Medical Device Packaging
Sample Size and Statistical Rationale

Live Webinar: April 28, 2016

Karen Greene, Life Packaging Technology LLC and Life Pack Labs, Vista, CA
karen@lifepacktech.com
760 835 2260

LIFEPACKAGING TECHNOLOGY

Life Pack Labs™
A MOCON® Inc./ Life Packaging Technology Business

Life Packaging Technology and Life Pack Labs

Life Packaging Technology

Provides customized packaging engineering services on a global basis: design, prototyping, technical and quality systems consultation and low volume manufacturing for packaging feasibility.

www.lifepackagingtechnology.com

Life Pack Labs

Provides expert packaging testing services for healthcare/ pharmaceutical and medical packaging

www.lifepacklabs.com

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 ISO 16775 section 5.3: " Sampling plans should be acceptable to packaging systems, **reflective of risk tolerance, and be based on statistically valid rationale**".
  - TIR ISO 16775 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 TIR ISO 16775
  - 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, discrete value**
  - **Variable data– numerical 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 =

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

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 AAII.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:**
  - [1] **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%**

[1] 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**

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

- ISO 11607, Packaging for Terminally Sterilized Medical Devices, Parts 1 and 2. 2006th ed. AAMI, 2006.
- "Medical Devices." U S Food and Drug Administration Home Page. 07 June 2009 <http://www.fda.gov/MedicalDevices/default.htm>.
- ISO/TS 16775:2014, Guidance on the application of ANSI/AAMI/ISO 11607, Packaging for Terminally Sterilized Medical Devices, Part 1 and Part 2:2006.
- 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.
- Juran's Quality Handbook, fifth edition, by Joseph M. Juran, A. Blanton Godfrey, 1998, page AAII.36.