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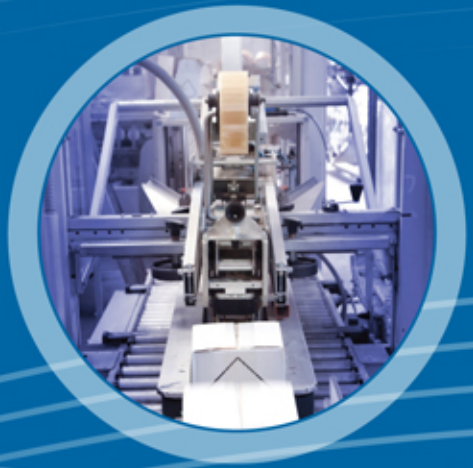
Munich



Qualifying Integral Container Closure Systems

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Integral Package

Conformance

Product-Package Maximum Allowable Leakage

Impact on Product Quality

Evidence

Package Seal Quality

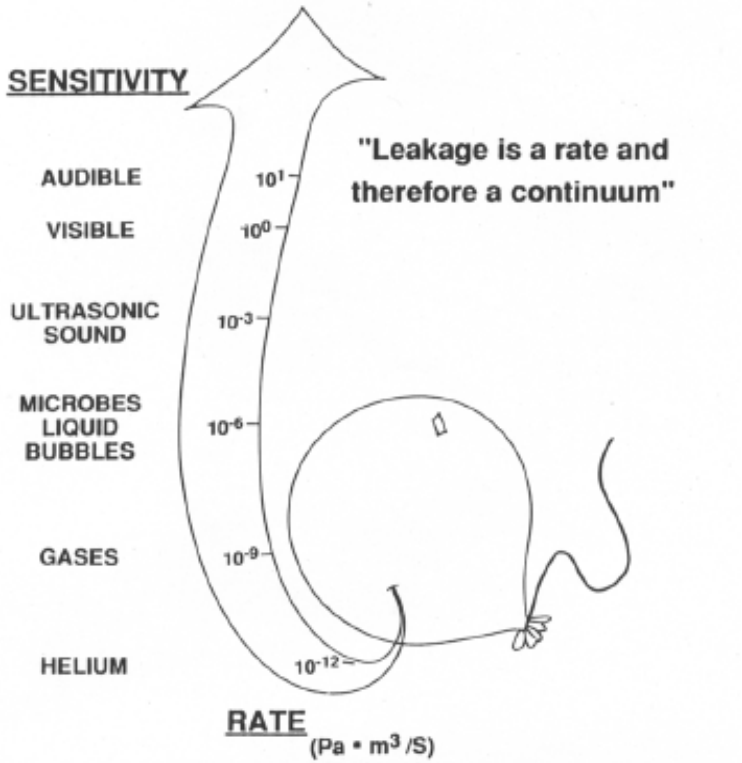
Container Closure Integrity

Sterile Packaging: Regulatory Expectation

- Provide descriptions of:
  - Overall process for the filling, capping and aseptic assembly of the drug product.
  - Method and results demonstrating container closure integrity.
  - Container/closure compatibility with the drug product to include the results of compatibility studies.
  - Washing, sterilization and depyrogenation process and the associated validation data for containers, closures and equipment.

BLA Filing Review Letter Excerpts http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm268638.htm

Package Integrity (CCI)



All package seals allow <u>some</u> leakage.

- **"Smallest"** diameter leaks allow **gas flow** only
- **"Larger"** diameter leaks can also allow **liquid flow**
- **"Largest"** leaks may allow **microbial ingress**

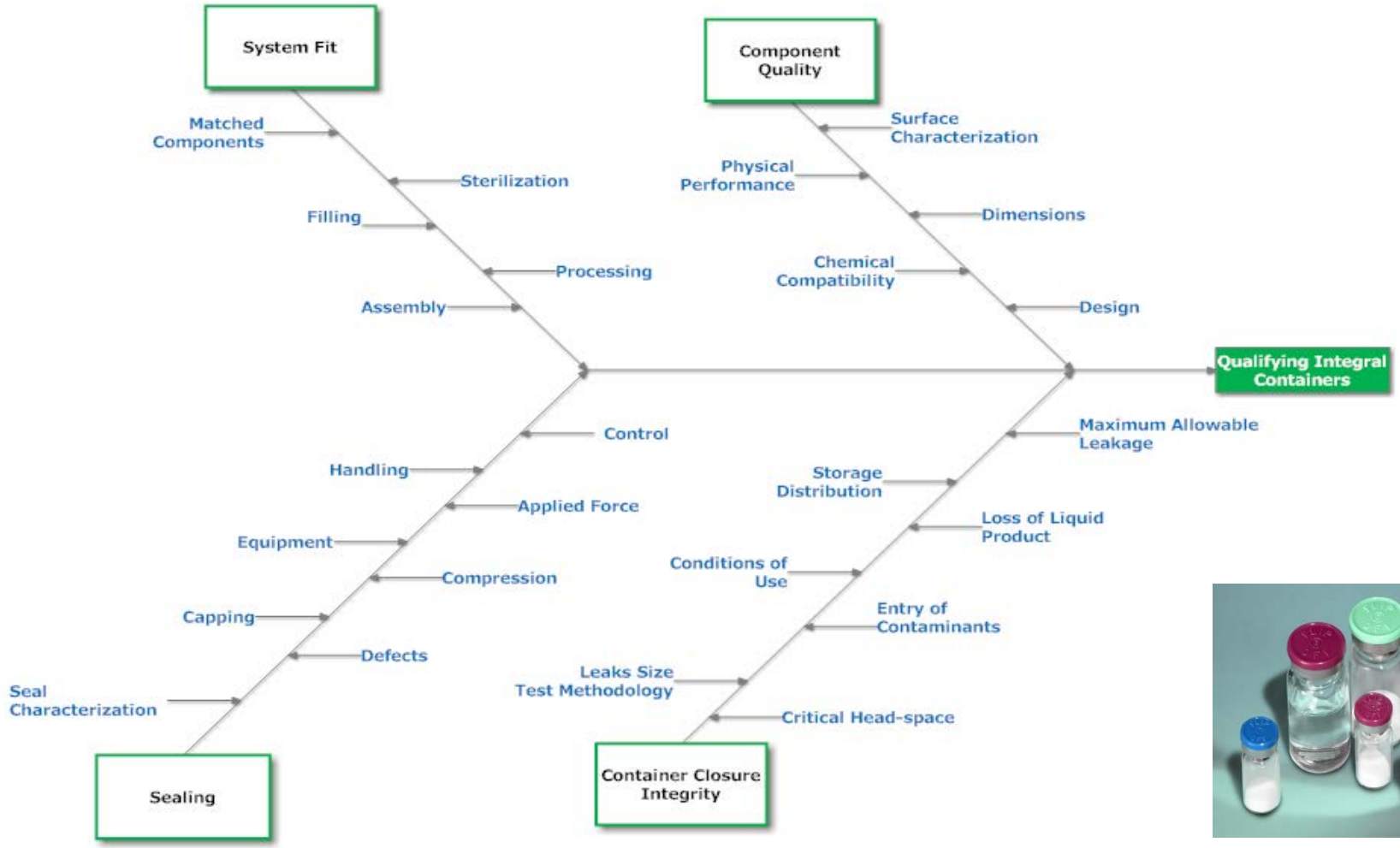
D Guazzo, RxPax, LLC, 2013 Mar 6, Prague Czech

Risks to Product Quality

- **Material Compatibility**
- Leaching
- Particles
- Product loss/Degradation
- Product Stability
  - Increase in moisture
  - Deterioration of lyocake
  - pH shift
  - Protein modification /aggregation
- Storage/Distribution

- **Container Closure Integrity** Failure
  - Leakage
  - Loss of product
  - Increased concentration
  - Contamination
  - Sterility failure
  - Critical headspace Loss
  - Over pressure
  - Under pressure

Integral Package Input Variables



Matching Component Attributes

- Closures Rubber

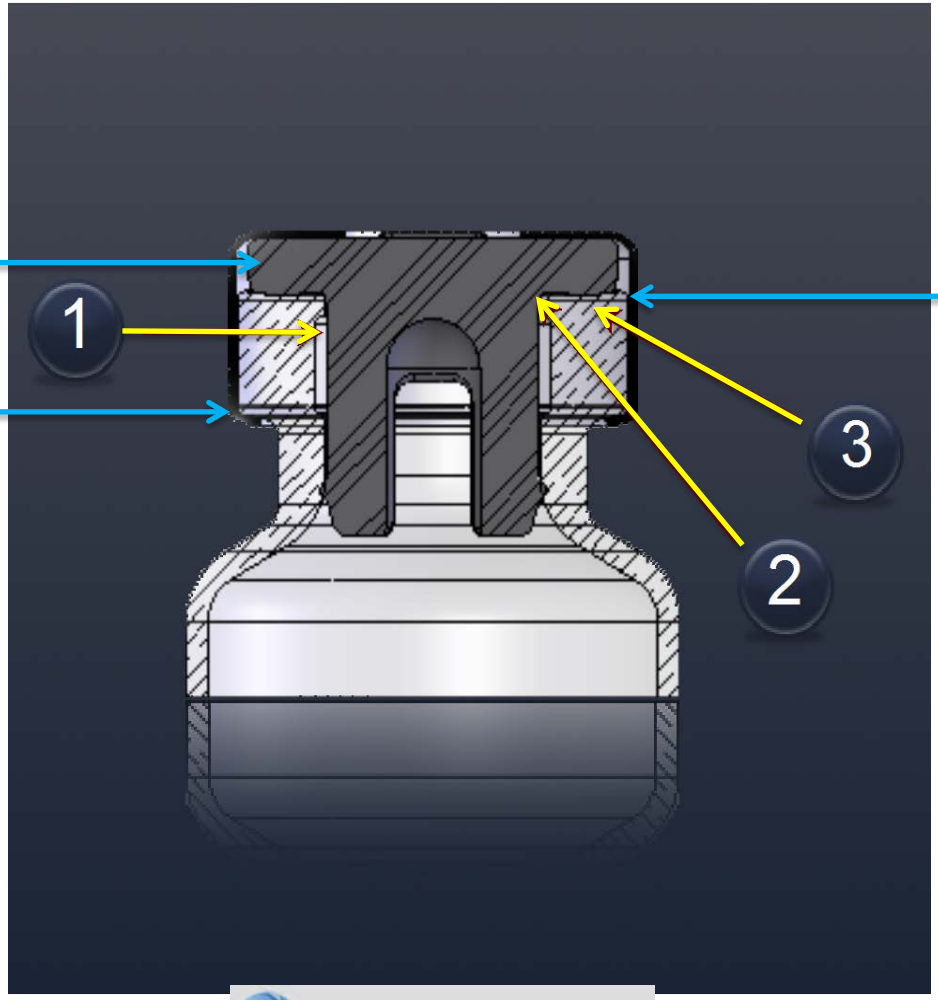
- Glass and Plastic Containers

Dimensionally stable
Withstand temperature extremes
Lubricious
Sterilizable
Low extractability
Low gas transmission
Machinability
Cleanliness

Hardness
Elasticity/resealability
Compression strength
Flow properties
Low moisture retention
Low abrasion

Transparent
High tensile and compressive strength
Smooth sealing surface
Low fracture/ breakage
Scratch resistance

Components of a Vial Seal



Component Quality and System Fit

- **Component**
  - Chemical compatibility
  - Physical performance
  - Design/dimensions
  - Surface characteristics

- **System**
  - Fit
  - Component performance
  - Processing
  - Assembly

Sealing Risks

- Inference fit of primary seal
  - Surface defects
  - Closure plug design
  - Improper position into vial neck
  - Vial out-of-round
- Aluminum seal skirt length
- Maintain integrity prior to crimping
- Controlling land compression seal
  - Machining applied force

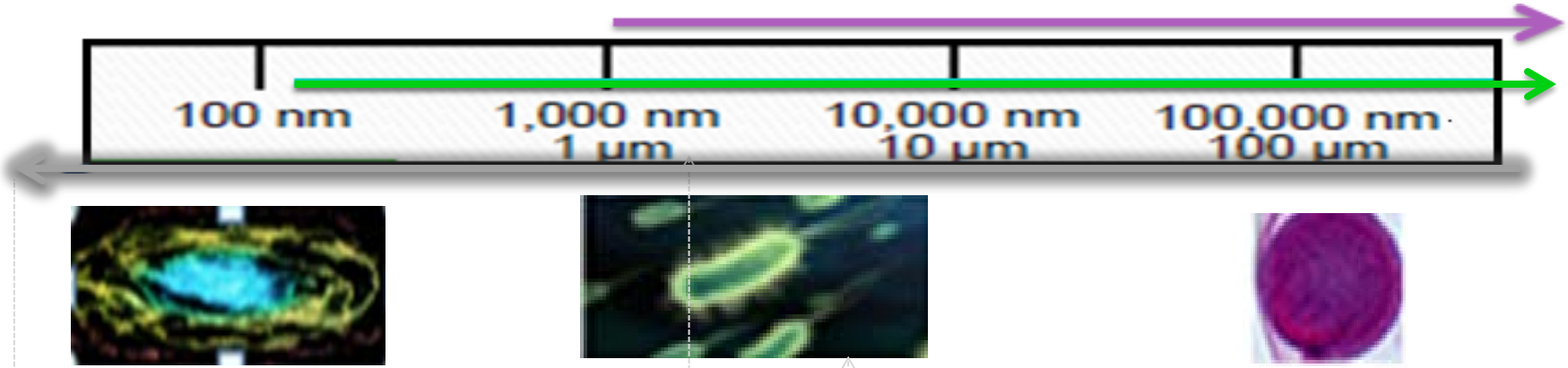
Seal Quality Evaluation Methods(1)

Method	Application
Dimensional Analysis	Critical review of component technical specifications Dimensions and tolerances, variabilty (Cp, CpK) Stacking, interference, worst case probability
Visualization of Component Design and Fit (2)	Component fit analysis for pre-capping integrity Lessens risk of headspace loss Lessens risk of misassembly
Raised Stopper Test	Monitors stopper position just prior to capping Lessens risk of headspace loss Lessens risk of misassembly
Finite Element Anaylysis (3)	Break down components into elements Apply laws of physics at the element level Solve for physical state elements (e.g.: temperature, stress, strain, pressure, etc.)
X-Ray Tomography	Evaluates, component fit, elastomer deformation
Residual Seal Force (RSF)	Verifies compressive force of crimped closure on vial land seal surface Indirect measure of elastomer compression (deformation) Ensures seal force Consistency
Experimental Design	Identify and evaluate factors that affect seal integrity and capping forces. Design optimization and critical parameter settings

(1) Adapted from D.Guazzo "Selection and application of CCI and seal quality tests throughout parenteral product life cycle" PDA Contaiiner/Closure Workshop, May 2013, Bethesda, MD USA
(2) P.Lam, A.Stern, PDA J Pharm Science and Technology 2010, 64
(3) R.Paul, "Functionality and fit through-oit shelf life: Applying Finite Element Analysis to Container Closure Systems" PDA Contaiiner/Closure Workshop, May 2013, Bethesda, MD USA

Measuring Leakage

- **Detrimental gases**
- **Liquid/microorganism**
- **Extraneous debris**



Laser Base Gas Headspace
(leak rate %O2;Moisture; ∆atm.)

Tracer Gas
(leak rate≥10^{-11} std cc/s)

HVLD (Pass/Fail)

Vacuum Decay
leak rate (∆Torr)

Liquid Ingress (Probabilistic)

Case by Case - Method Development - Method Validation

Leak Test Outcomes

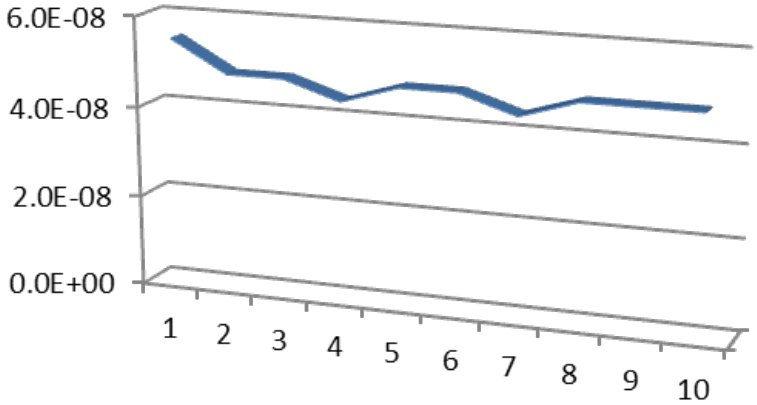
- Define the package's inherent integrity
  - *Maximum allowable leakage*
- Means of optimizing package design based on use challenges
- Check CCI as a function of product stability
- Routine manufacturing
- Commercial product stability

Proposed Revisions to USP <1207> Sterile Product Package – Integrity Evaluation

Initial Development

He Leak

Stack-up
Flange thickness
Crown height:
Skirt length:
Stack-up:
RSF:
(%)Compression



Component fit • Component material • Component processing

Container Closure Integrity

Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control.

No single package leak test or package seal quality test method is applicable to all product-package systems. Some product-packages may require more than one test method during the product life cycle.

Product Life Cycle Testing

Integral Packaging: Verify-Validate

Design to Build Assurance of Integrity Throughout the Products' Market Life

- Quality
  - Consider type of materials
- System Fit
  - Conditions of use
- Sealing
  - Optimal capping equipment and processes
- CCI
  - Establish maximum allowable leakage

Vigilant Monitoring of Components and Processes

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