A Holistic Strategy for Optimizing an Integral Parenteral Package to Ensure Container Closure Integrity

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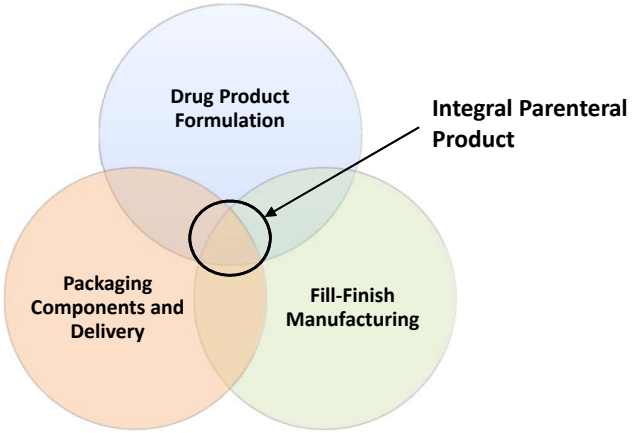
Background and Overview

- Purpose and Scope
- What is an Integral Parenteral Package?
- Package Integrity
- Establishing an Integrated Strategy
- Selecting Packaging Components
- Process Flow for Package Development
  - Determining MALL Criteria
  - Seal Quality Optimization



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Purpose and Scope

- To define a holistic strategy for an **integral parenteral package** that maintains container closure integrity throughout shelf life
- A holistic strategy **integrates** key attributes of (1) drug product formulation, (2) primary packaging materials/components, and (3) fill-finish manufacturing
- Examples described focus specifically on a development of a **vialed packaging system**
- Factors considered are applicable to any sterile package configuration

What is an Integral Parenteral Package?

An integral package **must:**

- Preserve sterility (i.e. absence of microbial ingress)
- Drug product quality (i.e. meet specified physicochemical requirements)
  - Includes loss of drug product dosage or ingress of contaminants
  - Maintain internal headspace gas (if applicable)

A product is not considered "integral" until capped and sealed

- Thus, package integrity is explicitly related to the maintenance of a product's "integral state" after being sealed

Package integrity is not defined as product sterility

Package Integrity

Package Integrity = Container-Closure Integrity (CCI)

- Defined as absence of leakage greater than the product package **maximum allowable leakage limit (MALL)** that could compromise drug product quality
- MALL is the smallest gap or leak rate that could put drug product quality at risk throughout shelf life
- Integrity evaluated on system as a whole, not on any singular component

Integral packages conform to the established, product-specific MALL criteria

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Establishing an Integrated Strategy

Three key functional areas impact development of optimal packaging system for a given product

1. Drug product formulation
   - *Critical Considerations*—Dosage Form (TPP), Storage & Transportation Temperature, Compatibility/Stability, Supply Chain Requirements
2. Packaging components and delivery
   - *Critical Considerations*—Material Attributes, Dimensional Tolerances, Component Design, Quality, and Processability
3. Fill-finish manufacturing
   - *Critical Considerations*—Capping Process Parameters, Sealing Technology and Equipment, CCIT Methodology

Note: Drug's target product profile (TPP) and supply chain requirements are primary driving forces for individual component selection

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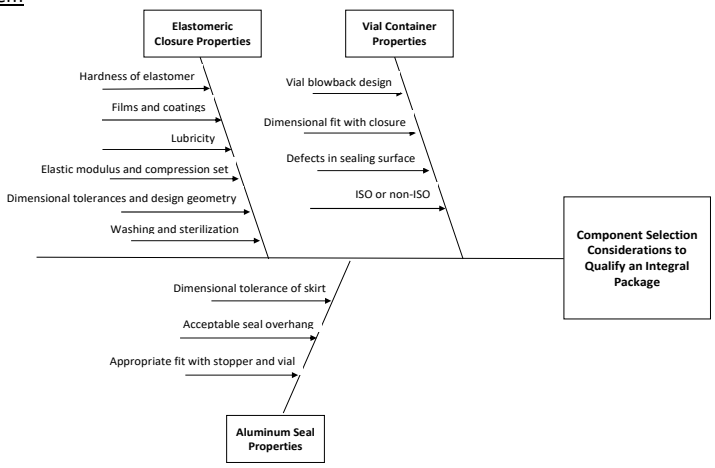
Selecting Packaging Components

Example: Vialed Packaging System



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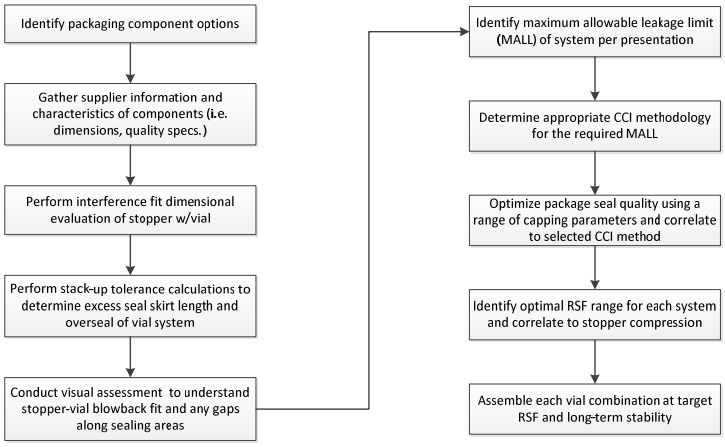
Process Flow for Package Development



Determining MALL Criteria

MALL criteria is product-specific and dependent upon drug dosage form

Liquid or Frozen Liquid DP

CCI Concerns

- Prevent microbial ingress (liquid or airborne)
- Prevent loss of drug contents
- Prevent entry of debris or detrimental gases

MALL: $<1 \times 10^{-7}$ mbar*L/s

Lyophilized DP

CCI Concerns

- Maintaining vacuum
- Limiting moisture content
- Gas effusion and exchange
- Prevention of microbial ingress (liquid or airborne)

MALL: $<1 \times 10^{-8}$ mbar*L/s

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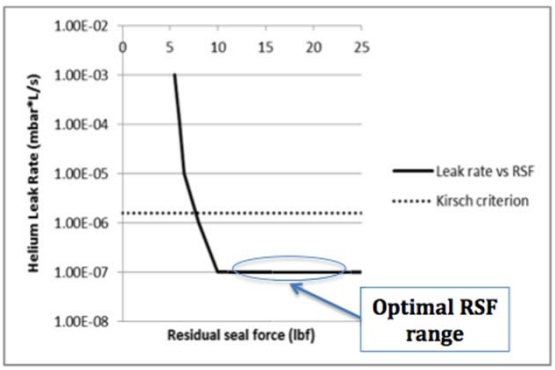
Sealing Quality Optimization: RSF Correlated to Helium Leak Rate

- Establish design space for vialed package seal quality
- Cap across wide compression forces (low to high) to generate range of residual seal force (RSF) values
- Vials capped at each setting tested via deterministic CCI method (i.e. helium leak)
- **Result:** Correlation of RSF to leak rate and stopper compression
- **Note:** Inherent package integrity has to be below product-specific MALL to be acceptable



Ref. L Kirsch, L Nguyen, C Moekly, R Gerth. Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials. PDA J Pharm Sci & Tech 51, 1997, 195-202.

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Implementing Package Optimization at Fill-Finish Manufacturing

Three types of sealing technologies used during fill-finish manufacturing

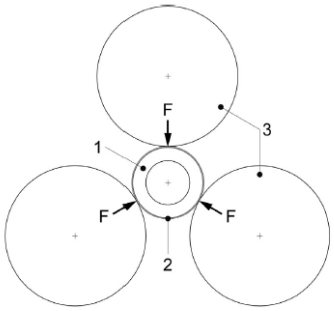
1. Spinning rollers (Two or Three)
2. Fixed capping rail
3. Free rotary capping plate (single or multiple heads) – Most commonly used

- Constant force or constant distance capping
- Potential sealing issues increased with 13mm neck/stopper combinations
  - 13mm stoppers have smaller flange thickness w/larger percent dimensional variability (RSF function of flange thickness)
- Softer elastomer formulations (lower compression set and hardness)
- Elastomers w/film on top of flange

Note: Aim for optimal RSF obtained from seal quality assessment by altering process parameters of capping equipment. RSF can be used as a universal indicator of seal quality, independent of capping equipment and sealing technology

Spinning-Roller Capper

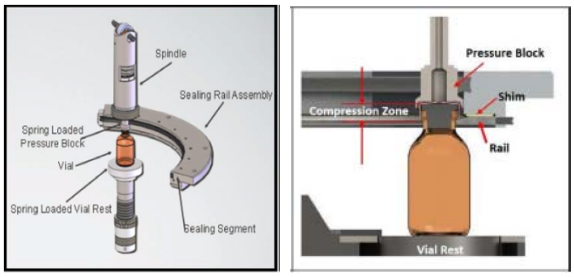
- Single head w/multiple rollers
- Vial is raised or head lowered to compress stopper against sealing plunger
- Rollers constrict (pull inwards) to crimp skirt under vial flange
- Symmetrical positioning of capping plates around vial head



Ref. Mathaes R et al. The Pharmaceutical Vial Capping Process: Container Closure Systems, Capping Equipment, Regulatory Framework, and Seal Quality Tests. Eur. J Pharm Biopharm. 2016. 99, 54-64.

Fixed Capping Rail

- Semi-circular, fixed sealing rail assembly
- Decreasing angle of rail performs crimp as vial is compressed between spring loaded plates (pressure block head and vial rest)
- Vial rotates during capping with the skirt against sealing/crimping rail
- Asymmetrical sealing process



Images courtesy of Roger Asselta, Genesis Packaging. Parenteral vial sealing and integrity webinar. 2017

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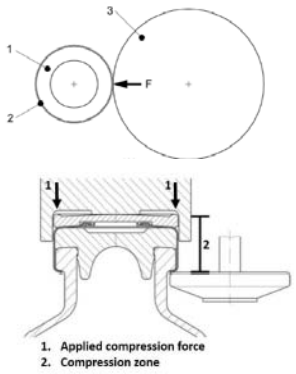
Free Rotary Capping Plate

- Similar to spinning-roller sealing technology
- Single or multiple heads with a single roller
- Capping force can be applied from below or above vial
- Capping plate moves freely w/rotating vial and folds skirt under vial flange
- Free-rotary plate can be adjusted in horizontal and vertical directions to influence RSF
- Asymmetrical sealing process



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Fill-Finish Capping Process Validation

- Capping process validation establishes the robustness and operational range of the equipment
- Operational range of capper is assessed via DoE by varying critical process parameters and correlating to seal quality optimization data for a specific vialed package combination
- **Result:** Design space of fill-finish package assembly obtained for CCS

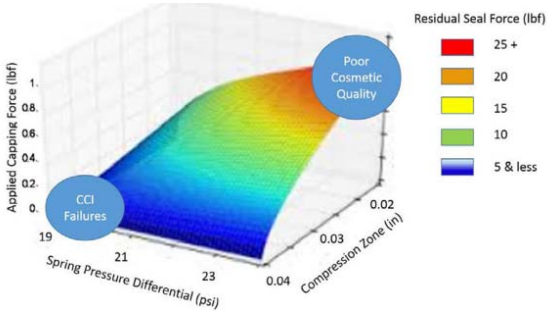

Image courtesy of Roger Asselta, Genesis Packaging. Parenteral vial sealing and integrity webinar. 2017

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CCIT Methodology: Suitability Throughout Product Lifecycle

Deterministic

- Tracer gas (vacuum) – i.e. helium-leak test w/MS detection
- Laser-based headspace analysis (FMS): O_2, CO_2, pressure, water vapor concentration
- Vacuum and/or pressure decay
- High voltage leak detection (HVLD)
- Mass extraction

Probabilistic

- Bubble emission
- Microbial challenge
- Dye ingress
- Tracer gas detection (sniffer)

Criteria for Method Selection

- Package contents
- Physicochemical or microbiological
- Deterministic or proababilistic
- Materials of construction
- Package design
- Established MALL criteria
- Sensitivity and range
- Destructive vs. nondestructive
- High speed vs. slow speed
- At-Line, In-Line, On-Line, Off-Line
- Quantitative or qualitative

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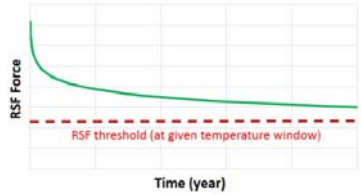
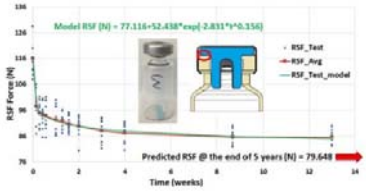
Predictive Modeling of Seal Quality and CCI During Shelf Life

- GMP stability samples can have RSF tested at various timepoints and temperatures throughout stability
- RSF can be plotted to trend stress relaxation of stopper over time
- As relaxation plateaus, modeling curve can be fit to empirical RSF data to predict seal quality at end of shelf life
- As RSF correlation to CCI leak rate established for specific, qualified vial packaging system





Images Ref. Zeng Q and Zhao X. Time-Dependent Testing Evaluation and Modeling for Rubber Stopper Seal Performance. PDA J Pharm Sci and Tech. 2018, 72 134-148.

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Summary

- An integrated, holistic strategy has to be devised to establish and optimize an integral parenteral package capable of ensuring CCI over product shelf life
- An E2E approach incorporating key input about (1) drug product formulation attributes , (2) packaging component material attributes, and (3) fill-finish manufacturing process parameters
- Inherent package integrity has to be determined and deemed acceptable per MALL
- Seal quality optimized via correlation to CCI
- Sealing design space defined by fill-finish capping process validation
- Determine suitability of CCIT methods at each stage of product lifecycle
- **Ultimate goal**: Generate predictive seal quality and CCI data using GMP stability batches in support of product quality throughout expiry

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