Container Closure Integrity Evaluation for Sterile Product Packages

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PDA Parenteral Drug Association

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Content

- What is CCI?
- Importance of CCI
- Regulations and Guidances
- CCI Understanding
  - Materials
  - Measurements
  - Environments
- Summary

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- **What is CCI?**
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Sterile Products

- A parenteral package must keep the product sterile.
- Sterile product is “free from viable microbial contamination throughout the product’s entire shelf life or dating period”

FDA Guidance for Industry,

Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, February 2008

Terminology

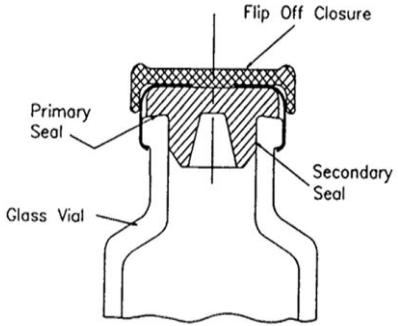
- CCI IS THE SAME AS
  - Package integrity testing
  - Package leak testing

- CCI is NOT simply defined as microbial barrier protection
- CCI is NOT solely determined via microbial challenge tests

CCI is achieved when a package meets the
MAXIMUM ALLOWABLE LEAKAGE LIMIT
required to ensure product quality attributes of
sterility and physicochemical stability through expiry

Inherent Package Integrity

- *The leakage rate of a **no-defect, well-assembled** package*
  - Leakage occurs between mechanically fitted components
  - Leakage may occur between physiochemically bonded components
- ***Leakage > inherent integrity leak** rate caused by*
  - Poor assembly
  - Component defects



Maximum allowable leakage limit (MALL) is that ***smallest gap*** or ***leak rate*** that puts product quality at risk (called “critical leak”)

INHERENT package integrity must be ≤ MALL

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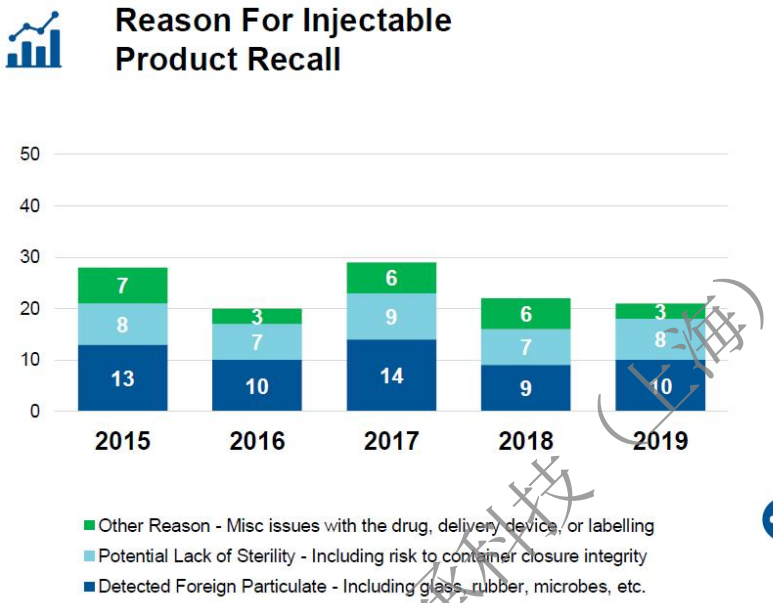
Particulates and lack of sterility cause most product recalls



Referenced from U.S. FDA. (2020). Recalls, Market Withdrawals, & Safety Alerts. Retrieved from https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts.

Importance of CCI

- CCI is one of the major concerns, leading to recalls and risk to patient safety.
- CCI testing is a growing concern for all packages because:
  - Packaging is becoming more complex
  - More CCI tests are being developed, but no one method works for all applications
  - Better understanding about CCI, e.g., CCI of lyo drug product and CCI at cold storage temperatures
  - Regulatory encouragement to use CCI test instead of sterility test

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Regulations and Guidances

Prior to Mid-1990s	Sterility testing alone is sufficient
1994	FDA Guidance: • The microbial barrier properties of a parenteral product package be verified • Sterility testing alone is insufficient
2008	FDA guidance: • Encourages using CCI test instead of sterility tests (Note that CCI test cannot replace sterility test prior to release) • Does not require comparison of Physical methods to Microbial ingress risk
2014 (Proposed)/ 2016 (Official)	USP <1207>: • A simple microbiological challenge test is not considered sufficient • Recommends deterministic methods over probabilistic methods

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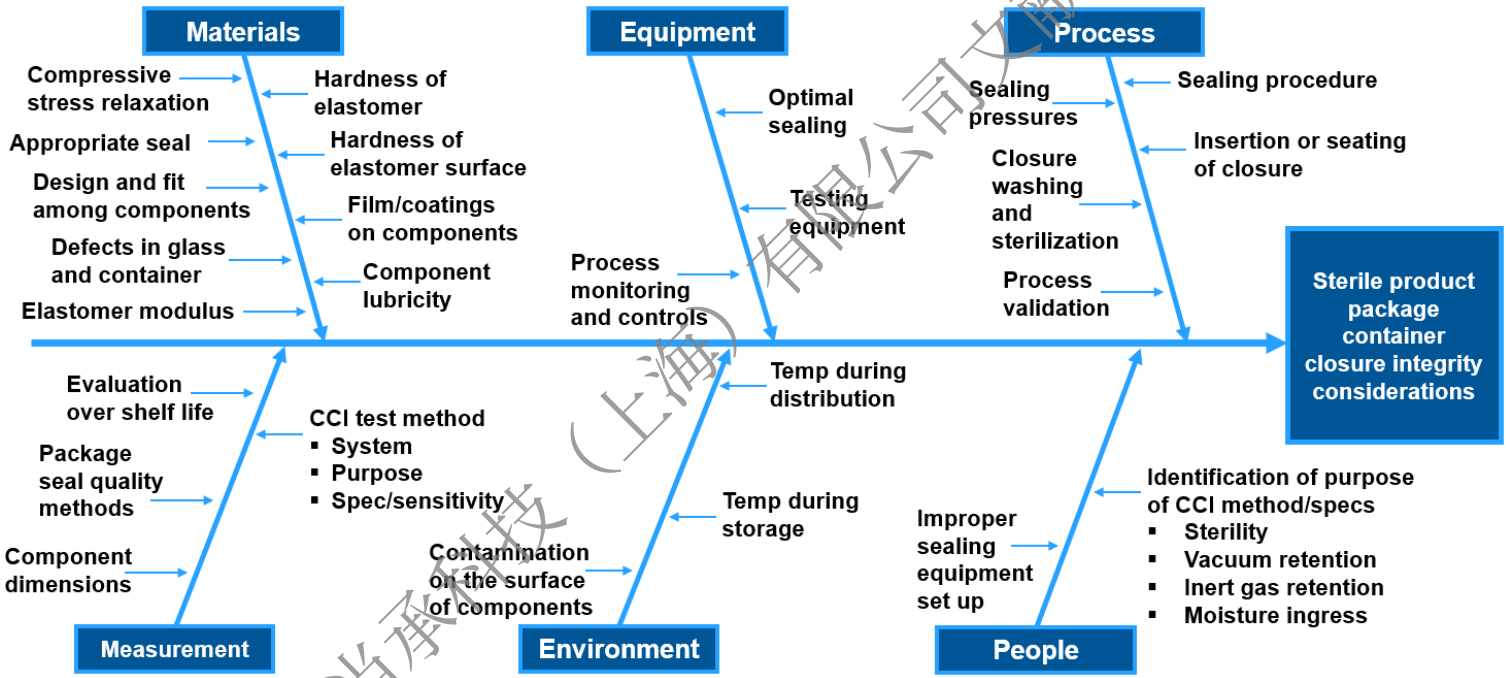
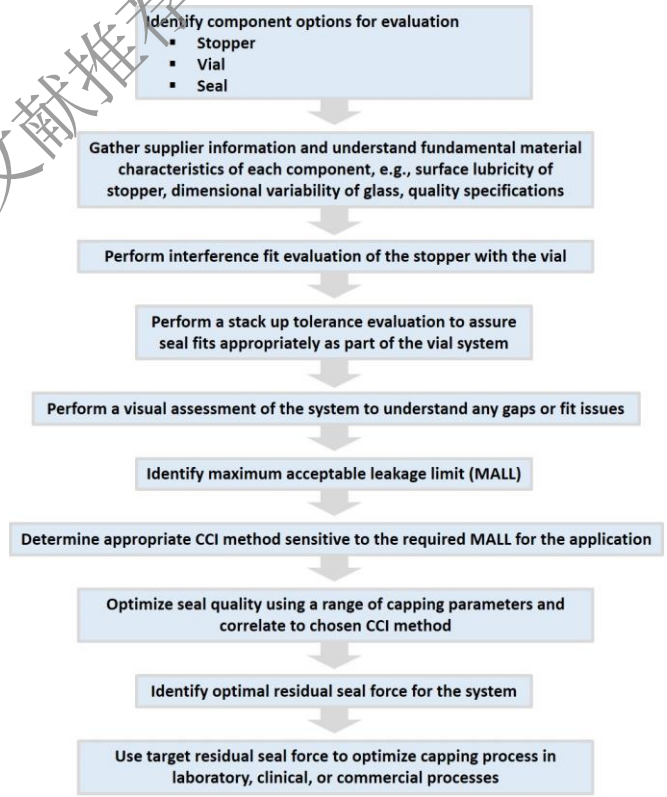
CCI Understanding



Referenced from Degrazio FL. 2018, 'Holistic Considerations in Optimizing a Sterile Product Package to Ensure Container Closure Integrity', *PDA J Pharm Sci Technol.*, vol. 72, no. 1, pp. 15-34.

Process Flow for Selecting Packaging to Ensure CCI

- Each factor needs to be gauged together- not independently- to ensure an optimized package
- There's no industry best practice standard defined for qualifying an acceptable container closure system platform for CCI currently



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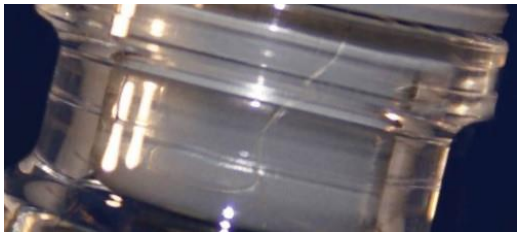
Materials

- Glass Vial Container
- Elastomeric Stopper
- Films/Coatings for Closures
- Fit among the Components

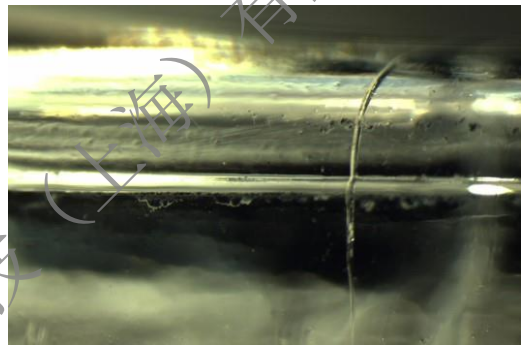
Typical Primary Parenteral Vial System

Glass Vial Container

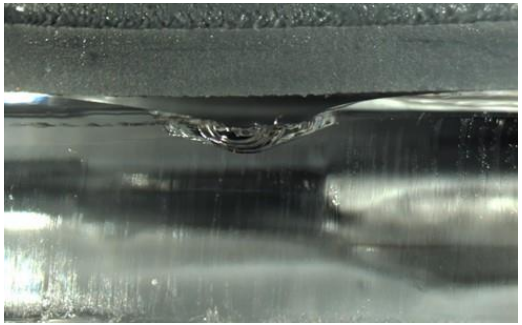
- Examples of quality defects that can affect the CCI of a vial system. Defects of either the stopper or the glass vial have the potential to affect integrity



Fiber in the stopper



Crack on vial lip



Chipped lip of vial

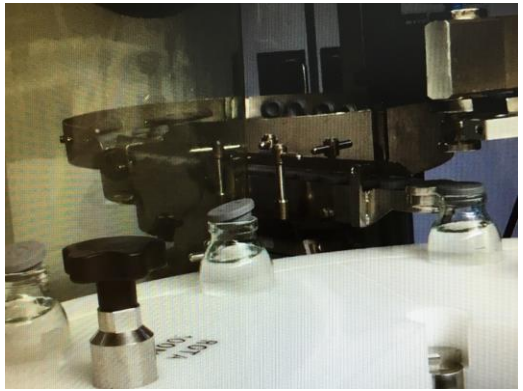
Elastomer Stopper

- Hardness of Elastomer
- Material Modulus
- Elastomer Viscoelasticity
- Component Surface Lubricity

Stopper Pop-up Following Lyophilization

Example of stopper pop-up phenomenon that can occur immediately after completion of the lyophilization process but before flip-off seals are used. The stopper pop-up can vary in amount; however, any stopper movement can cause a breach in integrity. Photo courtesy of Ed Trappler and Lyophilization Technology. Inc.

Stopper Insertion Problems Due to Lack of sufficient Lubricity

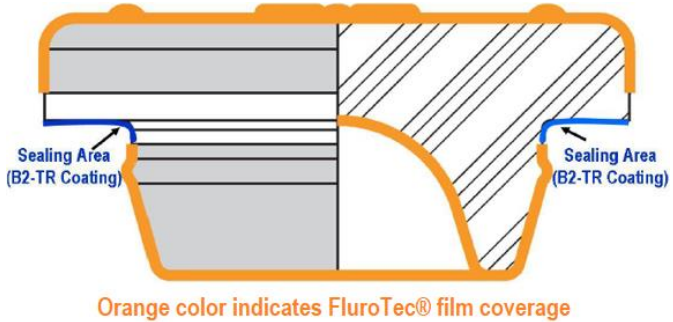


An example of a stopper that does not have enough surface lubrication. This leads to the stopper popping-up following insertion into ta glass vial. Friction between the interface of the stopper and glass may affect machinability or other issues that indirectly lead to poor integrity. Photo courtesy of West Pharmaceutical Services Scientific Insights Lab, Exton, PA.

Referenced from Degrazio FL. 2018, 'Holistic Considerations in Optimizing a Sterile Product Package to Ensure Container Closure Integrity', *PDA J Pharm Sci Technol.*, vol. 72, no. 1, pp. 15-34.

Films/Coatings for Closures

- Coating: B2-Coating, Polyvinylidene fluoride (PVDF)
- Film: Fluoropolymer films (FluroTec®)



Fit among the Components

- Closure Design
- **Interference Fit**
- Stack-up Tolerance
- Visual Analysis

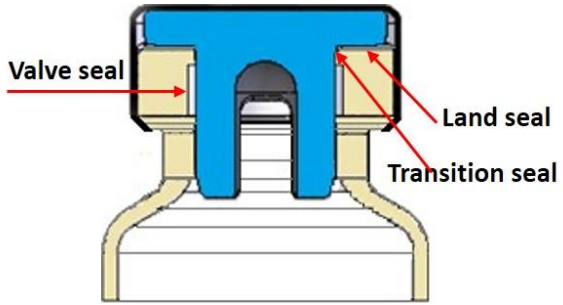
$$\frac{\text{Stopper Plug (O.D.)} - \text{Vial Neck (I.D.)}}{\text{Stopper Plug (O.D.)}} \times 100$$

Fit among the Components

- Closure Design
- Interference Fit
- **Stack-up Tolerance**
- Visual Analysis

$$(Skirt\ Length - Aluminum\ Ferrule\ Thickness) - [(Vial\ Crown\ Height) + (Stopper\ Flange\ Thickness) \times (1 - \%Stopper\ Compression)] = Excess\ Skirt\ Length$$

Primary and Secondary Sealing



Sealing between the stopper and vial typically occurs in three places. The primary seal is between the flange of the stopper and the top surface of the glass, this is the land seal. The other seals are located between the plug of the stopper and the inner surface of the neck of the vials and at the transition between the plug and the flange. Image courtesy of West Pharmaceutical Services Scientific Insights Lab, Exton, PA.

Fit among the Components

- Closure Design
- Interference Fit
- Stack-up Tolerance
- **Visual Analysis**

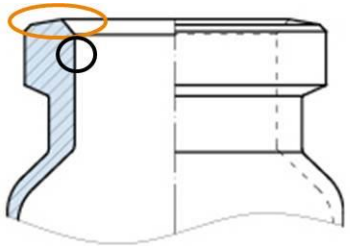
Acceptable

Unacceptable

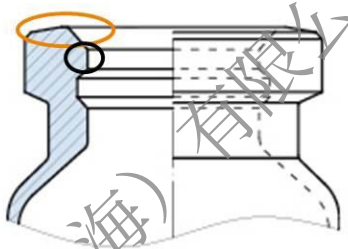
On the left is a picture of an acceptable quality seal, and on the right is an unacceptable seal from a visual quality or cosmetic standpoint. Typically it is a combination of a sealing process that has been validated through the use of an appropriate CCI method and an acceptable cosmetic appearance that qualifies a package for use.

Fit among the Components

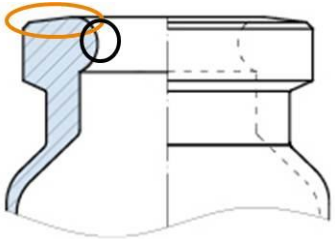
Typical Glass Variations



No Blowback



North America Blowback



Europe Blowback

Sealing after crimp

Sealing before crimp

There are multiple styles of glass vial designs. These show representative styles of vials with no blowback, a North American blowback, and a European blowback. Photos courtesy of Schott AG, Mainz, Germany.

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How to Select A Test Method?

Criteria mentioned in USP<1207.1>

- Package contents
- Package design, materials of construction, and mechanic
- Closure type and mechanics
- Maximum allowable leakage limit (MALL)
- Deterministic or probabilistic method
- Physicochemical or microbiological methods
- Method limit of detection
- Leak test detection limit
- Leak test method range
- Method outcome
- Quantitative or qualitative
- Non-destructive or destructive
- On-line or off-line

Three categories of product-package quality requirements

1. Sterility and product formulation content must be preserved.
2. Sterility, product formulation content, and gas headspace content must be preserved.
3. Sterility must be preserved: product access is required.

Measuring Leakage – MALL

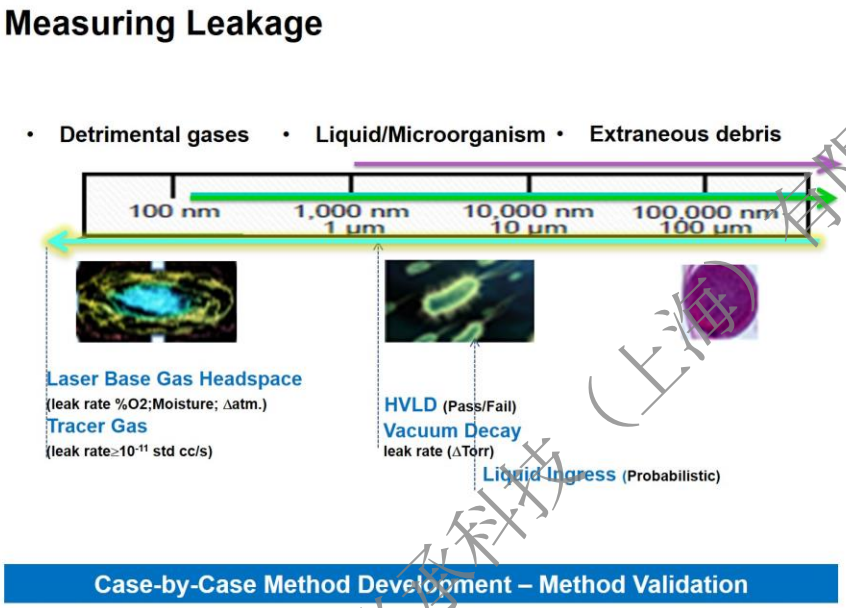

Figure taken from Paskiet, D.; Asselta, R. Qualifying Integral Container Closure Systems. Presented at the PDA Annual Meeting, San Antonio, TX, 2014.

- A Comparison of Leak Size Relating to Various Materials That Can Flow into or out of a Packaging System
- An array of test methods are available for proving CCI. The chart visualizes the need for more sensitive methods when preventing gas leakage versus methods that may be more appropriate for correlation with microbial ingress.

CCI Test Method Options

Leak Method Comparison	
Deterministic methods	**Probabilistic methods**
Reproducible	Not reproducible
Sensitive	Insensitive
Highly instrumental	Little or no instrumentation used
Quantitative test result	Qualitative, interpretive results
Minimal sample preparation	Considerable sample preparation
Low risk of error	High risk of error
Common Examples of Analysis Techniques	
Electrical conductivity and capacitance test (HVLD)	Microbial challenge
Laser-based headspace analysis	Liquid tracer tests (e.g., dye)
Tracer gas (vacuum mode)	Bubble tests
Vacuum decay	Tracer gas (sniffer mode)
Pressure decay	-

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Environment Considerations

Storage Condition Varies among Drugs

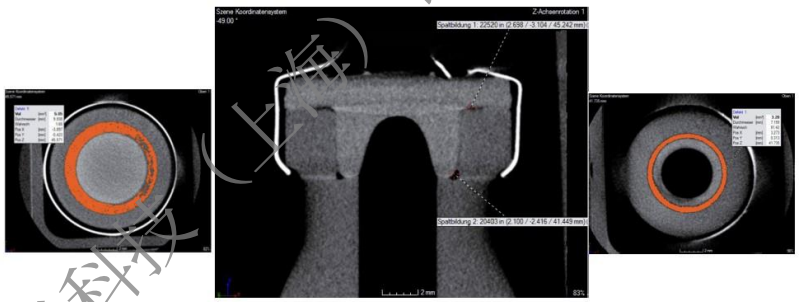
- Typical recommended storage condition for drugs is at 25℃
- Most vaccines require storage and distribution at 2 – 8℃
- Many biologics must be kept frozen, whether at -20℃ or -80℃
- Cell-based therapies should be shipped and distributed at cryogenic temperatures(<=-150℃)

Tg of a typical rubber stopper formulation is from -50ºC to -70ºC

Environment Considerations

Considerations during transportation must also be taken because temperatures can fluctuate significantly during air flight or storage under strenuous conditions such as using dry ice during shipping.

Leakage in Cryo Packaging(X-ray Tomography at -196℃)



Under extreme environmental conditions, such as cryogenic storage, a physical shrinkage of some of the components can occur. This can be visualized through techniques such as x-ray tomography.

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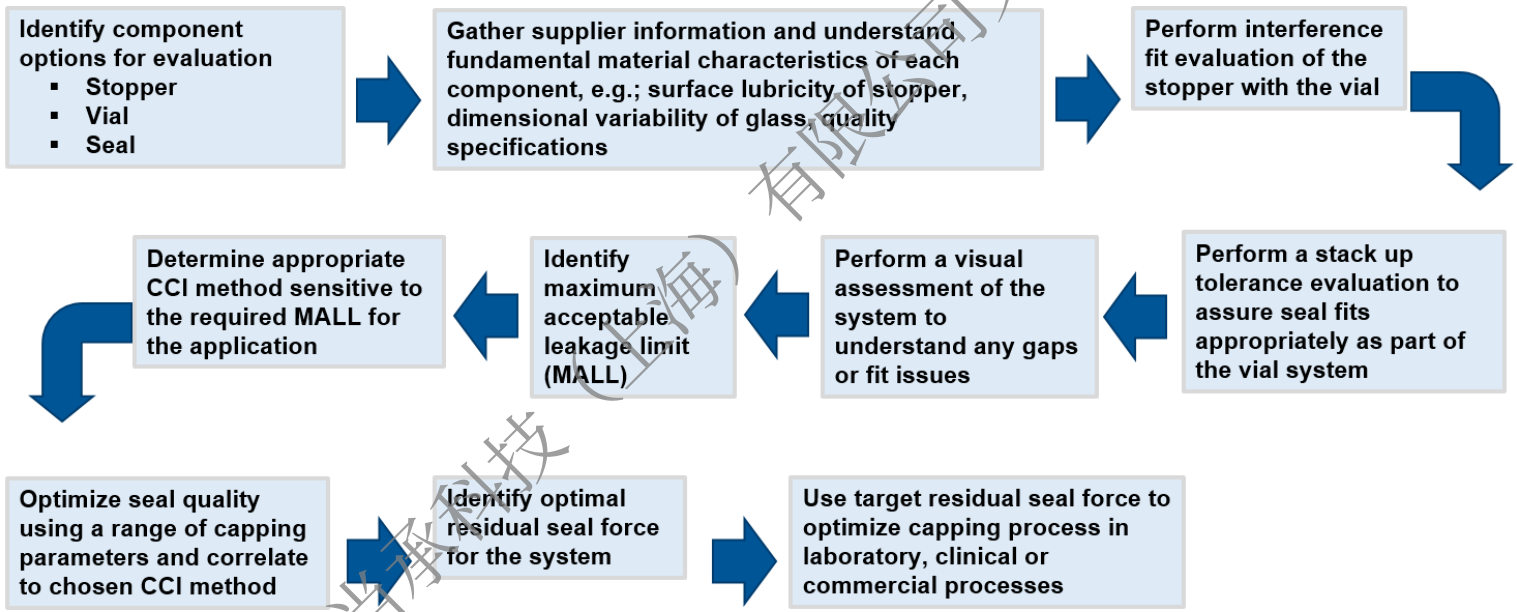
Holistic Process to Optimize Integral Container Closure System



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