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衛生福利部食品藥物管理署委辦計畫

「提升國內無菌與新興生醫藥品品質管理之研究」

無菌產品製造 GMP 作業論壇(一)

日　期　：(北區)民國 111 年 5 月 6 日

(南區)民國 111 年 4 月 22 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講　師　資　料

黃恩琪　經理/美商輝瑞健康生醫(股)公司技術服務部

時　間　表

時 間	內　　容	講　師
13:00-13:30	報　　到	
13:30-13:40	➢ 長官致詞	TFDA 監管組代表
13:40-14:50	➢ 玻璃瓶(Vial)的處理最佳實務 ➢ 導入風險評估於玻璃瓶處理流程 ➢ 玻璃瓶(Vial)處理製程考量要點	輝瑞 黃恩琪經理
14:50-15:10	休　　息	
15:10-16:20	➢ 玻璃瓶(Vial)處理製程考量要點(續) ➢ 防止非預期損害考量 ➢ 案例分享	輝瑞 黃恩琪經理
16:20-17:00	**交 流 討 論 及 課 後 測 驗**	TFDA 長官 及講師群

目　　錄

頁次

"Current Best Practices for Pharmaceutical Glass Vial Handling and Processing“

- PDA Technical Report TR87

ANGELA HUANG

Agenda

13:40-14:50	➢ 玻璃瓶(Vial)的處理最佳實務 ➢ 導入風險評估於玻璃瓶處理流程 ➢ 玻璃瓶(Vial)處理製程考量要點
14:50-15:10	休　　息
15:10-16:20	➢ 玻璃瓶(Vial)處理製程考量要點(續) ➢ 防止非預期損害考量 ➢ 案例分享

PDA

Technical Report No. 87
Current Best Practices for Pharmaceutical Glass Vial Handling and Processing

Technical Report Portal (pda.org) - Free online portal

- TR43: Glass Defects
  "Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing"
- TR85
  "Enhanced Test Methods for Visible Particle Detection and Enumeration on Elastomeric Closures and Glass Containers"
- 2017 PDA Glass Quality Survey
- PDA Journal of Pharmaceutical Science and Technology
  "Failure of Glass Tubing Vials during Lyophilization"

Purpose

to provide an understanding about the glass, various load/stress damages to the glass and to provide best practices guidance for glass handling during empty glass transportation, receipt, storage at manufacturing sites as well as handling of the glass during preparation, filling, stoppering, capping, terminal sterilization, inspection, and packing of the pharmaceutical finished product to minimize glass damage.

Glass- benefit & challenges

- ◆ Glass is a rigid, durable and non-permeable material to water, air and gas.
- ◆ Glass is compatible with a wide range of Pharmaceutical drug products.
- ◆Glass can be shaped into many forms and sizes (vials, syringes, ampules, sizes from 1mL to 3L), can be provided in Flint (clear), and colored (Amber) forms, and is easy to clean, sterilize and inspect.
- ◆ Amber colored glass can protect a drug product from UV light.
- ◆ Glass can be recycled.

- ☐ Glass is not compatible with all drug formulation/drug substances, drug products with high risk factors e.g., high pH or certain buffers or chelating, high ionic strength etc. can react with the glass
- ☐ Glass manufacturing is not free from flaws,
- ☐ Glass can break, chip, crack

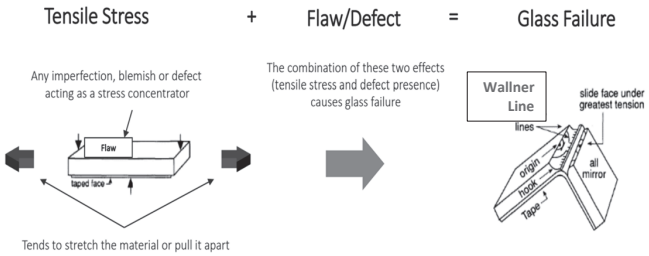
→ Glass breakage can result in processing down time, an increased number of production interventions, injury to operator/user, increased particulate load, sterility failure and a loss of product. The container sterility failure can put patient safety at risk.

Glass breakage occurs when…

- Glass is inherently a strong material, but the condition of its surface plays a major role in its resistance to breakage.
- For glass to break,
  - significant stress (Load) and
  - a critical surface flaw

  must be present at the same place and at the same moment.
- Sometime delayed fracture can occur due to slow crack growth from preexistent flaws. The loading conditions and stresses may initially be insufficient to cause breakage, but a flaw may slowly grow when it is under load until it reaches a critical condition and then triggers breakage.
- The rate of crack growth is very sensitive to the stresses and stress intensities acting on a flaw, and growth can be very slow or rather fast.

Glass failure main causes:



Fractography is a powerful tool for the analysis of fractured glasses, that can identify the cause of failure through the interpretation of fracture surface characteristics and can even provide quantitative information about the tensile stress.

Stress and Flaws-

- Stress is defined as applied force divide by area, magnitude of stress increases with increasing of forces and decreasing cross sectional area. Stress may be applied in the form of various loads like internal pressure, vertical loads, thermal shock and impact.
  - Stress applied from impact or loads is generally temporary and these stresses are present only when the loads are applied, removal of the loads eliminate the stress example, removing the closure from a beverage bottle containing a carbonated liquid will remove the stresses.
- Flaws, however creates a permanent stress to the glass.
- Surface flaws are results from handling of the glass container or from the glass manufacturing process.
- Example of stress from glass manufacturing process are poor annealing, compositional cord and inclusions etc. Surface damage induced early in the manufacturing process may manifest itself as failure later in the process or in the field as the container is subjected to subsequent stresses.
- The failure of glass container will occur only when the tensile stress equals or exceeds the strength of the glass container.

Examples of stress- (1/2)

The loads applied during handling, storage and processing induce stress to the glass and reduce the strength of glass. The various loads which can occur during handling, use, and storage of glass are described below:

- Internal Pressure: Internal pressure may occur during lyophilization process, storage (heat or freezing etc. Internal pressure normally creates tensile stress to body, bottom and shoulder -neck joining area.
- Vertical Load: Vertical load may lead to breakage of glass container. The vertical load mainly occurs during capping/crowning and storage. The vertical load normally generates tensile stress to heel and shoulder area of the container.
- Thermal Shock: A sudden change in the temperature applied to glass container which can lead to crack, check and breakage to the glass container. The thermal shock generate stress to complete glass container

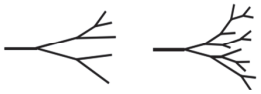
Examples of stress- (2/2)

- Impact: Impact may occur due to various reasons e.g.
  - Glass to Glass Contact,
  - Glass to Metal Contact, and
  - Friction at the time of container running at Line.

  Impact generate stress mainly to the impacted area or weaker portion near to impact.
- Hydrodynamic: Hydrodynamic loads are produced in liquid (and vacuum) filler containers that experience a sudden acceleration due to an impact event.
  - An impact to the filled vial causes the vial to pull away from the product, producing a small void or bubble in the liquid. Once the product catches up with the vial, this void collapse, producing a high-level, but localized stress on both the inside and outside surfaces of the lower sidewall/heel area. If the fractures originate on the inside surface, the load is referred to as "water pick."

Typical Breakage Patterns

Forking –

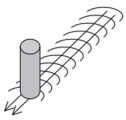


Low stress? High stress?

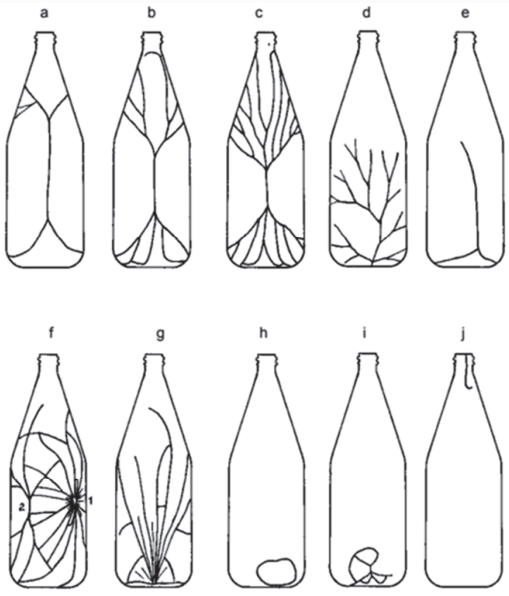
Hertzian cone –

(schematic illustration from cross sectional view)

Chatter mark -



(created by friction, curves concavity toward rubbing direction)



Picture-1: Bottle fracture patterns. (a-c) sidewall fractures due to internal pressure at progressively greater pressures; (d) internal pressure fracture starting from the base; (e) is a thermal fracture from sudden cooling of the base; (f) is an impact fracture on the right side (labeled 1) with a hinge fracture on the side (labeled 2); (g-i) show water hammer fractures and (j) shows a fracture from diametral rim clamping.

Reference- NIST Recommended Practice Guide Special Publication 960-16e2: Fractography of Ceramics and Glasses. George D. Quinn.)

Glass Breakage Mechanism

Crack propagates by tensile stress that concentrated at the origin, which is a small damage as cracks on the glass surface, or in the glass body.

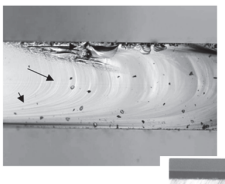
The relation of the failure stress and size of origin is explained:

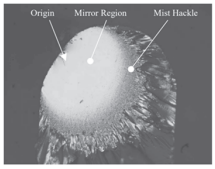
$$\sigma = \frac{1}{Y}\frac{K_{IC}}{\sqrt{c}}$$

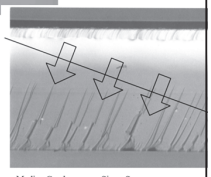
where :
Y is constant depending on the crack and sample shape ;
K_{IC} is the fracture toughness, and
c is crack size.

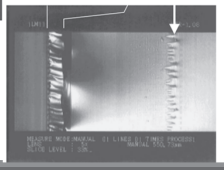
Fracture surface information-

- Wallner lines
- Hackle marks
- Mirror region
- Sharra scarp
- Origin



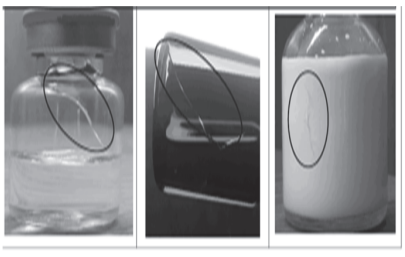


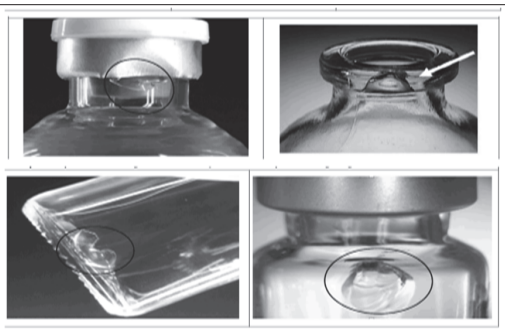


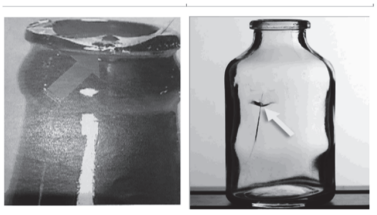


Reference- “Fracture Analysis: a Basic Tool to Solve Breakage Issue”, CORNING Technical Information Paper, 2004

GENERAL GLASS HANDLING GUIDANCE TO AVOID DAMAGES





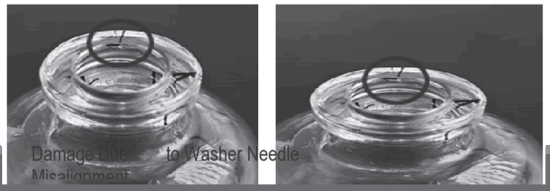


The glass breakage typically occurs due to too high applied force, poor processing equipment generating surface defects, manufacturing defects, improper handling, and not due to the inherent material limitations.

Typical candidates for lowering the strength of glass are static glass-to-glass contacts on accumulation tables, dynamic glass-to-glass contacts, due to sudden stops (impacts) at the end of conveying belts, glass-to-metal contacts with parts unintentionally protruding into the conveying path of containers.

GENERAL GLASS HANDLING GUIDANCE TO AVOID DAMAGES

Processing of glass containers on equipment and lines always presents some level of risk for container damage. To reduce the risk for certain flaws (e.g., scratches, scuffs, checks, bruises) on glass containers and generating glass particles, abrasions, cracks, and breakages, friction and force exerted upon the containers should be minimized throughout the entire process.



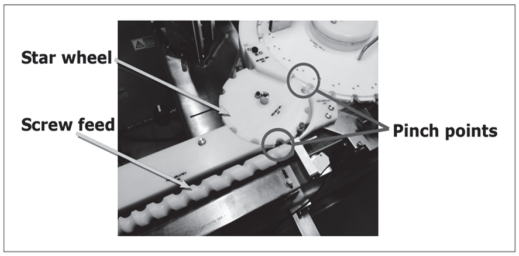
Best Practices/ General Considerations & Point to Address

Handling Consideration	Points to Address
Limit Glass-to-Glass Contact (Frictive and Impact)	
Limit Glass-to-Metal Contact	
Reduce Friction whenever Possible	
Overall Process Management	
Minimize Transitions and Accumulation of Containers	
Limit Areas of Back Pressure	
Assess Thermal Stressors	
Mitigate the Impact of Glass Breakage Events	
Investigate Breakage Events	

New Equipment Design & Consideration

Full range of dimensional variability and consideration of critical dimensions required for optimal container handling must be accounted for in equipment design.

- Container dimensional variability (lot-to-lot or vial-to-vial)
- Component stack-up tolerance (vial + stoper + seal)
- Container design appropriate for equipment use
- Technical drawing details (e.g. contact points on the rails, star wheels, screw feeds, grippers), including specifications on shoulder angles, radii, concentricity and roundness)



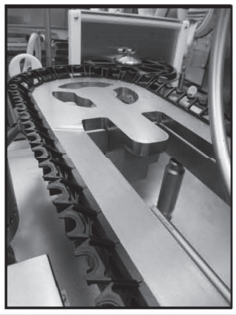
Aligning measurement techniques among and within pharma company, equipment suppliers and component suppliers

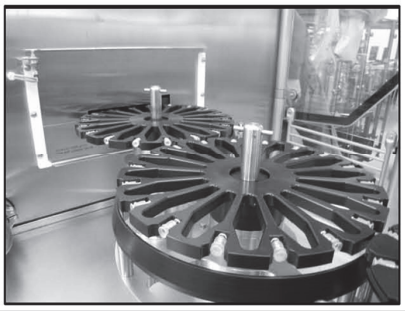
New Equipment Design & Consideration

Liquid Vials Line

◆ Minimization of glass to glass contact during production
- Single vial transport where applicable (washing, filling+closing, inspection)

◆Minimization of metal to glass contact during production
- Format parts made of polymer materials where applicable

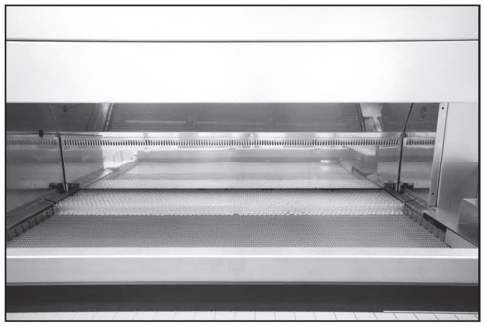


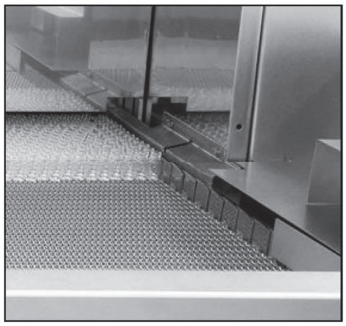


New Equipment Design & Consideration

Liquid Vials Line

◆ Reduced friction
- Objects are moved in a static position (e.g. grabber and vacuum star wheels)
- No contact to guide rails where applicable
- Synchronized running belts as lateral guidance inside sterile tunnel

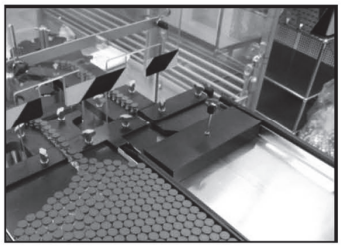


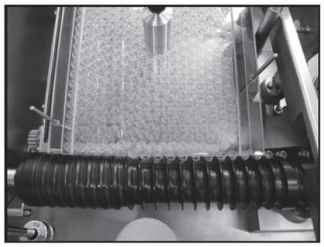


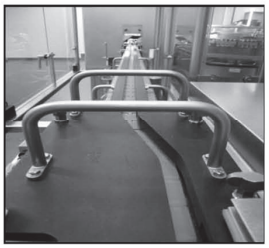
New Equipment Design & Consideration

Liquid Vials Line

◆ Further optimizations
- Analysis of visual inspection findings
- Conveyor belts stop automatically if following process stops
- Teflon coating for large surfaces like buffer tabled and eject plates







Real-Time Stress Monitoring

EXAMPLE

◆ Vial Diagnostic Drone and Associated Data Visualization Technology

Smart Drone (vial 形狀的傳感器)

Quantifeel™ System – Single-Site Pilot – 4 Months

- One Microsoft Surface Pro tablet, pre-loaded with Quantifeel™ software with 4-month license
- Allows for two (2) sensor drone formats from our existing library of available designs. (See list of available designs which is always growing.)
- Sensor drones can be exchanged for other available designs during the pilot period. The customer must provide Smart Skin with four (4) weeks' notice of any exchange request.
- The pilot includes full use of the system for the duration of the pilot period including access to all software updates, new design features and new cloud sync features for remote data access.
- Includes unlimited remote training, technical support and analytical support.
- Hardware and software are fully warrantied for all perils for the duration of the pilot.
- All hardware and software remain the property of Smart Skin and must be returned at the conclusion of the pilot.
- Special offer – Smart Skin will supply one (1) custom sidewall pressure design with initialization of the pilot. (Standard cost is $20,000). Note that format still counts as one of the 2 formats on-site for the subscription.

www.smartskintech.com

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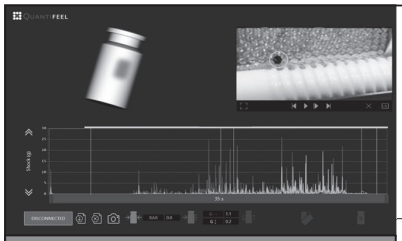
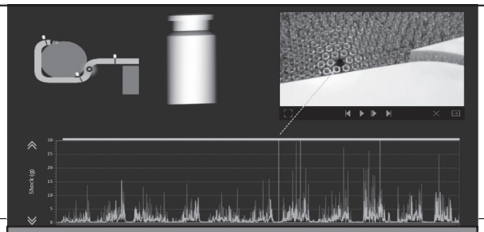
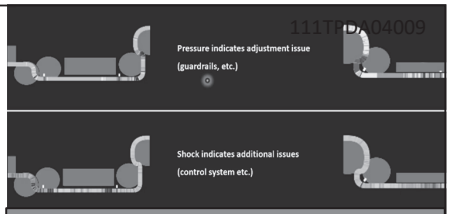


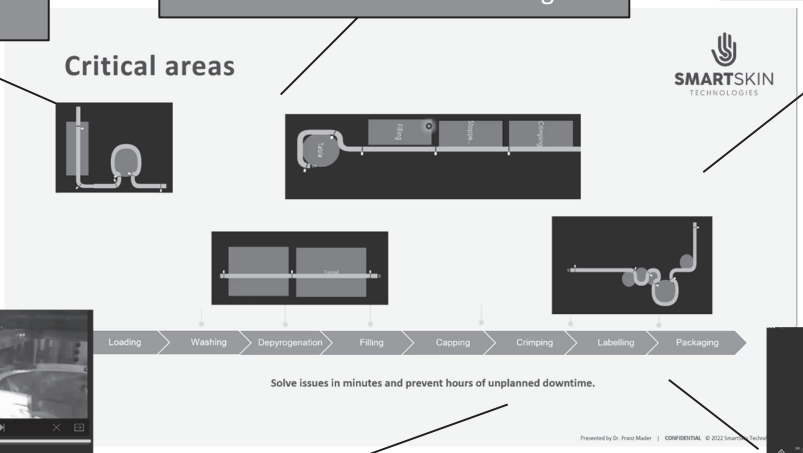
Washer infeed – conveyor to feeding screw

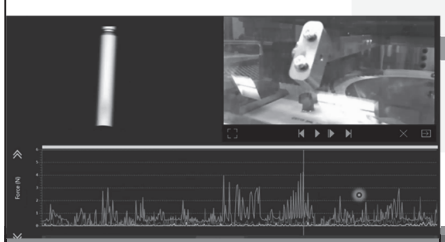


Buffer table and transition to single file

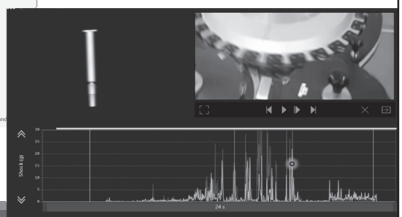


Filler/Stopper/Crimper. Conveying





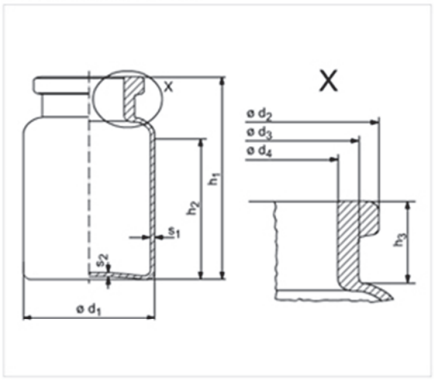
Inspection / Mass flow to starwheel



Labelling

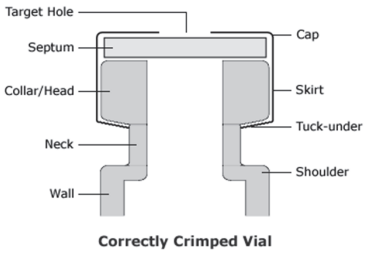
Source: SmartSkin Tech, Unlock New Potential in Productivity ; Dr. Franz Mader ; March 2022

STANDARD VIAL CRIMP NECK

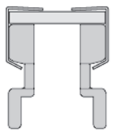


SPECIFICATONS ISO 8362-1 STANDARD VIAL CRIMP NECK

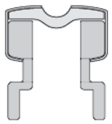
Type	full capacity ml	D1	D2+0.2-0.3	D3 max	D4 ±0.2	H1	H3	S1
2R	4.0	16±0.15	13.0	10.5	7.0	35±0.5	8.0±0.50	1.0±0.04
4R	6.0	16±0.15	13.0	10.5	7.0	45±0.5	8.5±0.50	1.0±0.04
6R	10.0	22±0.20	20.0	16.0	12.6	40±0.5	8.5±0.50	1.0±0.04
8R	11.5	22±0.20	20.0	16.0	12.6	45±0.5	8.5±0.50	1.0±0.04
10R	13.5	24±0.20	20.0	16.5	12.6	45±0.5	9.0±0.50	1.0±0.04
15R	19.0	24±0.20	20.0	16.5	12.6	60±0.5	9.0±0.50	1.0±0.04
20R	26.0	30±0.25	20.0	17.5	12.6	55±0.7	10.0±0.75	1.2±0.05
25R	32.5	30±0.25	20.0	17.5	12.6	65±0.7	10.0±0.75	1.2±0.05
30R	37.5	30±0.25	20.0	17.5	12.6	75±0.7	10.0±0.75	1.2±0.05



Correctly Crimped Vial

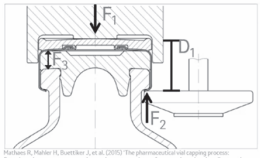


Under-crimped Vial



Over-crimped Vial

- Capping Equipment
  - Manual crimpers to high-speed automated cappers
  - Crimping mechanism; jaws (K-Head), rail, spinning rollers
  - Some equipment monitors pre-compression force
  - Most equipment is fixed height of roller/rail (component variations)
- Automated process
  - Assembled vial/stopper/seal applied a pre-compression force (F_1)
  - The aluminium seal is rolled under the vial flange
  - The roller or rail may exert additional force on stopper dependent on vial geometry (F_2)
  - When pre-compression force is removed, there is an immediate relaxation in stopper compression force (F_3).
- Monitoring the process
  - In cases were equipment measures pre-compression (F_1), not a measurement of stopper compression (F_3)
  - Component properties have impact on stopper compression (vial flange geometry, stopper properties)
  - Stopper compression can only be ***measured indirectly***



Markaert R, Mahler H, Buettiker J, et al. (2015) 'The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests' European Journal of Pharmaceutics and Biopharmaceutics, 95(2015) 54-64.

F1 - Pre-compression Force (cap to vial base)
F2 – Force exerted by crimping tool
F3 – Stopper compression force
D1 – Caliper, distance from crimping tool to pressure block

Source: Merck, Development of TopLoad Drone for Stopper Compression and Residual Force (RSF) ; Jeff Cremi

111TPDA04009

Risk Assessments – Typical tools

Risk Management Tool	Description / Attributes	Potential Applications
Basic Tools		
• Diagram Analysis • Flowcharts • Check Sheets • Process Mapping • Cause/Effect Diagrams (i.e., Ishikawa or fishbone diagrams)	Simple techniques that are commonly used to gather and organize data, structure risk management processes, and facilitate decision-making	Compilation of observations, trends, or other empirical information to support a variety of less-complex deviations, complaints, defects, or other circumstances
Risk Ranking and Filtering	• Method to compare and rank risks • Typically involves evaluation of multiple, diverse quantitative and qualitative factors for each risk, weighting factors, and risk scores	Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Statistical Tools	• Control Charts • Pareto Charts • Histograms	Visualization and evaluation of data to assist in the identification of trends, issues, and appropriate corrective actions
Advanced Tools		
• Fault Tree Analysis (FTA) • Hazard Operability Analysis (HAZOP) • Failure Mode Effects Analysis (FMEA)		

Examples of RPN Factor Determination

Criteria	Correlation Factor		Considerations
Severity	Will cause glass to crack or break/chip and enter container	10	How severe is the effect on the product? 10 = Previously observed glass break/crack 5 = May cause breakage or cracking, but has not been observed previously
	May cause glass to crack or break/chip and enter container	5	
	Will not cause glass to crack or break/chip and enter container	1	
Occurrence	Daily (1/2)	10	How often does the event occur (if observed in the past)? How often should the event be expected to occur (if not observed in the past)? Has the event ever occurred (if documentation exists)?
	Weekly (1/20)	7	
	Monthly (1/100)	4	
	Yearly (1/1000)	1	
	Remote or never (1/1,000,000)	1	
Detection/ Control	No possibility/highly unlikely to detect and/or control (< 50%)	10	How probable is it that the defect (crack or glass in product) will be caught before passing to the final customer?
	Unlikely to detect and/or control (50%–90%)	7	
	Somewhat certain to detect and/or control (90%–100%)	4	
	Certain to detect and/or control (100%)	1	

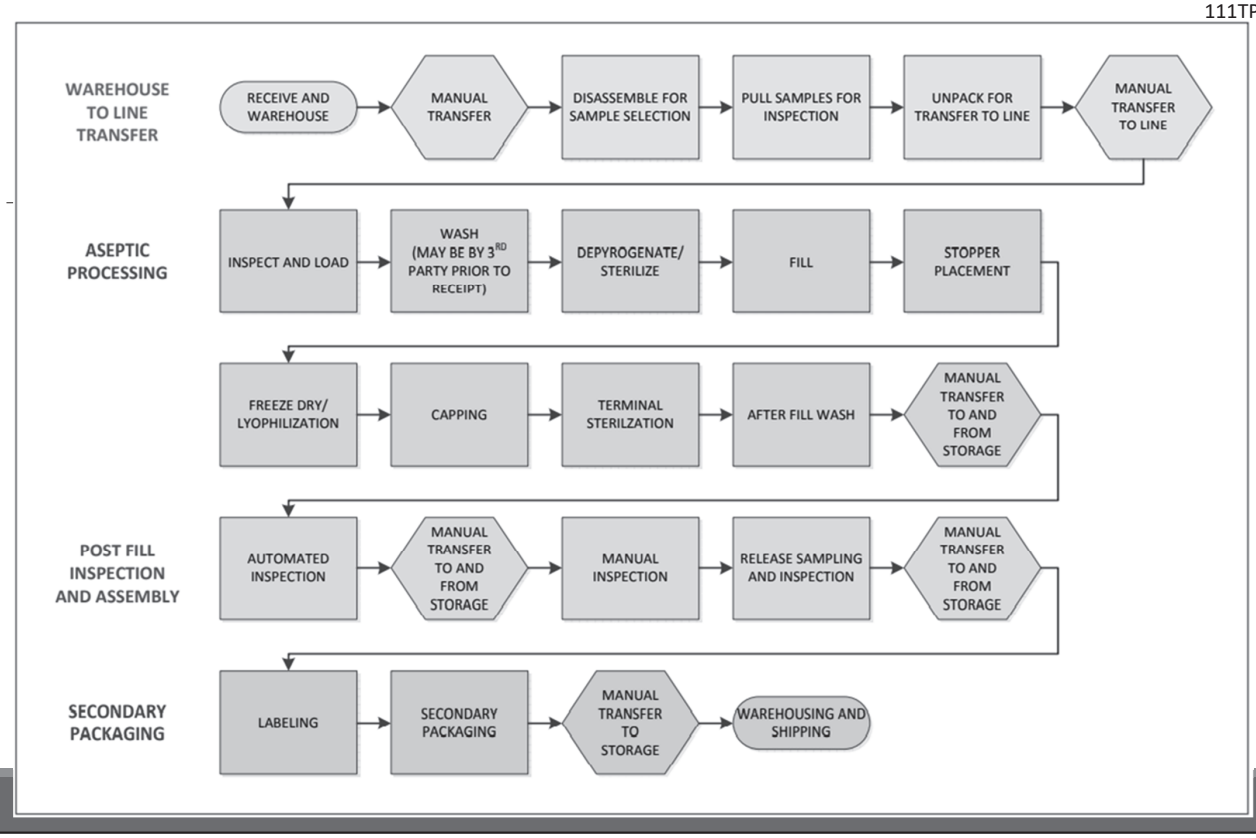
Glass Vial Handling Process

Glass-handling process begins at the glass vial manufacturer and continues through the final packaging at the pharmaceutical company and shipment to their customer.

Numerous transfers take place within that process. Consideration for glass handling must be taken into account for the transfer between process steps-

Some points to consider in transfers to and from the warehouse include ensuring

- ✓ the hand truck or lift wheels are in good condition,
- ✓ the operators are properly trained,
- ✓ the facility floor is in good condition with no potholes or deep cracks, and
- ✓ the floor of the transition from room to room is level.



Best Practices/ General Considerations & Point to Address

Handling Consideration	Points to Address											
	5.1 Transport storage	5.2 Line integral	5.3 Vial washing	5.4 Dry heat	5.5 Vial filling	5.6 Stopper placement	5.7 Lyo	5.8 Capping	5.9 Terminal sterilization	5.10 External washing	5.11 Inspection	5.12 Off-loading
Limit Glass-to-Glass Contact (Frictive and Impact)	v	v		v			v					
Limit Glass-to-Metal Contact	v	v			v			v				v
Reduce Friction whenever Possible		v					v					
Overall Process Management		v	v								v	
Minimize Transitions and Accumulation of Containers		v		v						v		
Limit Areas of Back Pressure		v		v						v		
Assess Thermal Stressors				v			v					

- Mitigate the Impact of Glass Breakage Events
- Risk Assessment
- Investigate Breakage Events

Glass Handling Process

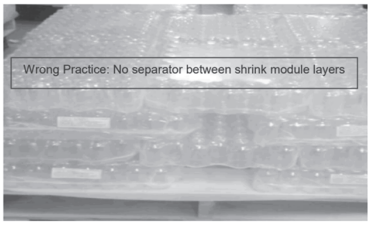
- Good glass handling practices can preserve the inherent strength of the glass containers, whereas poor glass handling practices can significantly reduce the practical strength of glass containers.
- Surface flaws induced due to damages early in the manufacturing process due to poor glass handling may manifest itself as failure later in the process or in the field as the container is subjected to subsequent stresses.
- To minimize the risk of creating flaws/damages (e.g., bruises/bump checks, scratches, scuff marks, cracks, checks, breakage, abrasions, etc.) during handling below mentioned recommendations are general glass handling guidance points to be considered and taken care of:
  - Documentation and Procedure
  - Best Handling Practice Recommendations

Glass Handling Process

- The glass-handling process at the pharmaceutical company starts
  - from glass receipt from the glass supplier
  - through the final packaging
  - for the shipment of finished product to their customer.
- Many transfers take place within the process. Each handling or processing step may introduce a surface flaws or may enlarge pre-existing one, which can result in a reduction of the overall strength of the glass.
- Therefore, each process steps from receipt of glass to loading of the product pallet into container should be considered for good glass handling practice to avoid any damage to the glass.

GLASS RECEIPT FROM GLASS SUPPLIERS: Packaging Configuration

Activity-
Supplier Pallet
for Transportation:



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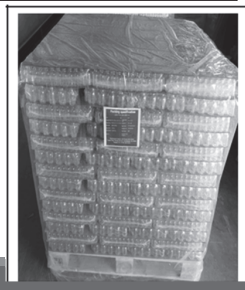
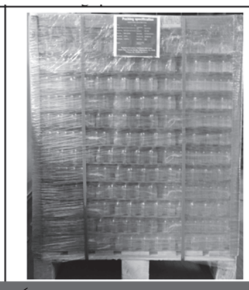


(O) Good Practice



- Configurations should be standardized for each container type and size: shrink-wrapped module type with glass-to-glass contact, or a tray with or without cell partitions or separators.

- Pack-out configuration should include a review of such factors as:
  - ✓Setbacks of the load from the edge of pallet
  - ✓Module-stacking
  - ✓Corner protection and straps
  - ✓Slip sheets between layers
  - ✓Method of securing the load to the pallet
  - ✓Total height of the pallet

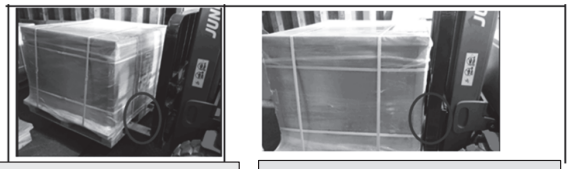
✓ Good Palletization with side and edge protector

Good Secured Palletization

UNLOADING AND TRANSFER OF SUPPLIER GLASS PALLET TO SITE PALLET

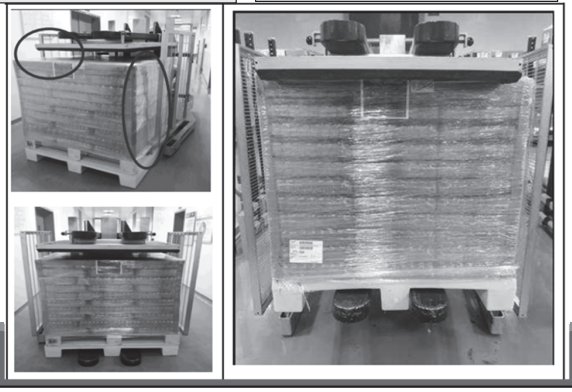
Activity-

- Material unloading from vehicle



(X) Not Good Practice (O) Good Practice

- During depalletization using Toppy

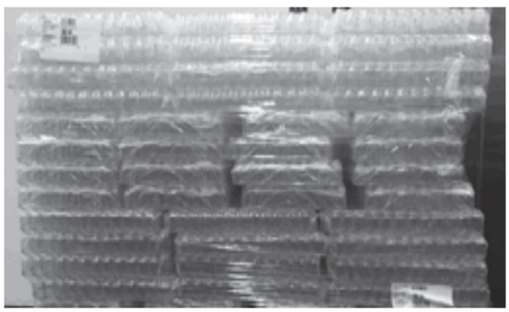


What's "Toppy"?
https://youtu.be/KLo73gKviZ8

Activity-

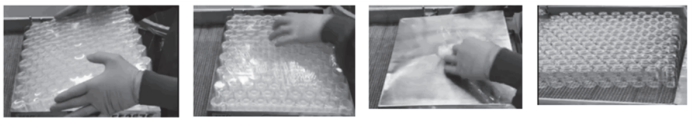
- Storage

(X) Not Good Practice (O) Good Practice

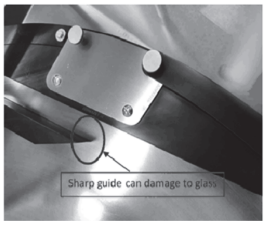


TRANSFER OF GLASS FROM STAGING AREA TO WASHER LOADING POINT, DEPACKING AND LOADING TO WASHER

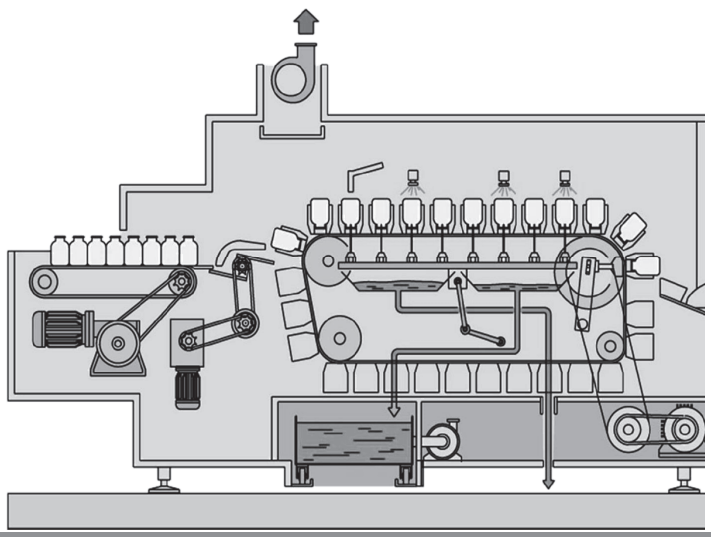
- Handle shrink wrap module carefully



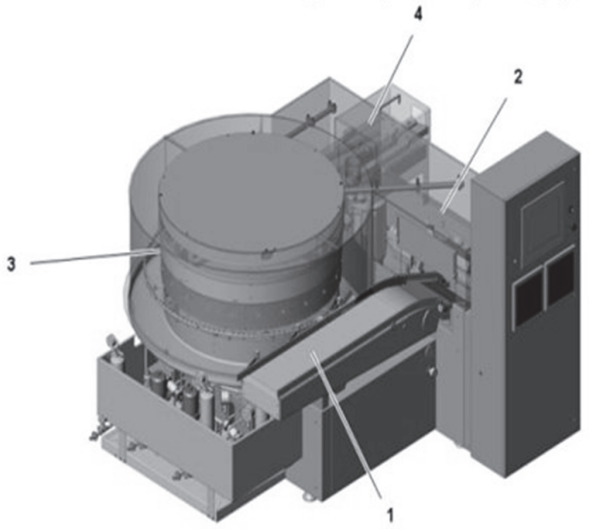
- Do not use sharp edge guide



Vial Washing Process – Linear or Rotary



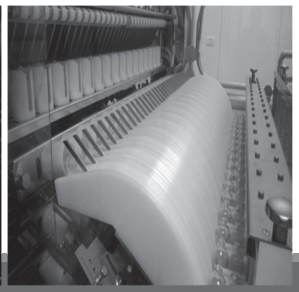
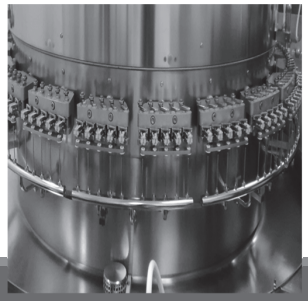
The machine RRU 3105 consists of the following main components and processing steps:



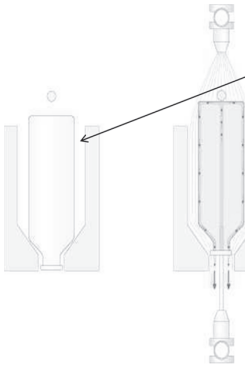
Loading and Infeed of Vials

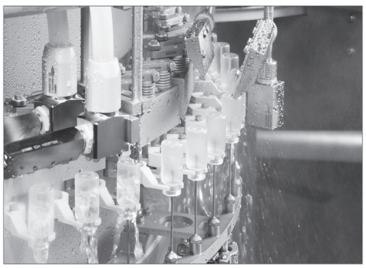
- The de-packed empty vials are loaded in the hopper of the unscrambler.
- The unscrambler sets the vials in upright position and deliver them to the infeed of washing machine.
- The infeed conveyor belt, carries the containers to the loading zone.
- Here the vials are arranged in several lines by specific sorting units that move back and forth.
- When the belt stops, a lift picks up the vials that are inserted into the conveying baskets by sliding on a spoke-shaped sector.



LIFTING NEEDLES / DIVING
- Optimum water distribution
- Flow effect on the glass surface



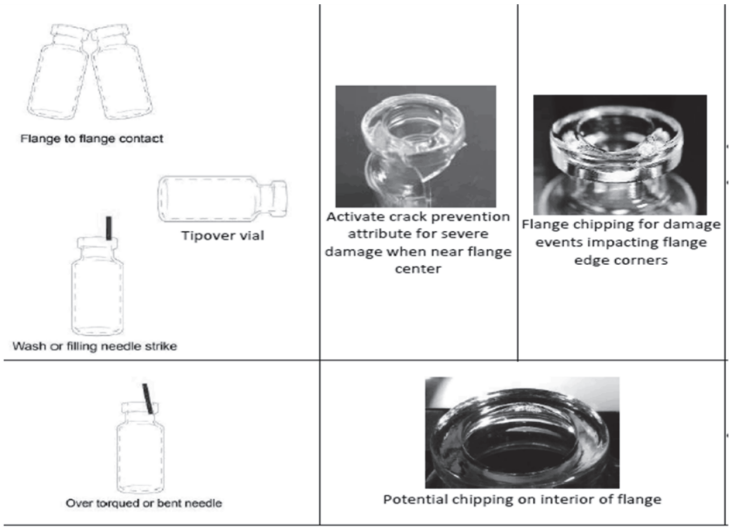


1.Position of vials in the basket is important so damaged baskets cannot be used.
2.Position of needle also plays an important role in vial washing.
3.Insertion of needles inside vials is important for effective washing.

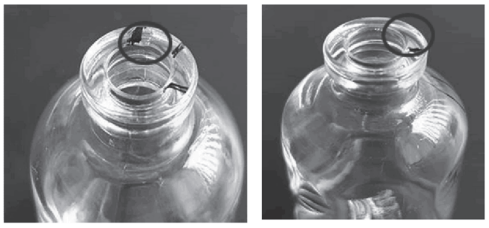
Needle motion:

- The vertical needle motion (the motion of the distributor and needles) is driven by a servo motor.
- The container specific insertion depth of the needles is stored as a recipe parameter on the HMI.
- The horizontal motion of the distributor and needles is driven by a mechanical cam.

Damage can occur due to needle misalignment

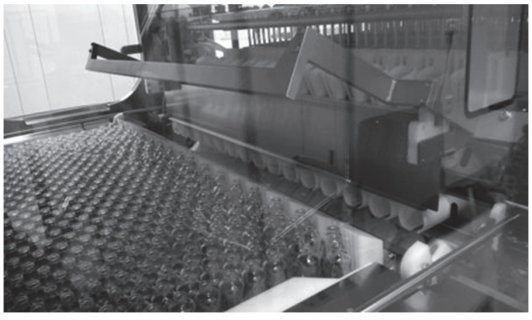


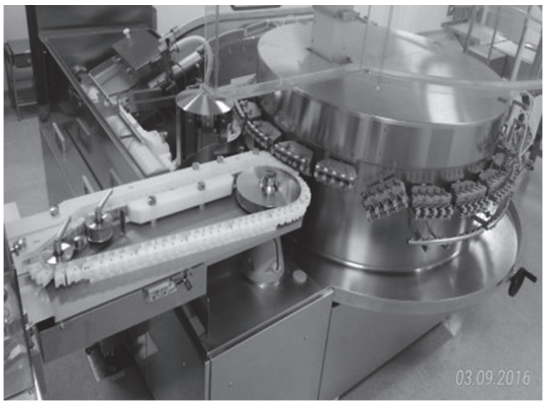
- Typical damage due to bent needle or wrong setup



- ✓ Ensure proper set-up of washing and filling equipment
- ✓ Avoid use of tipped, downed and rejected vials

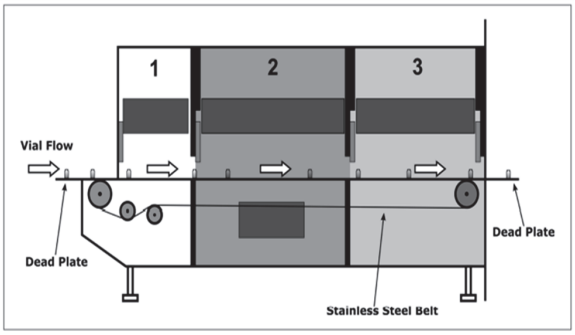
Vial Outfeed and Emptying (conveyed to downstream tunnel)





DEPYROGENATION OF GLASS

- Vials undergo a depyrogenation immediately after washing and depyrogenation is normally made at ~ 350 degree C temperature utilizing dry heat Process.
- This process effect lubricity of the glass surface and make the vials more susceptible to abrasion at external surface if vials are in contact with another vial (glass to glass contact) or glass come in contact with metal (glass to metal contact), this can create scratches/scuff marks at vial. This can generate glass fine glass particulates in the process.
- The scratches/scuff marks may weaken the glass surface, these defects can grow in further process.



Typical Depyrogenation Tunnel Layout with Preheat Zone , Hot Zone , Cooling Zone

Ideally the conveyor belt should be operated in a "pull mode" and run at a slightly higher speed than the feed rate from the washer in order to maintain a small space between the rows of vials.

Maintain a minimal downward transition of the vials is recommended to reduce the probability of damaging the heel region.

Tunnels typically include 3 zones: pre-heat zone, hot zone, cooling zone.

Vials are then pushed out of the tunnel, using slight back pressure, across a dead plate, and onto the next stage of process by an accumulator.

Although the glass structure is not impacted directly by the temperature used for depyrogenation, leaving the containers in the tunnel beyond the validated depyrogenation process time is not recommended.

The temperature removed the protective water skin from the containers, leaving them more vulnerable to surface damages. As a result, the exiting containers may be more prone to damage in general and have a higher COF than prior to depyrogenaiton, and make the vials more susceptible to abrasion.

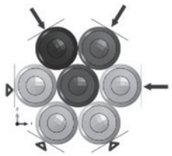
This type of friction is usually observed just below the shoulder and above the heel of the vials,

Though small and relatively minor in appearance, scratches and scuffs can potentially contribute to breakage under sufficient mechanical or thermal stress further downstream.

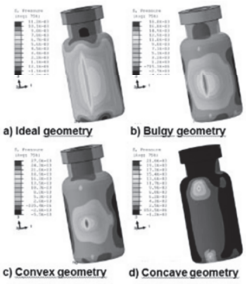
In a case where vials are in contact with on another, one vial may bond with the surface of another, causing the to stick together. Vertical marks will be apparent then the vials come apart.

These marks may act as stress concentrators and fracture origins as the vials are subjected to subsequent loads during downstream processing or handling.

Glass Surface Reactions: „Sticky Surface“

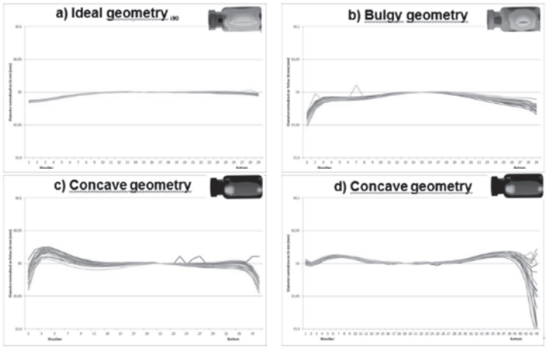


Packing scheme in tray



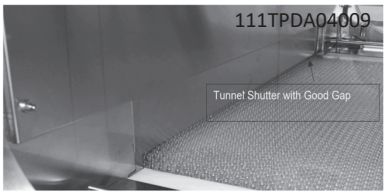
Pressure distribution along outer surface

Vial geometry performed by optical measurement technology



PHARMAVERSITY

SCHOTT glass made of ideas



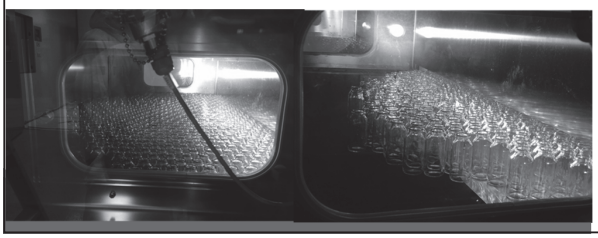
DEPYROGENATION OF GLASS: Tunnel / Batch Type Oven

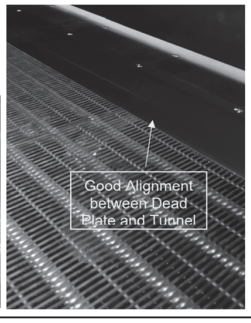
✓ Sufficient gap between shutter and the top of vial

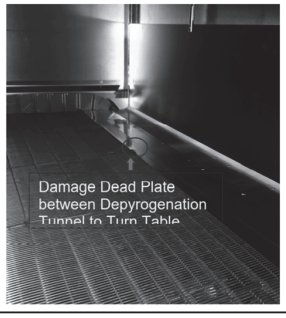
✓ Dead plate aligned properly with tunnel metal belt to ensure smooth transfer

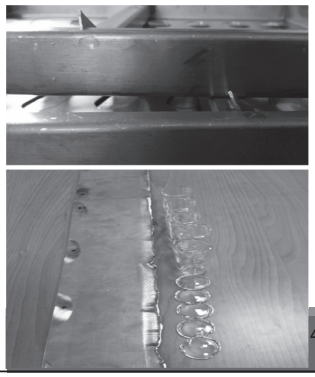
- misaligned dead plate can result in vial bottom damage, fallen vial, broken vial, overcrowding e.g. glass vial riding on another vial.

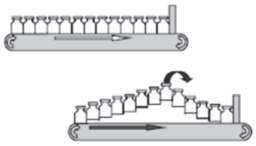
✓ Heating and cooling temperature gradient/cycle should be adequately defined and validated to avoid any thermal shock to glass



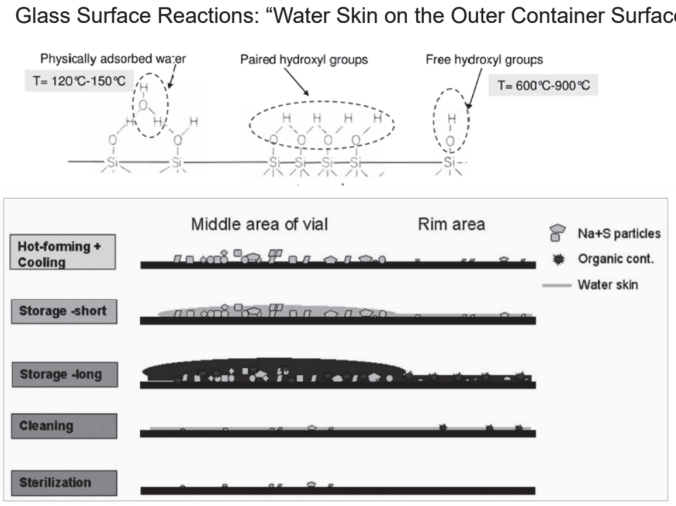




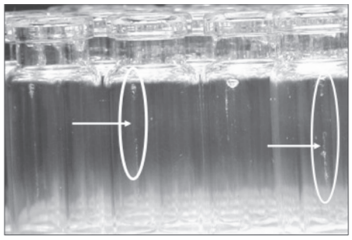




Glass surface phenomena



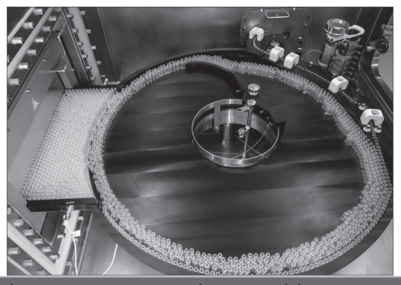
- Outer surface phenomena:
  - Sticky/ climbing vials
  - Scratches
  - Minor cracks
  - Roughness, friction



PHARMAVERSITY SCHOTT

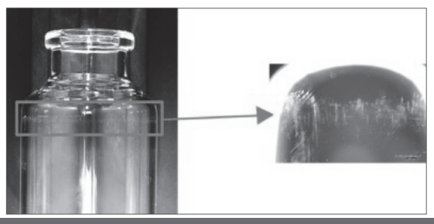
ACCUMULATION OF VIALS AT TURN TABLE / PRODUCT FILLING

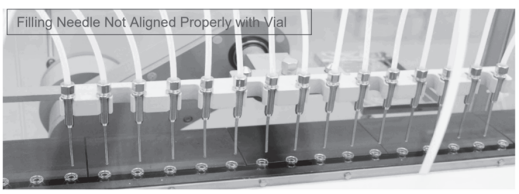
- Vials are transferred to the filling station after washing and depyrogenation, typically by a conveyor belt, with a star wheel or by a gripper the picks up the vial by the neck
- Either fixed nozzle or a diving nozzle apparatus
- Stoppered either by direct placement (stopper picked up by vacuum) or by a rotating wheel
- Ideally, grippers should be constructed of plastic rather than metal

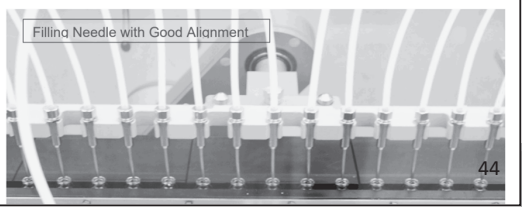


- Rotary Accumulation Table

Abrasion rings

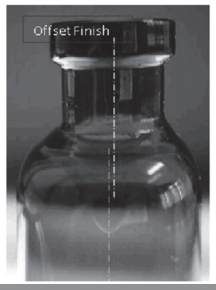


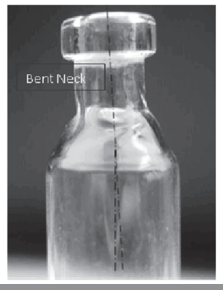




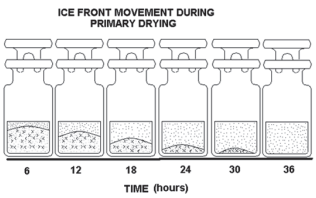
PRODUCT FILLING & STOPPERING

- Needle can also become bent when striking vials that have offset finishes
- Damage in the lip region of the vial can go unnoticed through inspection as the stopper and seal can mask the damage
- Regular inspection during the production batch should assess misalignment of and damage to filling needles.
- Vials attributes such as leaners (slanted bottoms), bent or offset finishes, or small inner diameter, can increase the risk of needle strikes.
- The risk of incurring damage during the stoppering process is very low as there is no glass-to-glass contact during stoppering. Any breakage observed during stoppering is most likely due to damage that occurred upstream.

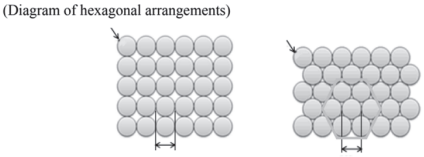


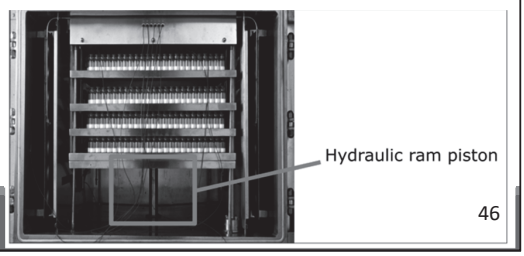


LYOPHILIZATION



- Lyophilization (freeze-drying) is a process though which water is removed from the liquid solution by freezing the product, subliming the ice (昇華), and desorbing residual water to low levels.
- Vials are filled with liquid product and stoppers are partially seated into the vials on the filling line prior to accumulation for the loading operation.
- The vials are loaded onto the freeze-dryer shelves, either manually using bottomless trays, or via automated mechanical loading system.
- Upon reaching the specified end condition of the process, the stoppers are fully seated into the vials with the hydraulic shelf-stoppering system. Vials are then unloaded from the chamber.
- Manipulation of the vials during loading, stoppering, and unloading processes, in addition to the freeze-drying process itself, can all be potential sources of glass vial handling issues.





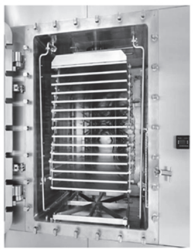
Vial Fracture due to
Expansion of Product Component

Lensed Vial

LYOPHILIZATION

- Loading & Unloading
  - Traying, transfer, loading and unloading: glass-to-glass and glass-to-metal interactions occur similar to other manipulation operations: close-packed configuration
  - Over time and repeated use, cleaning and sterilization, earn on the bottom surface of the tray can become evident and warping of the ring may occur, leading to “pinched” vials when nested
- Lyophilization
  - Potentially significant stress imposed on the glass from the expansion of product during freezing and drying
  - As the product freezes, crystals from the product can expand, often upward from the bottom of the vial and outwardly and down from the product surface toward the bottom
  - Extent of this effect vary depending on the specific product formulation
  - Although this expansion would not initiate glass breakage by itself, the risk to vial breakage increases with the presence of a defect, such as a blemish due to scratches in the vial from glass-to-glass and glass-to-metal abrasion.
  - Vial design, especially in the heel area, may also have an impact on breakage during expansion. With a large fill volume, internal forces are increased significantly.

Stoppering mechanism in a production freeze dryer



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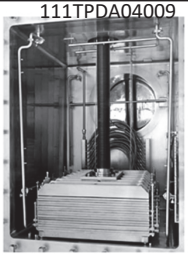


LYOPHILIZATION

- Seating the Stoppers
  - Final seating of the stopper occurs within the lyo chamber at the end of process, when the shelves are either lowered or raised to fully insert the partially seated stoppers.
  - The suspended shelved most often are driven by a hydraulic ram. Pressure exerted by the hydraulic system is set initially for the most demanding need, such as 1cc or 3 cc vials with a 13mm finish. Such small vials have greater density across the shelf surface area and require the greatest pressure (force per unit area) to fully seat the stoppers. In order to apply a uniform pressure to each vial across the shelves, the shelves should be level and planar. If there’s any significant variation to pressure distribution, the force can be localized significantly in one area, which could lead to glass breakage.
  - When a partial shelf-load of vials left at the end of filling operation are being placed on the lowest shelf, there must be sufficient number of vials, being evenly positioned across to accommodate the pressure evenly.
  - Failure to evenly distribute the vials across the shelves can lead to cokced selves and distortion of the shelf suspension hardware.
  - Some breakage observed may not be due to improper handling but may attributed to vial nonconformities, such as leaners, rocker or uneven bottoms, or an improperly designed or formed bottom radius

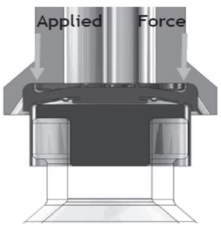
https://www.spscientific.com/freeze-drying-lyophilization-basics/

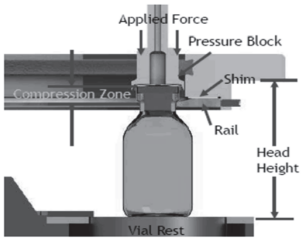
CAPPING

- Vial capping (crimping) is the last step in the aseptic process to fully seal a parenteral vial.
- The primary seal of a parenteral vial packaging system is the interface of the elastomeric stopper flange and the land sealing surface on the crown of the vial. Capping is the process of sealing the vial by compressing the flange of a rubber stopper against the to surface of the glass vial, forming the primary seal, and then crimping an aluminum ferrule around the stopper and vial finish.

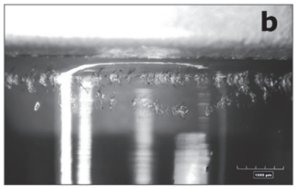
Sufficient vertical load force is necessary to optimally compress the stopper, achieve sufficient seal tightness, and assure container-closure integrity. A side load may also be imparted when the metal is crimped.

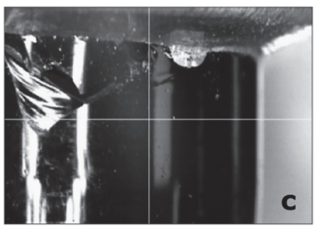
- Regardless of the sealing method, the stress created in the glass from these loads of an optimized capping process (<130N force) should be well below that where breakage would be expected. Breakage, however, is sometimes observed at the capper. Glass failure at capping is likely the manifestation of significant surface damage caused to the vial earlier in the process.

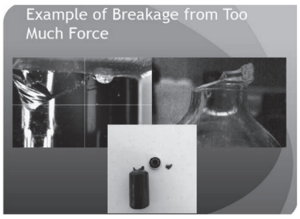




CAPPING - Examples of Surface Damage/Breakage & Vial Nonconformity







Examples of Surface Damage and Breakage Due to Contact with Sealing Disc or Rail
(a, b) Abrasion from sealing disc ;
(c) Chipping ; (d) Broken vial neck

The finish and plane of the seal surface is not perpendicular to the axis of the body.

Finish not concentric with the body.

Plane of the container bottom that is not perpendicular to the axis of the body.

Fold or overlap of glass on the exterior glass surface.

CAPPING

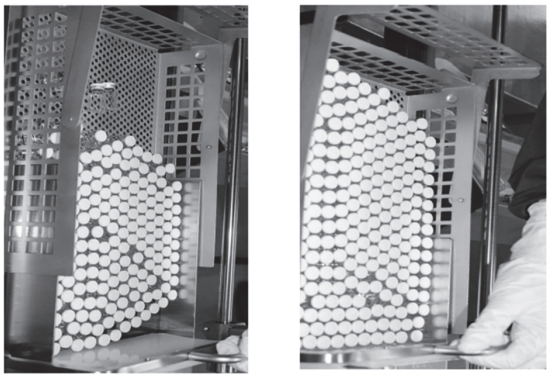
- Improper set-up of the capper or excessive vial variability (e.g., offset necks, bent necks, large necks, leaner, rocker bottoms, laps (folds) in the neck) could cause the neck to come in contact with the sealing rail or disc, causing surface damage to the neck of the vial that may propagate into fractures.
- Transfer of vials into and out of the capper usually consists of a combination of belts, screw feeders, and star wheels.
- That the sealing disc or rail will not contact vials within normal variability must be assured, and detailed capping equipment set-up parameters must be established and documented for each package combination. The parameters should be based on achieving sufficient stopper compression to achieve acceptable container-closure integrity without excessive force.
- Component variation and stack-up tolerance should be considered in establishing the capper parameters. Offsetting (top and bottom) springs or dampers are employed to compensate for total height variation.

Neck crack defect:
How the machine crimp the cap?

EXAMPLE

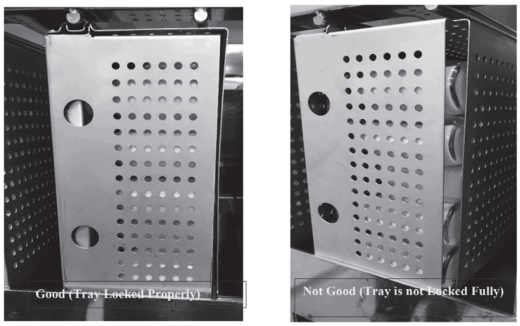
PRODUCT FILLED VIALS/AMPULE COLLECTION

Wrong Practice (Partial Tray Filling)



TERMINAL STERILIZATION / EXTERNAL WASHING

- Breakage of vials during terminal sterilization is most likely due to an upstream incident. The practical strength of the glass may have been reduced, thus reducing the burst pressure of the vials.
- Transitions that convey the glass containers into and out of the external washing unit operation (e.g., star wheels, screw feeds) must be aligned and synchronized.
- Feedback mechanisms or a sensor to detect proper functionality of the grippers should be used to prevent such glass breakage.

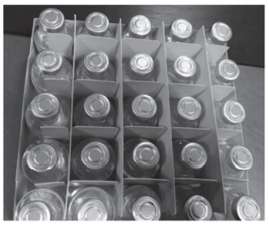


INSPECTION OF FINISHED PRODUCT FILLED GLASS CONTAINER / LABELLING

- Inspections may be carried out using manual, semi-automated, or automated.
- Most of the time inspection does not occur in-line just after the capping. Vials with finished product after filling are often packaged in intermediate packing material or in trays on pallets and then pallets are transported to the inspection line
- Most of the time labeling does not occur in-line just after the final glass container inspection. Vials with finished product after inspection are often packaged in intermediate packing material or in trays on pallets and then pallets are transported to the labelling and packing section. Normally transportation of pallets is made by hand truck/hand fork

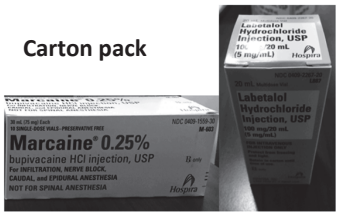
PACKAGING OF FINISHED PRODUCT FILLED GLASS CONTAINER

Divider/ Inner compartment

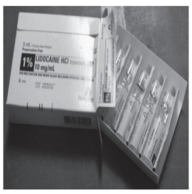


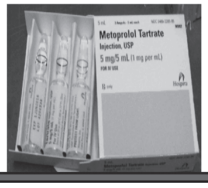
- Folding cartons, made of cardboard or coated paperboard, are often used.
- Carton properly sized, designed in a way that prevents glass breakage or damage, and made of materials with a lower friction factor and shock absorption.
- Multi-vial pack: prevent glass-to-glass contact

Carton pack



Shipper packing and Tray shrink wrapped packs





Fluted tray pack

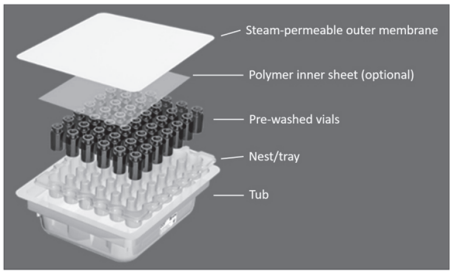
PALLETIZATION / LOADING OF PALLET INTO CONTAINER FOR DISPATCH:

Points to be Considered:

- Carton staking configuration
- Apply corner and edge protectors,
- Apply the slip sheet or separator between layers
- Ensure total height of pallet as per storage rack system,
- Avoid double stacking of pallet in warehouse and during transportation until or unless not validated for such storage.
- Secured load of pallet by stretch wrapping

- Ensure reefer Container/Vehicle is in good condition; and ensure door locking mechanism working properly
- Secured pallet properly by lashing or by putting air dunnage bag between gap to avoid movement of pallet during shipping

CONSIDERATIONS FOR PREVENTING ADDITIONAL DAMAGE



➢ Ready-to-Use vials
- Prevent glass-to-glass contact,
- Allow processing without unpacking

➢ Robotic Automation
- Reduce glass-to-glass contact,
- Precision pick-and-place units, provide consistent glass manipulation

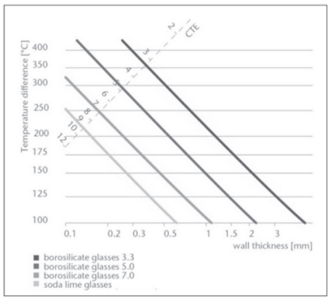
➢ Outer Surface Treatments or Coatings
- Strengthening the outer surface and/or applying a lubricating layer (maintain low COF)
- Molded-glass containers or tubular containers

Fundamentals of Glass Science

Table 8.0-1 Overview of Glasses Used in Pharmaceutical Primary Packaging by Classification and Standards

	Aluminosilicate	Borosilicate 3.3 Group Tubular	Borosilicate 5.0 Group Tubular	Borosilicate 7.0 Group Tubular	Borosilicate Molded	Quartz (Fused Silica)	Soda-Lime-Silicate Tubular/ Molded
Commonly Available Compositions							
SiO_2	70-80	80-82	72-75	70-74	65-70	> 99	70-75
B_2O_3	–	12-13	9-11	5-8	9-11	–	0-1
Al_2O_3	6-12	2	5-7	4-6.5	3-7	–	2-4
Na_2O/K_2O	8-13	4	6-9	9-12	9-10	–	12-16
MgO/CaO/BaO	3-7	0	1-3	5-7	4-5	–	10-15
Physical Data							
CTE [10^{-6} K^{-1} (20 °C; 300 °C)] as specified by ASTM E438	Not described	3.2-3.3	4.8-5.6	Not described			90-93
CTE [10^{-6} K^{-1} (20 °C; 300 °C)] as specified by ISO 12775	Not described	3.3	4.9-5.5	Not described			8-10
CTE [10^{-6} K^{-1} (20 °C; 300 °C)] as mainly found on the market	3.5-7.0	3.3	4.9-5.4	6.3-7.0	5.8-6.5	< 1.0	7.1-9.3
Annealing Point (°C) by ASTM E438 or common	560	560	560-575	550-580	550-570	> 1150	525-540

- Coefficient of Thermal Expansion (CTE) 熱膨脹係數
  - Main factor in determining the resistance of glass to sudden temperature change
  - Increasing resistance to thermal shock is correlated with decreasing CTE
- Due to the fact that glass has poor thermal conductivity, a thinner wall thickness is recommended for thermal resistance while a thicker wall will withstand greater mechanical loads



Comparison of Different Glass Types and Wall Thicknesses (according to CTE) (© SCHOTT AG)

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Stress Inside the Glass

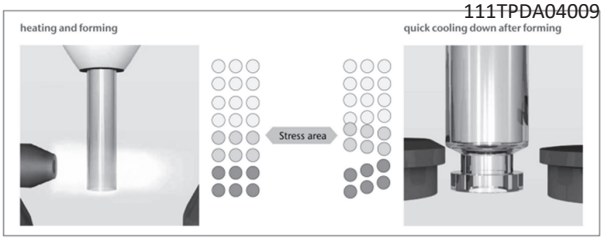


Figure 8.2.2.1-1 Schematic Representation of Heating* and Forming of a Glass Tube into a Vial (© SCHOTT AG) (1)

- Melting and Solidification Behavior of Glass
- Thermal Stress During Container Manufacturing
  - Vial annealed by heating to about 20C above Tg and then slowly cooled in a strictly controlled process in an annealing lehr(oven)
  - If the stress is not released properly, the risk of glass breaking at the zone of tensile stress is greater
  - Residual stress can be determined by polariscopic measurement devices

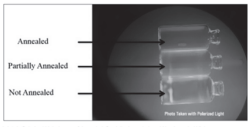


Figure 8.2.2.1-2 Polarized Light Image of Annealed, Partially Annealed, and Not Annealed Vials

  - Except for ampoule sealing, residual thermal stress cannot be introduced in the filling process as the temperature never exceeds Tg
  - If the temperature difference at a certain spot on the glass exceeds the particular thermal shock parameter, micro-cracks can result
  - Depyrogenation poses no risk in terms of thermal stress. It does, however, facilitate the introduction of scratches that decrease the mechanical strength which is discussed

Stress Inside the Glass

➢ Thermal Stress During Container Manufacturing (cont'd)

- The lower the CTE, the more stable the glass is in terms of thermal shock resistance, but the rate of change must be extremely high for thermal shock breakage.
- Use of glass with lower CTEs may reduce the breakage risk due to rapid rate of change; however surface defects still play the major role in glass breakage.
- Breakage during exposure to cold temp are primarily due to flaws present in the glass and the outward pressure of the internal materials, not thermal stress.
- The fewer defects there are on the bottom area and area of drug contact, the less likely the glass will break.
- Vial breakage during lyophilization process is usually due to the mechanical stress from the expanding solution rather than thermal stress.
- Likewise, the thermal stress does not contribute to breakage when glass is immersed in liquid nitrogen, but the sole cause of the failure is the outward expansion force of the frozen material.

Stress Inside the Glass

➢ Mechanical Strength of Glass

- Ductile versus Brittle Materials

- Practical Strength

Realistically predicting the practical strength of different glass is difficult. → Breakage only occurs if both stress and flaw or stress riser are present on tandem, and the combined phenomena exceed the practical strength of the particular piece.

- Tensile and Compressive Stress

Glass always breaks at the point of tensile stress location.
When compressive stress is exerted from one side, it always induces tensile stress in certain other places, but these areas of tensile stress are not always clearly detectable piece.

- Surface Condition and its Impact on Practical Strength

Griffith's theory of Fracture:

$$K = \sigma \cdot Y\sqrt{c}$$

σ = stress (induced by an applied force)

Y = geometric factor (which considers the location of the defect among other factors)

$\sqrt{c}$ = critical dimension (e.g., depth of defect)

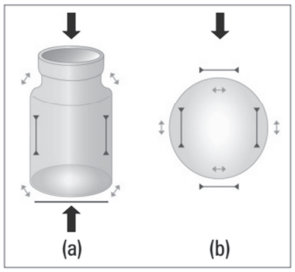


Figure 8.3.3-1 Vial with Compressive and Tensile Stress Areas (© SCHOTT AG)

Figure (a) has force applied to sealing surface of the vial creating tensile stress in the outer surface of the neck and heel and compressive stress in the side wall. Figure (b) has force applied to the side wall creating tensile stress on the interior surface at the exterior load location and exterior surface 90 degrees from load. Long Blue arrows are compressive stress and short orange arrows are tensile stress. Large red arrows represent load forces.

Adsorption Layer on the Glass

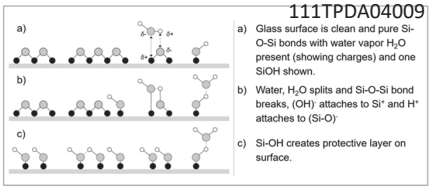


Figure 8.4-1 Visualization of the Reaction of Water Vapor from Humidity and the Glass Surface (© SCHOTT AG)

- Glass surface reacts with adsorbates from ambient air that then saturate the surface.
  - This layer acts like a cover on the glass and protects it from scratches.
  - This phenomenon of building up and evaporating is equally valid for all glasses.
  - The water layer not only protects the glass from scratches, but it also plays as a lubricant, decreasing the friction between glass containers or between glass and metal.

Chemical Strengthening

- Chemical strengthening by ion exchange creates a residual compression layer on the inner and outer glass vial surfaces that resists the applied tensile stress required to propagate flaws.
- Applying an additional protective coating to the outer surface will lower its COF and minimize surface damage during frictive sliding contact

Appendix II: Investigations

EXAMPLE

Fishbone Diagram - Root Cause Analysis (Report #xx)

ISSUE: Customer complaints reported for leaking vials of product xxxxxx from batch xxxxxx. Area: Filling line #xxxxxx

1. Define the problem (Plan)

Supplier advised that there was a discontinuity present in some vials which may crack if another ouside force is applied to the vial.
This RCA is to determine the cause of metal incisions present on the affected vials and any other "trigger" that may have caused the cracks to appear

2. Analyse the problem (Plan)

1. Man
Vial dispensing
forklift handling
manual stacking on trolleys
manual transfer to CPR
manual loading onto washer (knife used to cut packaging)
manual loading onto filling machine

2. Machine
washing machine metal guide
walking beams on filler
infeed turntable
reject starwheel and rail
guide rail transition from walking beams to outfeed scroll
decon machine nozzles
Seidenader volume sight guide
labeller
sheather
packing machine (pushing vials into cartons)

3. Material
discontinuity in glassware (identified by supplier)
metallic mark on vials from supplier
manufacturers lot number across multiple MP#s

product xxxxxx - 3 x broken vials in batch xxxxxxxx

4. Method
no change to method same method used for all vials

5. Environment
Canada weather conditions
regional location within Canada

6. Transport
transport between supplier and Mulgrave
transfer between buildings (Mulgrave)
transport Mulgrave to Canada
transport within Canada

Appendix II: Investigations

- Production personnel must be aware when a failure occurs. Any failure should be immediately investigated.
- Personnel should be well trained in proper glass handling, conducting initial-failure assessments, sample collection, and sample preparation for fracture analysis.
- In order for breakage to occur there must be
  - Force applied to the item to generate stress in the glass
  - Flaw to act as the origin of the fracture
- The general aim of fracture analysis is to identify the
  - Type and magnitude of force that was applied to the container
  - Type and severity of the defect at the fracture origin
  - Cause of the breakage, whether due to
    - Defective container that failed at normally expected levels of applied force
    - Excessive force applied to a commercial-quality container

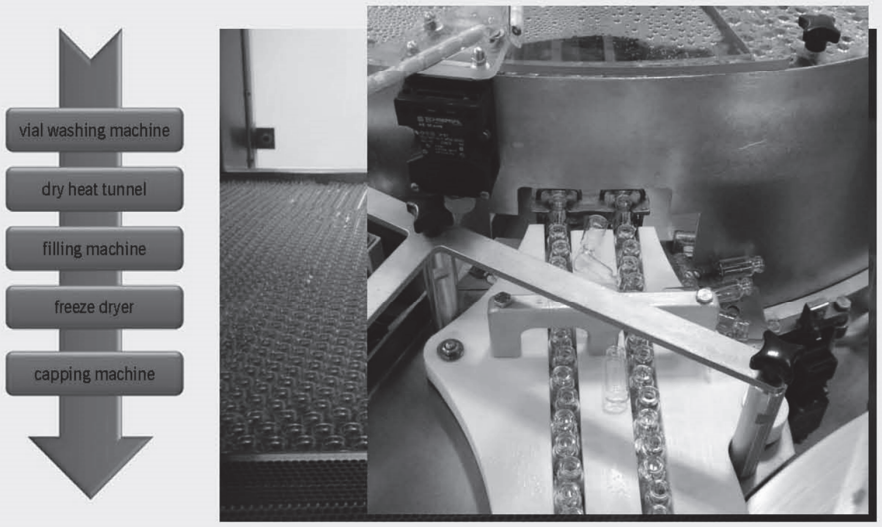
Root Cause Analysis & Mitigation

- ✓ Fracture Analysis
- ✓ Supplier Evaluation
- ✓ Incoming Inspection
- Equipment and Handling
- Line Clearance Procedures
- Training
- Metrics
- Visual Inspection
- Packaging and Distribution

EXAMPLE: Safe glass handling - possibilities for risk mitigation

Process flow – Filling of parenterals

EXAMPLE



Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage

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EXAMPLE: Safe glass handling - possibilities for risk mitigation

Method: Risik analysis

EXAMPLE

Speed:

0: low / without guidance
5: low / vial guidance
10: high / vial guidance

Format parts vial guidance:

0: no e.g. conveyer belts
5 : vial packages(e.g. dry heat tunnel)
10: strong guidance/ vial positioning

Height differences:

0: no,
5: yes – high to low in moving direction
10: yes – low to high in moving direction

Turning tables:

0: no
5: turning table simple outlet
10: turning table forced/sorted outlet

Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage

EXAMPLE: Safe glass handling - possibilities for risk mitigation

Risk Assessment: Cracks, Splinters and Breakage

EXAMPLE

	Speed	Guidance	Height differences	Turning tables	Risk level
Detraying	0	0	5	0	5
Vial washing machine	5	10	5	5	25
Dry heat tunnel	0	5	10	0	15
Filling machine	10	10	10	5	35
Format table	5	5	5	0	15
Transfer system	0	5	5	0	10
Freeze dryer	5	5	5	0	15
Intermediate storage	0	5	5	0	10
Raised stopper control camera	10	10	5	5	30
Capping machine	10	10	10	10	40
Traying	5	10	5	0	20

- Risk level 5-10: low - Risk level 15-25: medium - Risk level 30-40: high

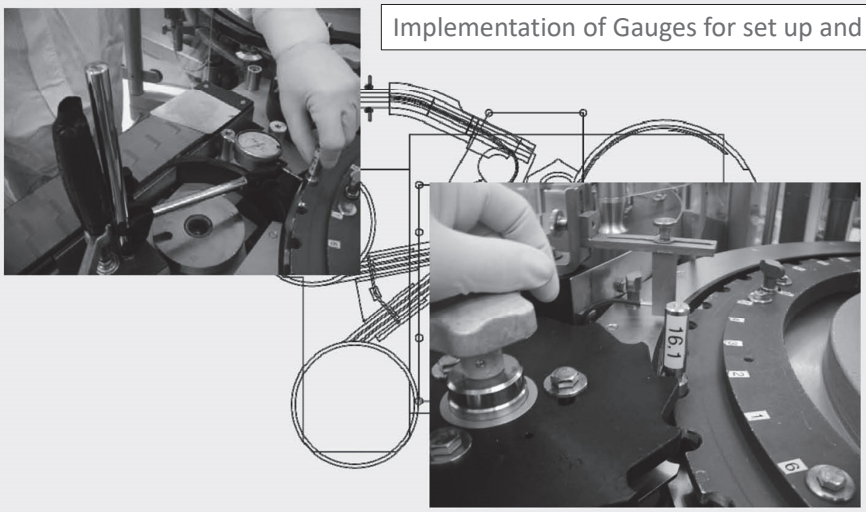
Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage

111TPDA04009

EXAMPLE: Safe glass handling - possibilities for risk mitigation

Safe guard measures: Example Vial filling machine

EXAMPLE



Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage

General conclusions/remarks/quotes

- Disadvantage of polymers vs glass: poor water vapor and oxygen barrier
- Fractography is a powerful tool to find out the reasons for fracture
- Quote Ingo Presser: "*If ppm glass breakage is comparable with airplane crashes, what is the issue?* "
- Most speakers emphasized the importance of **trending** defects
- Quote Wenzel Novak: *"Are cosmetic defects unwanted. One can easily make a line with no glass-glass contact with an increase in cost of 30%."*

Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage

PDA Journal of Pharmaceutical Science and Technology

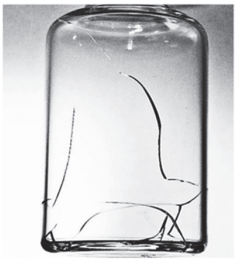
"Failure of Glass Tubing Vials during Lyophilization"

PDA J Pharm Sci and Tech 2019, 73 30-38

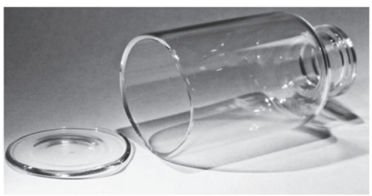
Examples of vials that failed due to an internal pressure force

a) Failure at relatively high pressure

b) Failure at relatively low pressure



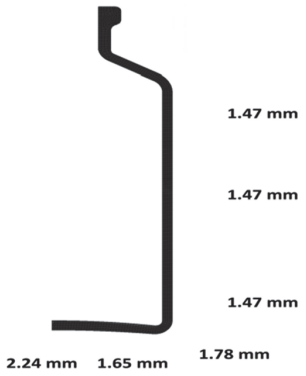
a) Failure at relatively high temperature differential



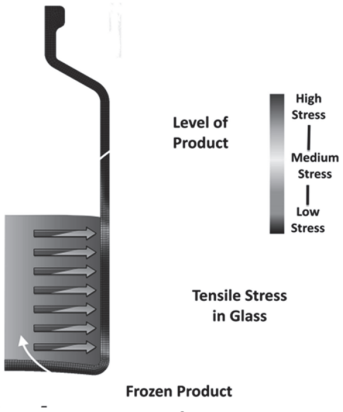
b) Failure at relatively low temperature differential

Examples of vials that failed due to a thermal shock force

"Failure of Glass Tubing Vials during Lyophilization"

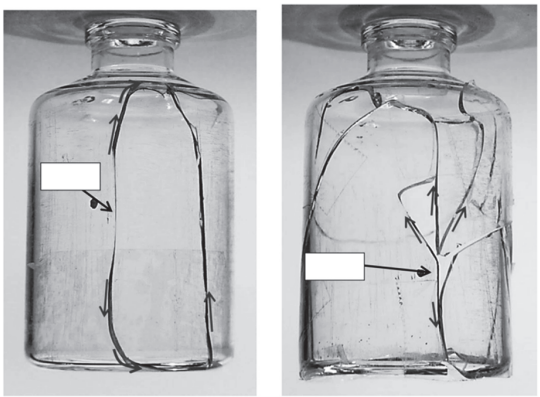


Glass thickness distribution



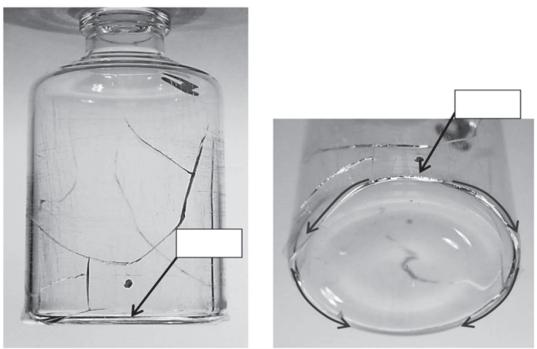
Finite element analysis of the tensile stress pattern due to expansion of frozen product

"Failure of Glass Tubing Vials during Lyophilization"



Typical fracture pattern from liquid nitrogen immersion breakage

Typical fracture pattern from oven to cold-water bath

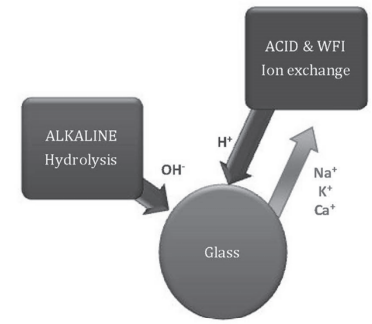


"Failure of Glass Tubing Vials during Lyophilization"

- Based on the nature of the fracture patterns, on the measured breaking stresses of tubing vials that fail during commercial lyophilization, and on the calculated stress values from thermal differentials,
  - it was concluded that the common type of lyo-breakage discussed in this paper is due to the outward expansion force generated by the frozen pharmaceutical product and not due to thermal gradients.
  - Thus, changes to the thermal properties of the glass vials (design changes to the vials or the use of glass having a lower coefficient of thermal expansion) are unlikely to make any significant difference in the frequency of breakage that may be experienced in typical lyophilization processes.
- Solutions to lyo-breakage can be best realized by performing detailed fracture analyses.
  - Such analyses will clearly differentiate the cause of breakage as either due to excessively high forces due to the expanding product or due to low glass strength caused by problems during vial production, transportation, or filling.

Challenges for Glass Containers: Breakage and Delamination

Chemical Mechanisms of Glass Attack depend on pH



Origin	Characteristic	Mechanism	Effect
Acid solution	pH < 7	**Ion exchange** between protons of aqueous environment and glass network modifiers : H^+ ¡ê Na, K, Ca	Alkali ions leaching from glass surface; SiO network not affected
Alkaline solution	pH > 7	**Hydrolysis** : OH^- attack the SiO rich islands of glass network	SiO network disintegrates and Si anions are dissolved, so that the glass decomposes as a whole; process is linear and time related
Water (e.g. WFI)		Similar to acid corrosion it leads to **Ion exchange** and to leaching of ions	At high temperature water corrosion can become significant

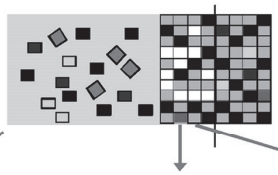
EXAMPLE

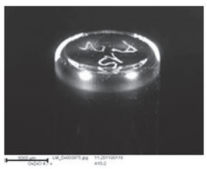
Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage – Delamination

Challenges for Glass Containers: Breakage and Delamination

Combination of Methods to characterize Glass Attack

2. Selective Dissolution





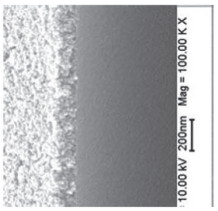
Info:

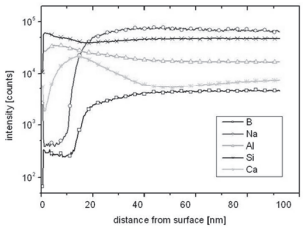
Concentration of glass elements that have gone into solution

Morphology
Layer thickness
Chemical composition

Chemical composition change as a function of depth

	Sample 1 [mg/L]	Sample 2 [mg/L]
B	2.3	0.44
Na	4.0	1.1
Al	0.24	0.02
Si	5.4	1.0





Method:

Inductively Coupled Plasma Mass Spectroscopy

Scanning Electron Microscopy
Energy Dispersive Spectroscopy

Secondary Ion Mass Spectroscopy

Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage – Delamination

111TPDA04009

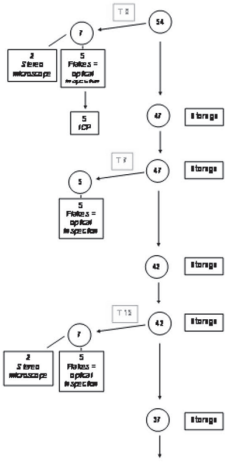
Challenges for Glass Containers: Breakage and Delamination

Accelerated Testing to predict Delamination Behavior

- Delamination usually seen after months or years of stability storage - **test must be much faster**
- Optical inspection gives a YES/NO answer and relies partly on chance - **complementary analytical tools needed to see early indicators**
- Delamination risks depends on drug - **test needs to use drug or placebo**

Study protocol example for accelerated testing at 60°C

	Reference (empty)	0 days	7 days	15 days	30 days	45 days	60 days
Optical inspection		x	x	x	x	x	x
Stereo microscope	x	x		x	x	x	x
ICP analysis		x			x		x
SEM/EDS morphology	x			x			x
SIMS depth profiling	x						x
SEM/EDS flakes (option)							x



Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage – Delamination

Challenges for Glass Containers: Breakage and Delamination

Conclusions

- Fractography is a powerful tool to find out the reasons for fracture
- Prediction of failure rates deserves overload test and tailored statistical evaluation
- Glass delamination
  - Glass delamination is not new (research started already 40 years ago)
  - There is no safe pH
  - Formulation more important factor than API
  - Risk assessment via screening tests
    - A combination of different analytical techniques needed
- Accelerated ageing tests are suitable to predict delamination risk

Source: Summary Pharma-Kongress Produktion & Technik / ECA Conference Glass – Glass Breakage – Delamination

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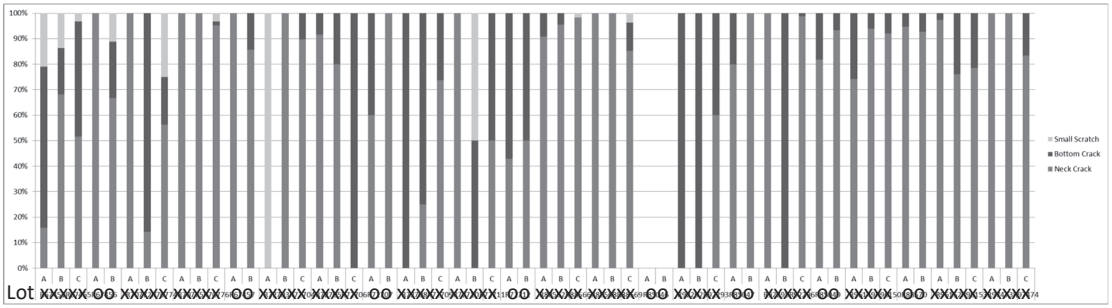
Case sharing

Where is the defect?

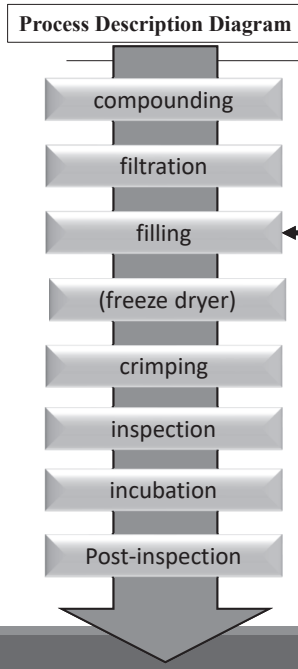
Case Sharing : Defects at manufacturing

EXAMPLE



Most of the defects contribute from Neck Crack
Some defects contribute from Bottom Crack
Small Scratch is cosmetic defect

Case Sharing : Defects at manufacturing – Impact & Investigation



EXAMPLE

Packaging component sterilization

A contaminated unit found at incubation …?!?

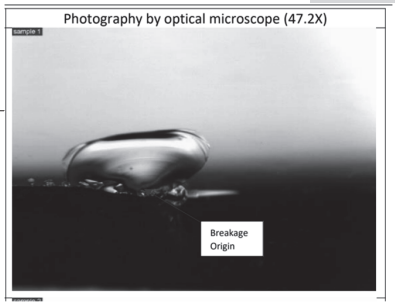
- When/how the vial damage happened?
- When/how the microbial gets in the vial?
- Pre-inspection?
  (why not rejected during pre-inspection?)
- Or post-inspection?
  (during transportation?)
- **Can we locate the root cause** away from the aseptic operation?

Case Sharing : Damage Analytics

EXAMPLE

Optical Microscopy

- Failure-inducing damage:
  - contact damage, or
  - melting induced discontinuity?
- Glass-to-Metal or Glass-to-Glass contact?
- Failure trigger: Direction and type of mechanical load
  (bending, side squeezing, axial load, internal expansion, temp gradients…)



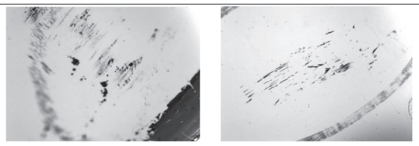


Fig.8 Fig.9

Scratches (Fig.8 and Fig.9) observed in vials with Scratches were generated by glass to metal contact basing on OOO manufacturing experience.

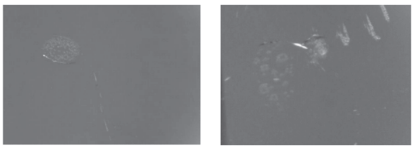


Fig.10 Fig.11

Scratches (Fig.10 and Fig.11) observed in vials with Scratches were generated by glass to glass impacted with the force basing on OOO manufacturing experience.

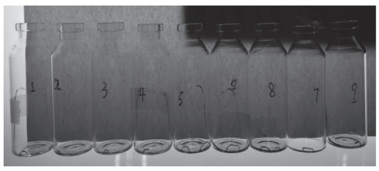


Fig.12

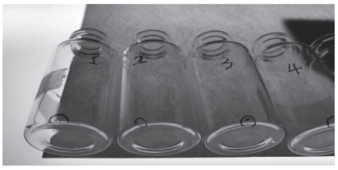


Fig.13

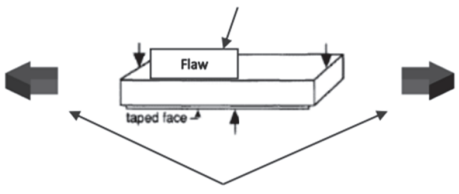
OOOOO performed the study of photography taken by optical microscope for the vials with the crack or lensing (Refer to the below table), it is possible to indicate the potential causes.

Case Sharing : Damage Analytics - Fractography

Glass failure main causes

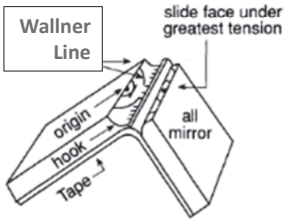
Tensile Stress + Flaw/Defect = Glass Failure

Any imperfection, blemish or defect acting as a stress concentrator



Tends to stretch the material or pull it apart

The combination of these two effects (tensile stress and defect presence) causes glass failure



Fractography is a powerful tool for the analysis of fractured glasses, that can identify the cause of failure through the interpretation of fracture surface characteristics and can even provide quantitative information about the tensile stress.

Case Sharing : Damage Analytics - Fractography

EXAMPLE

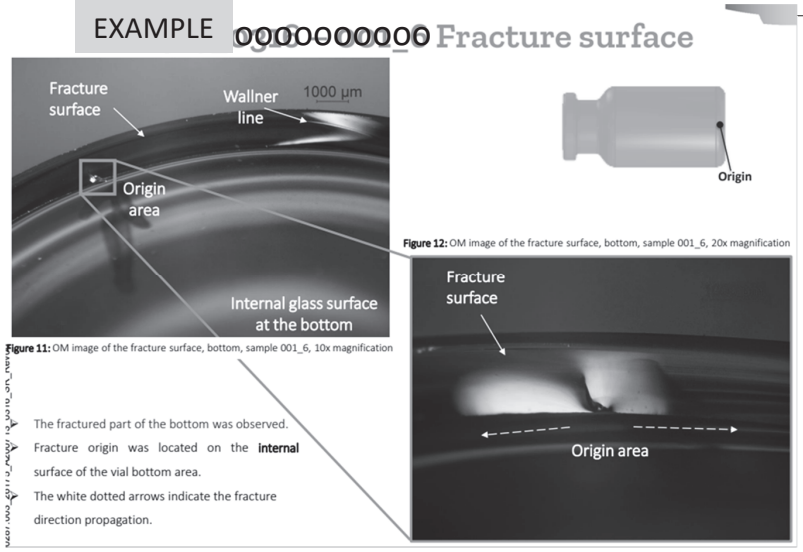


Figure 11: OM image of the fracture surface, bottom, sample 001_6, 10x magnification

Figure 12: OM image of the fracture surface, bottom, sample 001_6, 20x magnification

- Failure analysis investigation was performed on # vials, broken by lensing, with the bottom detached from the body.
- The fracture origin was identified onto the internal glass surface at the vials heel for all the observed vials.
- It was not possible to identify uniquely the failure root cause. The fracture probably originated from the presence of micrometric inclusions.

PDA Parenteral Drug Association

Technical Report No. 76

Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging

Nomenclature- Stopper

Figure 4.1.1-1 Stopper Nomenclature — Standard Terms (Serum & Lyo)

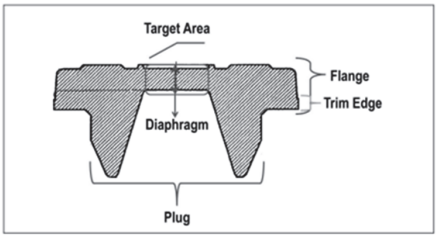


Figure 4.1.1-2 Stopper Nomenclature — Additional Common Features (Serum & Lyo)

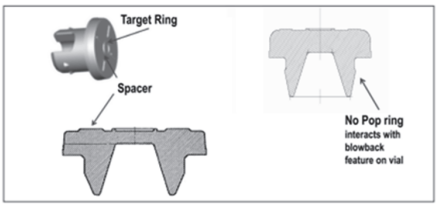


Figure 4.1.1-3 Stopper Nomenclature — Additional Common Features

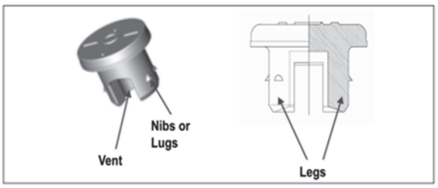
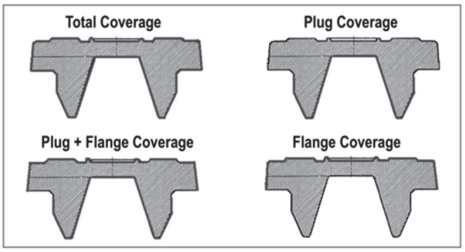


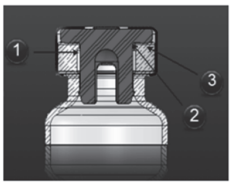
Figure 4.1.1-4 Stopper Nomenclature — Coatings and Laminates (Serum & Lyo)



4.1.2 Vial Container Closure Integrity (CCI) Considerations

A critical defect is one that has the potential to negatively impact the integrity of a container closure system. The integrity risk posed by a specific closure (vial stopper) defect is dependent on defect severity, defect location, and the level of protection required of the closure as the package is being assembled and after package assembly. The illustration below defines the different areas where sealing between the stopper and vial will occur.

Figure 4.1.2-1 Vial Container Closure Integrity (CCI) Considerations



1. **Valve seal:** A surface-to-surface compression seal formed between the vial neck and the vertical sides and/or beads of the closure plug. Synonymous with "plug seal."
2. **Transition seal:** The compression seal formed between the top of the closure plug and the vial mouth. This seal is a combination of land and valve seals.
3. **Land seal:** A surface-to-surface compression seal formed between the closure flange and the horizontal plane of the vial finish.

Elastomeric Vial Stopper Nonconformity

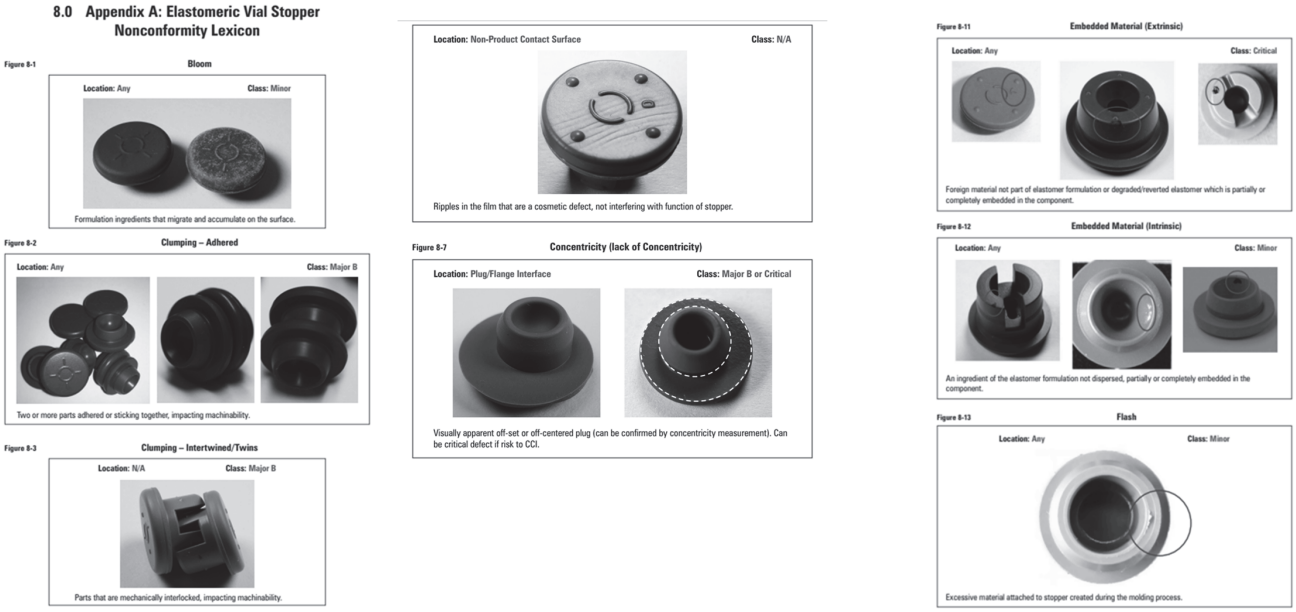
Table 4.1.3-1 Elastomeric Vial Stopper Nonconformity List

Nonconformance	Description		Location	Classification	Figure #
Bloom	Formulation ingredients that migrate and accumulate on the surface.		Any	Minor	8-1
Clumping — Adhered	Two or more parts adhered or sticking together, impacting machinability.		Any	Major B	8-2
Clumping — Intertwined/Twins	Parts that are mechanically interlocked unable to be machined.		N/A	Major B	8-3
Coating or Laminate — Film Incomplete	Disruption in film or coating, exposing the elastomer to drug product.		Product contact area	Critical	8-4
			Non Product Contact Surface	Major B	
Coating or Laminate — Other Defects	Irregularities including folds, abrasions, bubbles, cracks, and blisters.		Any area	Minor	8-5
Coating or Laminate — Wrinkles	Ripples in the film that are a cosmetic defect, not interfering with function of stopper.		Non-product contact area	N/A	8-6
Concentricity (Lack of Concentricity)	Visually apparent off-set or off-centered plug (can be confirmed by measurement).		Plug/flange interface	Major B	8-7
			If risk to CCI	Critical	
Contamination (Extrinsic) — Biocontamination	Loose or embedded visually identified biological materials such as hair, blood, skin, insects, etc.		Any	None Allowed	8-8
Contamination (Extrinsic) — Bulk Stoppers	Material not part of the elastomer formulation but part of processing such as oil, grease or other residues.	Not removable by washing	Any	Critical	8-9
		Is removable by washing	Any	Major A	
Contamination (Extrinsic) — Ready-to-Sterilize / Ready-to-Use	Material not part of the elastomer formulation such as oil, grease, environmental particulate, etc.		Any	Critical	8-10
Embedded Material (Extrinsic)	Foreign material not part of elastomer formulation or degraded/reverted elastomer which is partially or completely embedded in the component.		Any	Critical	8-11
Embedded Material (Intrinsic)	An ingredient of the elastomer formulation not dispersed; partially or completely embedded in the component.		Any	Critical	8-12
Flash	Excessive material attached to stopper created during the molding process.		Any	Critical	8-13
Knit Mark	A surface irregularity that results from material flow during molding process.		Any	Critical	8-14
Loose (Extrinsic) Material — Bulk Stoppers	Loose material not part of the elastomer formulation such as fibers, paper, plastic, foreign stopper material, not embedded. Removeable by washing.		Any	Critical	8-15
Loose (Extrinsic) Material — Ready-to-Sterilize / Ready-to-Use	Loose material not part of the elastomer formulation such as fibers, paper, plastic, foreign stopper material, not embedded.		Any	Critical	8-16
Loose Elastomer Material (Intrinsic) — Bulk	Loose elastomer of the same elastomer formulation, no embedded. Also called trim debris. Removable by washing.		Any	Minor	8-17
Loose Elastomer Material (Intrinsic) — Ready-to-Sterilize / Ready-to-Use	Loose elastomer of the elastomer formulation, not embedded. Also called trim debris.		Any	Major A	8-18
Malformed	Distorted or deformed stopper.		Sealing surface, risking CCI	Critical	8-19
			Any, impacting Machinability	Major B	

Table 4.1.3-1 Continued

Nonconformance	Description		Location	Classification	Figure #
Mixed Component(s)	Intermixing of foreign component(s), piece of a component, remnant differing in formulation, color or designs.		N/A	None Allowed	8-20
Mold Cavity Damage	Defects on sealing surface caused by damaged mold cavities (scratches, pits, blisters or dents).	Risk to CCI	Sealing surface	Critical	8-21
		No potential to impact CCI or Machinability	Other than sealing surface	Minor	
Non Fill (aka Void)	Incompletely formed elastomeric closure or liner.	Risk to CCI	Sealing surface	Critical	8-22
		Potentially impacting machinability, posing no risk to CCI	Any	Major B	
		No potential to impact CCI or Machinability	Any	Minor	
Split (aka Tear)	Disruption in continuity of elastomer surface.	Risk to CCI	Sealing Surface	Critical	8-23
		Potentially impacting machinability, posing no risk to CCI	Any	Major B	
		No potential to impact CCI or Machinability	Non-Sealing Surface	Minor	
Sponge	Porous area on the surface of the stopper where air was not removed during molding process.	Potentially impacting machinability, posing no risk to CCI	Non-sealing Surface	Major B	8-24
		No potential to affect CCI or machinability	Non-sealing Surface	Minor	
Surface Feature – Missing or Incomplete	An incomplete mark (ie tool identification, space or target ring) when specified on drawing.		Top surface of Flange	Minor	8-25
Surface Finish Variation	Smooth or rough surface (inconsistent surface condition).		Any	N/A, unless specified	8-26
Surface Imperfections	Cosmetic flaw on the surface caused by damaged mold cavities (scratches, pits, blister or dents).		Any	Minor	8-27
Trim Defect – Excessive Trim Lip	Excessive portion of webbing remaining after trimming > 0.254 mm / 0.010 inch. May impact machinability or capping.		Flange	Major B	8-28
Trim Defect – Off Cut Flange	Removed portion of stopper flange.	Risk to CCI	Flange	Critical	8-29
		No potential to affect CCI or machinability		Minor	
Trim Defect – Rough Trim Edge	Irregular trim surface.		Flange	Minor	8-30
Trim Defect – Fringed Trim Edge (aka Tails, Yarn)	Threads of elastomer attached to stopper at trim edge with the potential to become loose and enter product vial.		Flange	Major A	8-31

Nonconformity Lexicon



8.0 Appendix A: Elastomeric Vial Stopper Nonconformity Lexicon

Figure 8-1 Bloom

Location: Any Class: Minor

Formulation ingredients that migrate and accumulate on the surface.

Figure 8-2 Clumping – Adhered

Location: Any Class: Major B

Two or more parts adhered or sticking together, impacting machinability.

Figure 8-3 Clumping – Intertwined/Twins

Location: N/A Class: Major B

Parts that are mechanically interlocked, impacting machinability.

Location: Non-Product Contact Surface Class: N/A

Ripples in the film that are a cosmetic defect, not interfering with function of stopper.

Figure 8-7 Concentricity (lack of Concentricity)

Location: Plug/Flange Interface Class: Major B or Critical

Visually apparent off-set or off-centered plug (can be confirmed by concentricity measurement). Can be critical defect if risk to CCI.

Figure 8-11 Embedded Material (Extrinsic)

Location: Any Class: Critical

Foreign material not part of elastomer formulation or degraded/reverted elastomer which is partially or completely embedded in the component.

Figure 8-12 Embedded Material (Intrinsic)

Location: Any Class: Minor

An ingredient of the elastomer formulation not dispersed, partially or completely embedded in the component.

Figure 8-13 Flash

Location: Any Class: Minor

Excessive material attached to stopper created during the molding process.

Nomenclature- Aluminum Seal Components

Figure 4.2.1-1 Composition of a Vial Seal

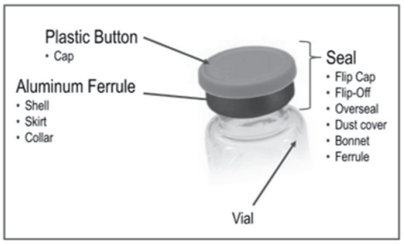
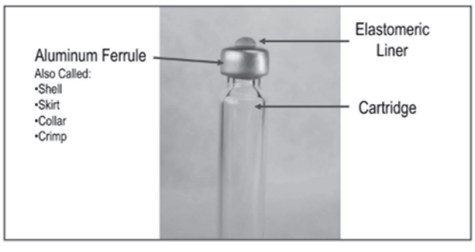


Figure 4.2.1-2 Composition of a Lined Seal



Aluminum Seal Nonconformity

Table 4.2.2-1 Aluminum Seal Nonconformity List

Nonconformance	Description	Location	Classification	Figure #
Bent, Crushed, or Out of Round	Deformation caused by external force resulting in the ferrule becoming misshapen to prevent machinability.	Ferrule	Major B	9-1
Bite Mark	Piece of aluminum removed by the forming equipment.	Ferrule	Minor	9-2
Broken Bridges	Bridges of the ferrule which have lost integrity prior to removal of the plastic button.	Ferrule	Major A	9-3
Burrs	Thin ridge or area of roughness produced during cutting or shaping of metal; irregular shaped aluminum on edge, often on Inner Diameter (ID), notch or hole (not resulting in loose aluminum/slivers).	Ferrule	Major B if large; Minor if small	9-4
Earring	The formation of scallops around the edge of the seal skirt.	Ferrule	Major B if specified % of overall height	9-5
Incomplete or Incorrect Feature	A design feature designated in the drawing is incomplete or incorrect.	Ferrule	Major A	9-6
Incomplete Score	Due to the score not being complete or not deep enough, the seal does not fracture properly.	Ferrule	Major A	9-7
Lacquer Incomplete	An interruption in the lacquer surface. Can include thin, swirled, uneven, or chipped lacquer.	Ferrule	Major B	9-8
Lacquer Missing or Incorrect	Lacquer is absent from surface or incorrect color.	Ferrule	Critical	9-9
Lacquer Scratches	Scratches in the lacquer coating exposing aluminum to environmental effects.	Ferrule	Minor	9-10
Lip	A localized aluminum protrusion which extends past the edge of the ferrule.	Ferrule	Major B	9-11
Missing, Insufficient, or Excessive Groove	Groove in aluminum is absent, too shallow, or too deep.	Ferrule	Major B	9-12
Missing Score or Bridges	Lack of an intended design attribute (either score or bridge) that is necessary in order for the seal to function appropriately.	Ferrule	Major A	9-13
Projection / Protrusion	Removal of the button causes raised metal around target area. Also called "cheese grater effect". Creates potential for hazards for practitioner, such as a torn glove.	Ferrule	Major A	9-14
Pull Through	Pull-through occurs when the button is removed but the aluminum bends rather than break the aluminum bridges/score to expose the target area.	Ferrule	Major A	9-15
Wrinkles	Vertical folds in the aluminum generated by the forming process.	Ferrule	Major B	9-16
Chipped or Broken Button	Damage to the button including a section or fragment that has been physically detached from the whole.	Button	Minor; Major B if impacting machinability	9-17
Damaged, Incomplete, or Small Melt	Melt that is missing a portion, or the diameter is not sized as specified.	Button	Major A	9-18
Embeded Contamination	Foreign substance on the surface or within the plastic that cannot be removed.	Button	Minor	9-19
Flash	Includes long gates, long injection site, or other excess plastic material.	Button	Major B	9-20
Incomplete Button	Also referred to as a "short shot". Includes sunken plastic injection sites or other lack of plastic material.	Button	Major B	9-21
Lifted Finger(s)	One or more fingers of the button which are not flush with the surface of the aluminum.	Button	Minor	9-22
Mangled Buttons	Buttons that are mangled during the assembly process by getting caught in assembly equipment. Will not machine in filling equipment.	Button	Major B	9-23
Missing or Damaged Fingers	Fingers of the button which are no longer present or misshapen prior to removal of the plastic button, but does not cause lack of function.	Button	Major B	9-24
Plastic Color Variation	Includes variation in color (streaks, blotches, swirled, etc) or samples exceeding agreed to color standards.	Button	Minor	9-25

Table 4.2.2-1 Continued

Nonconformance	Description	Location	Classification	Figure #
Printing Incomplete, Missing, or Illegible	Printing either not present, not complete, or not able to be read when required by the product drawing. Defect critical if printing is for patient safety purposes per USP<1>.	Button	Critical (patient safety); or Major A	9-26
Contamination (Non-Biologic)	Processing aids (grease or lubricants) inherent to the manufacturing process or extrinsic material.	All	Minor	9-27
Intermix	Stranger item within a carton or shipment of product.	All	None Allowed	9-28
Inverted Assembly	During the assembly process, the shell is assembled to the button incorrectly.	All	Major B	9-29
Unassembled	Absence or loss of attachment between the ferrule and button such that the flip cap is no longer a merged unit.	All	Major B	9-30
Visible Aluminum Particulate	A loose aluminum fragment that is present on the surface of the product.	All	Critical for Lined Seals; Minor otherwise	9-31
Inverted Liner Material	Laminated liner inserted wrong side up.	Lined Seal	Critical	9-32
Missing or Multiple Liner	Liner material not present or multiple liners present.	Lined Seal	Major B	9-33
Incomplete Liner	Off cuts of elastomeric liner, also called "mouse bites".	Lined Seal	Critical	9-34
Liner Loose or Not Flush	A liner which is not properly positioned or not fixed in the position that is dictated in the product drawing.	Lined Seal	Minor	9-35

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Nonconformity Lexicon

9.0 Appendix B: Aluminum Seal Nonconformity Lexicon

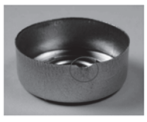
Figure 9-1 **Bent, Crushed, or Out of Round**

Location: Ferrule — Class: Major B

Deformation caused by external force resulting in the ferrule becoming misshapen to prevent machinability.

Figure 9-2 **Bite Mark**

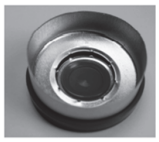
Location: Ferrule — Class: Minor



Piece of aluminum removed by the forming equipment.

Figure 9-3 **Broken Bridges**

Location: Ferrule — Class: Major A



Bridges of the ferrule that have lost integrity prior to removal of the plastic button.

Figure 9-7 **Incomplete Score**

Location: Ferrule — Class: Major A

Due to the score not being complete or not deep enough, the seal does not fracture properly.

Figure 9-8 **Lacquer Incomplete**

Location: Ferrule — Class: Major B

An interruption in the lacquer surface. Can include thin, swirled, uneven, or chipped lacquer.

Figure 9-9 **Lacquer Missing or Incorrect**

Location: Ferrule — Class: Critical

Lacquer is absent from surface or incorrect color.

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Acknowledgement / Reference

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- Merck, Development of TopLoad Drone for Stopper Compression and Residual Force (RSF) ; Jeff Cremi
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- And …