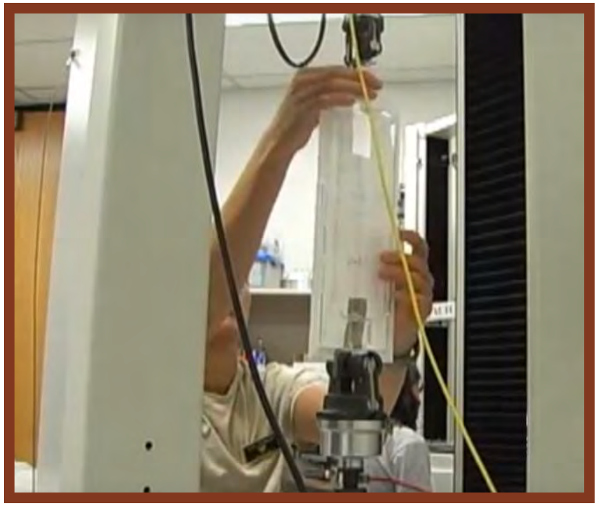


YouTube: Gross Leak Bubble Test per ASTM F2096

WESTPAK
EXCELLENCE IN TESTING

Solution Case Study #2 (cont'd.)

- Seal strength testing – 30 samples
  - 95% confidence and 90% reliability
    - Go / No-Go Testing



[YouTube: Seal Strength Testing per ASTM F88]

WESTPAK® EXCELLENCE IN TESTING

Solution Case Study #2 (cont'd.)

- **Question: How many samples would be needed if 99% confidence and 99% reliability is required?**

- **Answer: 459 samples**

Case Study – Wrap Up

- Seal strength testing
  - If it is a continuous characteristic, then depending on the standard deviation and delta (difference to detect), the confidence and reliability can change.

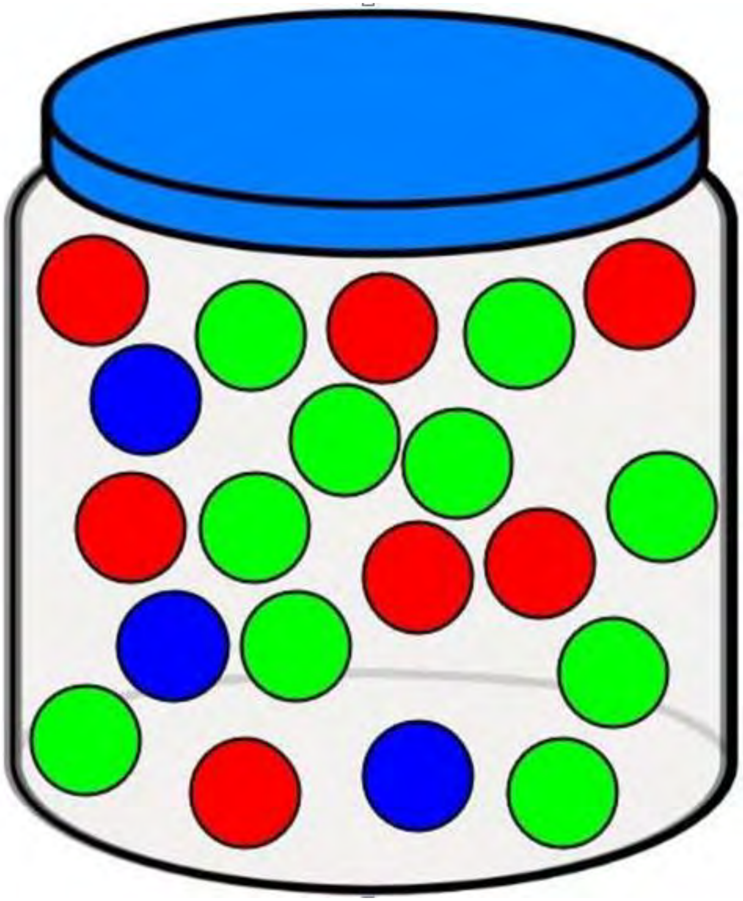
Statistics Overview

- Introduction
- Sampling Error
- Sample Size Calculations
  - Based on the Individual Values
  - Go/No-Go
  - ANSI Z1.4
  - Square Root of N + 1

Introduction

- Decisions are often based on our analysis of a sample.

- How we conduct a sample is very important.
  - Want:
    - Minimize bias
    - Sample reflects the characteristics of the lot or batch
    - Economical sample size



WESTPAK
EXCELLENCE IN TESTING

Sampling Error

- Sampling has inherent risks and potential error.
- The number of samples should be sufficient to minimize the risks.
- Cost versus benefit

		Reality	
Decision		Accept	Reject
	Accept	Correct Decision	Type II Error (β) Consumer Risk
	Reject	Type I Error (α) Producer Risk	Correct Decision

Sample Size for Individual Values

- Can develop sample sizes for individual values instead of the mean.

- Requires a confidence level and percent of future values expected to be in the interval (coverage or reliability).

- This approach is for all future observations (beta-content approach)

$$\overline{X} + k * S < U$$

$$\overline{X} - k * S > L$$

- Two-sided tolerance limits for normal populations-Some improvements. Howe, W. G. 1969, Journal of the American Statistical Association, Vol. 64, pp. 610-620)

WESTPAK® EXCELLENCE IN TESTING

Example

- How large a sample do I need to have 95% confidence with 95% reliability for a mean of 10.0 and standard deviation of 0.55?
- The specification are 8.5 to 12.0

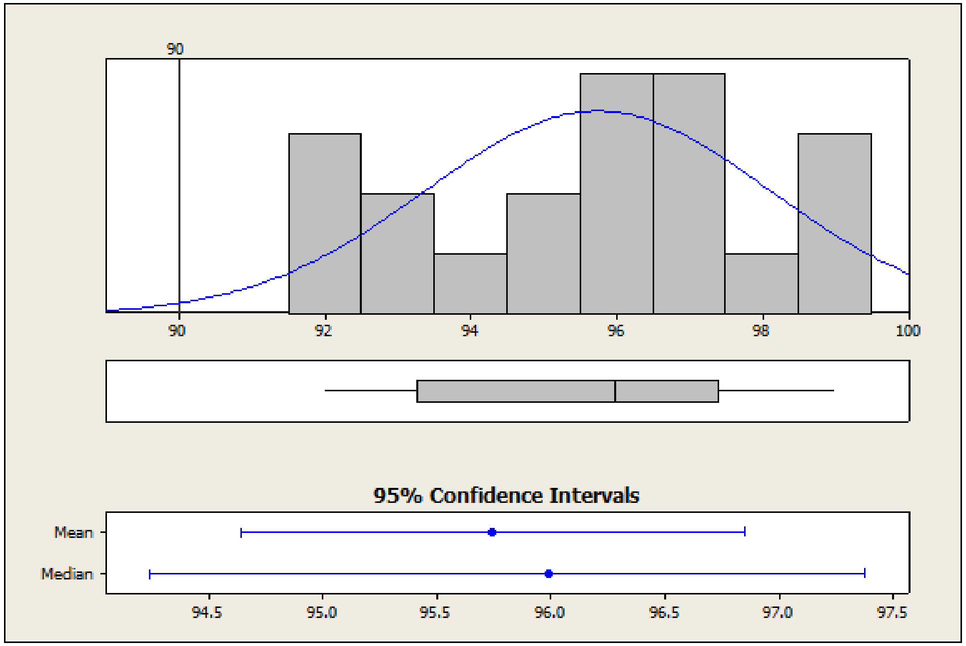
$$10 - k * 0.55 > 8.5$$
$$k = 2.727$$

- Since the mean is closest to the lower specification
- **Sample size is approximately 21**

WESTPAK®
EXCELLENCE IN TESTING

Compared with a Mean

- We collected 20 results
  - Mean = 95.7
  - Std Dev. = 2.4
  - LSL = 90
  - Min = 92
  - Max= 99



Which is Right?

- Want to test if the **MEAN** is greater than 90.
  - The 95% Lower Bound on 95.1 is 94.8. This implies if we sample 20 units from a population whose mean is 95.7 with SD=2.4, the average will be greater than 94.8; 95% of the time.

- Want to test if the **INDIVIDUAL** values are greater than 95.
  - The Lower Bound with 95% confidence and 99% coverage (reliability) is 87.9. This implies if we sample 20 units from a population whose mean is 95.7 with SD=2.4, 99% of the individual values would be greater than 87.9 with 95% confidence.

Which is Right? (cont'd.)

- The mean of 20 results would meet the specification.

- A sample of 20 results would have individual samples that would fail.

- Must be careful to specify what is the reportable value for the testing.

WESTPAK
EXCELLENCE IN TESTING

Attribute Sampling Plans When All Units Pass

- At 95% Confidence and 90% Reliability

- $n = \frac{\ln(1 - Confidence)}{\ln(Reliability)} = \frac{\ln(1 - 0.95)}{\ln(0.90)} = 28$

Confidence	Reliability	Sample Size
80%	80%	8
80%	90%	16
80%	95%	32
80%	99%	161
90%	80%	11
90%	90%	22
90%	95%	45
90%	99%	230
95%	80%	14
95%	90%	29
95%	95%	59
95%	99%	299
99%	80%	21
99%	90%	44
99%	95%	90
99%	99%	459

ANSI Z1.4

- Z1.4 is a standard developed for incoming inspection where the attribute is pass/fail.
- ANSI Z1.4 system is a collection of sampling plans with switching rules.
- Plans are intended primarily to be used for a continuing series of lots or batches.

WESTPAK
EXCELLENCE IN TESTING

Attribute Sampling Plans

- AQL: Acceptable Quality Level "is the maximum percent nonconforming (or the maximum number of nonconformities per hundred units) that, for purposes of sampling inspection, can be considered satisfactory as a process average." §4.2

- Note: AQL is not lot or batch specific but rather a process average.

- AQL is stated in the standard as a percent:
  an AQL = 0.15 is a rate of 0.15 nonconforming units per 100 units or 0.15%.

$\sqrt{N} + 1$

- There is no known statistical justification for the use of the 'square root of N plus one' sampling plan.

- "Despite the fact that there is no statistical basis for a 'square root of n plus one' sampling plan, most firms utilize this approach for incoming raw materials."

  – Henson, E., A Pocket Guide to CGMP Sampling, IVT.

WESTPAK
EXCELLENCE IN TESTING

Compare the Plans

ANSI/ASQ Z1.4

- Lot Size N=1000
- Sample size n=32
- Acceptance Ac=0
- Rejection Re=1
- AQL=0.160%
- LQ = 6.94%

Square root N plus one

- Lot Size N=1000
- Sample size n=33
- Acceptance Ac=0
- Rejection Re=1
- AQL=0.153%
- LQ = 6.63%

References

- H. Saranadasa, "The Square Root of N Plus One Sampling Rule: How Much Confidence Do We Have?" *Pharm. Technol.* 27 (5), 50 (2003).
- American Society for Quality (ASQ), ANSI/ASQ Z1.4-2008 (Milwaukee, WI, 2008).
- W. Taylor, *Guide to Acceptance Sampling* (Taylor Enterprises, Inc, Lake Villa, IL, 1992).
- Zero Acceptance Number Sampling Plans, 5th edition, by Nicholas Squeglia
- Howe, W. G. 1969, Journal of the American Statistical Association, Vol. 64, pp. 610-620)

QUESTIONS

WESTPAK
EXCELLENCE IN TESTING

More Questions Later? Need a Quote?

- RELIABILITY
- PACKAGING
- SUPPLY CHAIN
- HAZARDOUS MATERIAL
- LIFE SCIENCE
- MATERIAL ANALYSIS
- COLD CHAIN
- MILITARY/AEROSPACE
- SOLAR
- SUSTAINABILITY

Submit Test Questions or Request for Quote to WESTPAK via our website at www.westpak.com/contactus.aspx

Need Statistics Help? Contact Steven Walfish at Statistical Outsourcing Solutions www.statisticaloutsourcingservices.com

WESTPAK®
EXCELLENCE IN TESTING

Next Webinar Topic

Case Studies of Medical Device

Package Failures

Katie Tran
Principal Quality Systems Engineer
WESTPAK

Date: Thursday, February 22, 2018

Register at: www.westpak.com/page/resources/webinars

About WESTPAK

Two Locations

San Jose Laboratory
83 Great Oaks Boulevard
San Jose, CA 95119
408-224-1300

San Diego Laboratory
10326 Roselle Street
San Diego, CA 92121
858-623-8100

www.westpak.com

Contact Us

WESTPAK, INC.
ISO 9001:2008
10001175 & 10004260

ISO 17025
ACCREDITED LABORATORY

ista
CERTIFIED LABORATORY

WESTPAK
EXCELLENCE IN TESTING