



# Glass Handling Best Practices for Glass Primary Containers

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- Course Overview

- 1 Requirements for incoming inspection  
(Pharmacopoeia requirements)
- 2 How to do it in practice
- 3 What to consider or to avoid (case studies)
- 4 Coordination process between packaging  
manufacturer and customer

- General Remarks

- Packaging is an integral part of a pharmaceutical product
- It affects quality, stability and identification of drug product
- Provides an adequate degree of protection (air, humidity, light)
- Should not interact physically or chemically with drug product
- No risk of toxicity



## ● General Remarks

- Quality requirements for primary glass container for drug product filling are continuously increasing
- Fast running filling lines require smooth supply of packaging components
- Supply of material from different suppliers may result in certain variations within agreed tolerances, which may require re-adjustments of filling lines
- Special requirements for
  - Pen-Systems or Auto-Injectors
  - New products (Biologicals) or special applications



- Overview

- 1 Requirements for incoming inspection**
- 2 How to do it in practice
- 3 What to consider or to avoid (examples)
- 4 Coordination process between packaging manufacturer and customer





- Content
  - Legal Requirements
  - Acceptance Criteria & Test Parameter
  - Test Methods
  - Documentation
  - Defect Evaluation Lists / Technical Report

- EU GMP Guideline, Part I, Chapter 1



⇒ ***Pharmaceutical Quality System***

*Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain*

- EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines



## ANNEX 8

### SAMPLING OF STARTING AND PACKAGING MATERIALS

#### Principle

*Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.*

#### Packaging material

*5. The sampling plan for packaging materials should take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and what is known of the **Quality Assurance system** of the **packaging materials manufacturer** based on audits. The number of samples taken should be determined statistically and specified in a sampling plan.*



- Code of Federal Regulations 21 CFR 211  
Sec. 211.80 General requirements



- (a) *There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and **drug product containers** and closures; such written procedures shall be followed.*
- (d) *Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).*

- Code of Federal Regulations 21 CFR 211

Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures



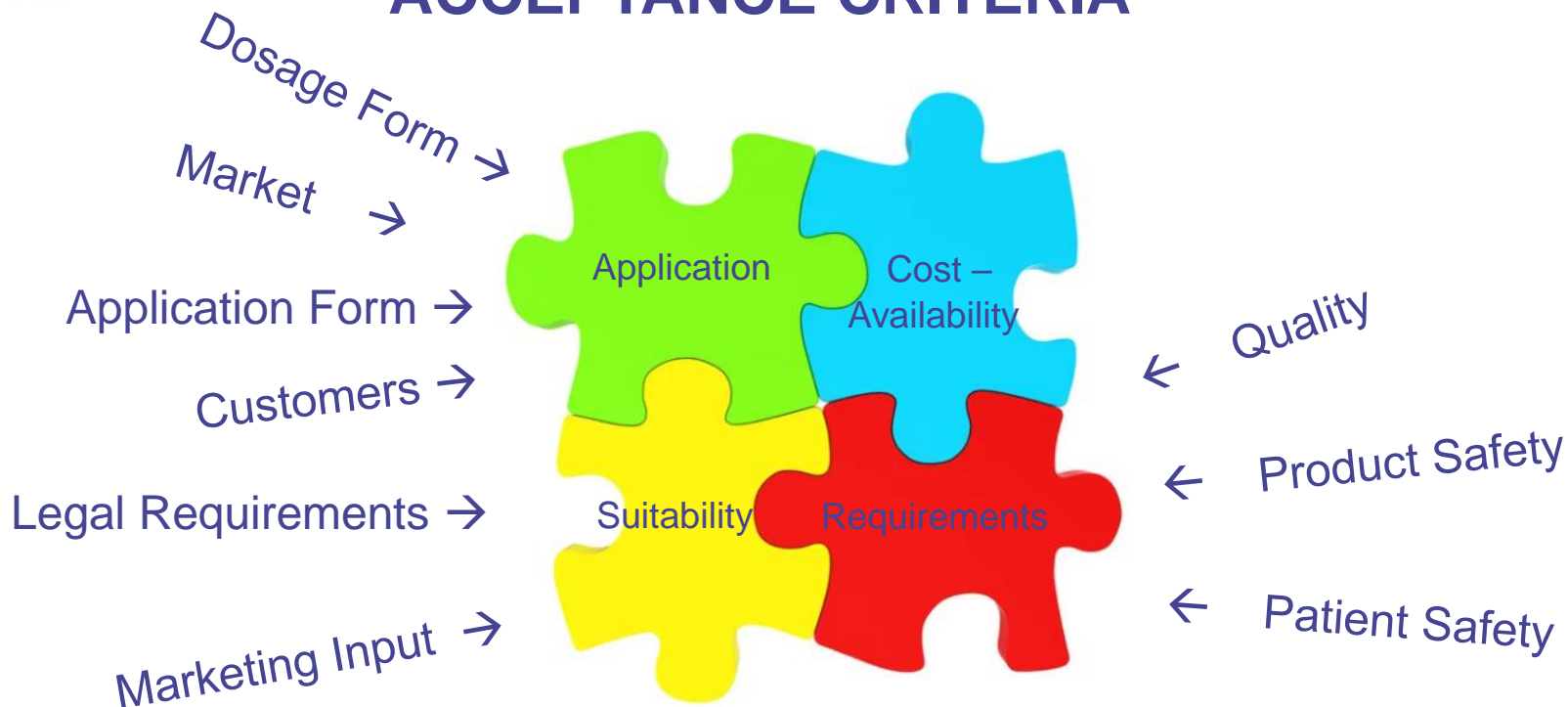
(5) *Sample containers shall be identified so that the following information can be determined:*

- *name of the material sampled,*
- *the lot number,*
- *the container from which the sample was taken,*
- *the date on which the sample was taken, and*
- *name of the person who collected the sample.*

*...Containers and closures shall be tested for conformity with all appropriate written specifications. ...*

- Specifications / Acceptance Criteria
  - What are acceptance criteria?
  - Who specifies these criteria?
  
- Test Parameter
  - Definition of test parameter
  
- Test Methods
  - Identification of methods based on test parameter

## ACCEPTANCE CRITERIA



**Nobody knows it better than you!**

## ACCEPTANCE CRITERIA

... based on the intended use of the glass container

- Dosage form?
- Which markets? EU – US – JP - other
- Kind of application? Oral, Parenteral, Inhalation
- Legal regulations & laws? AMG, Ph.Eur., USP, JP, CHP, cGMP

## TEST PARAMETER

... can be defined based on Acceptance Criteria

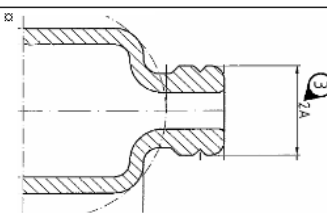
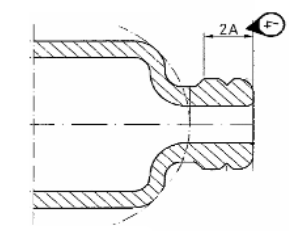
<ul style="list-style-type: none"> <li>Physical / Chemical</li> </ul>	Pharmacopeia Regulations Standards
<ul style="list-style-type: none"> <li>Microbiological</li> </ul>	Pharmacopeia Internal conditions
<ul style="list-style-type: none"> <li>Dimensional</li> </ul>	Technical drawings Engineering standards Product & process requirements
<ul style="list-style-type: none"> <li>Visual - Inspection by attributes</li> </ul>	Product & process requirements PDA Technical Report 43 Defect Evaluation List

## TEST PARAMETER

- Requirements from pharmacopeias, regulations and defect evaluation lists are important and can be used in general
- Specific requirements may need to be defined individually and mutually agreed with the supplier!
- Supplier data may complement or replace incoming test parameter (risk-based approach)





- Example of an individual defect categorization

Maß-Nr. □	Technical Drawing	Nomenclature	Risk prod technical	Classification
3#		Flange (Collar) Outside Diameter	<input type="checkbox"/> 1# <input checked="" type="checkbox"/> 2A# <input type="checkbox"/> 2B# <input type="checkbox"/> 3#	Potential Impact on Container Closure Integrity
4#		Flange (Collar) Height	<input type="checkbox"/> 1# <input checked="" type="checkbox"/> 2A# <input type="checkbox"/> 2B# <input type="checkbox"/> 3#	Potential Impact on Container Closure Integrity

A joint risk assessment of packaging components with manufacturing can also increase the acceptance of incoming inspection activities!



Description Fehlerbeschreibung	Category / Kategorie	AQL-Level	EXAMPLES / BEISPIELE		
			Comment / Bemerkung	Defect sample / Schlechtmuster	Sample according to specification / Gutmuster
Form burrs and scars > 1 mm <sup>2</sup> on the outer surface of the glass barrel; closure integrity not impaired  <i>Formmarken und narbige Erscheinungen &gt; 1 mm<sup>2</sup> auf der Glaskörperaußenoberfläche; Dichtigkeit nicht beeinträchtigt</i>	cosmetic  <i>kosmetisch</i>	6.5	Marks on head of cartridge  <i>Rattermarken am Konus</i>		
			Wrinkles on head of cartridge  <i>Quetschfalten am Bördekkopf</i>		

Define the risk of the individual parameter and acceptance level!

- **Test Methods** finally derive from established **Test Parameter**
  - Accuracy of the method
    - Tolerance (decimal place) of dimensions in the technical drawing?
  - Extent of inspection
    - What needs to be tested for individual batches (inspection level)?
    - Supplier data on Certificate of Analysis
  - Test interval
    - Complete / reduced testing
    - Identity, monitoring or skip lot?



- CHEMICAL TESTING

- Determination of the hydrolytic resistance is an important parameter to guarantee the quality of the glass composition.

- **Just to resume ...**

Type I glass: borosilicate; only for tubing; in compliance with Pharmacopeia requirements for injectable liquids because of its high chemical durability; lower thermal expansion; flint or amber

Type II glass: soda-lime treated on inner surface ( 0.5 mm) to remove free alkali ions; high chemical durability; only for tubing; high thermal expansion; non suitable for injectable liquids; only light amber

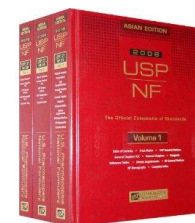
Type III glass: soda-lime; moderate chemical durability; for tubing and molding; high thermal expansion; non suitable for injectable liquids; variously colored.

- **CHEMICAL TESTING**

## Relevant USP Glass Testing Procedures

USP/NF Section <660> Type I Highly Resistant Borosilicate Glass

- Hydrolytic Resistance – Glass Grains
- Surface Glass Test
- Arsenic USP <211>
- Light Transmission (Amber)



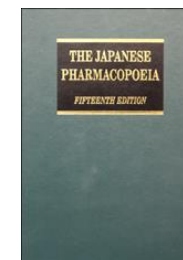
## Relevant European Pharmacopeia

EP 3.2.1 Glass Containers for Pharmaceutical Use

## Relevant Japanese Pharmacopeia

JP 7. Test for Containers and Packaging Materials

7.01 Test for Glass Containers for Injections



- MICROBIOLOGICAL TESTING

## Endotoxin- / Bioburden- Testing



Endotoxin

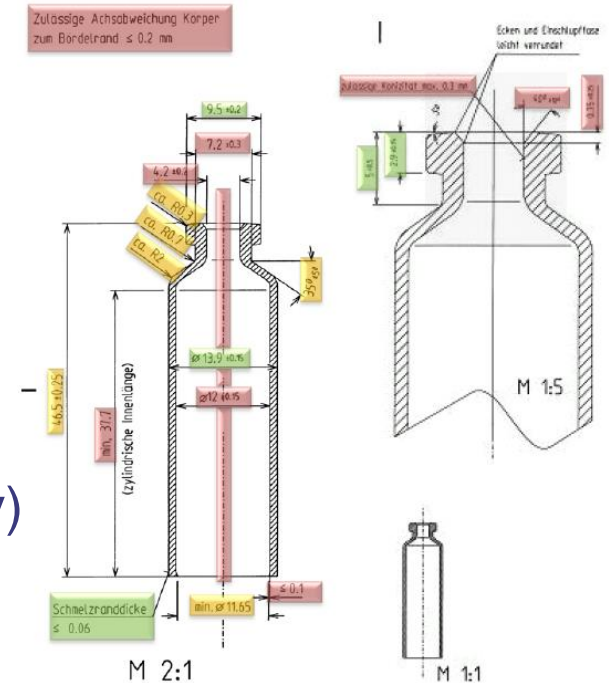
LAL-Test (according to Ph. Eur. 2.6.14 ; USP <85>, JP)

Bioburden

(according to Ph. Eur. 2.6.1; USP <71>, JP)

## ● DIMENSIONAL TESTING

- Caliper
- Micrometer caliper
- Outside micrometer
- Plug gauge
- Profile projector (manual or electronically)
- Electronic camera measuring system



- VISUAL INSPECTION - INSPECTION BY ATTRIBUTES

- Special attention should be taken on visual nonconformities to align incoming inspection parameters with the relevant control units of the filling / inspection lines

- Defects are described and classified

- PDA Glass Task Force Technical Report 43
- Edito Cantor Defect Evaluation List



- These reports provide a general overview of defects including a classification of the potential criticality

## CRITICAL - MAJOR - MINOR

to support a quality decision-making process

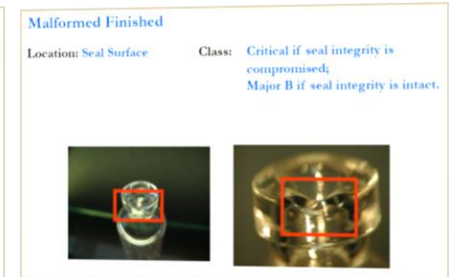
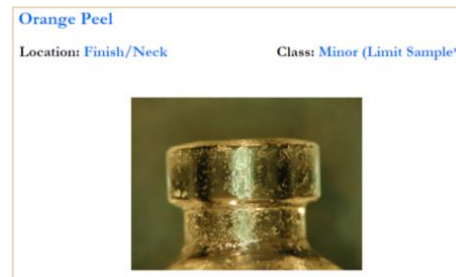
- The characteristics of these defects can vary, therefore the acceptance level should be individually defined
- The sensitivity of camera control units should also be taken into consideration
- Defects may not be equally distributed across the batch manufacturing process (nested)

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Excerpt TR 43 PDA Glass Task Force

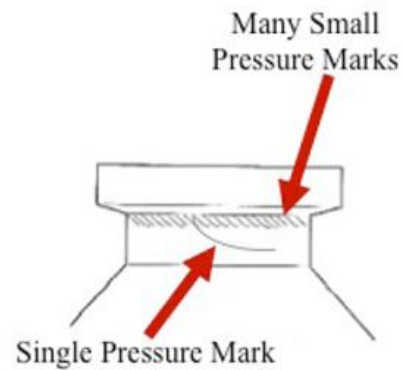
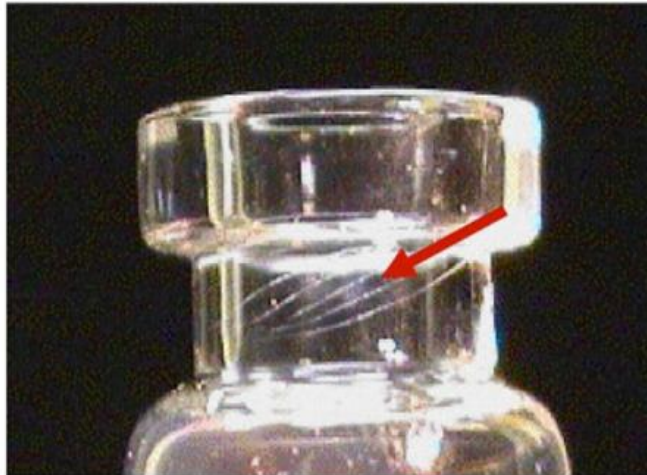




### Glass Nonconformity Lexicon (PDA TR 43)

<b>CRITICAL</b>	<i>A Nonconformity that is likely to result in personal injury or potential hazard to the patient (including defects that compromises the integrity of the container)</i>
<b>MAJOR A</b>	<i>... leading to serious impairments e.g. a malfunction that makes the packaging unusable</i>
<b>MAJOR B</b>	<i>Impairments of a lesser degree e.g. reduced efficiency in production</i>
<b>MINOR</b>	<i>Nonconformity that does not impact product quality or process capability</i>
<b>N/A</b>	<i>An imperfection not classified as nonconformity</i>

- The characteristics of defects can vary



Surface diagonal lines around the neck that may give a feathery or frosty appearance.

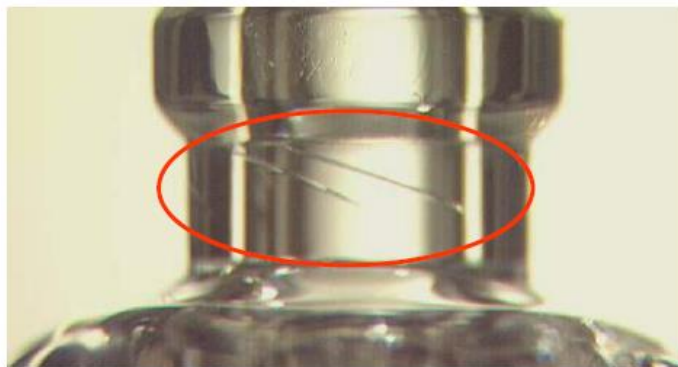


- Minor defects can result in significant disruption and yield losses on the filling / inspection lines

## Folds

Location: Neck

Class: Minor (Limit Sample\*)



Excerpt TR 43 PDA Glass Task Force

- Sampling for Incoming Inspection

- 21CFR820.250 – Statistical Techniques

- “(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

- (b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.”

- Defects and Acceptance Levels
  - Prevailing method for evaluation of defects:  
Commonly used Acceptance Sampling Plans
  - Widely used sample inspection system originally developed as U.S. military standard 105E plans
  - The AQL system (Acceptable Quality Limits) has been accepted by national and international quality associations (DIN ISO Norm 2859, ASQ/ANSI)
  - Provides acceptance and rejection rates based on normal statistical distribution



- Defects and Acceptance Levels
  - Control Sample Unit (Tailgate samples) is important for evaluation of a batch
  - Samples should be representative and randomized across the entire batch
  - Sampling often delegated to supplier
  - The number of samples for incoming inspection depends on batch size and defined AQL
  - AQL represents the percentage of defects routinely accepted

- DIN ISO 2859 has different levels for reduced, normal and tightened inspection
- Influencing on the certainty when accepting or rejecting material and the inspection cost

Losumfang	Special Inspection Levels				General Inspection Levels		
	S 1	S 2	S 3	S 4	I	II	III
2 Lot Size	A	A	A	A	A	A	B
9 bis 15	A	A	A	A	A	B	C
16 bis 25	A	A	B	B	B	C	D
26 bis 50	A	B	B	C	C	D	E
51 bis 90	B	B	C	C	C	E	F
91 bis 150	B	B	C	D	D	F	G
151 bis 280	B	C	D	E	E	G	H
281 bis 500	B	C	D	E	F	H	J
501 bis 1 200	C	C	E	F	G	J	K
1 201 bis 3 200	C	D	E	G	H	K	L
3 201 bis 10 000	C	D	F	G	J	L	M
10 001 bis 35 000	C	D	F	H	K	M	N
35 001 bis 150 000	D	E	G	J	L	N	P
150 001 bis 500 000	D	E	G	J	M	P	Q
500 001 und mehr	D	E	H	K	N	Q	R

Excerpt DIN ISO 2859

- Code letter defines the number of Tailgate Samples for inspection
- Acceptance / rejection numbers are listed in the AQL columns



Tabelle 2-A - Single Sampling Plan (Normal Inspection)

Kennbuchstabe für den Stichprobenumfang	Stichprobenumfang	Annehmbare Qualitätsgrenzlage, AQL, in Anteil fehlerhafter Einheiten in Prozent und Anzahl Fehler je 100 Einheiten (normale Prüfung)																											
		0,010	0,015	0,025	0,040	0,065	0,10	0,15	0,25	0,40	0,65	1,0	1,5	2,5	4,0	6,5	10	15	25	40	65	100	150	250	400	650	1 000		
A	2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
B	3	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
C	5	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
D	8	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
E	13	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
F	20	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
G	32	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
H	50	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
J	80	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
K	125	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
L	200	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
M	315	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
N	500	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
P	800	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
Q	1 250	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	
R	2 000	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	

↓ - Man wende die erste Stichprobenanweisung unter dem Pfeil an. Ist der Stichprobenumfang gleich dem Umfang des Prüfloses oder größer, wende man 100%-Prüfung an.  
 ↑ - Man wende die erste Stichprobenanweisung über dem Pfeil an.  
 Ac - Annahmezahl  
 Re - Rückweiszahl

Excerpt DIN ISO 2859



- AQL 0.65

- Acceptance limit 10 - Rejection limit 11 defects
- 0.65% AQL Quality Statement:

“If you sample 800 and use the acceptance criteria to accept on 10, reject on 11, you have ~95% probability of accepting the batch if it contains 0.65% defects or less”

- In most cases Tailgate samples are pulled by the supplier during manufacturing
- Sampling is an important process
- Valid conclusions on the whole batch can only be made on representative samples
- Correct sampling is an essential part of the supplier Quality Assurance practice
- Samples are packed separately by the supplier and delivered with the batch shipment
- Sampling is delegated to supplier per contract, verification during audits & dual batch sampling





END OF PART 1

- Overview

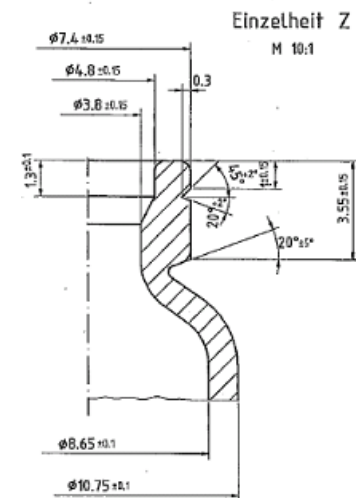
- 1 Requirements for incoming inspection
- 2 How to do it in practice
- 3 What to consider or to avoid (examples)
- 4 Coordination process between packaging manufacturer and customer



- Content
  - Specification
  - Sampling
  - Sample Size
  - Equipment, Tools
  - Documentation
  - Supplier Certification

## Specifications (EU-GMP; Cap. 4 )

- *Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation*
  
- *All documents describing the material belong to the specification*
  - *Technical Drawing*
  - *Material Characteristics*
  - *Regulatory Requirements (e.g. Ph. Eur.; USP; JP)*
  - *Test Parameter*
  - *Certification of Parameter*

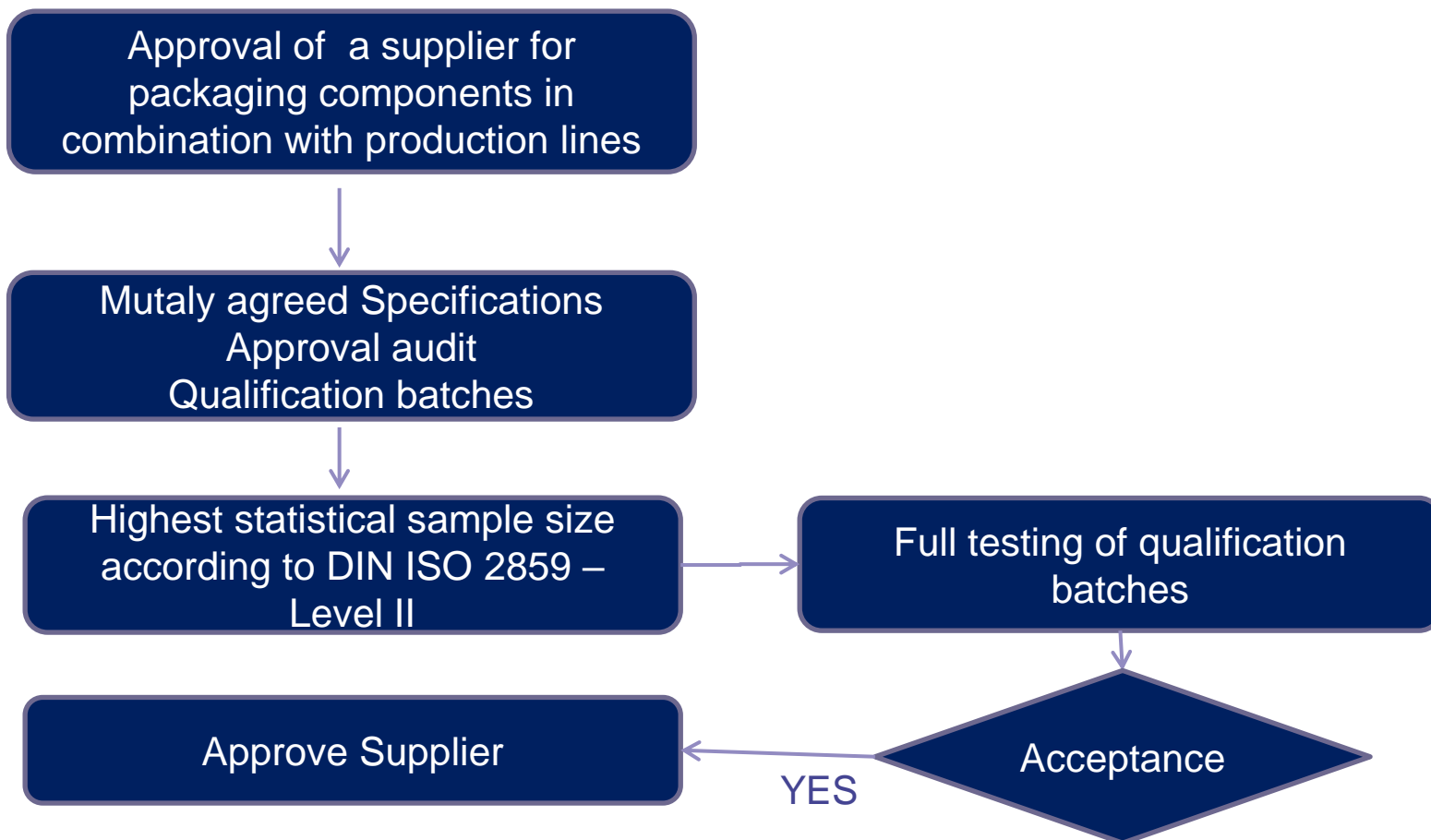


## Specifications (EU-GMP; Kap. 4 )

- Batch testing / release is based on these documents
- It is recommended to agreed on inspection methods upfront with supplier
  - Visual Inspection (limit sample, defect catalogue)
  - Specific methods not described in literature
  - Method comparison
  - Accuracy of measurement
  - Sample defect catalogue

**Quality Agreement!**

## Supplier Approval Process





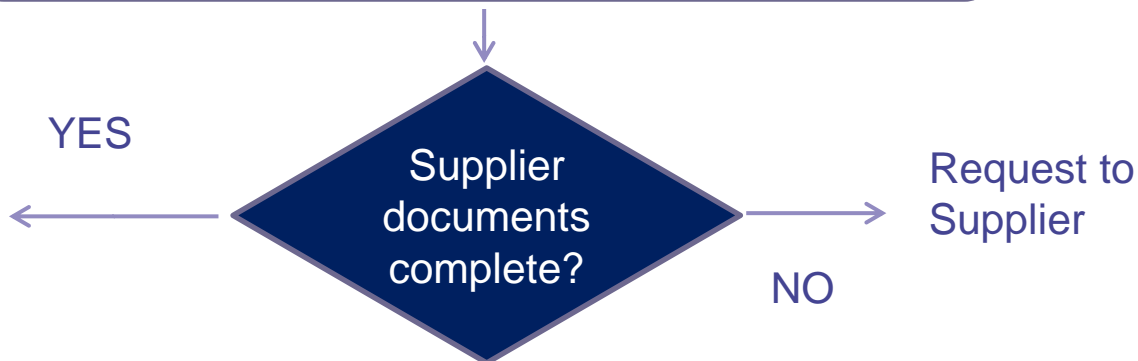
## Tailgate Samples with each Delivery

Samples collected by supplier in accordance to DIN ISO 2859 Level II and agreed Packaging Specification / Sampling delegation

Samples send with batch delivery

Delivery of batch including  
Certificate of Analysis

Booking process  
creates test  
protocol, with all  
parameter for  
incoming control  
testing /  
documentation



## Index of a Packaging Material Specification (Example)

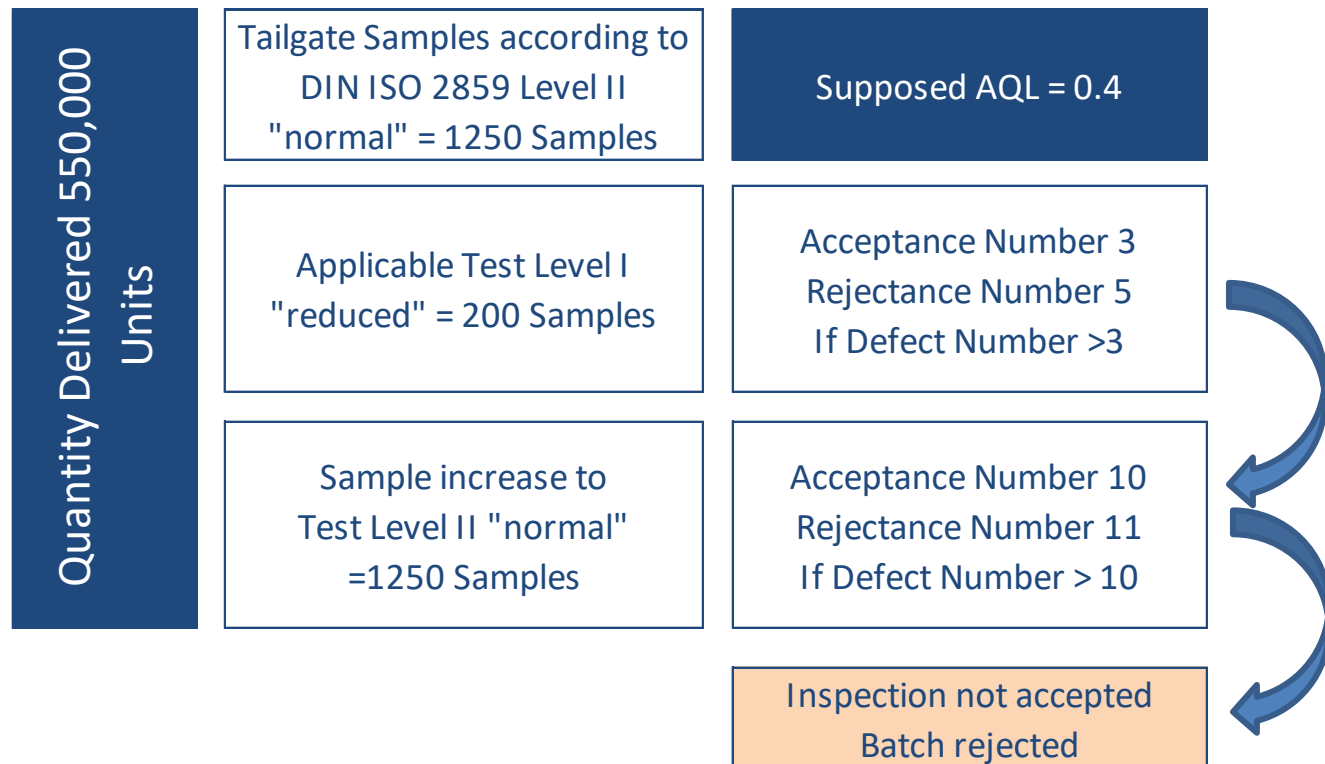
1. Material Specific Chapter – Technical Drawing
2. General Chapter
  - 2.1 Material & Design
  - 2.2 References & Standards
  - 2.3 Packaging Instructions
  - 2.4 Quality Acceptance Criteria
  - 2.5 Supplier control samples (sampling plan)
3. Characteristics / Specifications
  - 3.1 Criteria for Batch Release
  - 3.2 Additional Criteria e.g. glass grain test annually
  - 3.3 Specific Criteria e.g. microbial testing
4. Sample Procedure & AQL Acceptance

... to be checked at delivery

- ⇒ Correct pallets used (heat treated)
- ⇒ Correct labeling
- ⇒ No visible transport damages
- ⇒ Documents complete (delivery note, certificate)
- ⇒ Correct supply chain (supplier - manufacturer)



## Example of a two phasic inspection approach (by attributes)



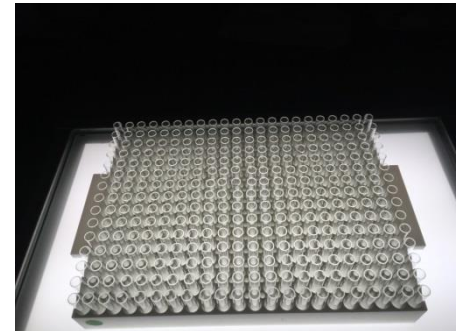
## Visual Inspection

- In order to standardize the inspection it can be helpful to use the method described in Ph. Eur. Method 2.9.20. Particulate Contamination: Visible Particles. Terms and conditions are defined.
  - Intensity of light
  - Duration under review
  - Viewing background



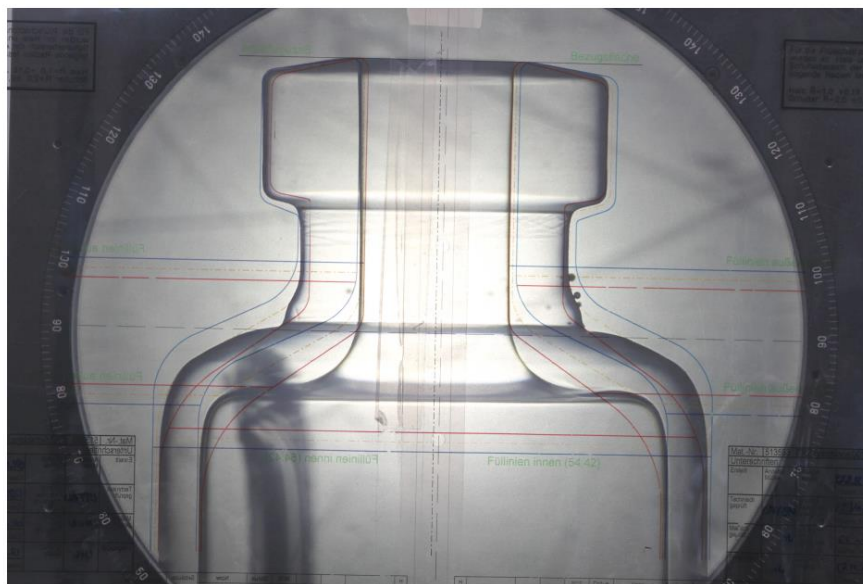
## Visual Inspection

- Documentation of inspection results
  - Reporting of individual inspection criteria e.g. scratches, cracks, dirt
  - One generic criteria, combined with a defect catalogue and the corresponding AQL



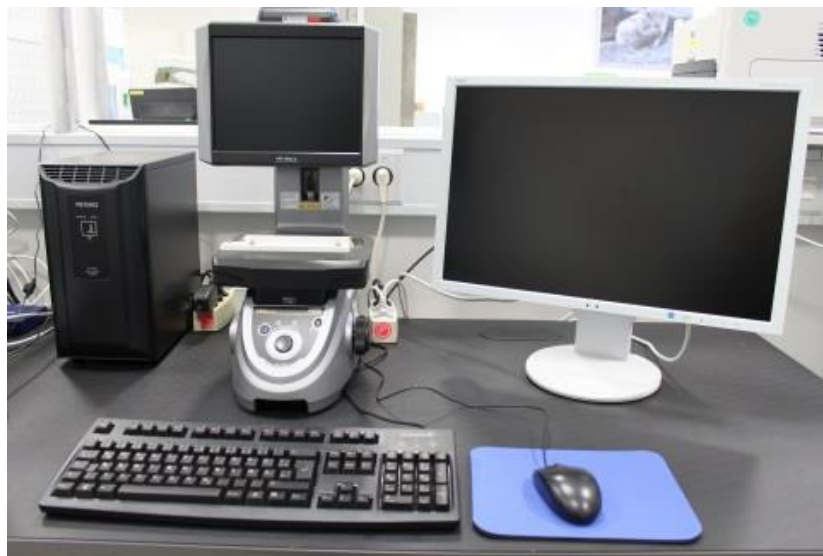
## Dimensional Inspection

- Manual Profile Projector: Dimensional evaluation with specification template without data storage



## Dimensional Inspection

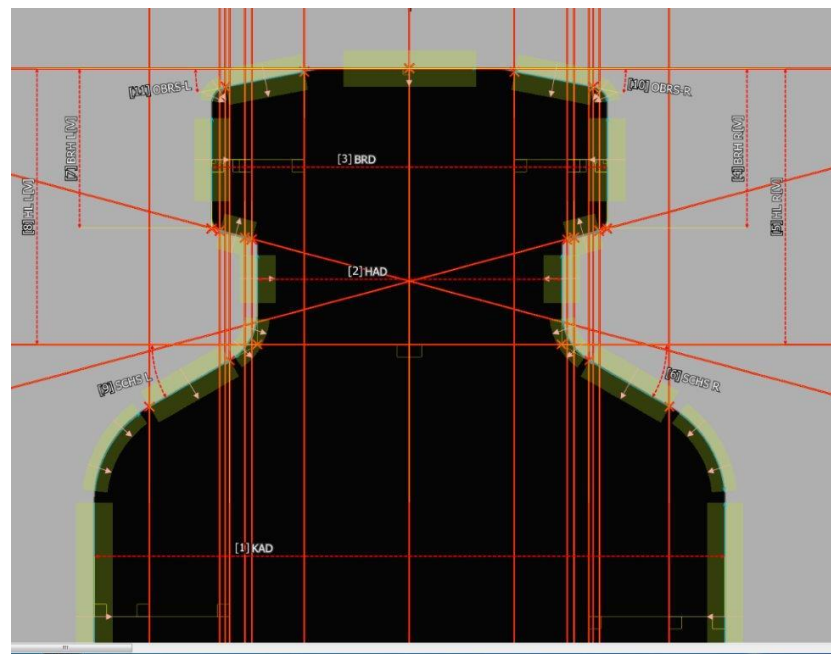
- Manual measuring devices or electronic camera systems





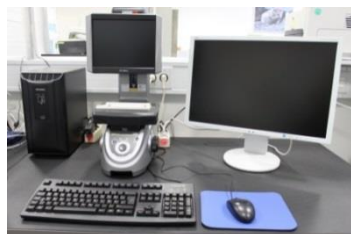
## Dimensional Inspection

- Set up of a camera system: Reference lines and intercept points to be defined
- Further developments for image processing



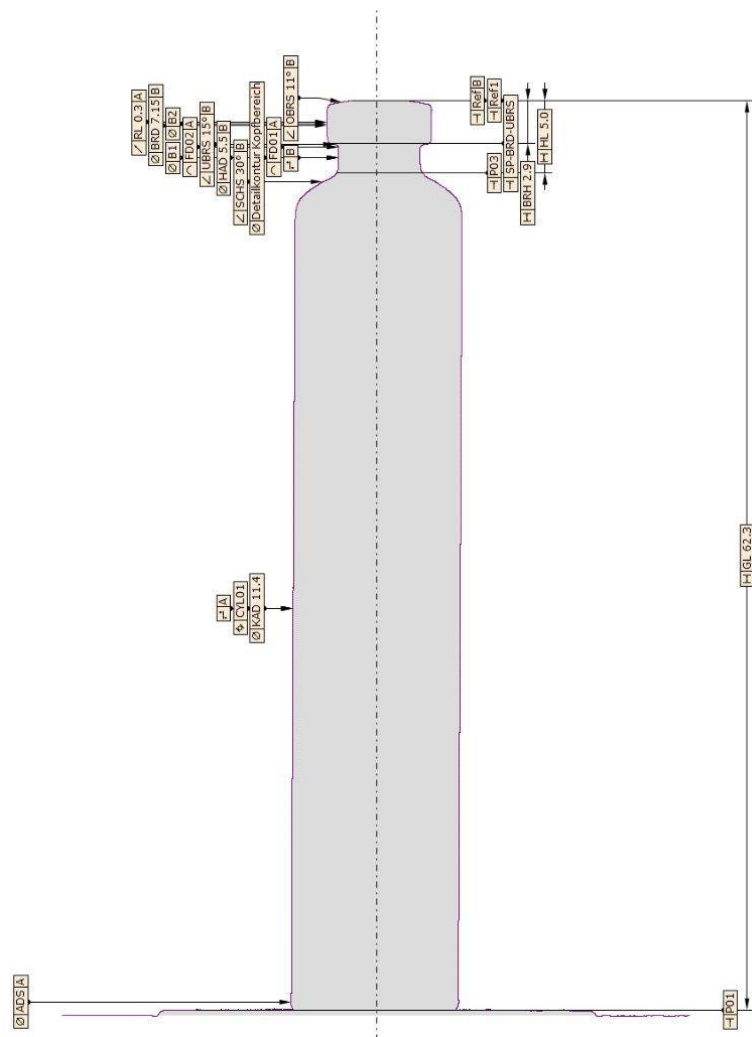
## Dimensional Inspection

2D 3D



## Dimensional Inspection

Unit of measurement	Characteristics
mm	Glazing ring diameter
mm	Body diameter
mm	Neck diameter
mm	Flange diameter
mm	Flange height
mm	Neck height
mm	Total length
°	Upper locking ring angle
°	Lower locking ring angle
°	Shoulder angle
mm	Excentricity



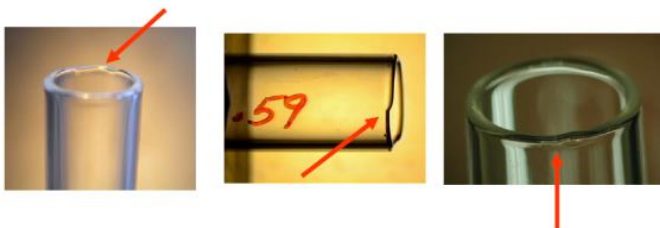
## Dimensional Inspection

- Three-dimensional rotation-symmetric results
- Contact-free measurement
- Evaluation of multiple parameter of complex bodies

### Bad Cut

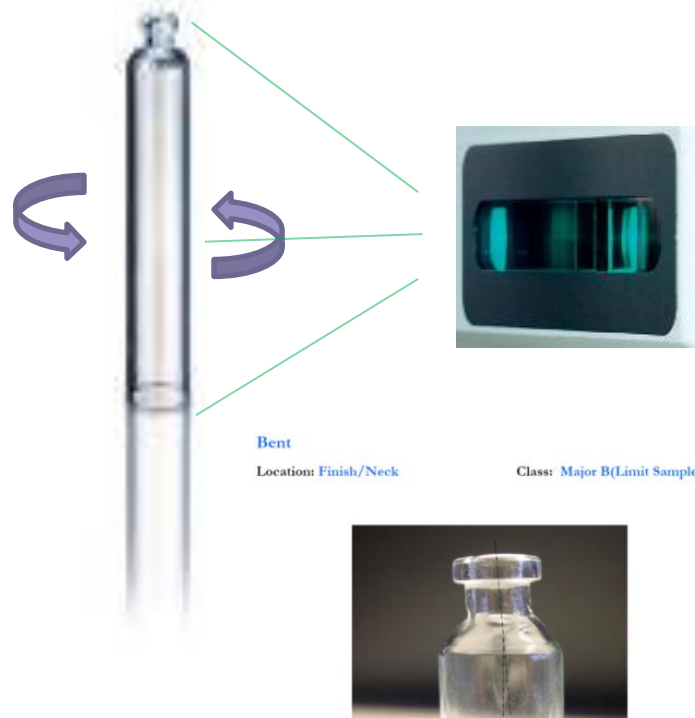
Location: Cut End

Class: Minor



Poor cut resulting in an irregular glazed end

### Rotating measurement



### Bent

Location: Finish/Neck

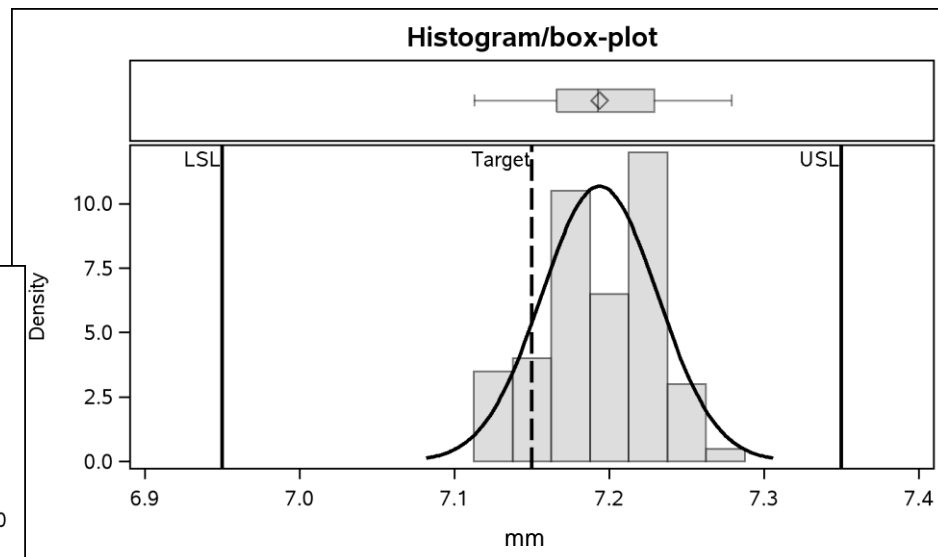
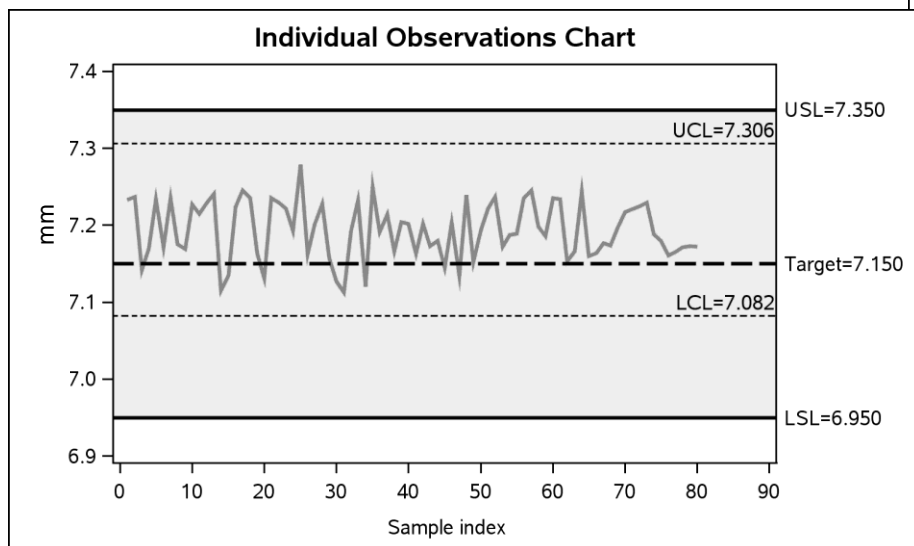
Class: Major B(Limit Sample\*)



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

## Dimensional Testing

### Results Collar Diameter



## ● Documents relevant for batch release

### • Supplier documentation

- Certificate
- Specifications
- Test Protocol
- Delivery slip



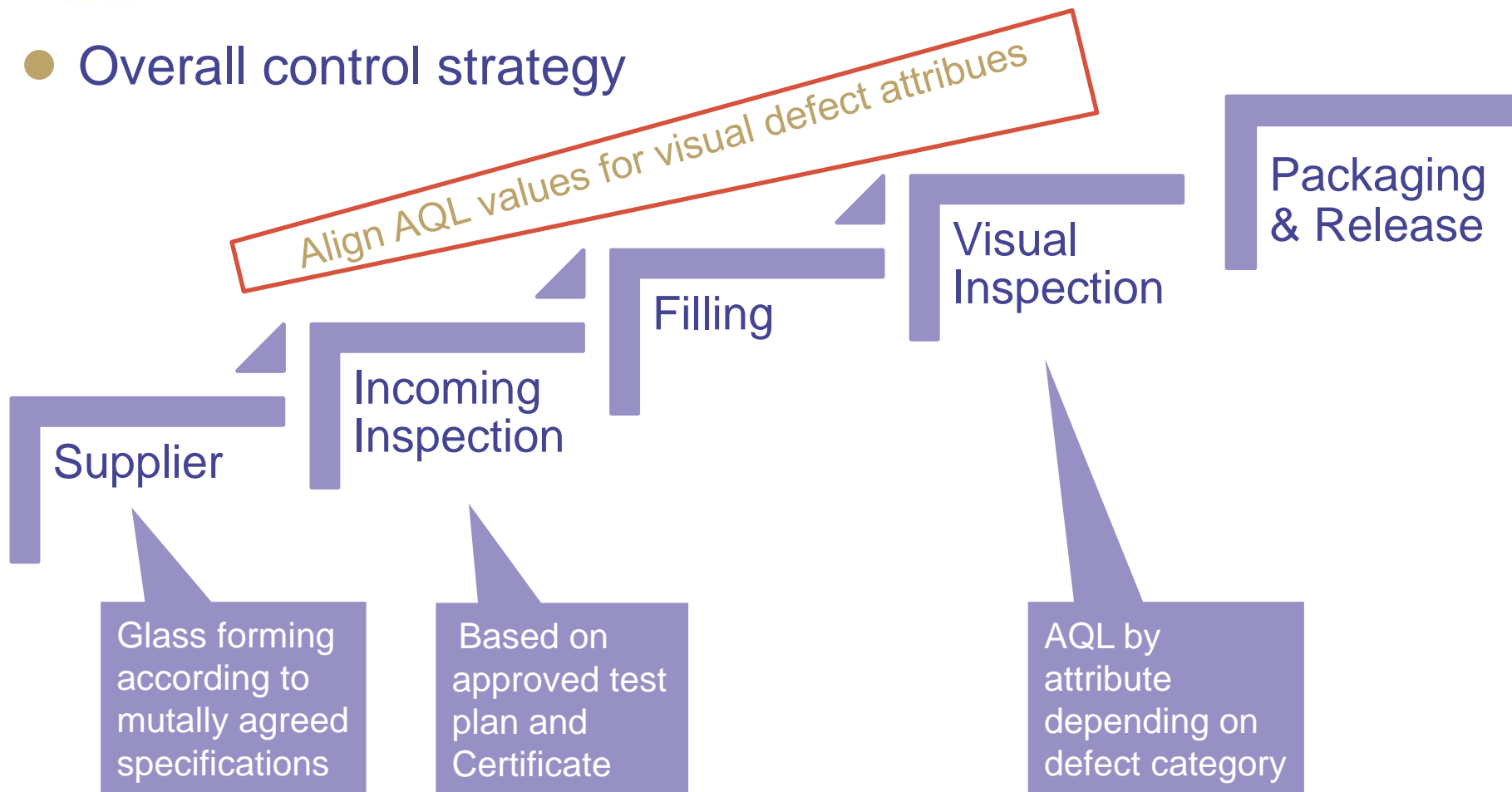
### • Test Methods

- Standard Operating Procedures
- Specifications
- Test Plan

### • Inspection documentation

- Dimensional Results
- Chemical Results
- Visual Results
- Test Protocols
- Log Books

- Overall control strategy





End of Part 2

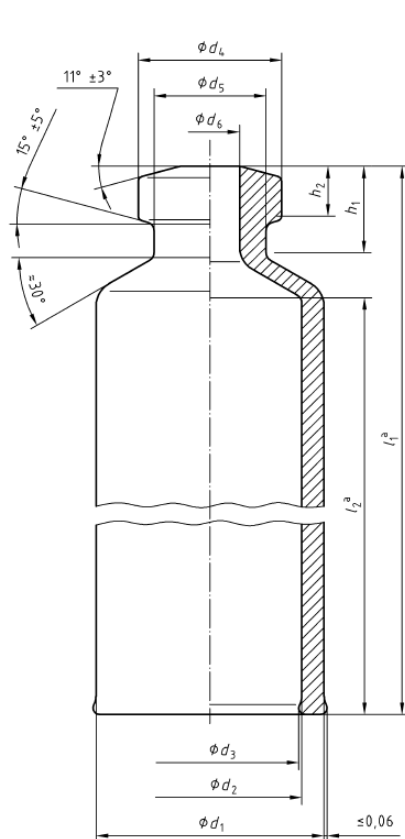


- Overview

- 1 Requirements for incoming inspection
- 2 How to do it in practice
- 3 **What to consider or to avoid (case studies)**
- 4 Coordination process between packaging manufacturer and customer



- Glass container for the pharmaceutical industry are standardized



Maße in mm  
Dimensions in mm

Maße in mm  
Dimensions in mm

$d_1$	Grenz-abm. tol. $\pm$	$d_2$	Grenz-abm. tol. $\pm$	$d_3$	$d_4$	Grenz-abm. tol. $\pm$	$d_5$	Grenz-abm. tol. $\pm$	$d_6$	Grenz-abm. tol. $\pm$	$h_1$	Grenz-abm. tol. $\pm$	$h_2$	Grenz-abm. tol. $\pm$
				min.										
8,65	0,1	6,85	0,1	6,55	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,85	0,1	8,65	0,1	8,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,95	0,15	9,25	0,1	8,95	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
11,60	0,15	9,65	0,1	9,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
14,00	0,15	12,00	0,15	11,65	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
14,45	0,15	11,85	0,15	11,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
18,25	0,15	16,05	0,15	15,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15

Excerpt DIN ISO 13926-1

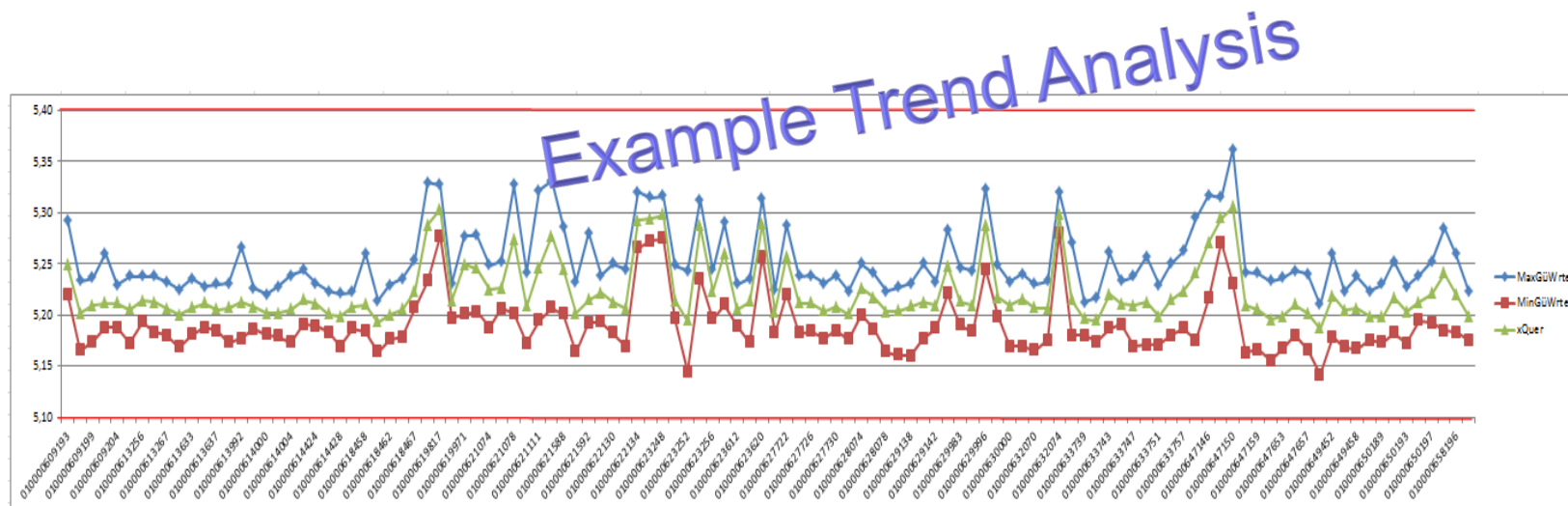
- However, these standardized tolerances might lead to unacceptable variances of certain dimensions especially on fast running filling lines
- See table h1 and h2 for flange height: This can result in variances of  $\pm 0,20$  mm to  $\pm 0,50$ mm depending on the format!

Maße in mm  
Dimensions in mm

$d_1$	Grenz-abm. tol. $\pm$	$d_2$	Grenz-abm. tol. $\pm$	$d_3$ min.	$d_4$	Grenz-abm. tol. $\pm$	$d_5$	Grenz-abm. tol. $\pm$	$d_6$	Grenz-abm. tol. $\pm$	$h_1$	Grenz-abm. tol. $\pm$	$h_2$	Grenz-abm. tol. $\pm$
8,65	0,1	6,85	0,1	6,55	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,85	0,1	8,65	0,1	8,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,95	0,15	9,25	0,1	8,95	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
11,60	0,15	9,65	0,1	9,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
14,00	0,15	12,00	0,15	11,65	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
14,45	0,15	11,85	0,15	11,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
18,25	0,15	16,05	0,15	15,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15

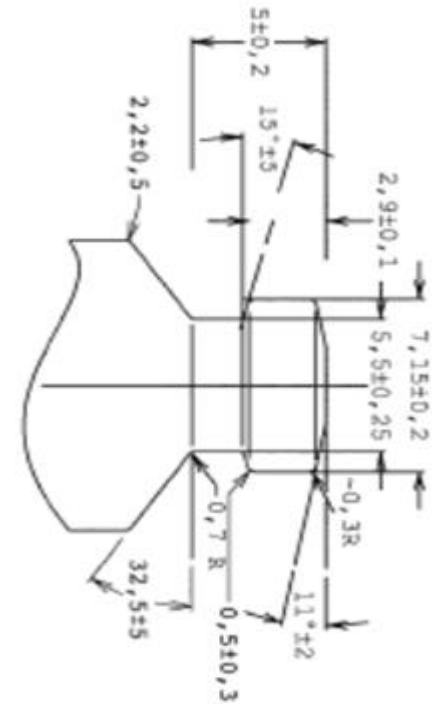
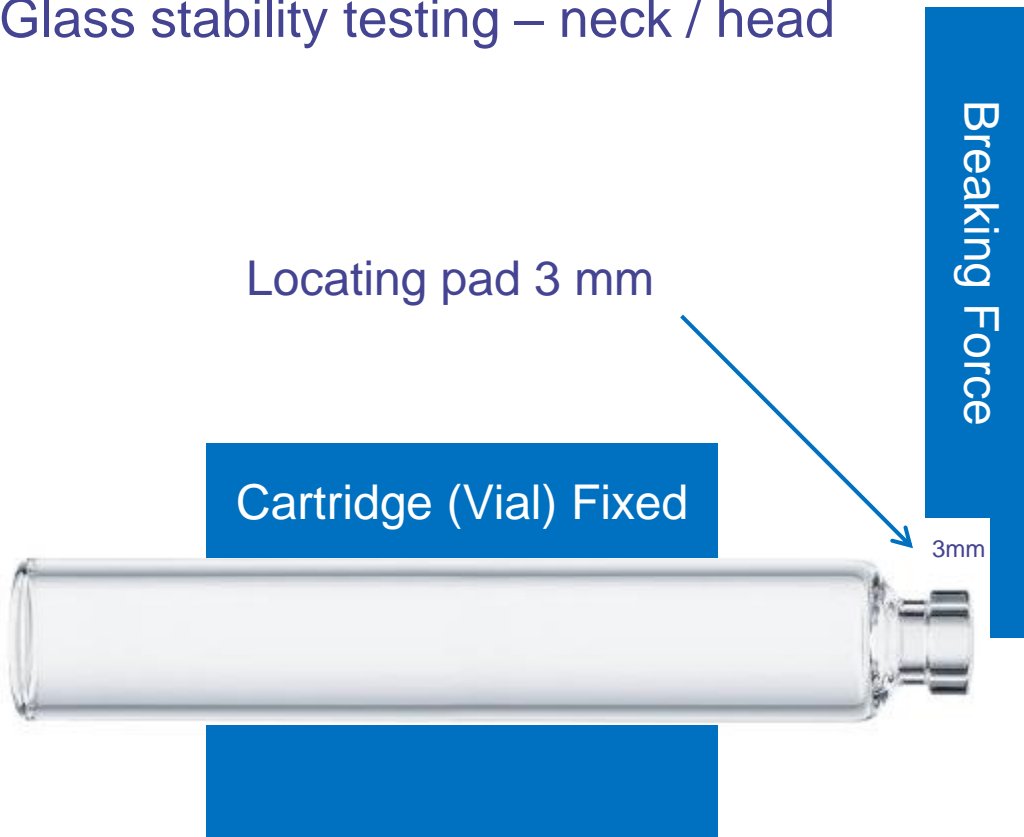
Excerpt DIN ISO 13926-1

- It can be important to know and understand the characteristics of the container of individual suppliers and their forming lines
- Monitoring of critical dimensional characteristics can give a good understanding of the packaging components

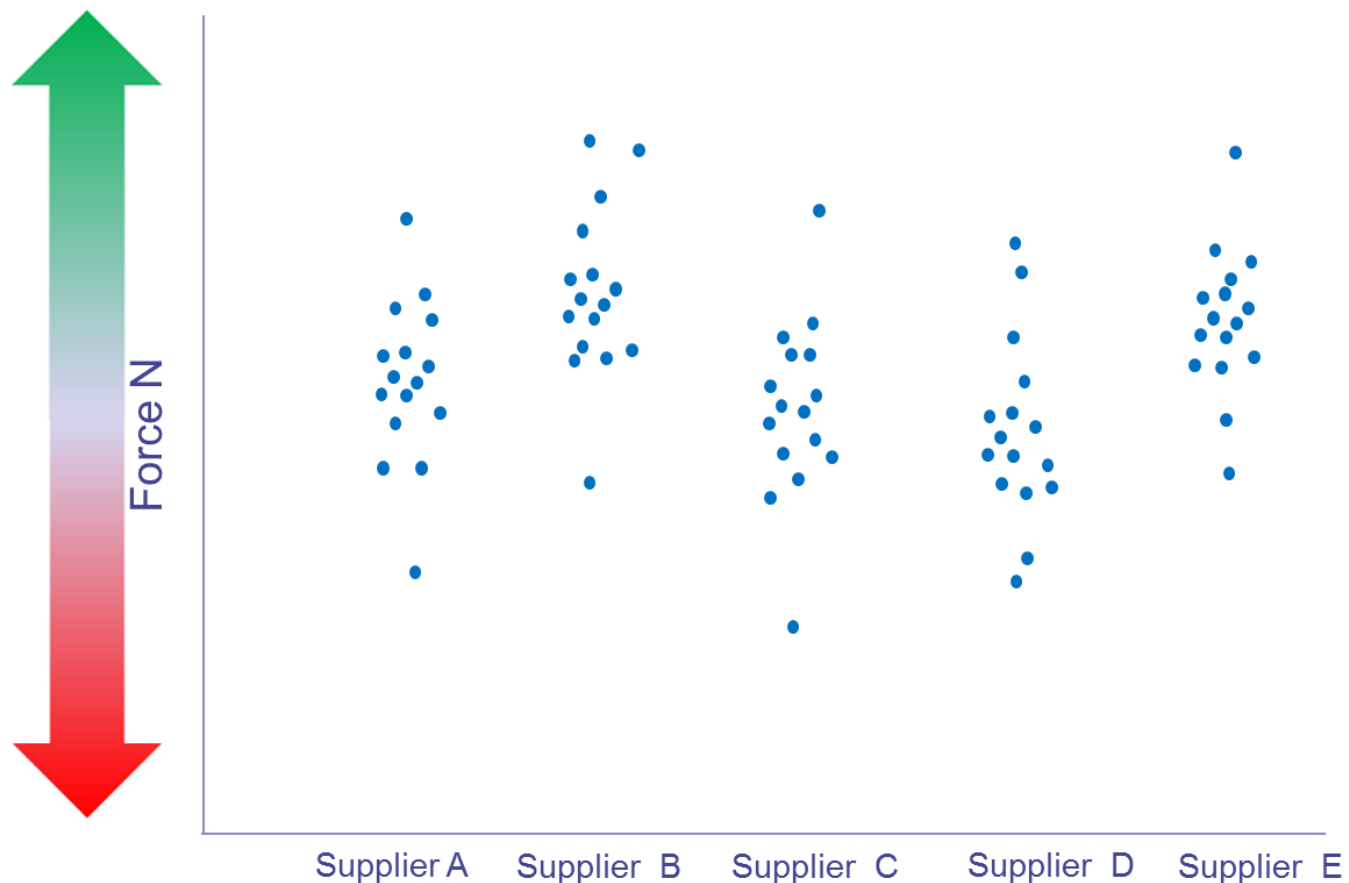


- Glass strength and breakage risk
  - Glass has no elastic constant for stability
  - Small superficial defects can have an impact on stability and breaking resistance
  - Glass to glass contacts during processing can be critical
  - Methods for investigation

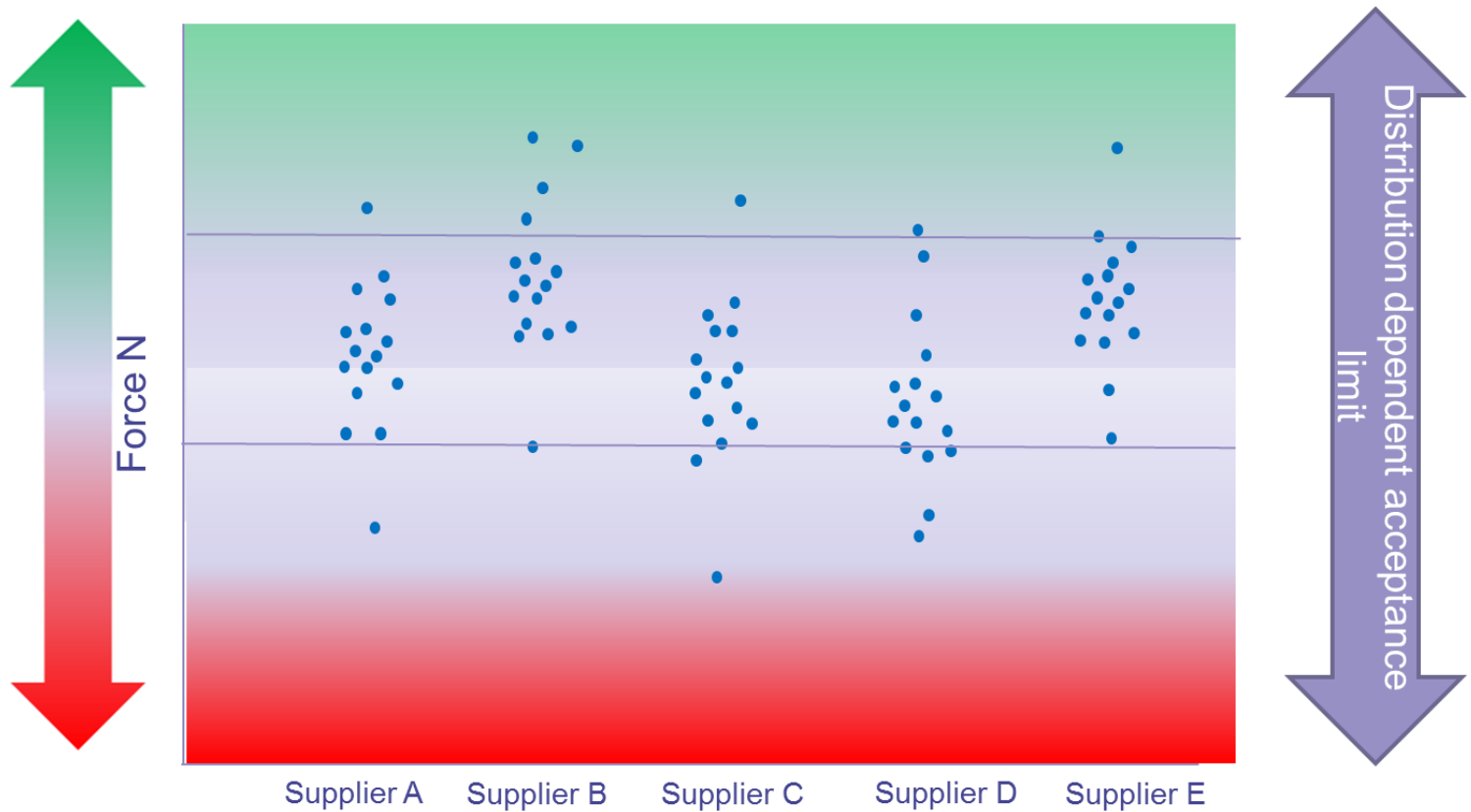
- Glass stability testing – neck / head



- Glass stability testing results

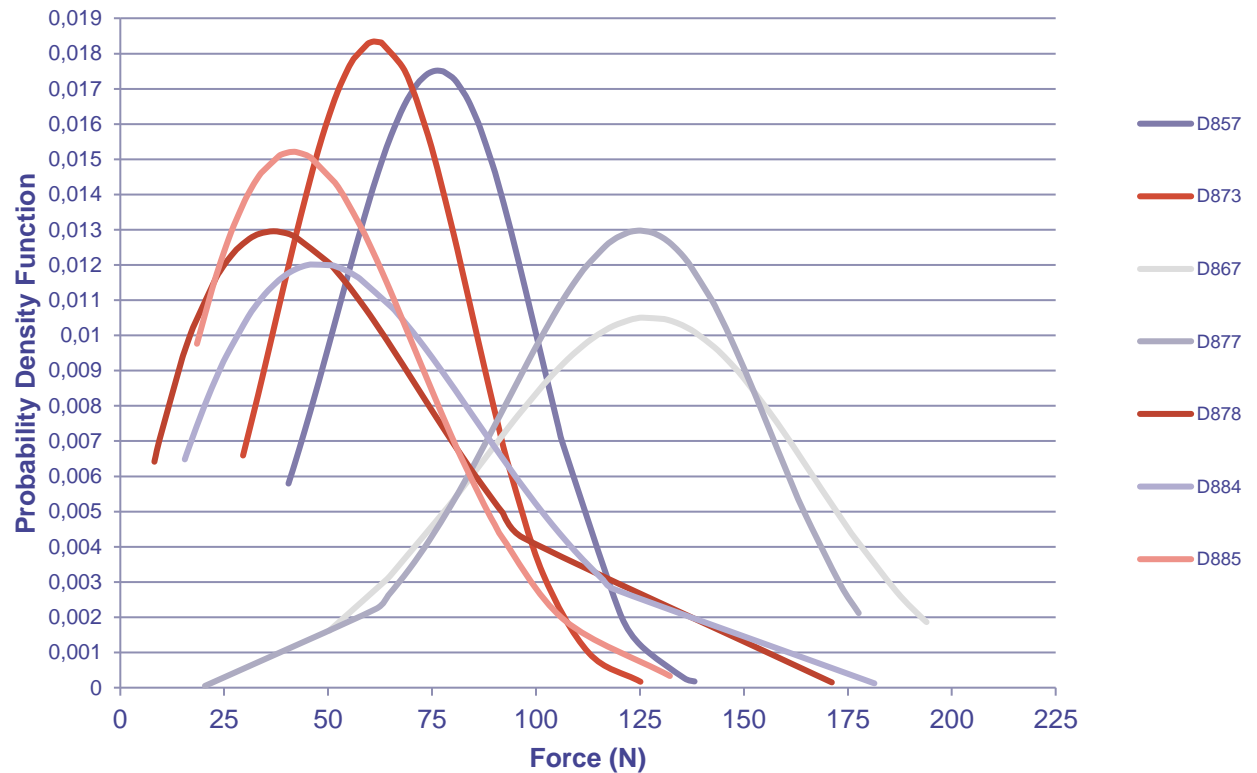


- Glass stability testing results

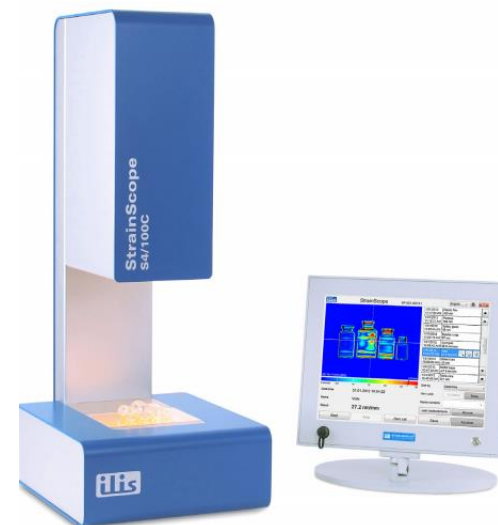
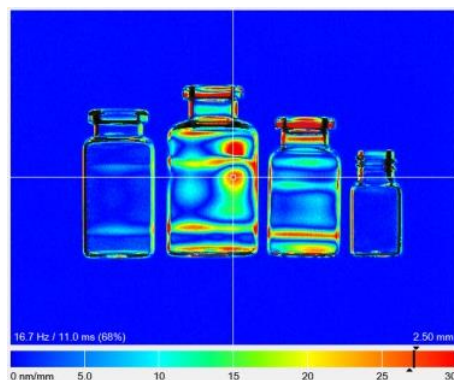




● Glass stability testing – stopper mouth



- Identification of residual stress




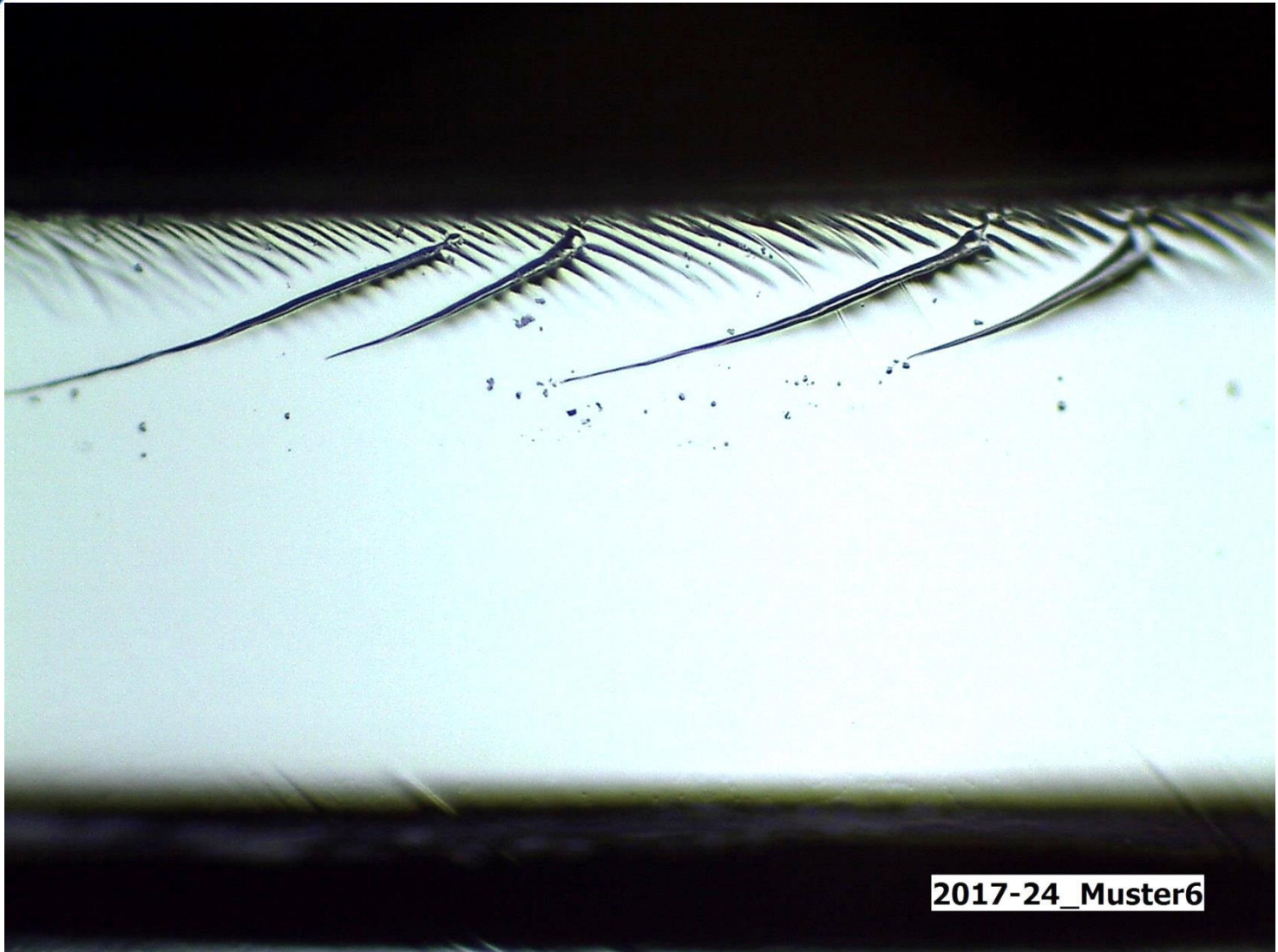
StrainScope S4 – ilis

- GMP compatible photographic documentation
- Fast multiple sample testing

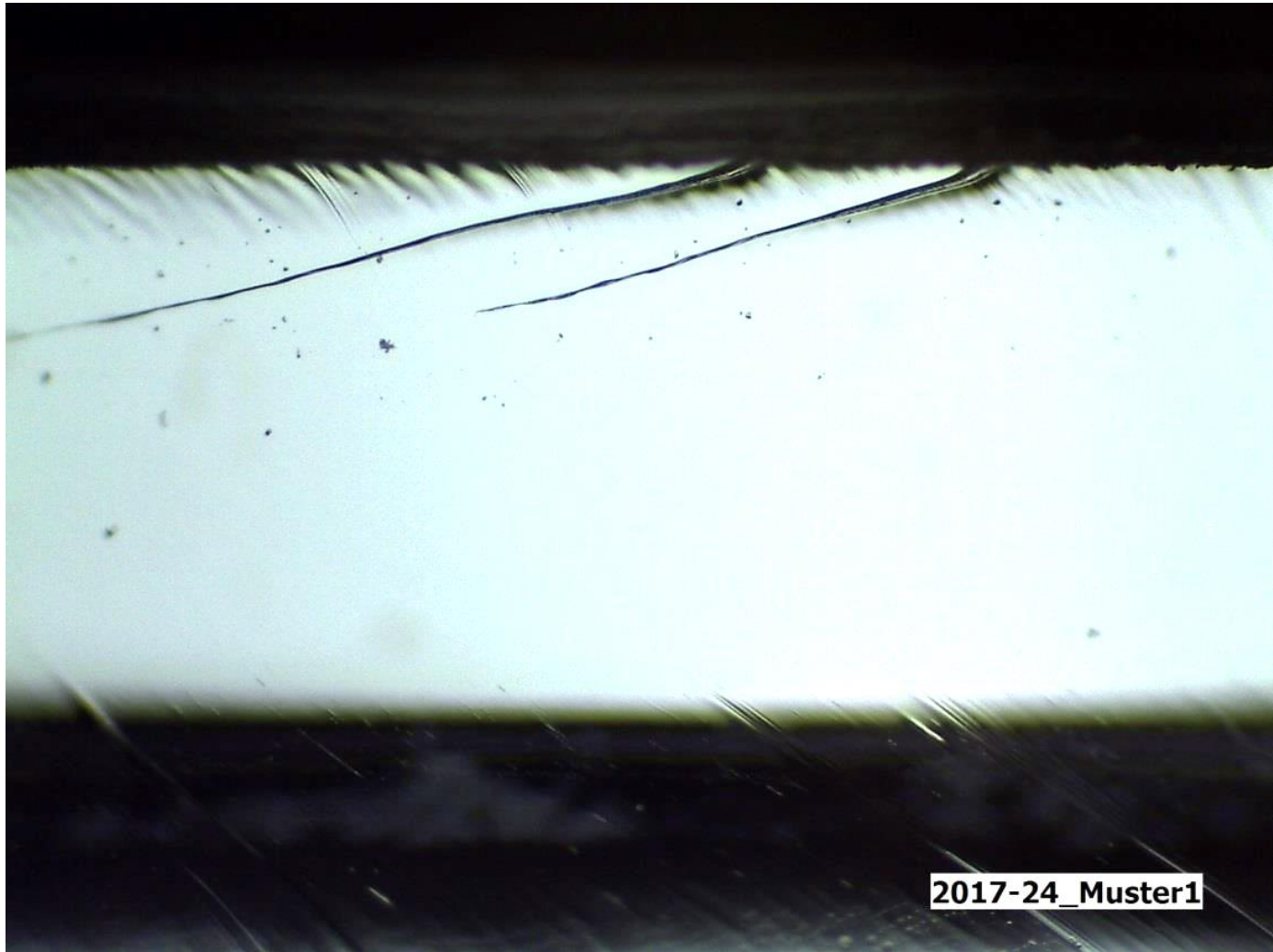
- Defects and Imperfections
  - Defects / Imperfections are not always distributed across the entire batch
  - Rare or nested defects may not be detected during incoming control
  - Glass forming process variability controlled by IPC & control cameras

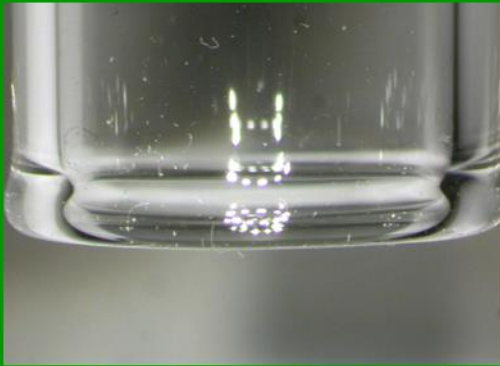
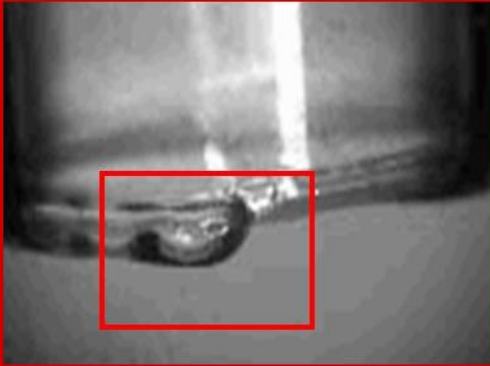


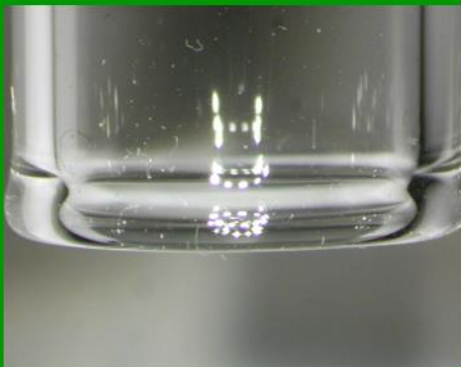

Description of Defect	Acceptable	Poor Quality
<p>Pressure / Tool Marks</p>	 <p>Faint tool marks - process related</p>	 <p>Tool marks with potential functional impact</p>



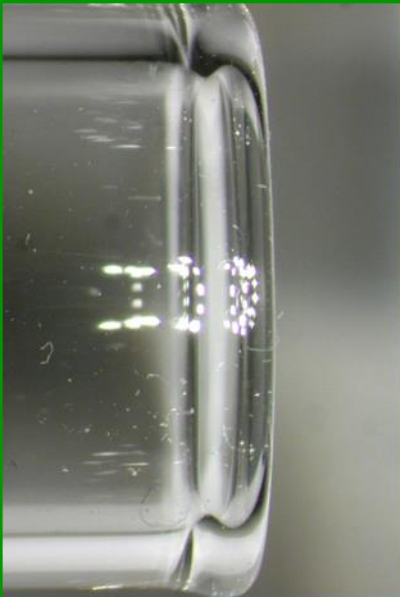
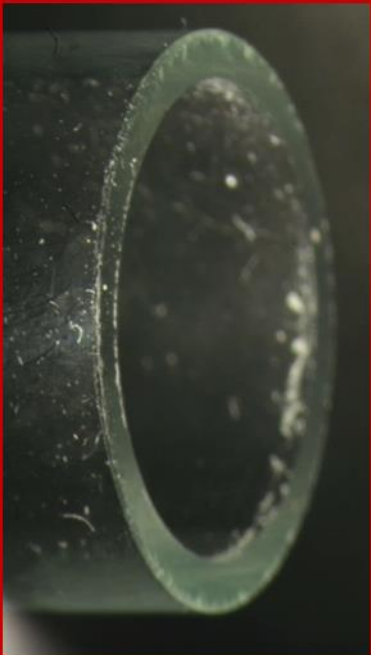
2017-24\_Muster6



Description of Defect	Acceptable	Poor Quality
<p>Deformed or damaged cartridges, function / processing impacted</p>		 <p>Melting ring deformed</p>

Description of Defect	Acceptable	Poor Quality
<p>Deformed or damaged cartridges, function / processing NOT impacted</p>		 <p>Molding ring slightly deformed</p>



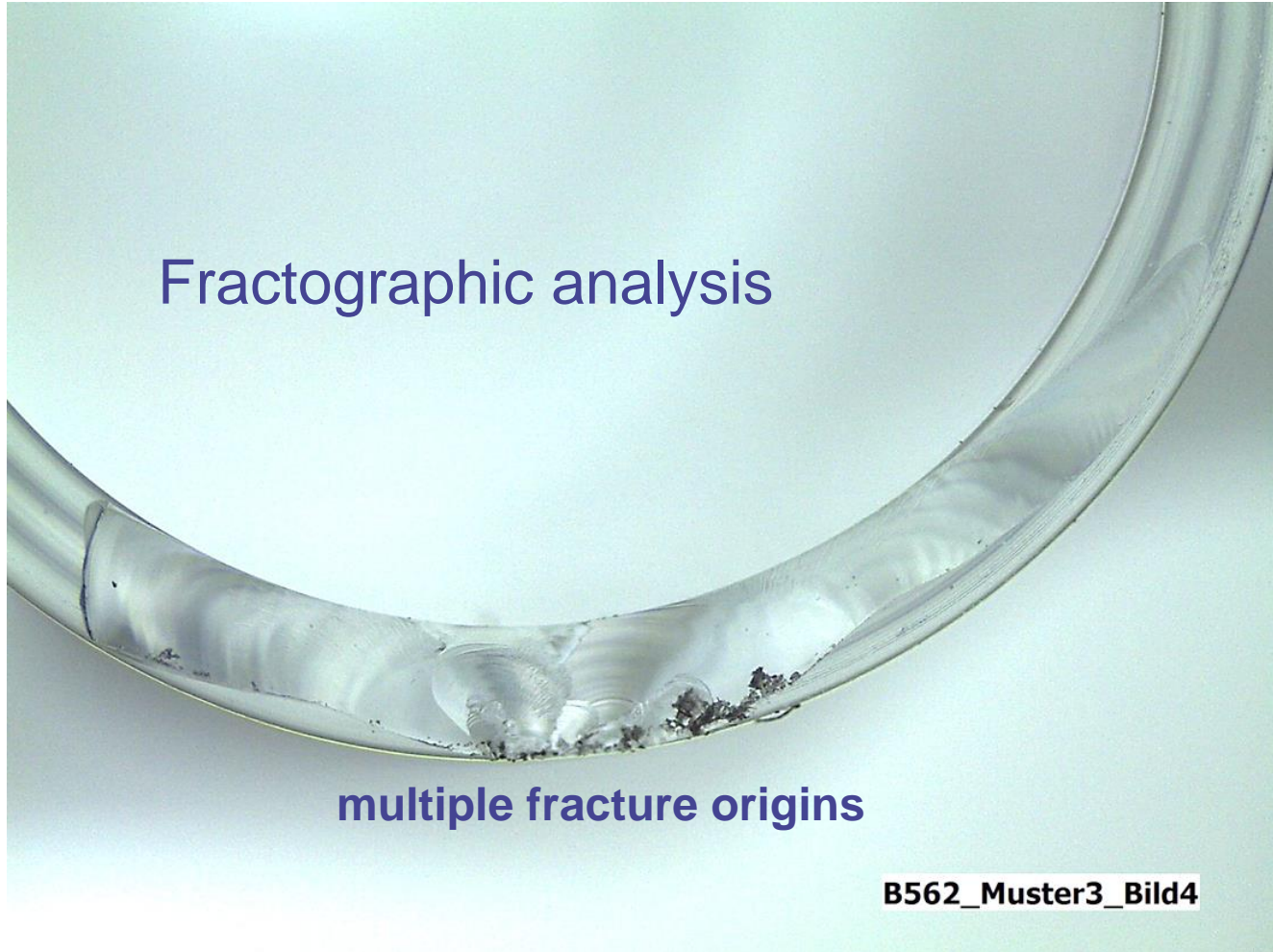
Description of Defect	Acceptable	Poor Quality
<p>Partially or not molded cartridges function / processing impacted</p>		

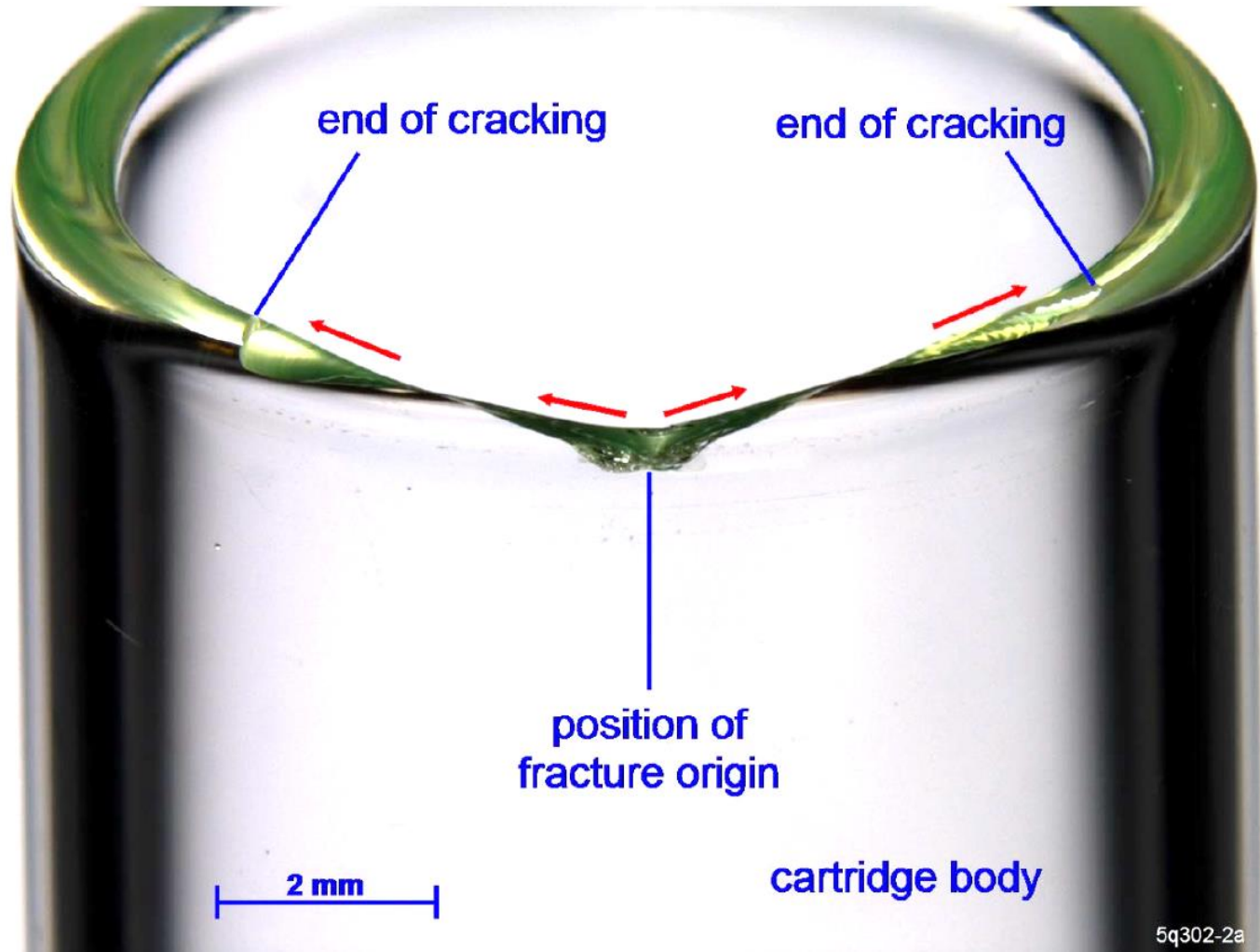


Fractographic analysis

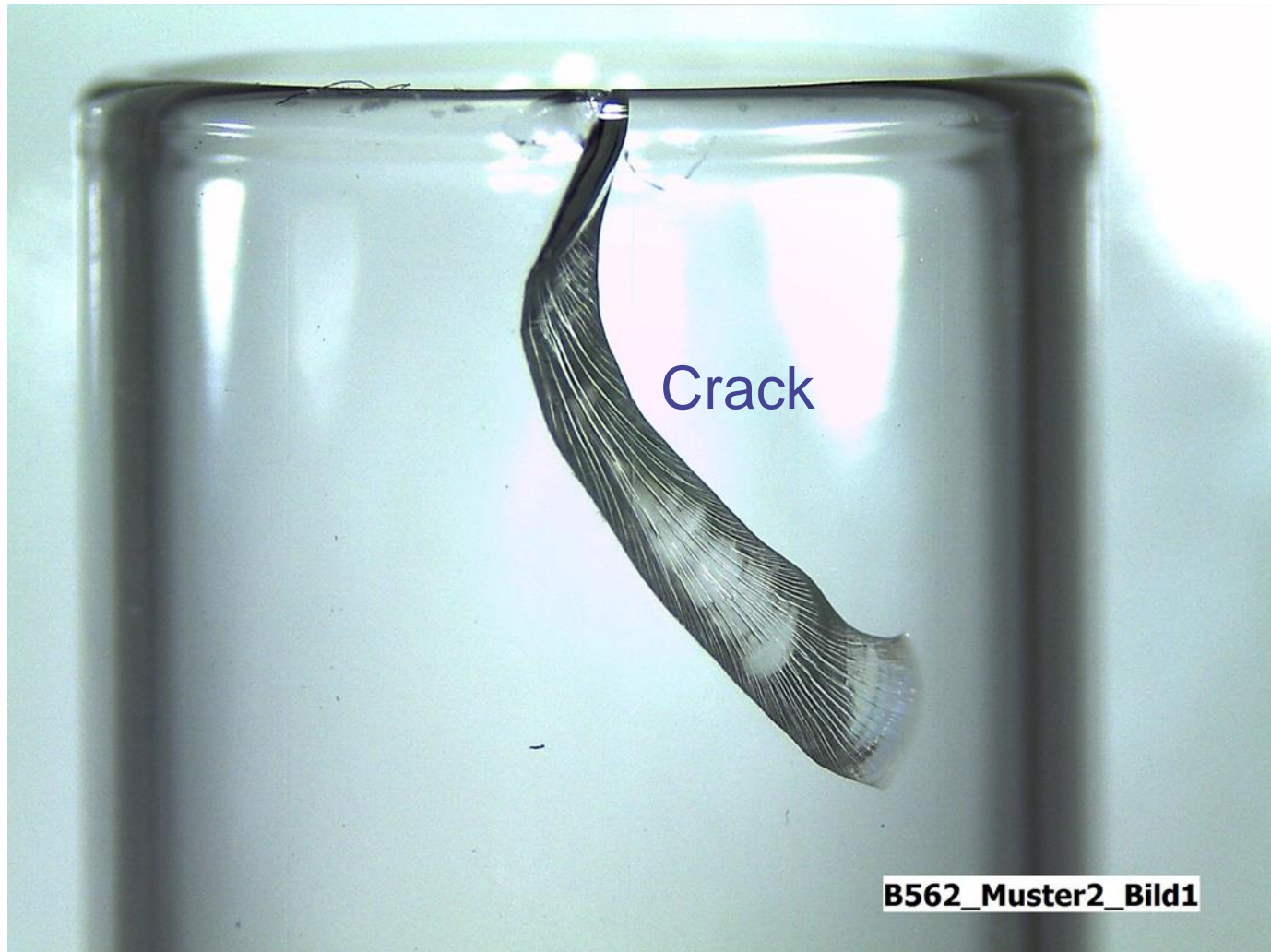
multiple fracture origins

B562\_Muster3\_Bild4

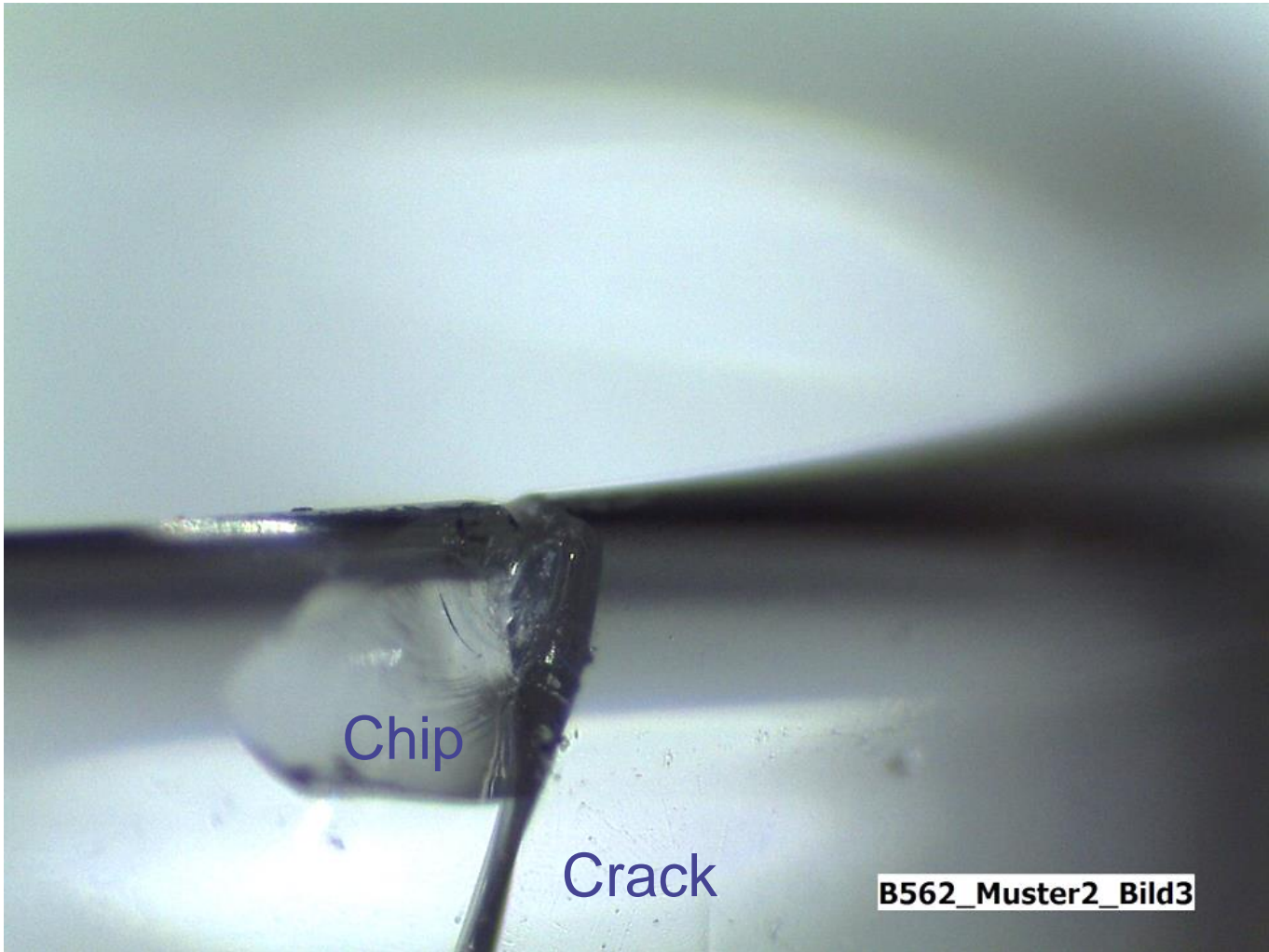






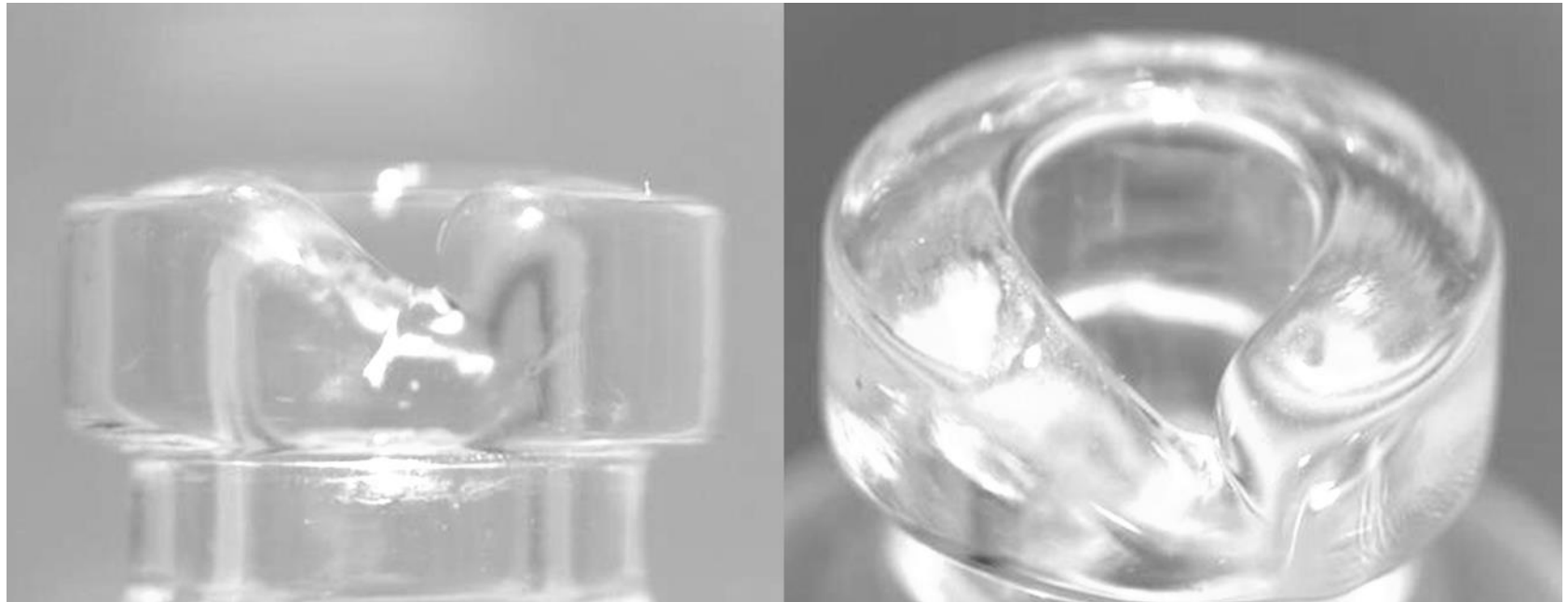
5q302-2a



## What to consider or to avoid (examples)


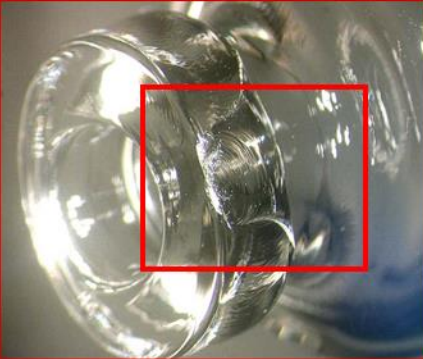


Description of Defect	Acceptable	Poor Quality
<p data-bbox="214 825 610 889"><b>Deformed cartridge</b> <b>Container closure impacted</b></p>		



Container closure impacted, example from a field complaint




Description of Defect	Acceptable	Poor Quality
<p>Chipped glass (Cracks)</p>	 A clear glass vial with a smooth, intact surface, set against a green background.	 A clear glass vial with a visible chip or crack on its surface, highlighted by a red rectangular box, set against a red background.

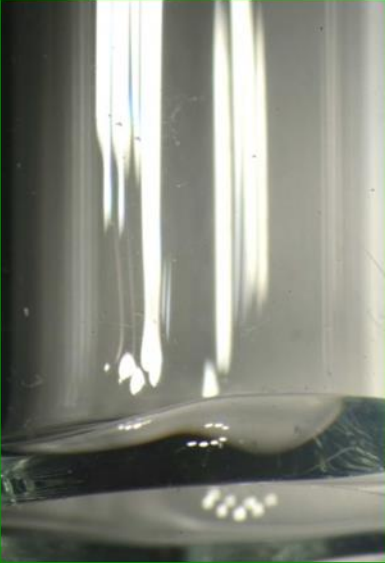
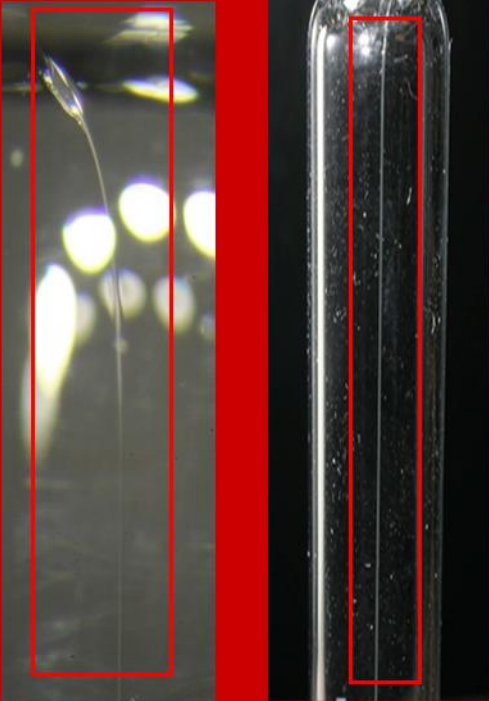
Container closure integrity impacted?  
Batch impact or singular event?


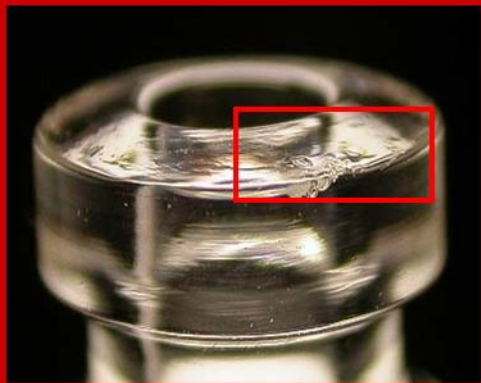


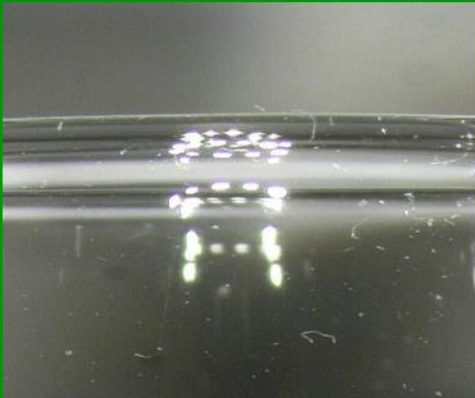
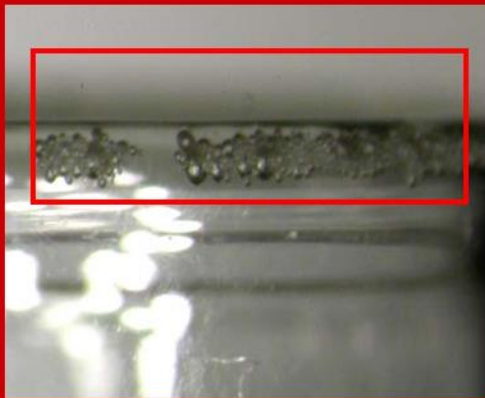
**B562\_Muster1\_Bild4**

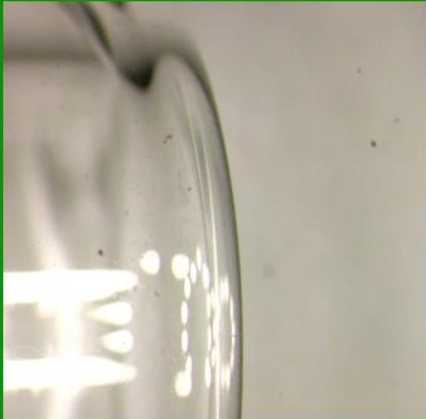

Description of Defect	Acceptable	Poor Quality
<p>Scratches / air lines outer surface</p>		 <p>Scratch or Air Line</p>



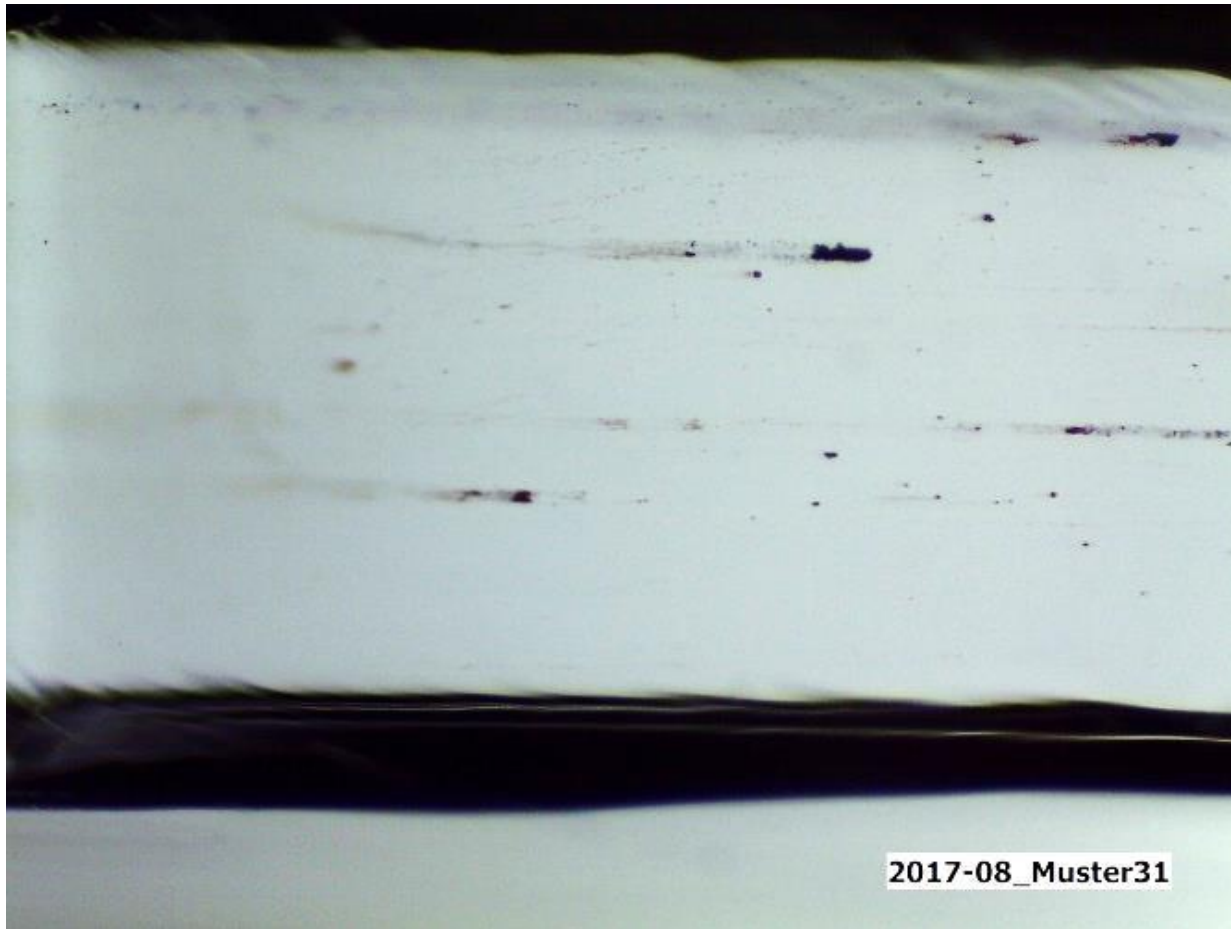
Description of Defect	Acceptable	Poor Quality
<p>Closed air lines</p>		




Description of Defect	Acceptable	Poor Quality
Air bubbles	 A clear glass vial stopper with a smooth, rounded top and no visible defects.	 A clear glass vial stopper with a red rectangular box highlighting a small, irregular air bubble trapped on the top surface.

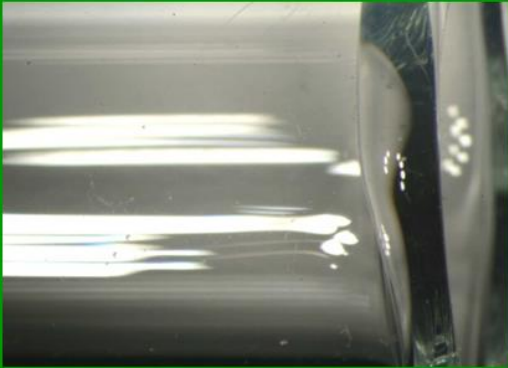
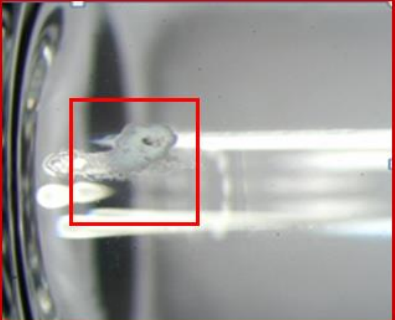
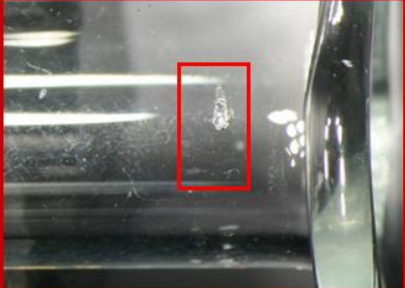
Description of Defect	Acceptable	Poor Quality
<p data-bbox="324 868 486 896">Air bubbles</p>		

Description of Defect	Acceptable	Poor Quality
<p>Contamination inside, not easy removable (not embedded)</p>		 <p>Abrasion</p>



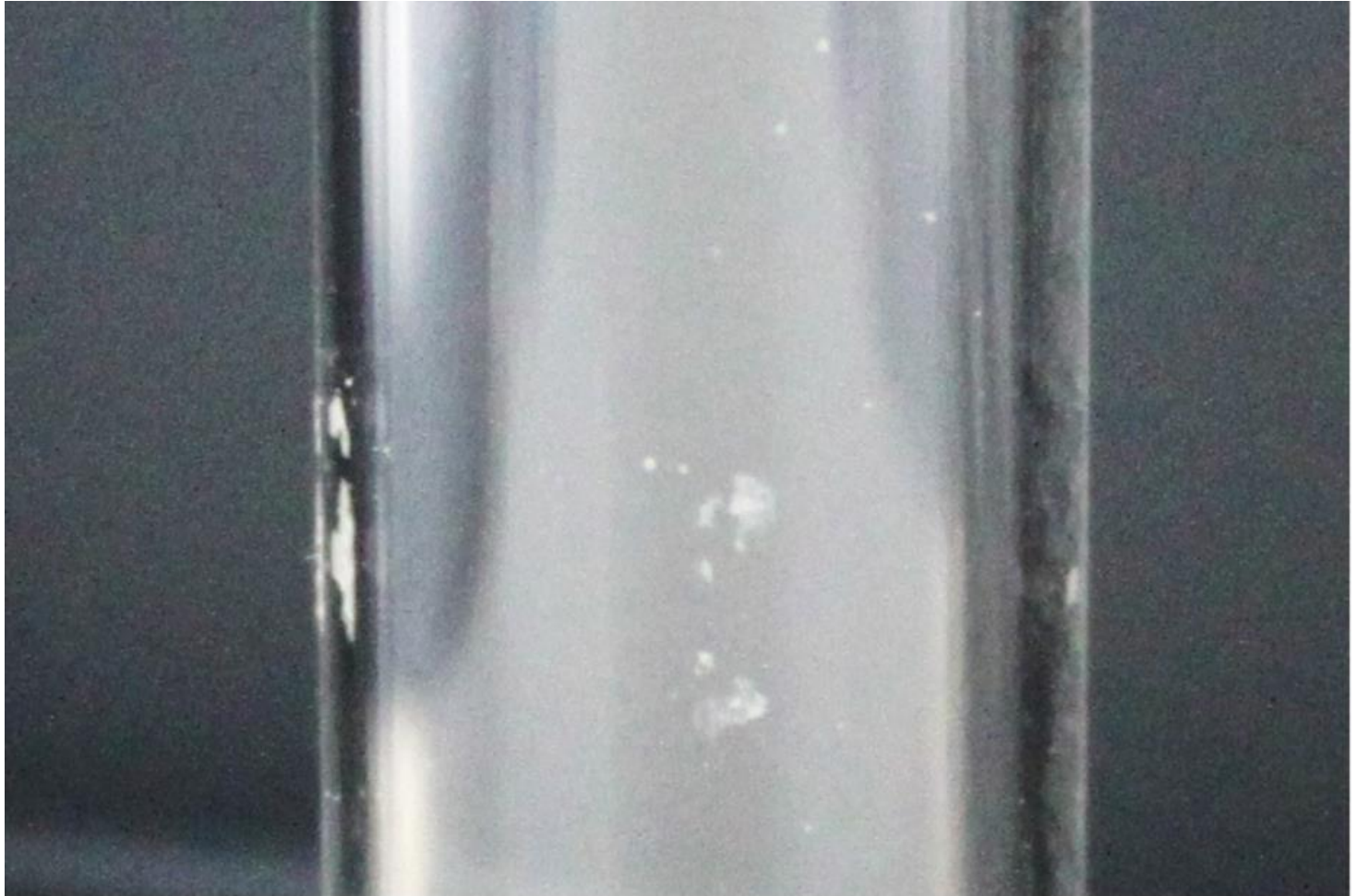


Description of Defect	Acceptable	Poor Quality
<p>Contamination outside or embedded not removable</p>		 

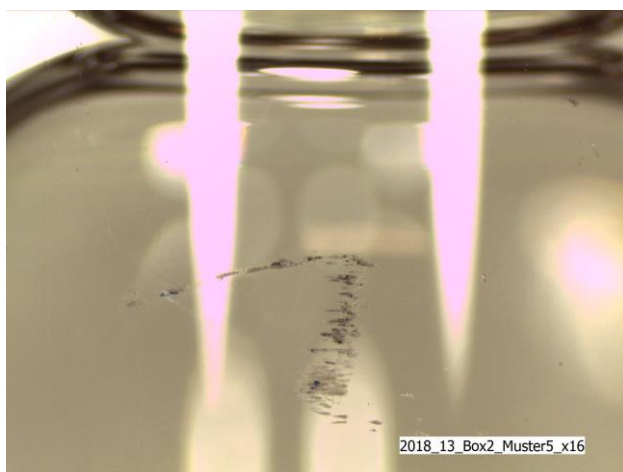
Description of Defect	Acceptable	Poor Quality
<p>Visible baked glass grit / chips On the glass surface</p>		 <p>Baked glass grit</p> 

Description of Defect	Acceptable	Poor Quality
<p>Visible baked glass grit / chips On the glass surface</p>		

## What to consider or to avoid (examples)



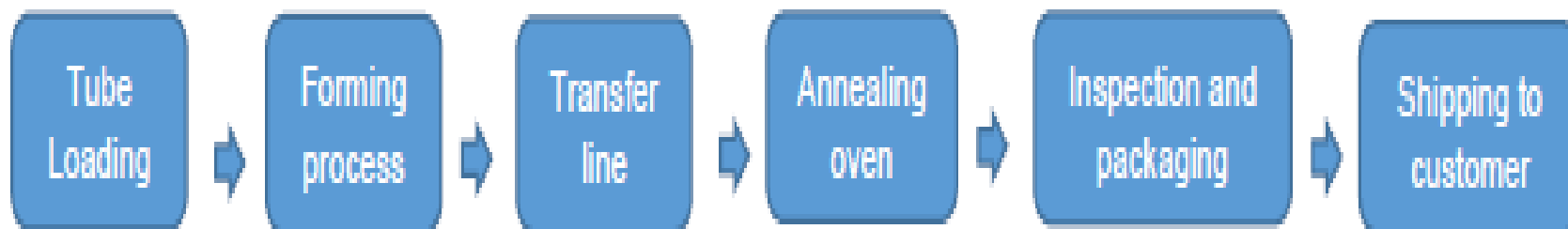
- Defects from filling operations – not always caused by supplier



*CASE STUDY I: Vial collar with contamination after sterilisation*

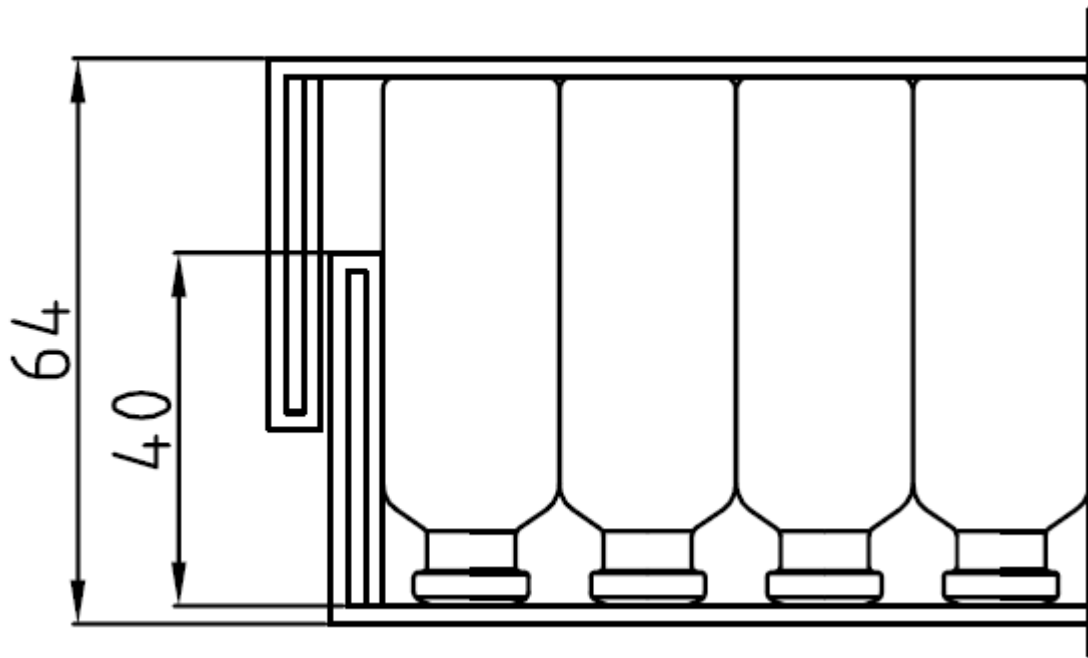


- Supplier Manufacturing Process Investigation





- Investigation inconclusive – no clear root cause identified
- Most probable cause: Oil contamination of the Polypropylen box



- Supplier Certification & Reduced Testing
  - Prerequisite for reduced testing
    - ⇒ Quality History
    - ⇒ Quality Management System
    - ⇒ Supplier Certification
  - Risk Analysis to evaluate potential impact
    - ⇒ Reduction of individual test parameter
    - ⇒ Supplier results disclosed on CoA
    - ⇒ Determination of verification strategy (dynamic testing)
    - ⇒ SKIP-Lot testing

- SKIP-Lot Testing
  - Not all incoming lots are inspected
  - ISO 2859-3:2005: Sampling procedures for inspection by attributes - Part 3: Skip-lot sampling procedures (industrial standard)
  - **Identity testing** for pharmaceutical products required
  - Should only be used when it has been demonstrated that the quality of the product is very good

- EU GMP Guideline, Part I, Chapter 5
  - *Manufacturers of finished products are responsible for any testing of starting material as described in the marketing authorisation dossier*

*They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform **identification testing** of each batch ...*
  - *Requirements to be fulfilled when accepting test results from suppliers*
    - *Audits at appropriate intervals (sampling & testing)*
    - *CoA signed by a designated person (qualification)*
    - *History of compliance*
    - *Full analyses at appropriate intervals*

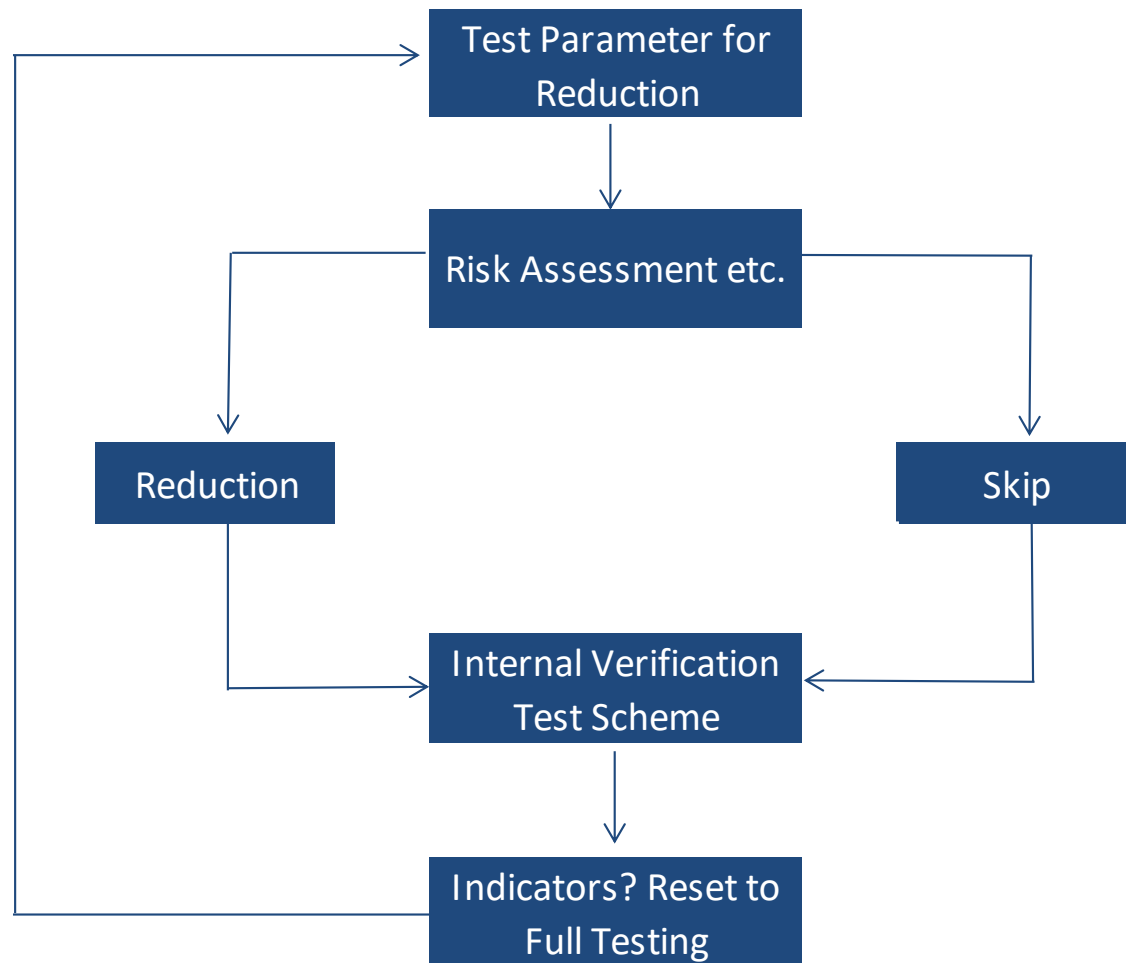
**Note: The same applies to packaging materials**

- US GMP Regulations – 21 CFR 211

⇒ *Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures*

*(d) (3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.*

## Reduced Testing Scheme



- Reference samples

**EU Guidelines to Good Manufacturing Practice, Volume 4  
Annex 19**

**Reference and Retention Samples**

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.

- Each packaging site should keep reference samples of each batch of primary and printed packaging materials.

- Risk of Delamination

- The phenomenon gained attention of pharmaceutical industry in 2010 as a result of products recalled from the market (vials).
- An advisory was published by the FDA informing drug manufacturers of the phenomenon and the conditions associated with elevated risk of delamination.

<http://www.fda.gov/drugs/drugsafety/ucm248490.htm>

- Glass delamination is a serious concern for parenteral products. The phenomenon represents a chemical reaction that results in the release of tiny glass particles called “lamellae” into the product container. Not only does the occurrence of lamellae indicate a product stability issue but may also present a risk to patient safety.



- Risk of Delamination
- Hot Topic in 2010

March 1, 2022 09:28 AM EST | FDA+

[🔗](#) [in](#) [🐦](#)

## FDA rejects Gilead's next big HIV drug over glass vial issues



**Zachary Brennan**  
Senior Editor

Gilead on Tuesday received a rejection letter for its latest potential first-in-class HIV drug, as the company said the FDA cited Chemistry Manufacturing and Controls (CMC) issues relating to the compatibility of lenacapavir with its proposed container vial.

Regulators previously slapped a clinical hold on 10 trials studying injectable versions of the experimental HIV treatment, known as lenacapavir, due to concerns that vials made of borosilicate glass could lead to the formation of sub-visible glass particles in the solution.

RELATED: [FDA slaps a hold on Gilead's injectable HIV treatment over concerns about potential glass contaminants](#)

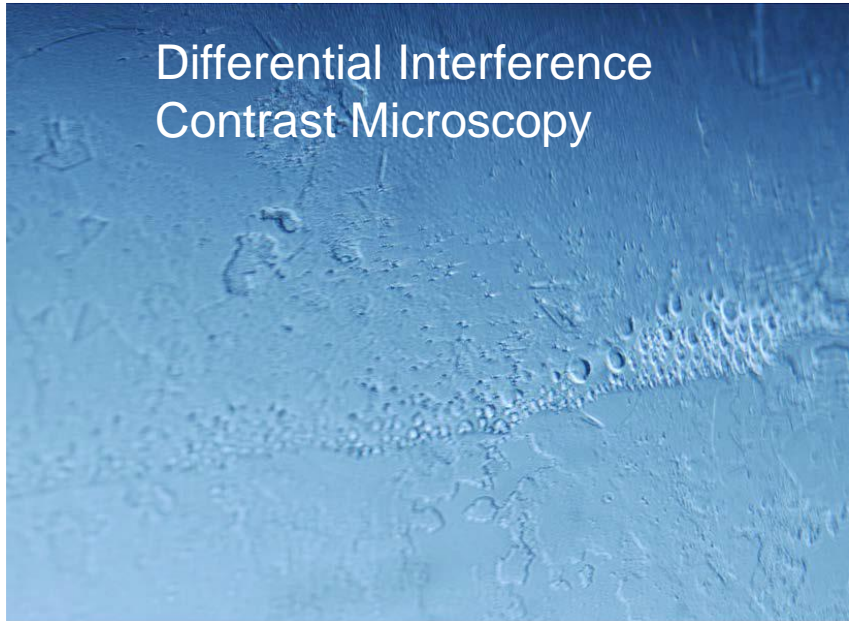


Merdad Parsey

“Gilead intends to provide FDA with a comprehensive plan and corresponding data to use a different vial type,” Gilead CMO Merdad Parsey said in a statement. “We look forward to discussing this further with FDA over the coming months so that we can make this investigational new therapy available to people living with multidrug-resistant HIV as soon as possible.”

On the positive side for Gilead, the FDA did not request any new clinical trials in its CRL. Analysts previously estimated that lenacapavir sales will reach almost \$900 million by 2026, according to [Evaluate](#).

- Conditions associated with formation of glass lamellae
  - High Heat During Glass Vial Manufacturing
  - High pH Buffer
  - High Ionic Strength
  - Long Shelf-life
  - Room Temperature Storage
  - Terminal Sterilization



- **Delamination Risk**

		Risk factor
Primary Packaging (PP)	Type I without or Silicone	1
	Type II with treatment	10
Product Formulation (PF)	pH	
	Buffer (B)	
	Ionic Strength (IS)	
	Complexing Agent (CA)	
	pH $\leq$ 7	1
	pH $>$ 7 & $\leq$ 8	5
	pH $>$ 8 or acetate, citrate, phosphate Buffer or IS $>$ 0,1M or CA	10
Without terminal sterilization	1	
Process (PR)	Terminal sterilization (1 cycle)	5
	Terminal sterilization (more than 1 cycle)	10
	PP x PF x PR	
Overall Risk Rating		

- Overview

- 1 Requirements for incoming inspection
- 2 How to do it in practice
- 3 What to consider or to avoid (examples)
- 4 **Coordination process between packaging manufacturer and customer**



- Selection and Qualification of Supplier
  - Pre-qualification (questionnaire, information, due diligence visit)
  - Negotiate contract(s)
  - Supplier audit
  - Agree upon specifications (sampling)
  - Quality Agreement
    - Mandatory if data from CoAs are accepted for incoming inspection
    - Sampling delegation
    - Quality requirements should be discussed and agreed with the supplier. This may include production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures

- Ongoing Monitoring of Supplier
  - Supplier relationship management
    - Classification
    - Assessment
    - Monitoring and Trend Performance
    - Complaint Management
    - Supplier Information
    - Shared Reviews & Feedback

- **Supplier Management**

- Specification Documents (contractual)
- Quality Agreements
- Supplier Audits
  - ISO 15378:2017 (en) Quality Management System for Medicinal Packaging Material Supplier

Specifies requirements for a quality management system for manufacturers of pharmaceutical and medical device primary packaging materials.

Manufacturers need to demonstrate their ability to consistently meet customer requirements, including regulatory requirements and international standards as applicable.



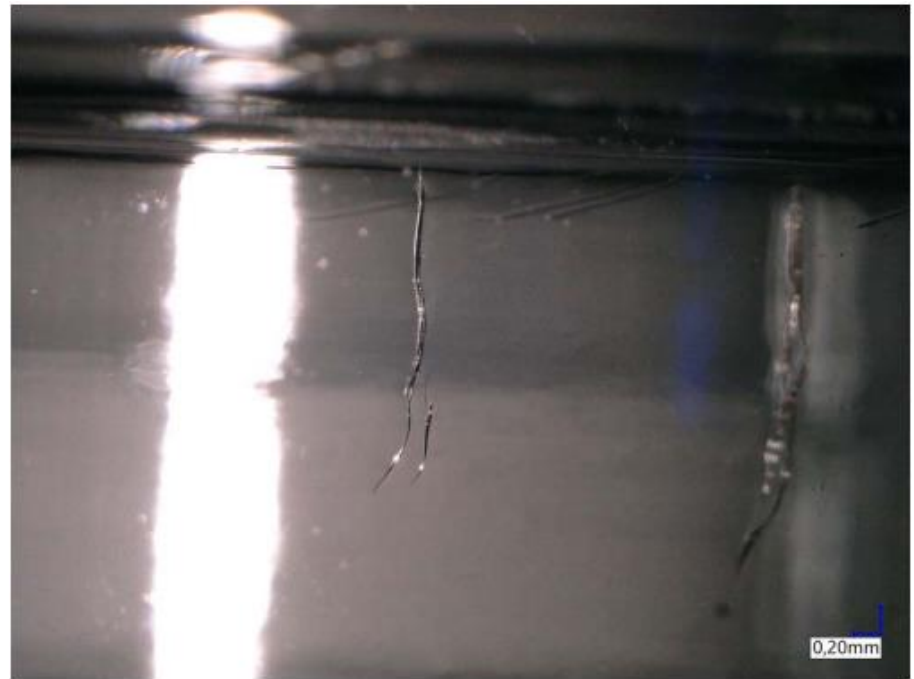
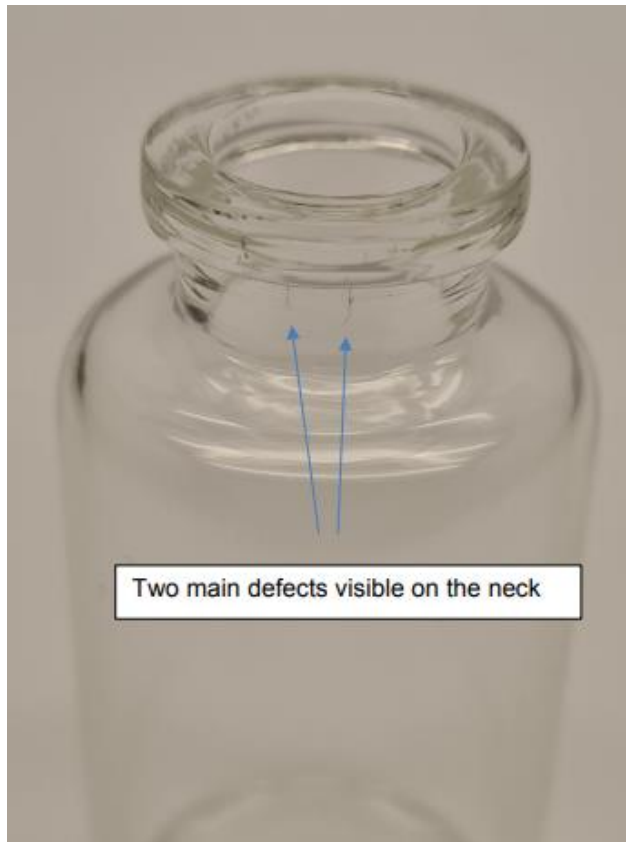
## Coordination process between packaging manufacturer and customer

- ISO 15378 standard enables the supplier to comply with legal requirements for pharmaceutical and medical device primary packaging materials
- The standard integrates the requirements of ISO 9001 as well as GMP principles, a regulatory requirement for the pharmaceutical and medical device industries as per all international regulations such as Code of Federal regulations (US), and European directives and regulations
- The standard also helps to reduce the risks of safety hazards and product contamination to ensure product efficacy and shelf life.
- The standard delineates GMP principles and specifies Quality Management System requirements applicable to primary packaging materials



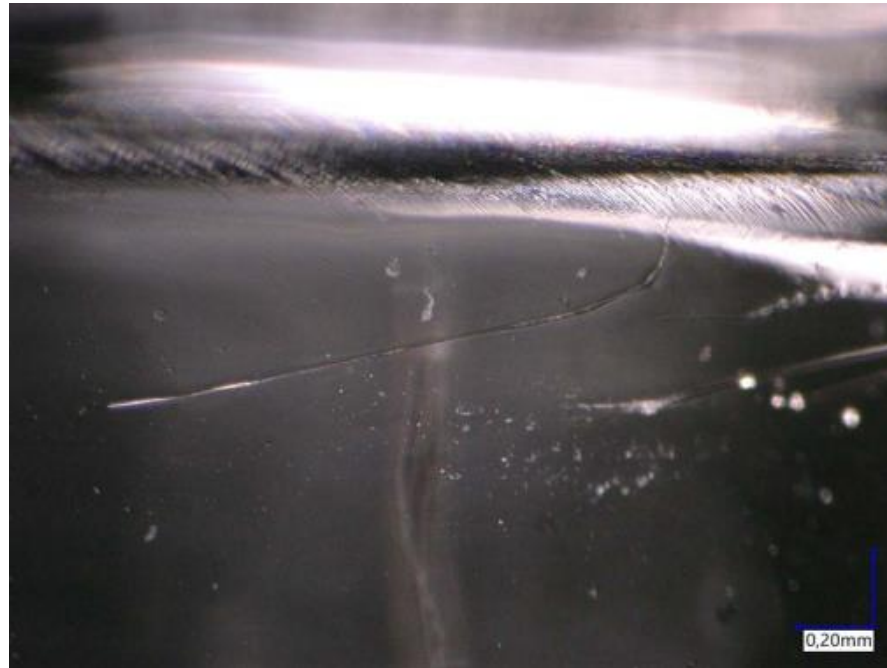
- Definition of defects
  - Can be quite subjective for visual parameter
  - Expected quality might be higher than described in official defect lists e.g. high value products
  - Some imperfections are process intrinsic
  - Other factors that may influence acceptance level, e.g. product delivery market e.g. Japan

- CASE STUDY II - Defect Vial identified during In-Process Control in combination with an unusual high reject rate



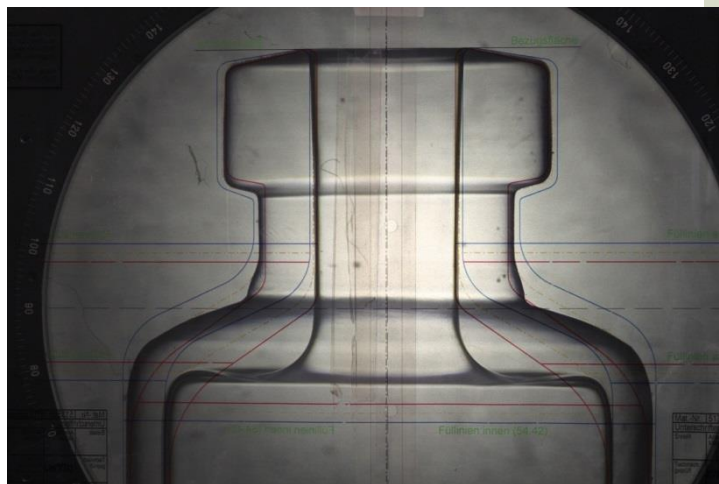
Picture 5: Vial nonconformity and visible tool marks (magnification 50x)

- Hypothesis: Poor glass batch
- Specific examination of 1250 vials resulted in 57 vials with declared imperfections – mostly pressure marks

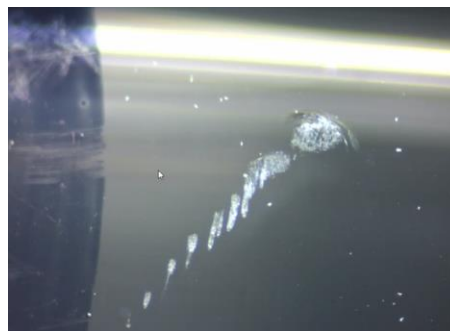
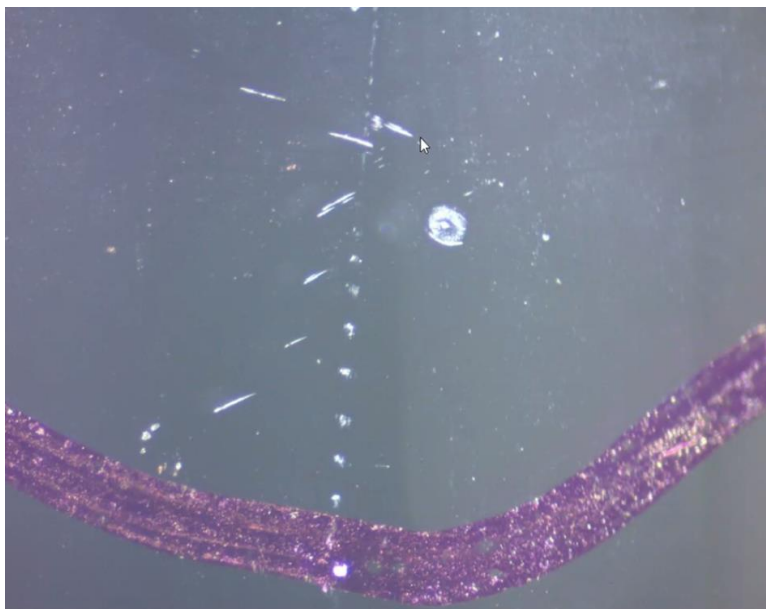


- Internal evaluation by Incoming QC:  
Quite faint imperfections
- Supplier complaint initiated and samples sent
- Complaint Investigation Result: The pressure marks do not effect the function or integrity of the glass and are considered conforming as no Limit Sample is defined.

- Limit Sample (optional)
  - Physical unit that is agreed between manufacturer and customer that defines the maximum degree of acceptability of an imperfection
    - Subjective Defect
    - Objective Defect



- CASE STUDY III: High rate of rejections during automated control of filled vials resulted in a very precise manual re-evaluation



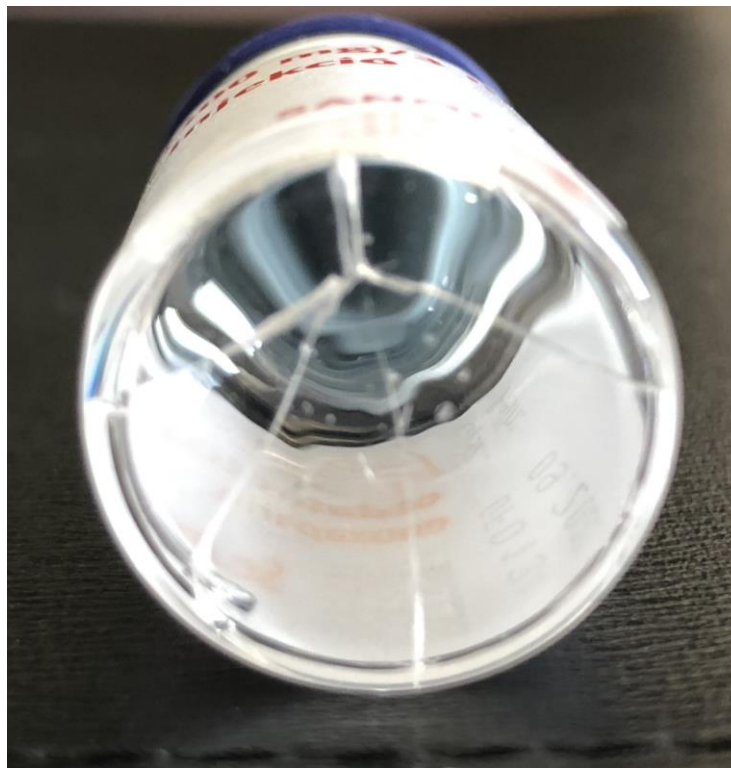
- Small bump checks also visible on not processed vials



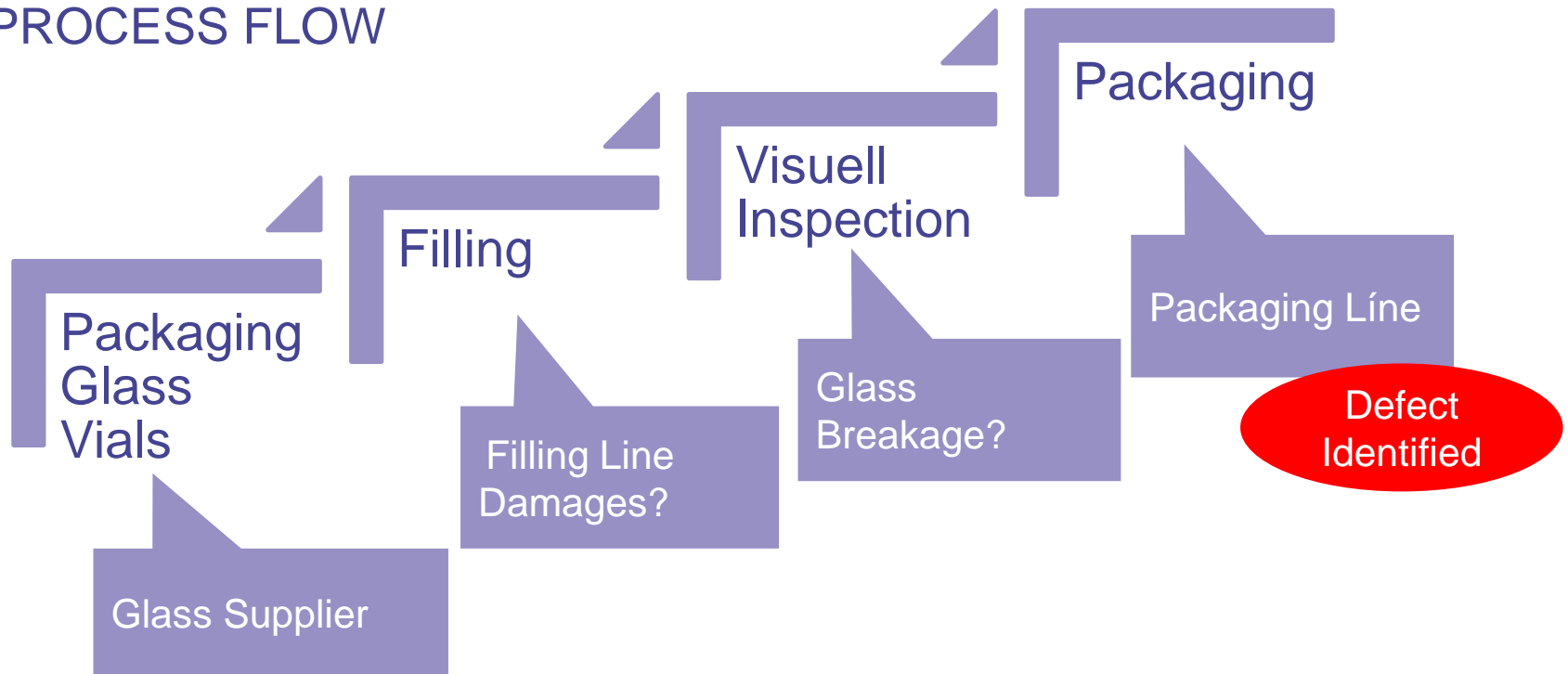
- CASE STUDY IV – Broken glass vials in packaging
- During packaging of a liquid product in 5 mL vials chipping of vial bottoms were observed
- During investigation, additional glass defects identified in retained samples
- Type of defect can not be identified during visual inspection
- Containment of affected glass / product batches not clear to be defined



- Case Study – Glass vial defect in Packaging

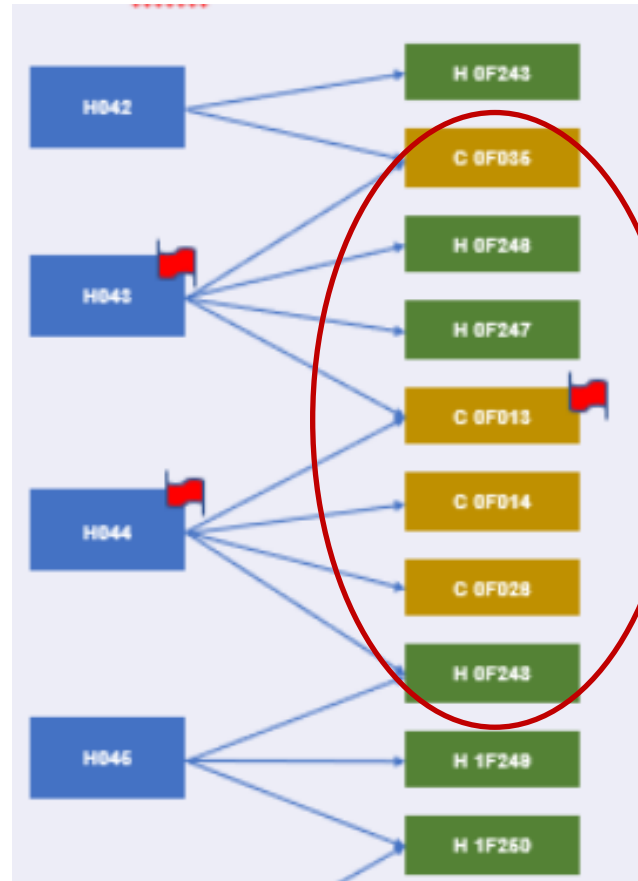


- PROCESS FLOW

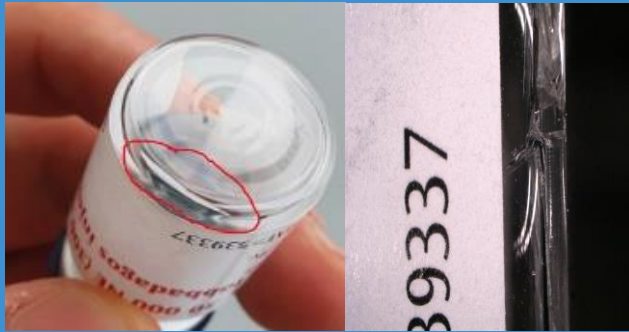


- Potential Product Impact

Vial Batch                      Drug Product Batch



- Investigation identified new phenomenon (B)



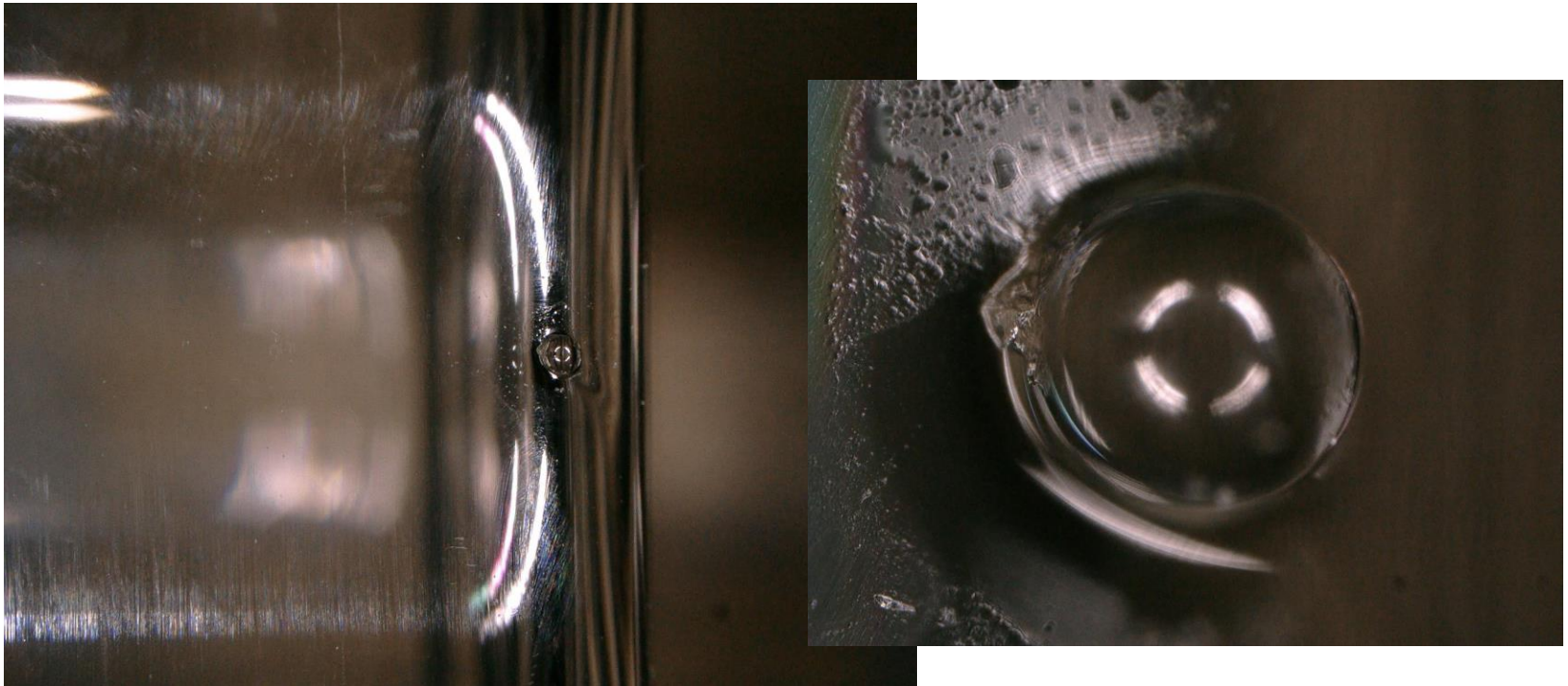
Phenomenon A – Chipped Bottom

≠



Phenomenon B – „Heel Stickers“/Scratches

- Heal Sticker





- Heal Sticker

**Heel Sticker**

**Location:** Heel or Bottom      **Class:** Major B



An external string of glass, usually rounded, extending out from the heel or bottom.

PDA Glass Task Force  
Tubular Glass Vial Lexicon

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### Nonconformity Classifications

*Critical:* A Nonconformity that is likely to result in personal injury or potential hazard to the patient. This classification includes any nonconformity that compromises the integrity of the container, and risks microbiological contamination of a sterile product.

*Major A:* A Nonconformity leading to serious impairments, for example, a malfunction that makes the packaging unusable.

*Major B:* A Nonconformity leading to impairments of a lesser degree, for example, reduced efficiency in production.

*Minor:* A Nonconformity that does not impact product quality or process capability.

*N/A:* An imperfection classification that is less than the size, magnitude and impact of a nonconformity is considered not applicable.



## Coordination process between packaging manufacturer and customer

- In-house Investigation
- Supplier complaint initiated
- Finally, Root Cause was identified as an incorrect set-up of the packaging line leading to high mechanical forces to the vials

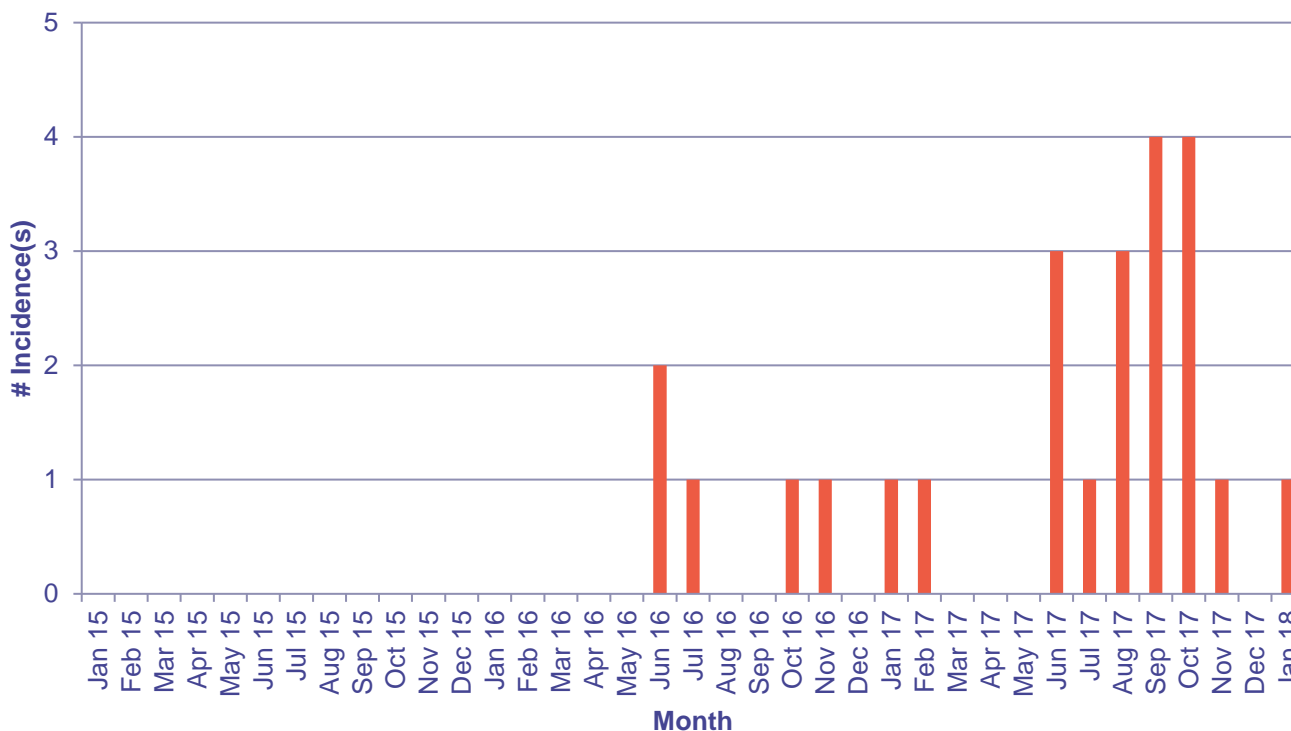
- CASE STUDY V

Glass chippings at the glazing end





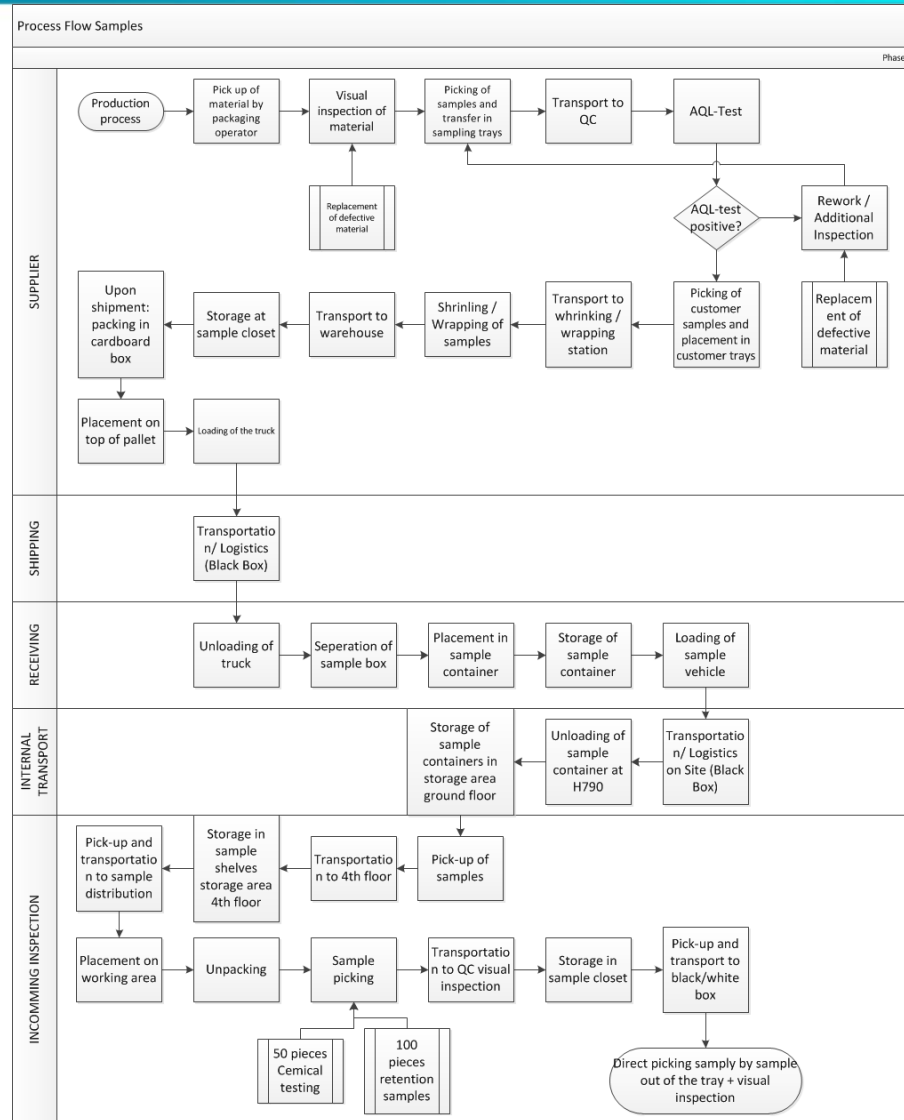
- Incidences during incoming inspection



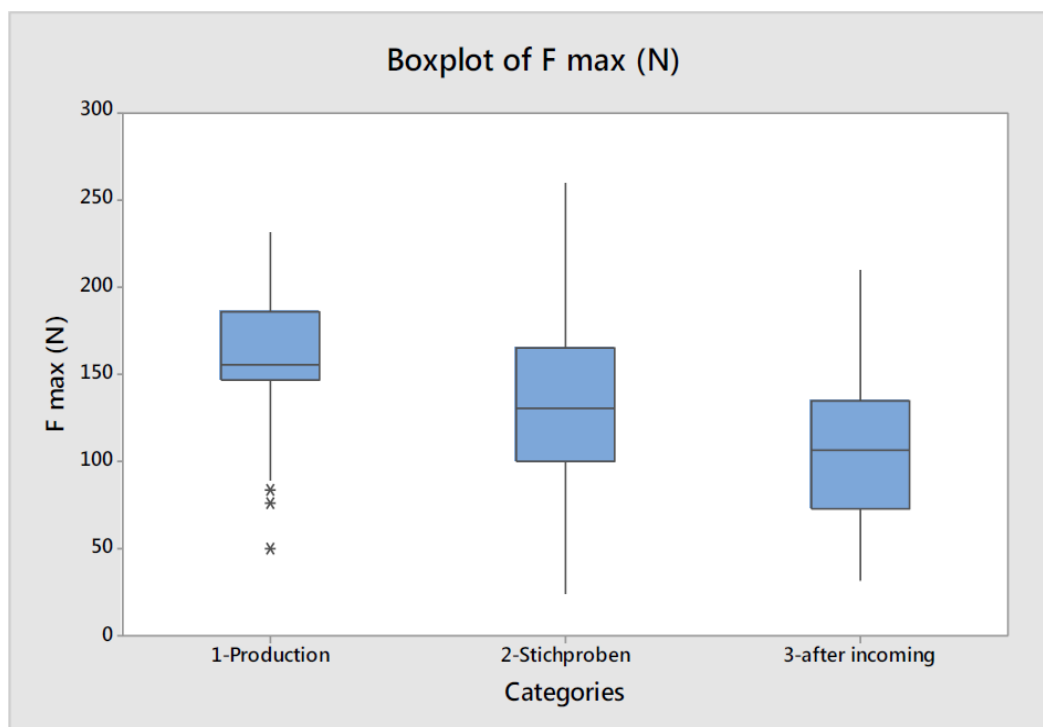
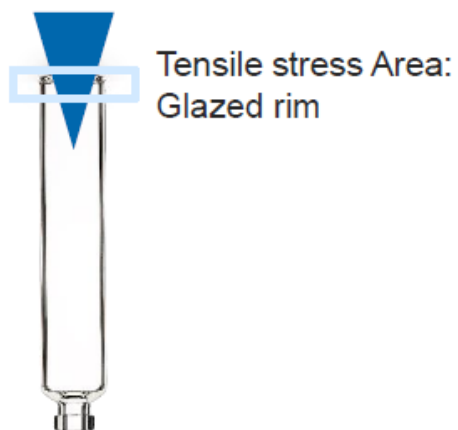
- Re-inspection results of selected batches

Batch	Defect Rate Tailgate	Sorted units	Defect Rate after sorting
A	1.5%	> 900,000	0.001 %
B	1.2 %	> 900,000	0.002 %
C	0.48 %	> 90,000	0 %

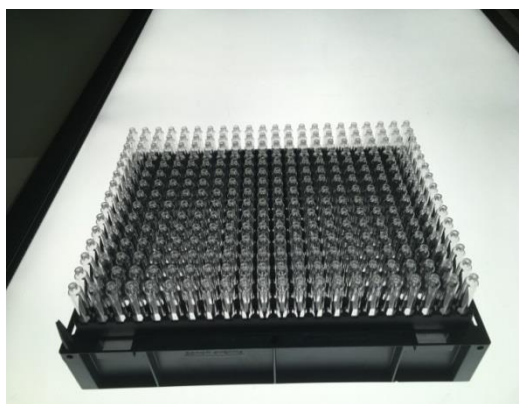
- Shared Investigation: Processing of Tailgate Samples vs. Material Batches



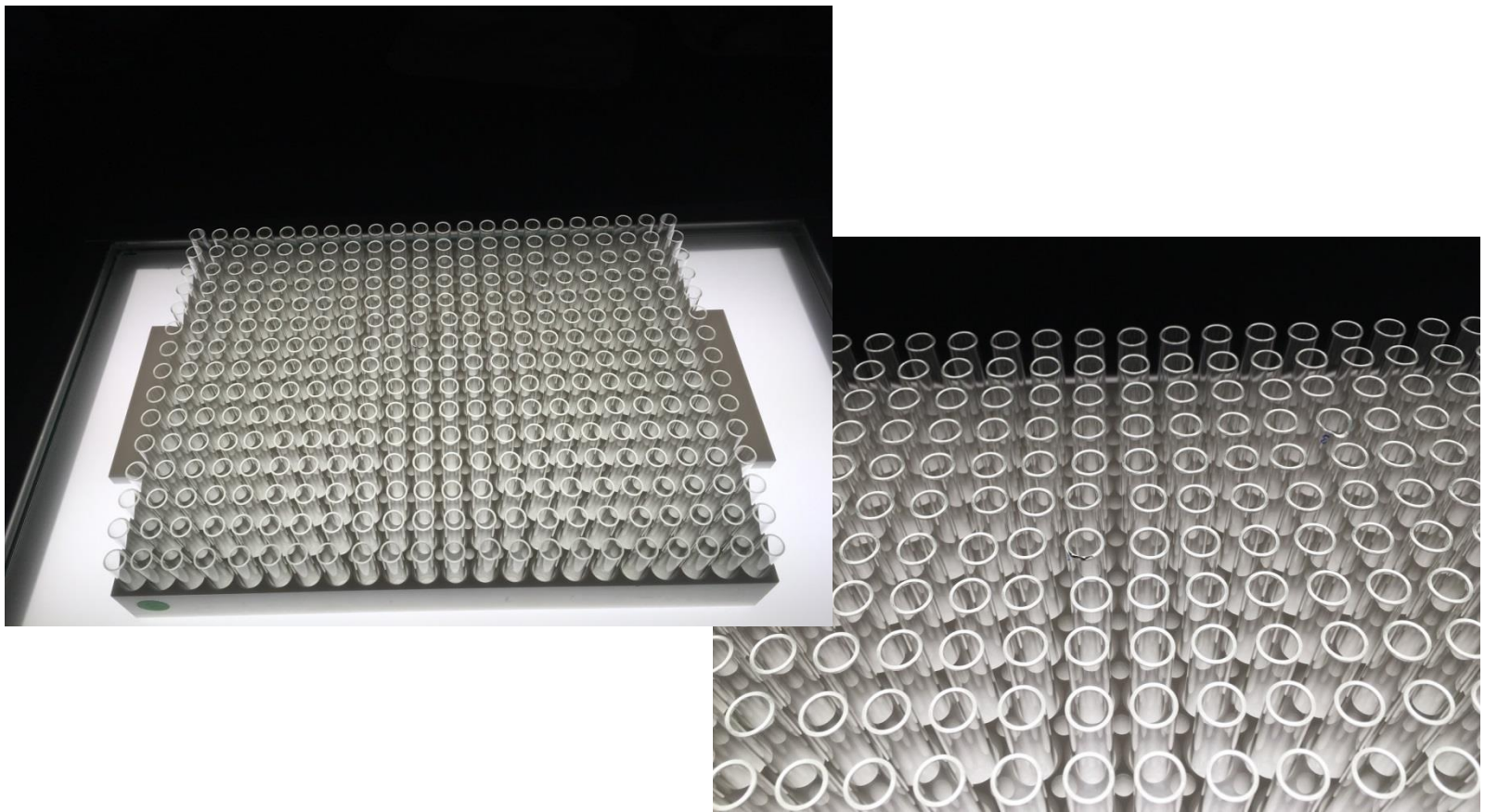
- Investigation of glass stability pre-/ post-shipment



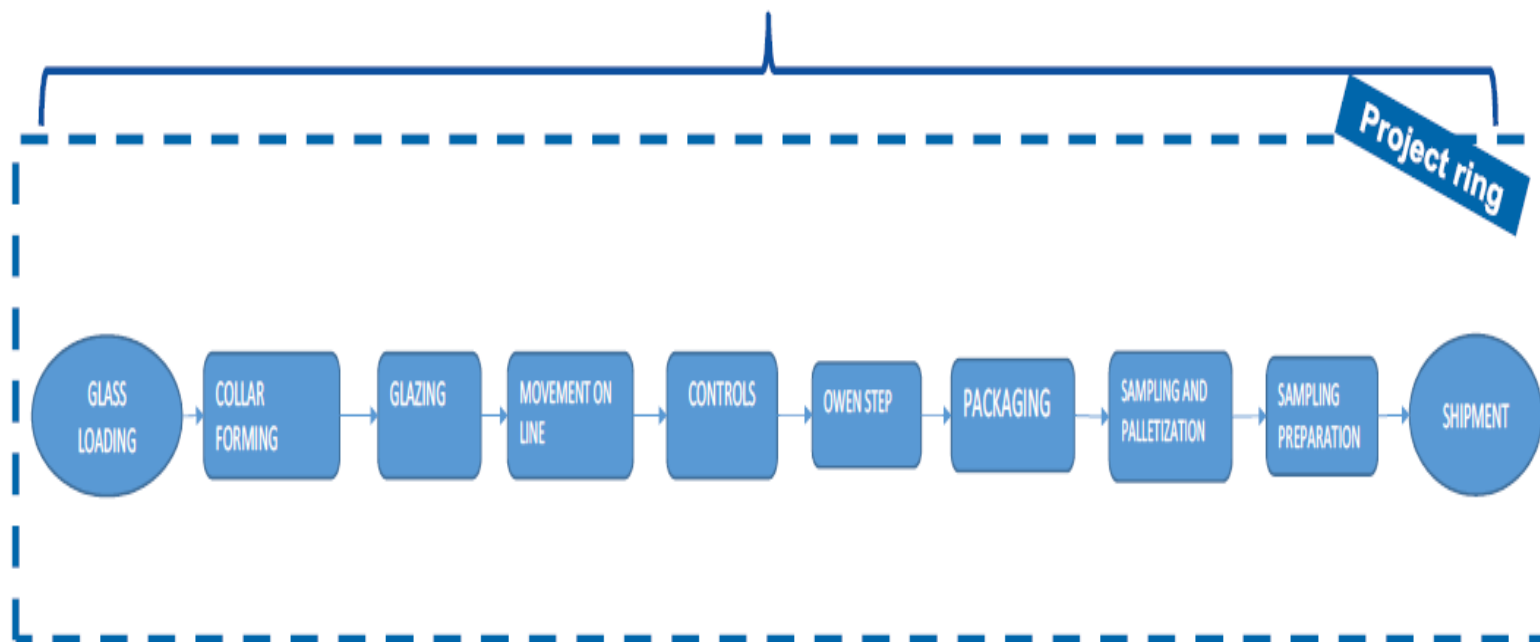
- Improvement potential identified for processing of Tailgate samples



- Improvement potential visual inspection (light box)



- System investigation at supplier



Outcome: Further standardization of glazing parameters on the hot forming lines to improve glass stability and therefore to prevent chipping defects

- CONCLUSION
  - Single root cause could not be identified
  - Several contributing factors have been identified and related improvements implemented at both parties
  - Since implementation of the related CAPAs no further batches have been rejected
  - Partnership with supplier is an important factor for resolution of this type of issues



- CHIPS – Single event or indicative for batch quality

- A fragment of glass missing or broken away from the surface. No malfunction
- Location: general

Source	Class	Remarks
FBL	Minor	Non-functional areas, no malfunction
PDA	Major A	If seal integrity in sealing area is not compromised
	Major B	otherwise



## Chipped Sealing Surface

**Location:** Seal Surface

**Class:** Critical if seal integrity compromised;  
Major A if seal is intact.



A finish that has a small section or fragment missing or broken away from the sealing surface.

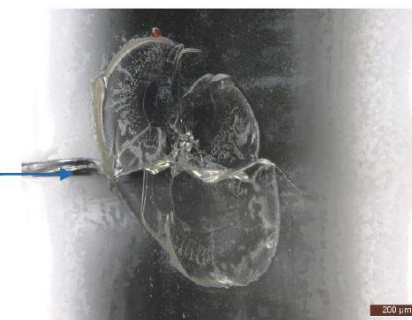
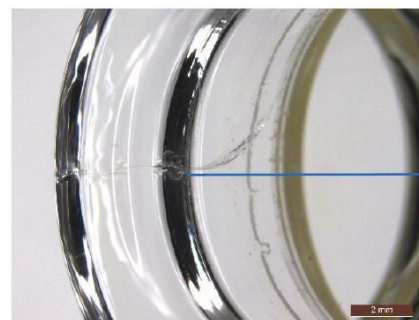
- **Rare single glass defects**



Glass defect with a hole in the shoulder area, causing leakage during use



Turbid vial identified during inspection with a passed-through crack that caused a loss of integrity



Defect is ascribable to a glassy spot – may function as a stress concentrator factor

## Summary of Controls

- Supplier
  - IPC: Inspection during processing
  - Final QC: Inspection of finished product
  - Reference Samples
- Pharmaceutical Manufacturer
  - Receiving/Incoming QC: Inspection for quality-determining parameters and/or the manufacturer's (supplier) certificate
  - Documentation: Recording of inspection data in suitable archives
  - Reference Samples



Thank You!

## ● References

- EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines
  - Part I, Chapter 1: Pharmaceutical Quality System
  - Part I, Chapter 4: Documentation
  - Part I, Chapter 5: Production
  - Annex 8: Sampling of Starting and Packaging Materials
  - Annex 19: Reference and Retention Samples
- Code of Federal Regulations 21 CFR 211
  - Section 211.80 General requirements
  - Section 211.84 Testing and approval or rejection of components, drug product containers and closures
- ISO 15378:2017 Primary packaging materials for medicinal products -- Particular requirements for the application of ISO 9001:2015, with reference to good manufacturing practice (GMP)
- DIN ISO 2859 Sampling Procedures for Inspection by Attributes, -3 Skip Lot Testing
- DIN ISO 13926 Pen Systems - part 1: Glass Cylinders for Pen-Injectors for Medical Use
- PDA Technical Report-43 Revised: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers, for Pharmaceutical Manufacturers, 2013
- Principles for the Defect Evaluation Lists for Packaging Material, Edito Cantor Verlag fur Medizin und Naturwissenschaften GmbH, 5th Edition 2017

- References Pharmacopeias
  - Glass Testing Procedures
    - USP/NF Section <660> Type I Highly Resistant Borosilicate Glass
    - Ph. Eur. 3.2.1 Glass Containers for Pharmaceutical Use
    - Japanese Pharmacopeia 7.01 Test for Glass Containers for Injections
  - Endotoxin- / Bioburden- Testing
    - Endotoxin LAL-Test (according to Ph. Eur. 2.6.14 ; USP <85>, JP)
    - Bioburden (according to Ph. Eur. 2.6.1; USP <71>, JP)
  - Visible Particles
    - Ph. Eur Method 2.9.20 Particulate Contamination, Visible Particles