IoPP Education Track Webinar
Medical Device Packaging
Sample Size and Statistical Rationale

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Presented by

Institute of Packaging Professionals
Medical Device Packaging Technical Committee
• 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

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• **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
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
A Process for Development of a Statistical Rationale
Risk Analysis
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
Design FMEA

Failure modes and effects analysis of the packaging/device system
## Risk Analyses

Device/Project: ____________________________  Performed by:  ____________

- Device part/model number(s): ____________________________
- Type: (Component/Subsystem/System) ____________________________

Date: ____________  ____________  ____________

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

\[
\frac{n! \cdot p^x \cdot (1-p)^{n-x}}{x! \cdot (n-x)!}
\]

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

<table>
<thead>
<tr>
<th>Minimum Sample Size</th>
<th>Acceptability</th>
<th>Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>60</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>300</td>
<td>99%</td>
<td>95%</td>
</tr>
</tbody>
</table>
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
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.
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–

Additional Sampling Plan Pointers
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
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
    • \( 74 = \frac{90}{1 + 90(.05)^2} \)
    • **Test**-- \( n = 74 \) packages for 95%/95%

Sample Size Development Process

Medical Device Companies
Sample Size
Survey
<table>
<thead>
<tr>
<th>Interview Question</th>
<th>Responses</th>
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<tbody>
<tr>
<td>7d) What is the typical sample size utilized for packaging validations?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Company #1—154</td>
</tr>
<tr>
<td></td>
<td>Company #2—15</td>
</tr>
<tr>
<td></td>
<td>Company #3—30 or 60 with use of corresponding k values</td>
</tr>
<tr>
<td></td>
<td>Company #3—60 (95%/95%) or 600 (95%/99.5%) depending on risk assessment</td>
</tr>
<tr>
<td></td>
<td>and statistical rationale</td>
</tr>
<tr>
<td></td>
<td>Company #4—30</td>
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<tr>
<td></td>
<td>Company #5—project specific</td>
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<tr>
<td></td>
<td>Company #6—30 or 40—pre and post sterile</td>
</tr>
<tr>
<td></td>
<td>Company #6—depends on risk assessment and statistical rationale</td>
</tr>
<tr>
<td></td>
<td>Company #7—30</td>
</tr>
<tr>
<td></td>
<td>Company #8—30=min requirement</td>
</tr>
<tr>
<td></td>
<td>Company #8—59=min requirement</td>
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<tr>
<td></td>
<td>Company #9—60-100</td>
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<td></td>
<td>Company #10—22</td>
</tr>
<tr>
<td></td>
<td>Company #11—30</td>
</tr>
</tbody>
</table>
Sample Size Development Process

Wrap Up
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??
Works Cited


