

# **Applying PAT to the Lyophilization Process:**

**What must be done to  
achieve real time release?**

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# FDA Definition of PAT

**A system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during process) of critical quality and performance attributes of raw and in-process materials and processes , with the goal of ensuring final product quality.**

Pharmaceutical CGMPs  
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# Quality

- **Product quality should be built-in to the process by design and not tested into the final product.**
- **Six Sigma – 3.4 defects per million**

# Lyophilization Process

## ■ Formulation

# Formulation

- **Reproducibility – current effort**
  - **Thermal Properties**

# Thermal Properties

- Presence of ice-like water clusters (freezing)
- Degree of supercooling (freezing)
- Depression of freezing temperature (freezing)
- Interstitial phase changes (freezing)
- Collapse or eutectic temperature (warming)
- Interstitial melting temperature (warming)
- Degree of crystallization (warming)
- Metastable States (warming)
- Activation energy (warming)

# Formulation

- **Reproducibility – current effort**
  - **Thermal Properties**
  - **Non-Stoichiometric Effects**

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# Formulation

- **Reproducibility – current effort**
  - **Thermal Properties**
- **Non-Stoichiometric Effects**
  - **Frequency Distribution**
    - **Mean Temperature**
    - **Standard Deviation**
      - **Skewed**

# Future Needs for Thermal Analysis

- **Statistical Significant of Measurements**

- **Rapid**

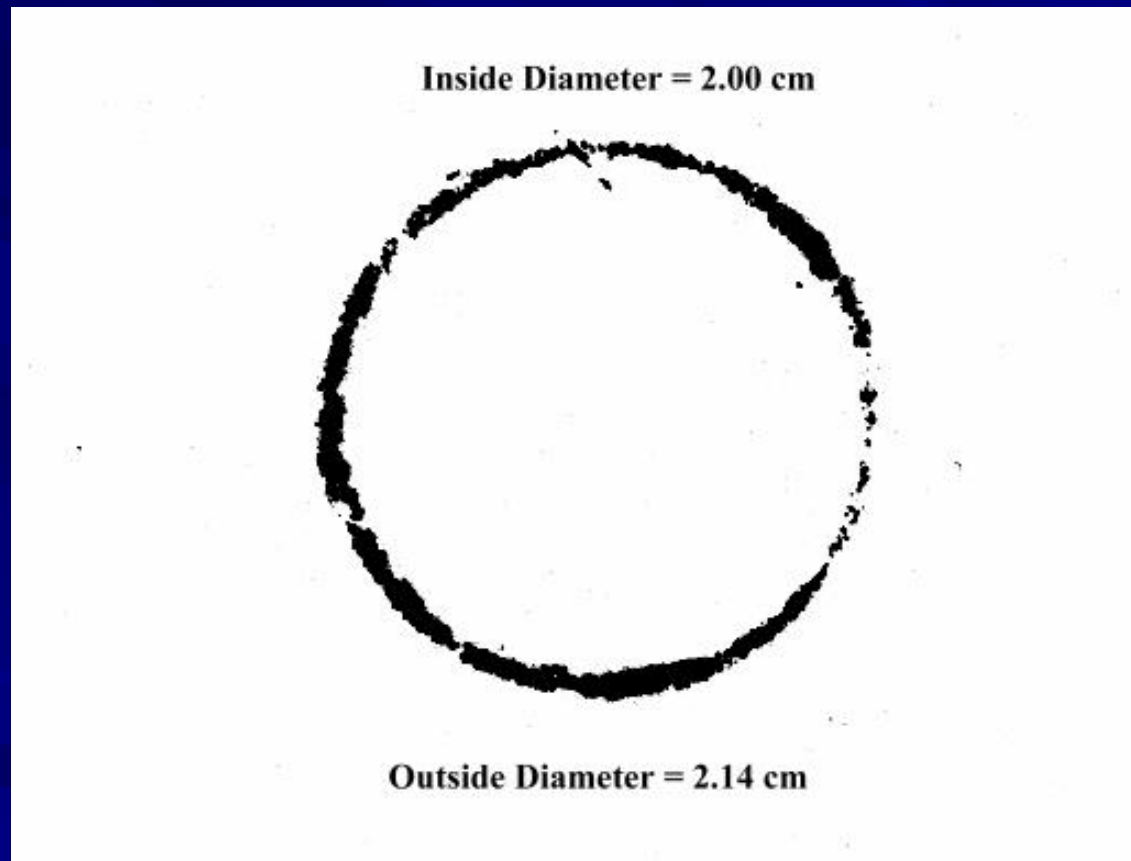
# Lyophilization Process

- Formulation
- Freezing Process
- Primary Drying

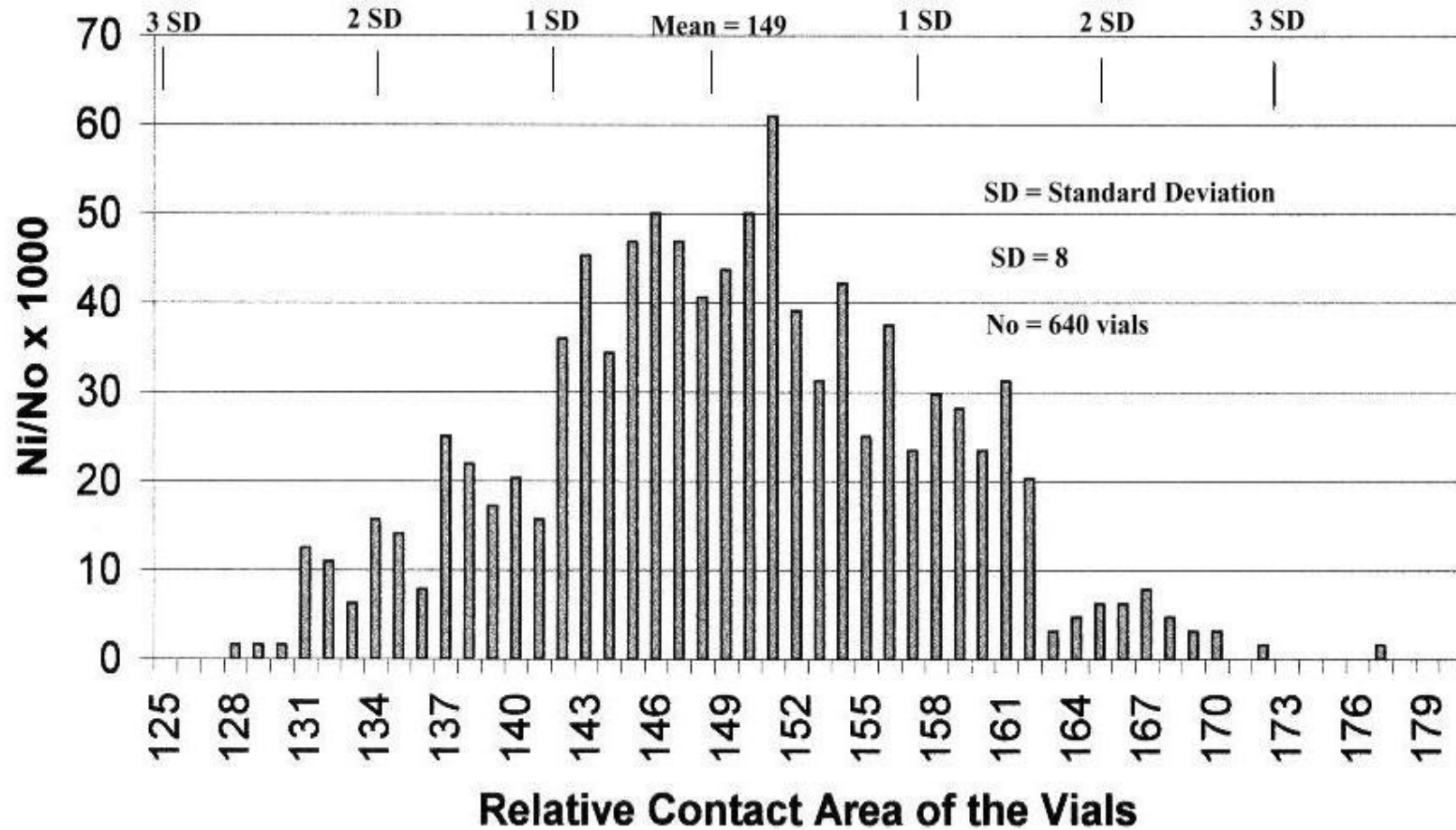
# Primary Drying

## ■ Container (Vial)

# Vial Surface Area



## Frequency Distribution of the Contact Area of Vials



# Primary Drying

- Container (Vial)
- Product Temperature

# Product Temperature

- Thermocouples – OUT
- Resistance Thermal Devices – OUT
  - What is needed in the Future
    - Non-intrusive method
- Statistically Significant Number of Temperature Measurements
  - Shelf-Shelf Measurements

# Primary Drying

- Container (Vial)
- Product Temperature
- Shelf – Surface Temperature

# Shelf Temperature

- Fluid Temperature – OUT
- What is needed in the Future
  - Non-intrusive method
- Statistically Significant Number of Temperature Measurements
  - Shelf-Shelf Measurements

# Primary Drying

- Container (Vial)
- Product Temperature
- Shelf – Surface Temperature
- Improved Equipment Design

# Lyophilization Process

- **Formulation**
- **Freezing Process**
- **Primary Drying**
- **Secondary Drying**

# Secondary Drying

- **Currently – Uncertain as to the residual moisture content of product until it is removed from the dryer. Testing is not statistically significant.**
- **Future - Statistically significant determination of the moisture content before the stoppering process.**

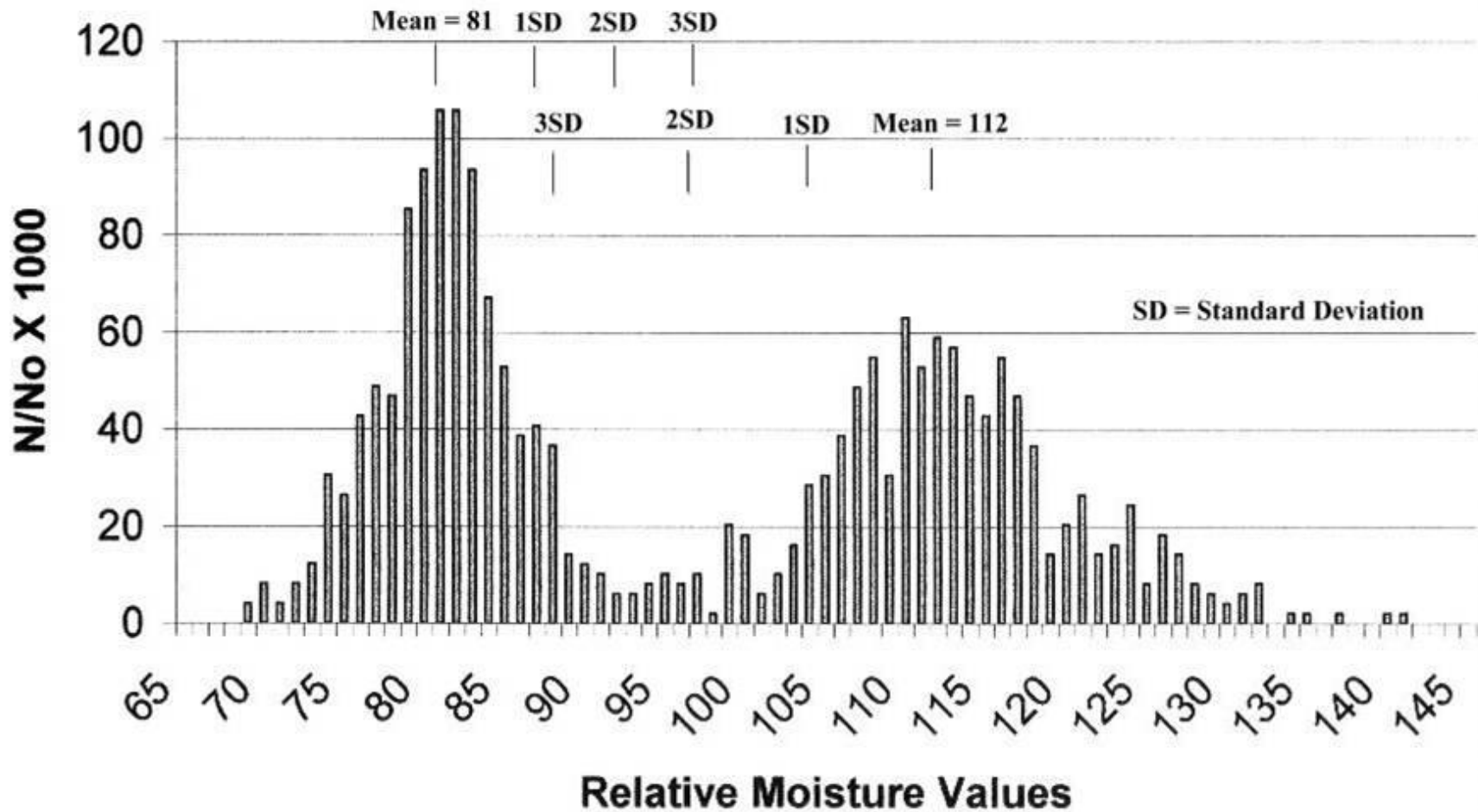
# Lyophilization Process

- **Formulation**
- **Freezing Process**
- **Primary Drying**
- **Secondary Drying**
- **Stoppering**

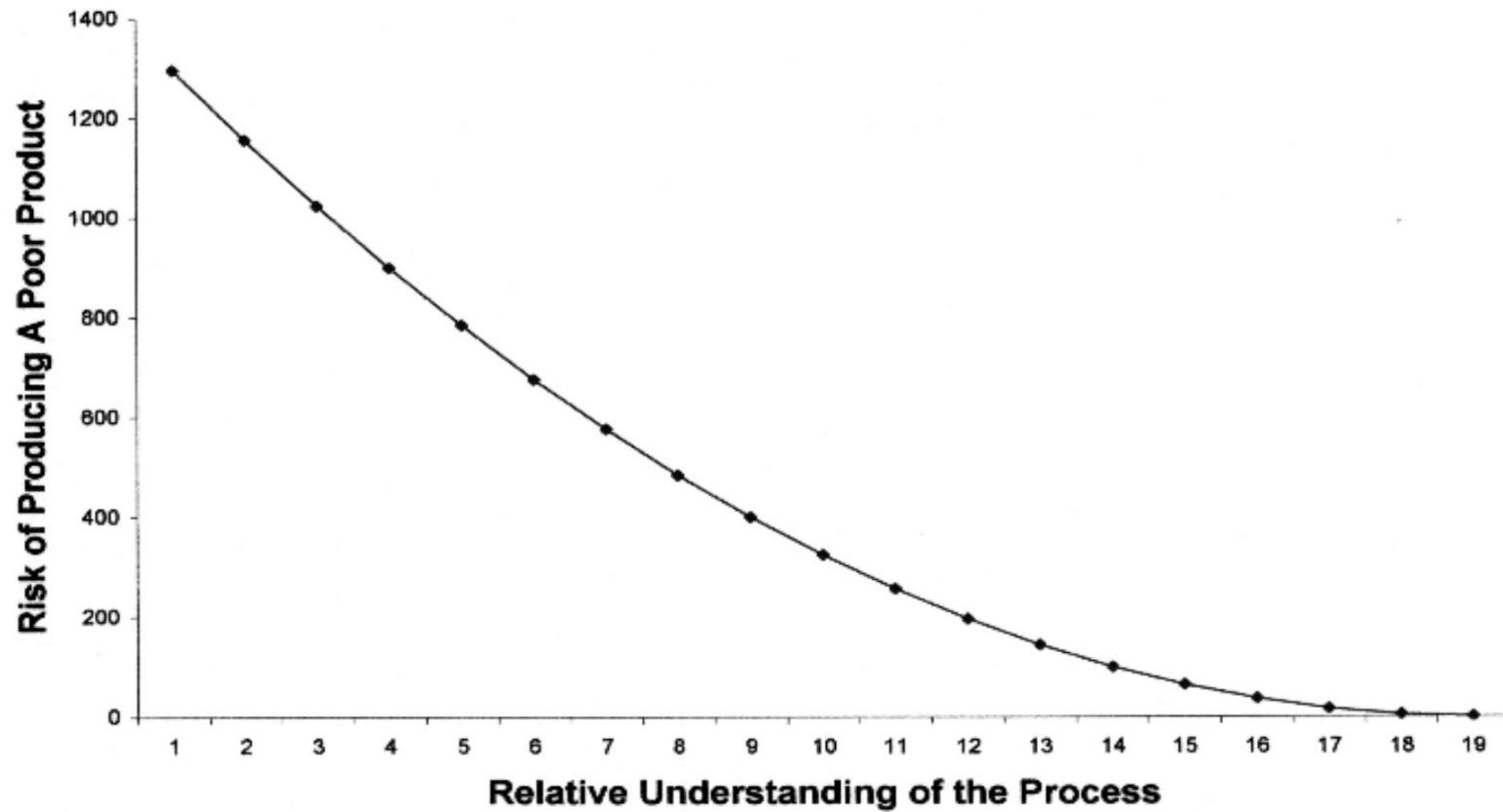
# Stoppering

- **Equipment – Flat shelves (top and bottom) to ensure complete seating of all closures on the vials.**
- **Moisture content of the closure**

## Frequency Distributions for Dried and Un-Dried Sterilized Closures



**Risk of Producing A Poor Product vs Relative Understanding of the Process**



# Acknowledgments

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**Thank YOU!!!**

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