

# *IoPP Education Track Webinar*

## Medical Device Packaging

### Sample Size and Statistical Rationale

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Presented by



# MDPTC: Mission Statement



- **Provide a forum for packaging professionals representing the Medical Device Industry for discussion, exchange and development of information on issues that affect them in areas of organization, problems and technical issues, regulations, standards and new technologies.**

# MDPTC: Vision Statement



- Provide the latest **information** on national and international regulatory requirements as they affect the packaging of medical devices.
- Provide a **forum** to voice the device industry packaging position on issues that affect them.
- Provide **education** to new members entering the medical device area of package engineering.
- Provide a timely list of **tools and documents** (guides, test methods and standards) that are helpful when performing the tasks related to the package engineering of medical devices.
- Exchange **non-proprietary information** regarding new materials, equipment and systems, which can improve the overall performance and quality of the medical device packaging industry.
- Act as a **liaison** for technical and regulatory updates between organizations of mutual interest such as AAMI, ISO, ASTM, ISTA and the U.S. FDA.

# MDPTC: Subcommittees



Medical Device Packaging  
Technical Committee

- **Labeling**
  - Dave Olson – AdvancedWeb,  
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- **Education**
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# Agenda

- **Statistical Rationales**---the importance and application of developing an appropriate sample size for testing
- Compliance and guidance for:
  - medical device sterile barrier systems
  - Food
- Determining sample size for sterile barrier systems (packaging systems)
  - A **process** for developing an appropriate and statistically valid test population
- Summary of key takeaways of non-statistically significant survey of medical device companies on statistical rationales
- Wrap Up
- Question and answer

# Statistical Sample Size Development

## Why Have a Statistically Significant Sample Size?

# Why have a statistically significant sample size?

- **For sterile medical devices– it is a requirement**

- ISO 11607:2006, part 1—section 4.3- “The sampling plans used for selection and testing of packaging systems shall be applicable to the packaging systems being evaluated. Sampling plans shall be based upon **statistically valid rationale**”
- TIR 22:2007 section 5.3: “ Sampling plans should be acceptable to packaging systems, **reflective of risk tolerance, and be based on statistically valid rationale**”.
- TIR 22:2007 section 12.2.3, Packaging system design validation: “Sampling plan to be used: Sample sizes must be large enough to provide for statistically significant analysis to provide a high degree of reliability, and will be **dependent on corporate risk policy, economics and regulatory requirements**”.

# Why have a statistically significant sample size?

- **For Food– Food Safety and Modernization Act--2011**

## **PREVENTION**

### – **Written food safety plan**– Includes:

- Evaluates hazards that are reasonably likely to occur (*risk analysis*)
- Steps put in place to minimize or prevent hazards—your mitigation
- Verification activities– might include validation that the preventive controls are adequate for their purpose and are effective in controlling the hazard
- Generally, cGMP provisions would still apply to facilities that would be exempt from the hazard analysis and risk-based preventive control requirements



# Statistical Sample Size Development

## A **Process** for Development of a Statistical Rationale

# Statistical Sample Size Development

## Risk Analysis

# Sample Size Development Process

## Statistical Rationale Development for Validation

### Process of product/package risk assessment

- Medical Device—corporate application of **ISO 14971:2007** “Application of Risk Management to Medical Devices”
- Formal risk analysis of SBS. Check out Annex H **TIR 22**
  - Most Risk Analyses and Design FMEA’s designate Loss of Sterile Barrier Integrity as a Critical Defect.
- Review and alignment of risk with corporate assignment of criticality of risk and statistical rigor related to testing methodologies, based on defect criticality

# Statistical Sample Size Development

## Design FMEA

**Failure modes and effects  
analysis of the packaging/device  
system**

# Sample Size Development Process

## Risk Analyses



Device/Project: \_\_\_\_\_

Performed by: \_\_\_\_\_

•Device part/model number(s): \_\_\_\_\_

•Type: (Component/ Subsystem/System) \_\_\_\_\_

Date: \_\_\_\_\_

Component /Function/ Procedure	Potential Hazard (or Failure Mode)	Effects of Hazard (or Failure)	Severity	Potential Cause(s)/Mechanism(s) of Failure	Occurrence	Current Risk or Design Control Measures	Detection	RPN	Recommended Action(s)	Responsibility & Target Completion Date	Actions Taken	Severity	Occurrence	Detection	RPN
Sterile Barrier System	loss of sterile barrier integrity	Nosocomial infection—human patient	4	device damaging primary sterile barrier packaging components	1	material specifications	5	20	Packaging Design Validation	Engineering		4	2	2	16

# Sample Size Development Process

## Statistical Rationale Development



So now that I have determined my defect criticality, now what?

### Definitions

- Response type for your specific packaging test (s)
  - **Attribute data**— pass/fail, leak/no leak—binary in nature
  - **Variable data**— discrete value— for example seal strength— XX lbs. force/inch width
- Confidence and reliability
  - **Confidence** or risk level—Central Limit Theorem
    - Average value of the attribute obtained by your test samples is equal to the true population value
    - 95% confidence level---95/100 samples will have the true population value within your range of precision specified
  - **Reliability**—percent defective in the population-based on zero failures for your testing

# Sample Size Development Process

## Attribute Data

# Sample Size Development Process

## Statistical Rationale Development

- Response type for your specific packaging test (s)
  - **Attribute data– SAMPLE SIZE DETERMINATION**
- The exact binomial distribution

### Sample Size Formula is based off of the Binomial Distribution

If n represents the sample size,  
p represents the proportion of success (1-p represents the proportion of failure),  
x represents the number of successes (n-x represents the number of failures),  
then the formula for the probability of x successes in n trials =

$$\frac{n!}{x! (n-x)!} p^x (1-p)^{n-x}$$

where  $a! = a*(a-1)*(a-2)*...*2*1$  (i.e.,  $6! = 6*5*4*3*2*1 = 720$ )



# Sample Size Development Process

## Statistical Rationale Development



- **Attribute data– SAMPLE SIZE DETERMINATION**

- **The exact binomial distribution:**

Statistical analysis statement with zero failures-- Based on a simple passing or failing of the test criteria (package leak). Using the exact binomial distribution with “X quantity” sample size and 0 failures, at least “Y%” of the population would meet the validation criteria. Specifically—sample size of 60, at least 95% of the population would meet validation criteria with 95% confidence.

Minimum Sample Size	Acceptability	Confidence
30	90%	95%
60	95%	95%
300	99%	95%

# Sample Size Development Process

## Statistical Rationale Development



- —95% confidence, 95% reliability--**This means that one can state with 95% confidence that no more than 5% of the population will exhibit the “defect” or unacceptable condition when tested as *specified* within the test protocol.**
  - Is 95%/95% okay? Depends....
    - Criticality of defect—risk assessment
      - Share survey data for sterile barrier breach
      - FDA has not published requirements, audience will have direct experience
    - Company history with—this type of package design, packaging process, device/product configuration, validation history

# Sample Size Development Process

## Variable Data

# Sample Size Development Process

## Statistical Rationale Development

- **Variable data— discrete value**

- for example—seal strength –lb. force/inch width.
- Typically a specification or specification limit is established for variable data, for example a *minimum seal strength value*.

- **Concept of Tolerance Limits for Variable Data, e.g. Seal Strength**

- Practical boundaries of process variability for seal strength
- Based on your seal strength distribution, the 95% tolerance limit will be greater than your specified minimum seal strength spec.

# Sample Size Development Process

## Statistical Rationale Development



- **Variable data– discrete value**

- Frequently, a **lower tolerance limit** is calculated at a specified confidence and reliability—for example, **95%/99%**

- The lower tolerance limit (LTL) calculation must be equal to or greater than the specified **minimum seal strength value**.
- A **lower tolerance limit** is calculated as follows---- mean of the test population - (k value) X standard deviation.

Mean – k\*s–

- The “k” factor can be obtained from Juran’s Quality Handbook, fifth edition, by Joseph M. Juran, A. Blanton Godfrey, 1998, page AAll.36.

# Sample Size Development Process

## Additional Sampling Plan Pointers

# Sample Size Development Process

## Statistical Rationale Development



- Some additional pointers:

- AQL Sampling Plans are for use in manufacturing sampling plans—NOT validation sampling plans
  - **WHY?**
  - **The Burden of proof of “good” shifts**
    - In manufacturing, the lot is assumed Good, until proven bad— biased towards the producer’s risk
    - Validation—it is assumed that the requirement has not been met unless testing demonstrates it is so

# Sample Size Development Process

## Some Alternative Sample Size Determination Methods



# Sample Size Development Process

## Statistical Rationale Development



- **Alternate Sample Size Determination Method:**

- <sup>1</sup> **Finite Population Correction for Proportions**

$$n = \frac{N}{1 + N(e)^2}$$

- Finite Population Correction for Proportions:
- **n = Validation test sample size—what we are solving for..**
- N = Validation lot Size from which you will sample, example- -90 packages
- e = level of precision, reliability, 95%
- Power or confidence level = 95%--assumed
- $74 = 90/1 + 90(.05)^2$
- **Test-- n = 74 packages for 95%/95%**

<sup>1</sup> Statistical Reference: *Determining Sample Size* by Glenn D. Israel, University of Florida IFAS Extension, PE0D6, published 1992 and reviewed 2009 and *Cliffs Quick Review Statistics* by David H. Voelker, Peter Orton and Scott V. Adams, Wiley Publishing, Inc. 2001, page 79.

# Sample Size Development Process

## Medical Device Companies Sample Size Survey

# Medical Device Companies--Survey

Interview Question	Responses	
	Variable	Attribute
7d) What is the typical sample size utilized for packaging validations?	Company #1-154	Company #1—154 invasive, 65– non invasive
	Company #2--15	Company #2--60
	Company #3—30 or 60 with use of corresponding k values	Company #3—60 (95%/95%) or 600 (95%/99.5%) depending on risk assessment and statistical rationale
	Company #4—30	Company #4--300
	Company #5—project specific	Company #5—project specific
	Company #6—30 or 40—pre and post sterile	Company #6—depends on risk assessment and statistical rationale
	Company #7--30	Company #7--59
	Company #8—30= min requirement	Company#8—59= min requirement
	Company#9—60-100	Company#9--230
	Company #10--22	Company#10--22
	Company #11--30	Company #11--60

# Sample Size Development Process

## Wrap Up

# Sample Size Development Process

## Statistical Rationale Development

### Wrap Up



- Understand your industry **compliance requirements** for a statistical rationale for validation
- Execute a **risk assessment** utilizing tools such as FMEA
- Once risk is assessed, work with your organization to establish the **criticality of the risk or failure**.
  - Major Defect
  - Critical Defect
- Develop your **statistical rationale based on the criticality of the defect**
- Review the “cost of quality” vs. the risk assessment
  - Dummy devices can be used in a packaging validation for a sterile barrier system
  - Packaging systems must be manufactured through a validated process using process extremes
  - Validated sterilization process
  - Part of the risk assessment should include the leveraging of previous validations
    - Similar packaging design validations?
    - Brand new packaging design and/or materials?

# Thank You

## Questions??



# References



## Works Cited

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