



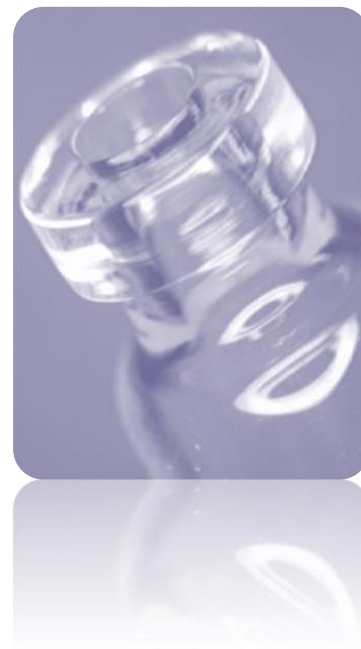
Glass Handling Best Practices for Glass Primary Containers

PDA Training Course, Mainz, October 18th/19th 2017

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Sanofi Site Frankfurt Insulin*

- **Course Overview**

- 1 Requirements (from pharmacopoeias) regarding 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**





- General Remarks
 - Packaging is an integral part of any pharmaceutical product
 - It affects the quality, stability and identification of drug product
 - Provides an adequate degree of protection
 - Should not interact physically or chemically with the drug product
 - No risk of toxicity

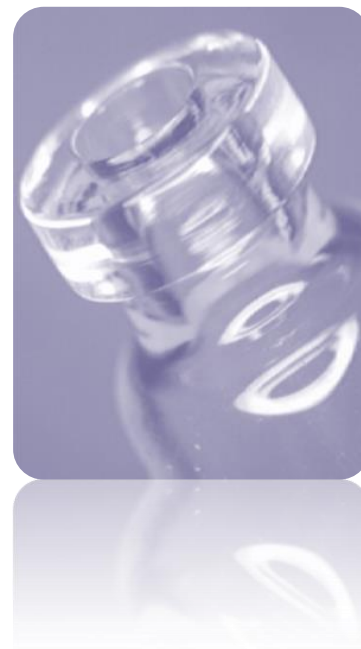
- General Remarks

- 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 packaging material from different suppliers may result in certain variations within the agreed tolerances, which may require readjustments of the filling line
- Special requirements for
 - Pen-Systems or Auto-Injectors
 - New products or special applications



- Overview

- 1 Requirements (from pharmacopoeias) regarding 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





- Contents
 - **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. ..

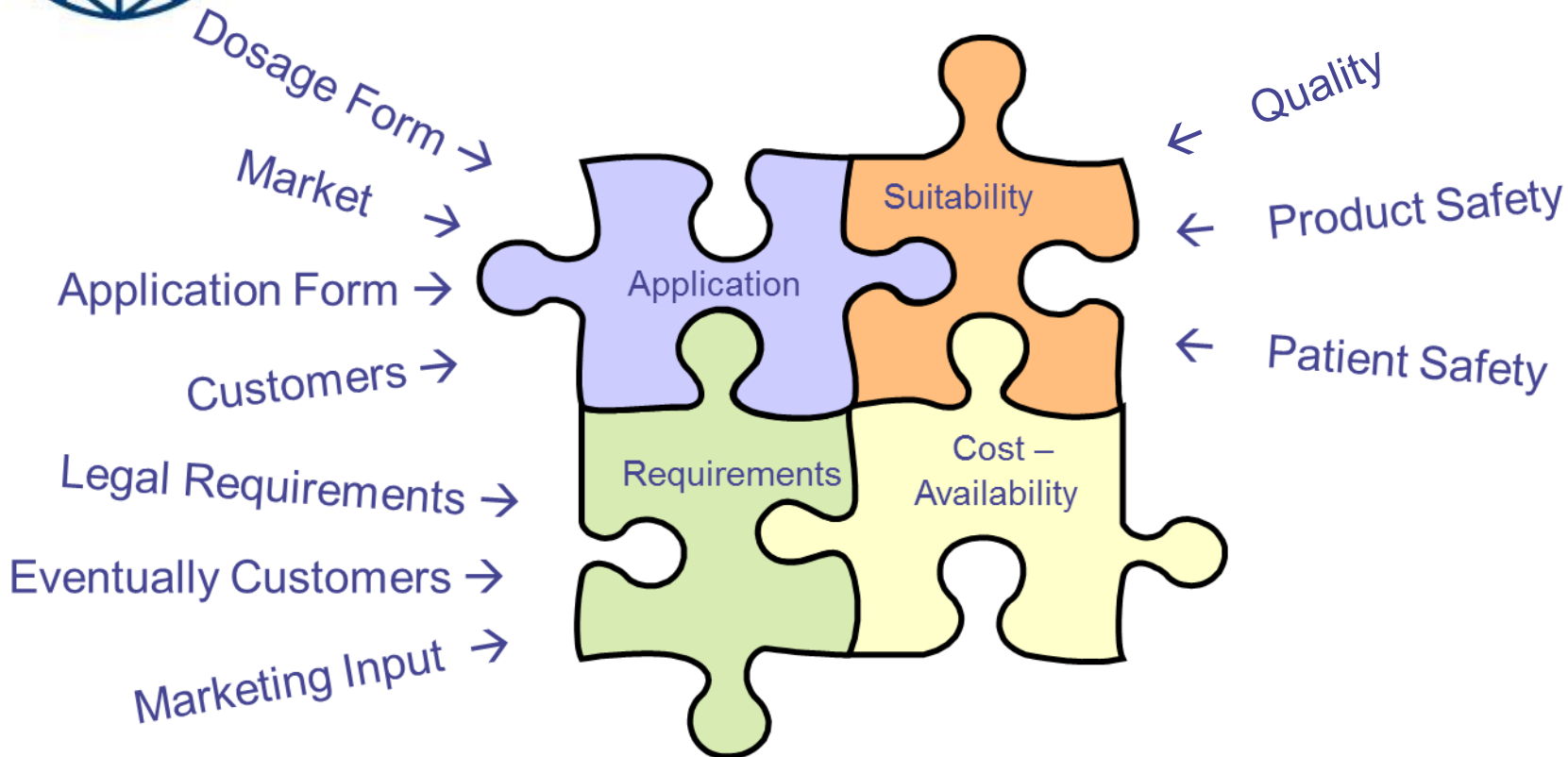
- Specifications / Acceptance Criteria
 - What are acceptance criteria?
 - Who specifies these criteria?

- Test Parameter
 - Definition of test parameter

- Test Methods
 - Identification of methods based on test parameter

ACCEPTANCE CRITERIA

- ... based on the intended use of the glass container
 - **Dosage form?**
 - **Which markets? EU/ US/ JP**
 - **Kind of application? Oral, injection, inhalation**
 - **Legal regulations and laws? AMG, Ph.Eur., USP, JP, cGMP**



Nobody knows it better than you !

TEST PARAMETER

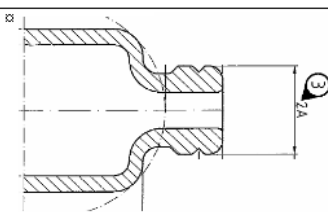
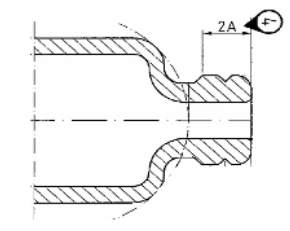
- ... can be defined based on Acceptance Criteria

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

- 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!



- Example of an individual risk based defect categorization

Maß-Nr. □	Technical Drawing	Nomenclature	Risk prod technical	Classification
3 □		Flange (Collar) Outside Diameter	<input type="checkbox"/> 1 ¶ <input checked="" type="checkbox"/> 2 A ¶ <input type="checkbox"/> 2 B ¶ <input type="checkbox"/> 3 □ ↓	Potential Impact on Container Closure Integrity
4 □		Flange (Collar) Height	<input type="checkbox"/> 1 ¶ <input checked="" type="checkbox"/> 2 A ¶ <input type="checkbox"/> 2 B ¶ <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 ² on the outer surface of the glass barrel; closure integrity not impaired <i>Formmarken und narbige Erscheinungen > 1 mm² 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 the 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)?
 - **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

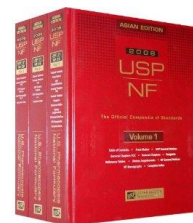
Type III glass □ soda-lime; moderate chemical durability; for tubing and moulding; high thermal expansion; non suitable for injectable liquids; variously coloured.

- 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)



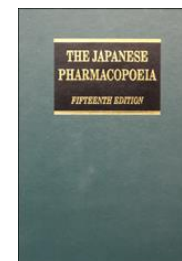
Relevant European Pharmacopeia Testing

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

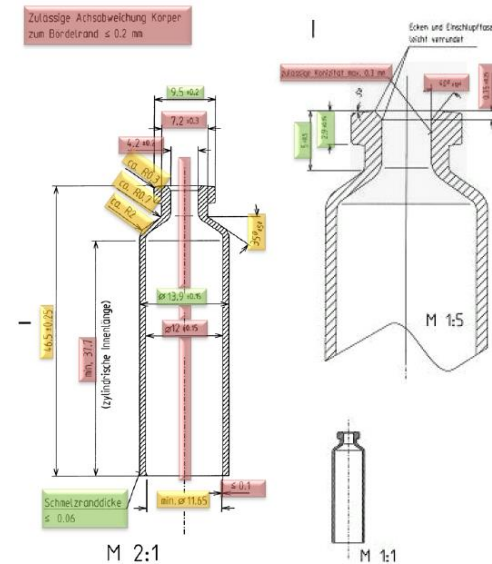
LAL-Test (according to Ph. Eur. 2.6.14 ; USP <85>, JP)

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)
- Three dimensional camera control



- VISUAL INSPECTION - INSPECTION BY ATTRIBUTES

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

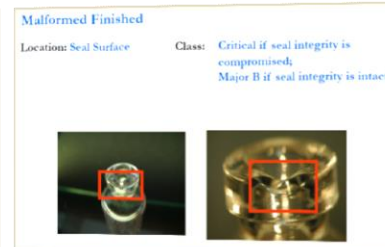
- Defects are described and classified

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



- 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 the control units should also be taken into consideration
- Defects may not be equally distributed across the batch manufacturing process

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Excerpt TR 43 PDA Glass Task Force

Glass Nonconformity Lexicons (PDA TR 43)

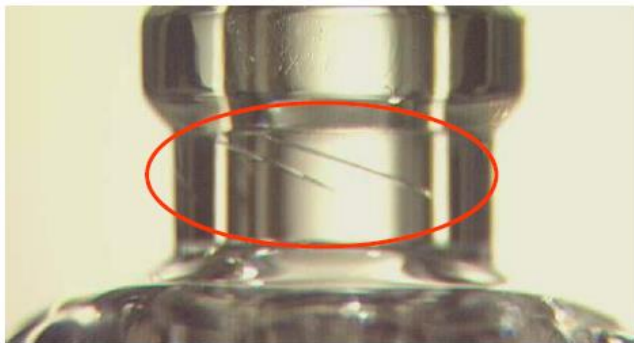
CRITICAL	<i>A Nonconformity that is likely to result in personal injury or potential hazard to the patient (including defects that compromises the integrity of the container.</i>
MAJOR A	<i>... leading to serious impairments e.g. a malfunction that makes the packaging unusable</i>
MAJOR B	<i>Impairments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

- 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

- Defects and Acceptance Levels
 - Prevailing method for evaluation of defects is the AQL system (Acceptable Quality Levels) based on DIN ISO Norm 2859. Acceptable defect rates for the control samples are defined.
 - The actual AQL – value for a sample unit defines the acceptance and rejection rates based on a statistical defect distribution.



- Defects and Acceptance Levels
 - The control sample unit is important for the evaluation of defects
 - Samples should be representative and randomized across the entire batch
 - The number of samples for incoming inspection depends on the batch size and the defined acceptable defect rate
 - The lower the acceptable defect rate the higher the number of samples

- DIN ISO 2859 defines different inspection levels
- Depending on the batch size and the inspection level a code letter is determined

Losumfang	Spezielle Prüfniveaus				Allgemeine Prüfniveaus		
	S 1	S 2	S 3	S 4	I	II	III
2 bis 8	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	L	N
35 001 bis 150 000	D	E	G	J	L	M	P
150 001 bis 500 000	D	E	G	J	M	N	Q
500 001 und mehr	D	E	H	K	N	Q	R



Excerpt DIN ISO 2859

- Code letter defines the number of control sample units
- Acceptance / rejection numbers are listed in the AQL columns

Tabelle 2-A — Einfach-Stichprobenanweisungen für normale Prüfung (Leittabelle)

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		
		Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	
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

- In most cases control samples are pulled by the supplier during manufacturing
- Sampling is an important process in operation
- 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 (Tailgate Samples)

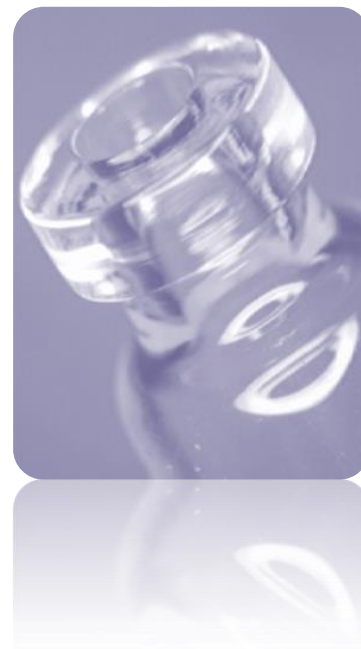




END OF PART 1

- Overview

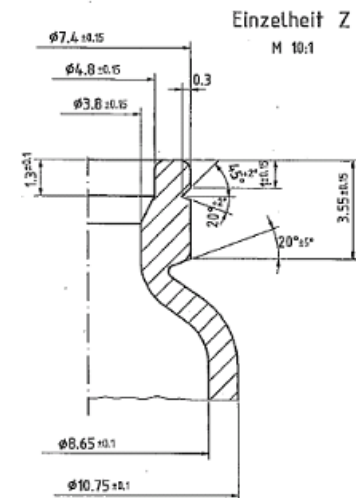
- 1 Requirements (from pharmacopoeias) regarding incoming inspection
- 2 **How to do it in practice**
- 3 What to consider or to avoid (examples)
- 4 Coordination process between packaging manufacturer and customer



- Contents
 - **Specification**
 - **Sampling**
 - **Sample size (AQL)**
 - **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*



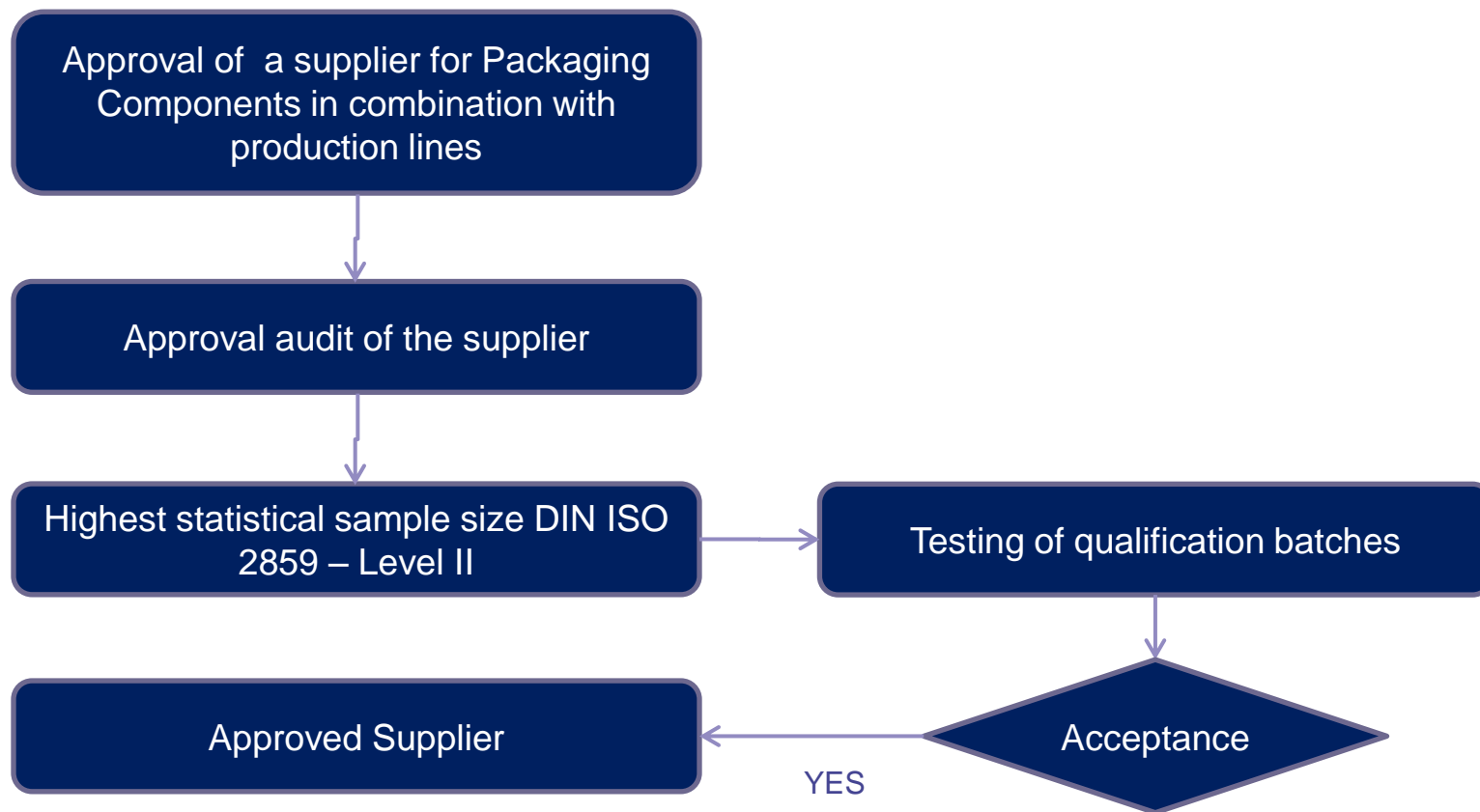
Specifications (EU-GMP; Kap. 4)

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



Quality Agreement!

Supplier Approval Process



Tailgate Samples with each Delivery

Samples are collected by supplier in accordance to the DIN ISO 2859 Level II and the agreed Packaging Specification

Samples are separated on the delivery

Delivery with CoA
(Certificates of Analysis)

Booking process creates a specific test protocol, which includes all parameters for incoming control



Index of a Packaging Material Specification (Example)

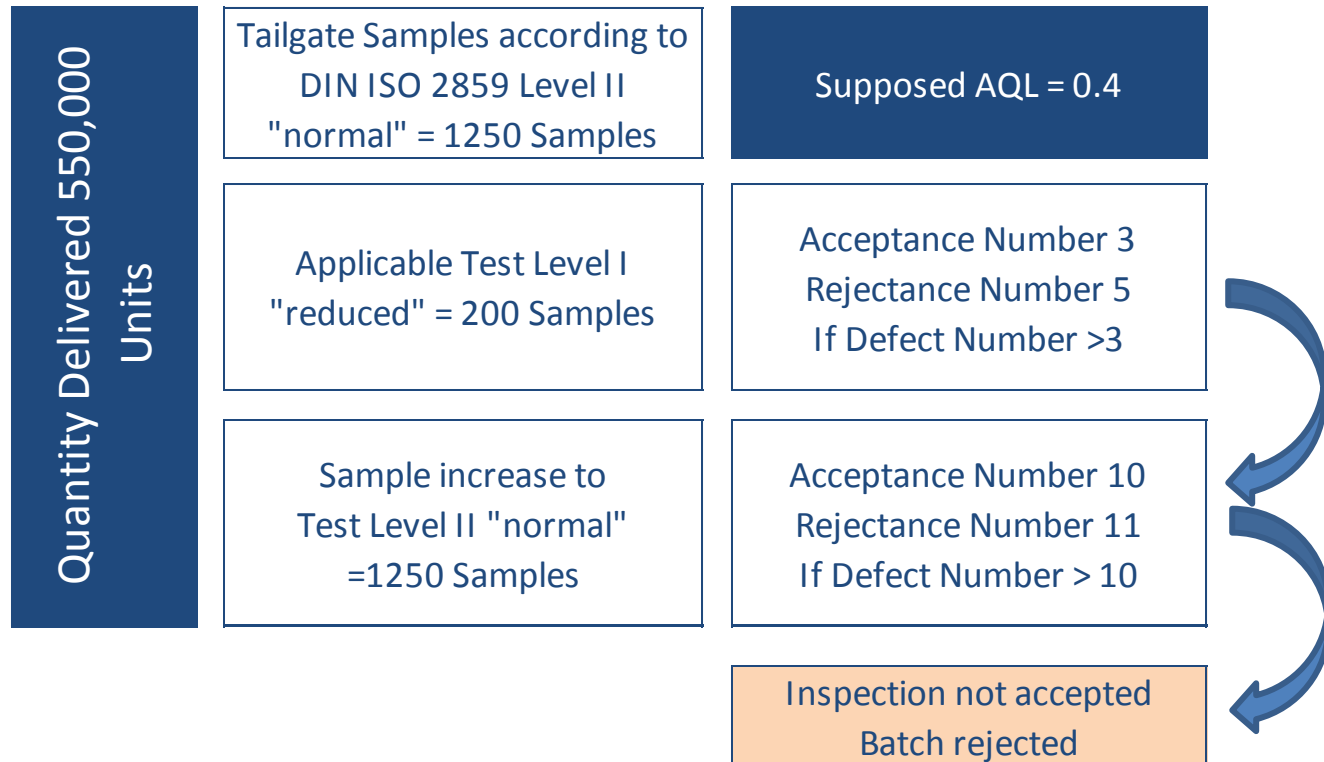
- 1. Material Specific Chapter – Technical Drawing
- 2. General Chapter
 - 2.1 Material & Design
 - 2.2 References & Standards
 - 2.3 Packaging Instructions
 - 2.4 Quality Acceptance Criteria
 - 2.5 Supplier control samples (sampling plan)
- 3. Characteristics / Specifications
 - 3.1 Criteria for Batch 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**
- ⇒ **Visible damage**
- ⇒ **Documents (Delivery slip, Certificates)**
- ⇒ **Correct supply chain**



Example of an inspection approach (by attributes)

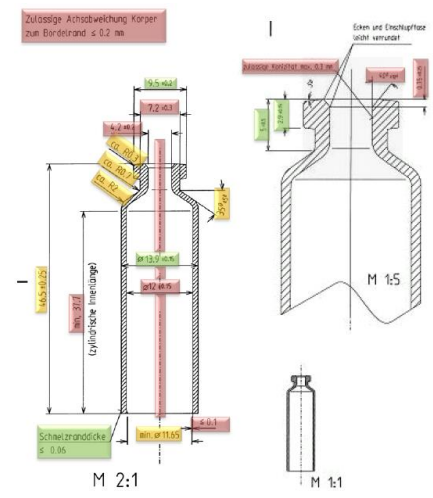
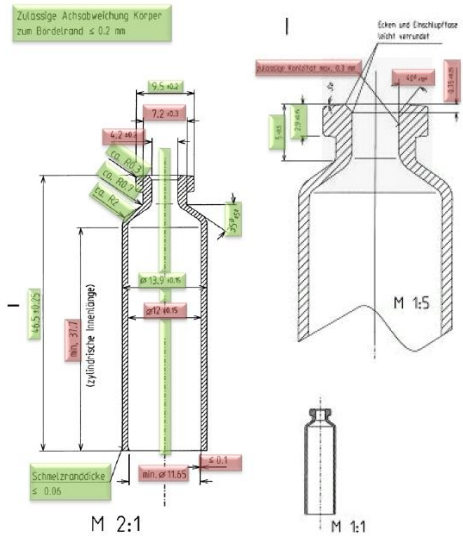


Visual Inspection

- 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
 - Period under review
 - Viewing background



Dimensional Inspection



Dimensional Inspection

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

Rotating measurement

Bent

Location: Finish/Neck

Class: Major B(Limit Sample*)

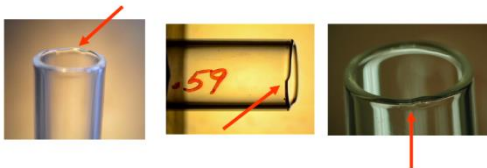


The finish and plane of the seal surface is not perpendicular to axis of the body.

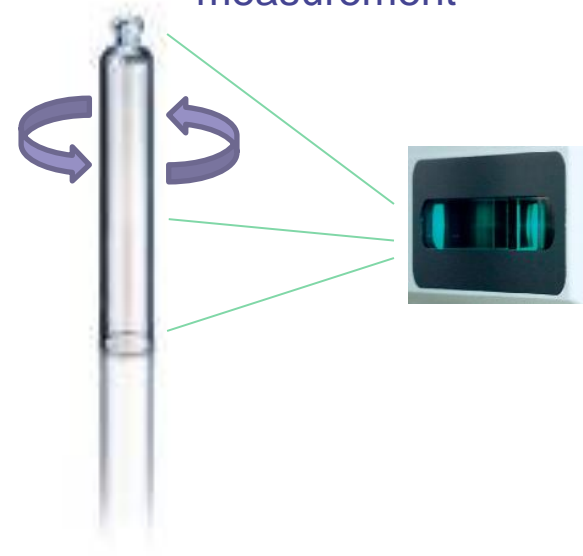
Bad Cut

Location: Cut End

Class: Minor



Poor cut resulting in an irregular glazed end



- Documents relevant for batch release

- Supplier documentation

- Certificate
- Specifications
- Test Protocol
- Delivery slip

- Inspection documentation

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



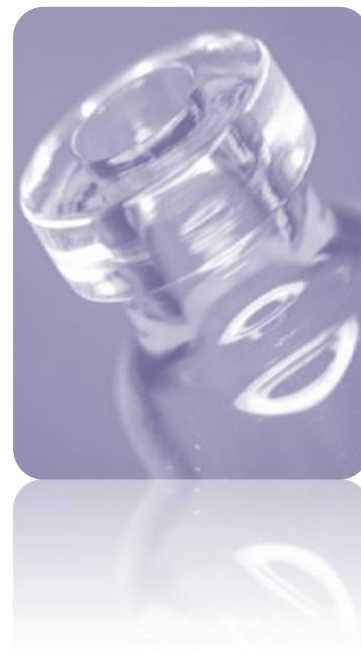
Test Methods
Standard Operating Procedures
Specifications



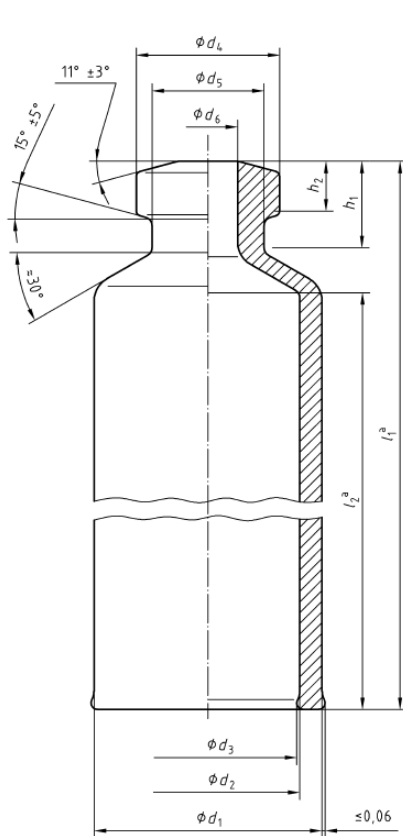
End of Part 2

- Overview

- 1 Requirements (from pharmacopoeias) regarding 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



- 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. ±	d_2	Grenz-abm. tol. ±	d_3	d_4	Grenz-abm. tol. ±	d_5	Grenz-abm. tol. ±	d_6	Grenz-abm. tol. ±	h_1	Grenz-abm. tol. ±	h_2	Grenz-abm. tol. ±
				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

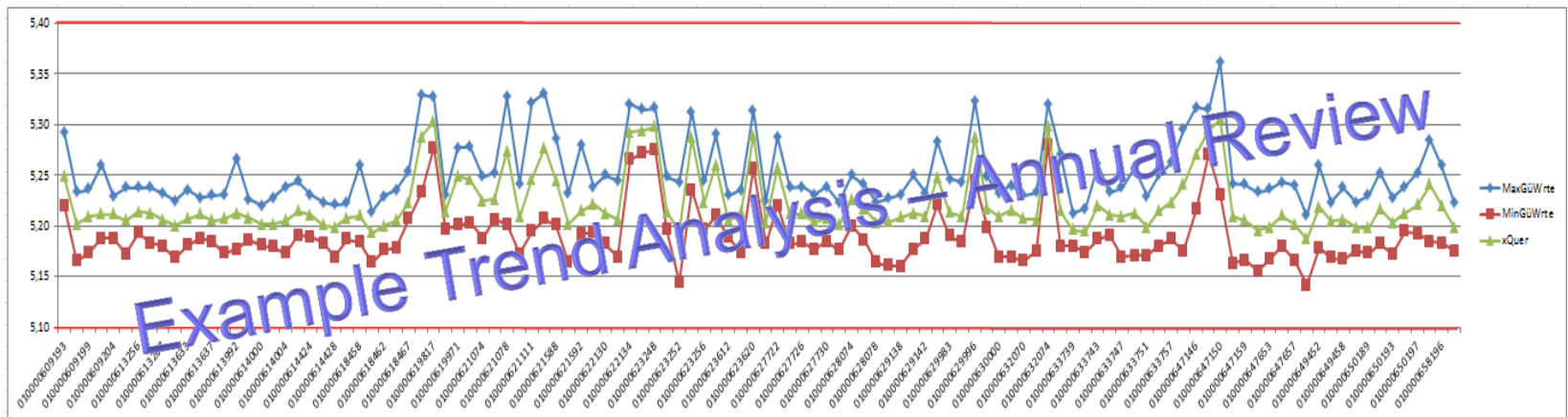
- However, these standardized tolerances might lead to unacceptable variances of certain dimensions especially on fast running filling lines
- See table h1 and h2 for flange height: This can result in variances of $\pm 0,20$ mm to $\pm 0,50$ mm depending on the format!

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

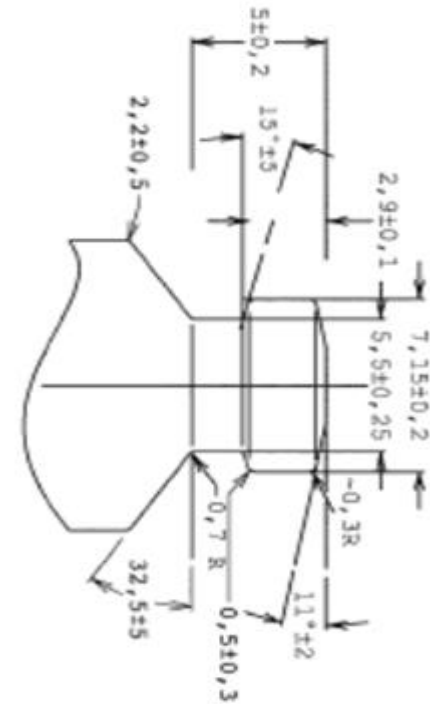
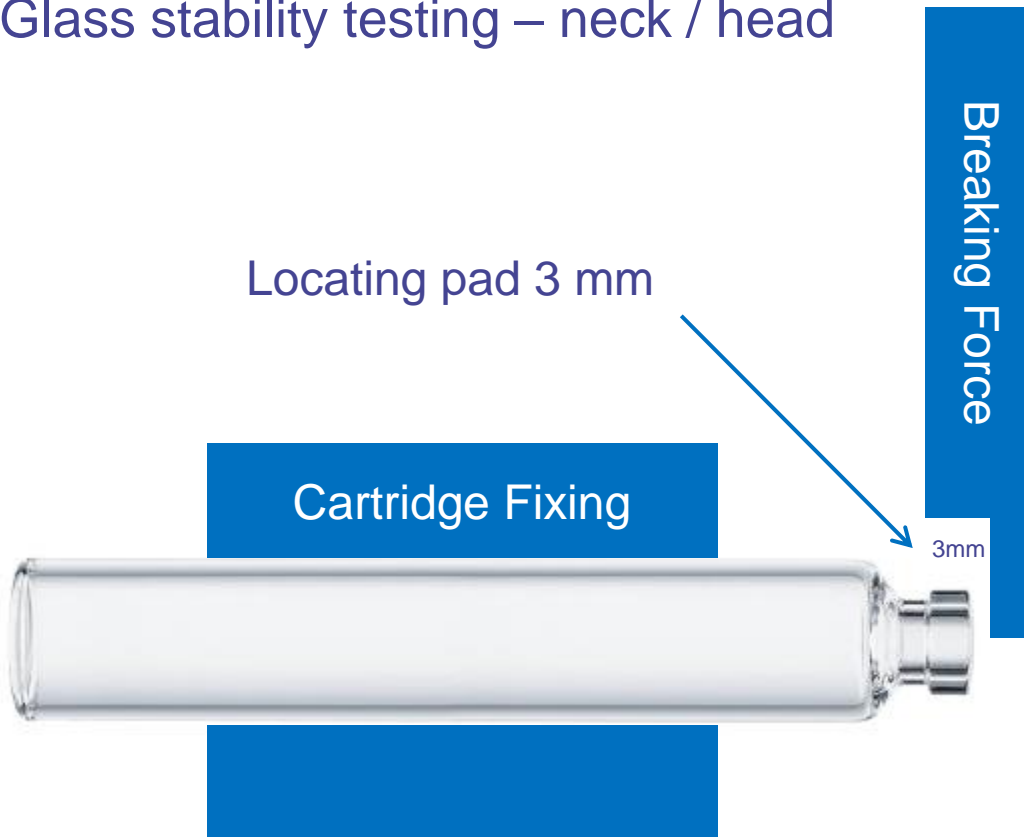
Excerpt DIN ISO 13926-1

- 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 (annual review) 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 strength**
 - **Glass to glass contacts can be critical**
 - **Methods for investigation**

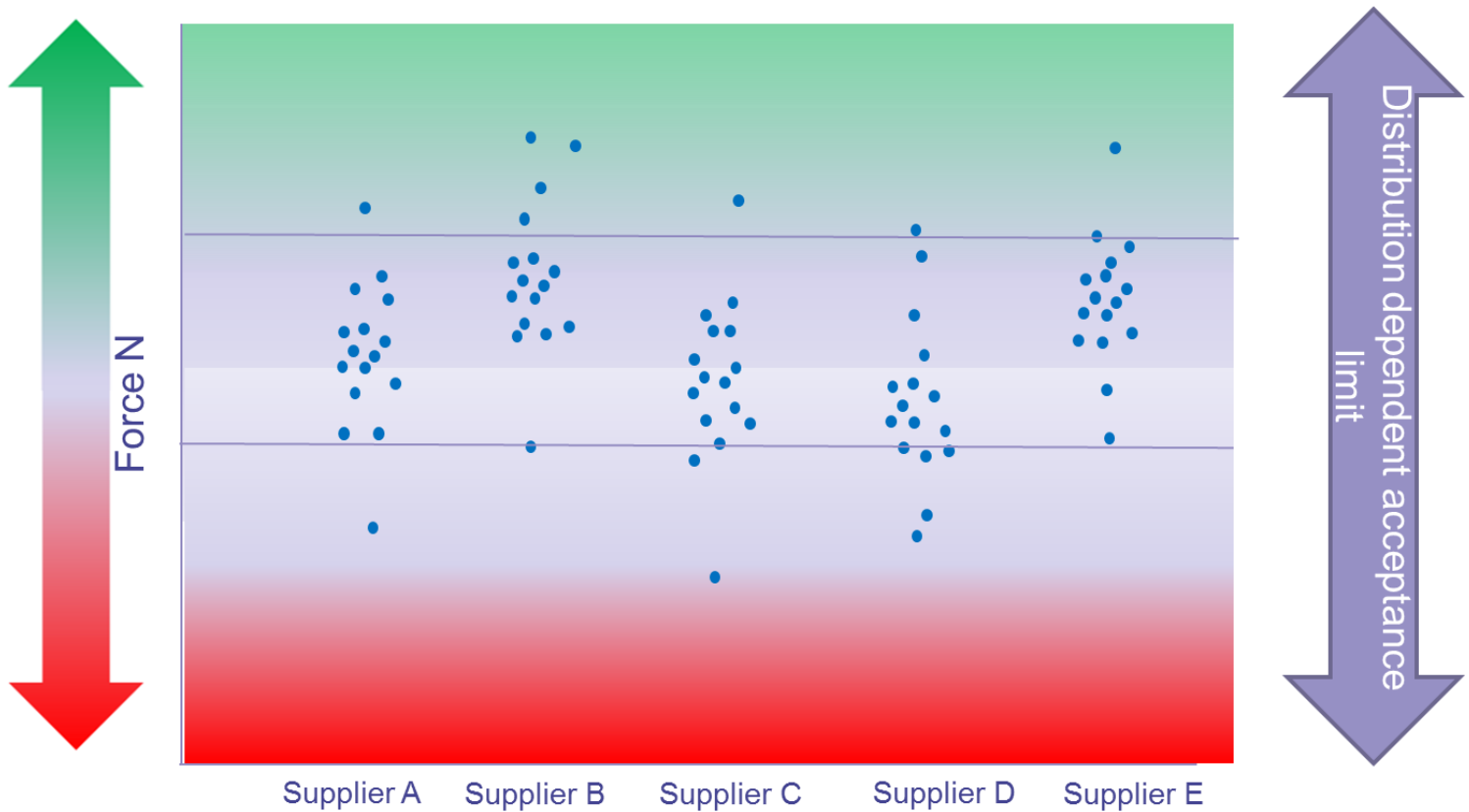
- Glass stability testing – neck / head



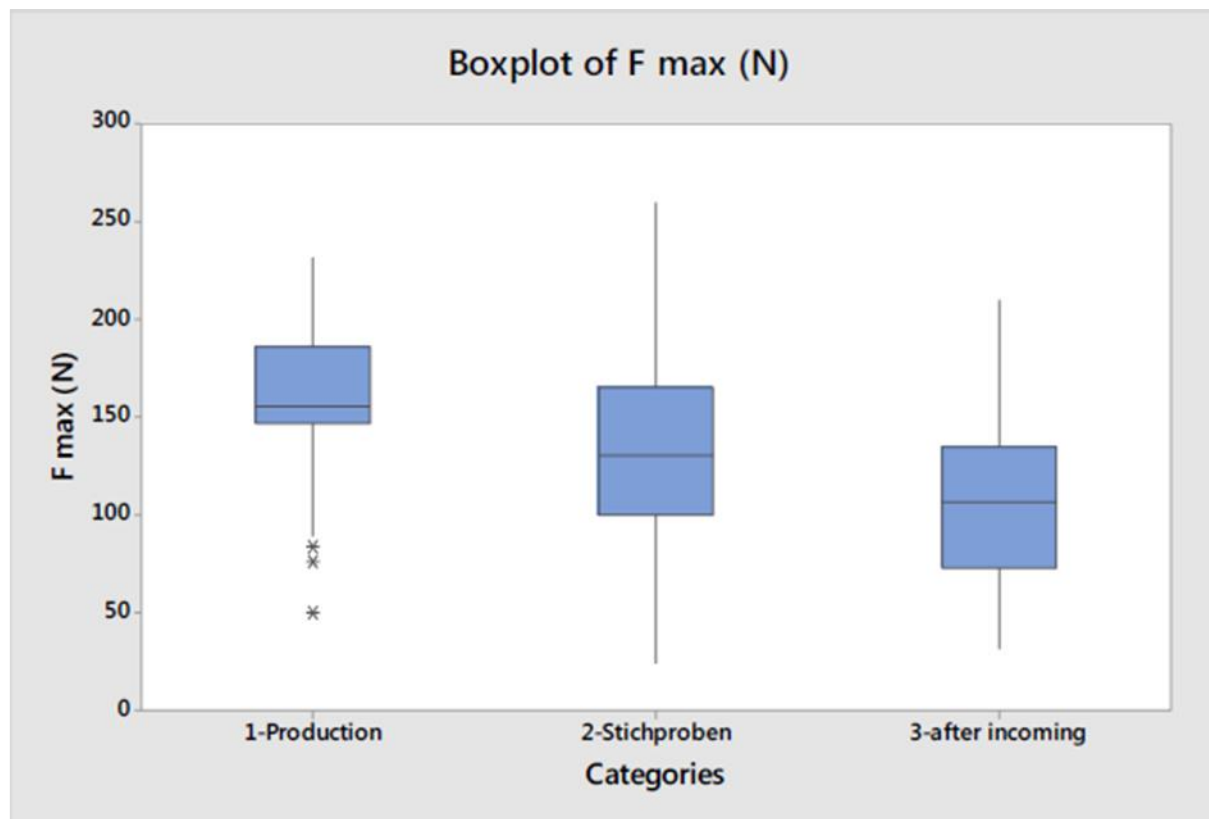
- Glass stability testing results



- Glass stability testing results

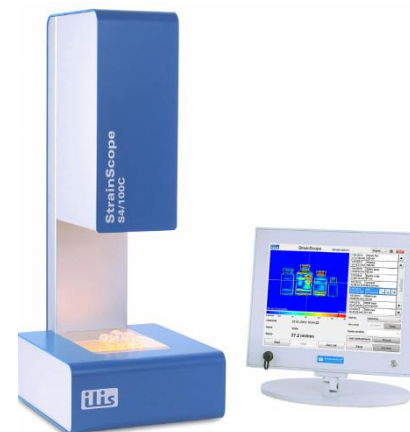
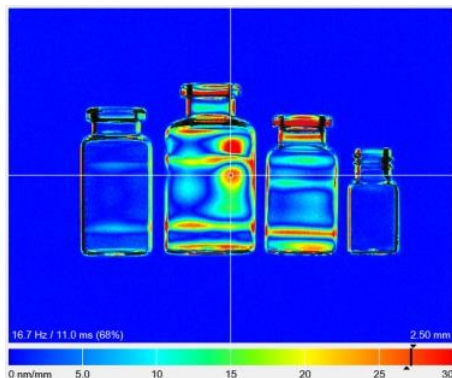


- Glass stability testing – stopper mouth



Decrease of glass stability during monitored processing steps


- Identification of residual stress



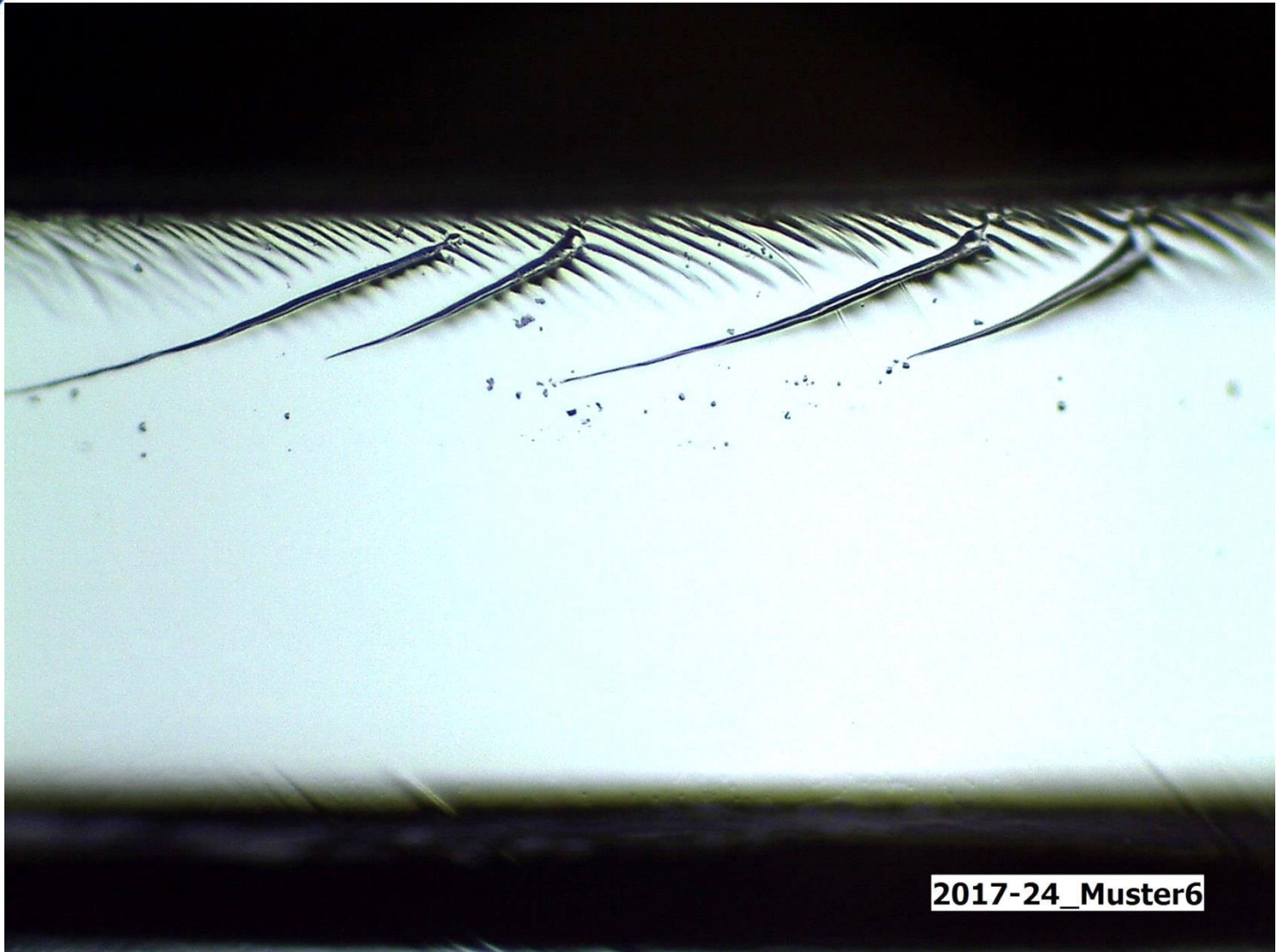
StrainScope S4 – ilis

- GMP compatible photographic documentation
- Fast multiple sample testing

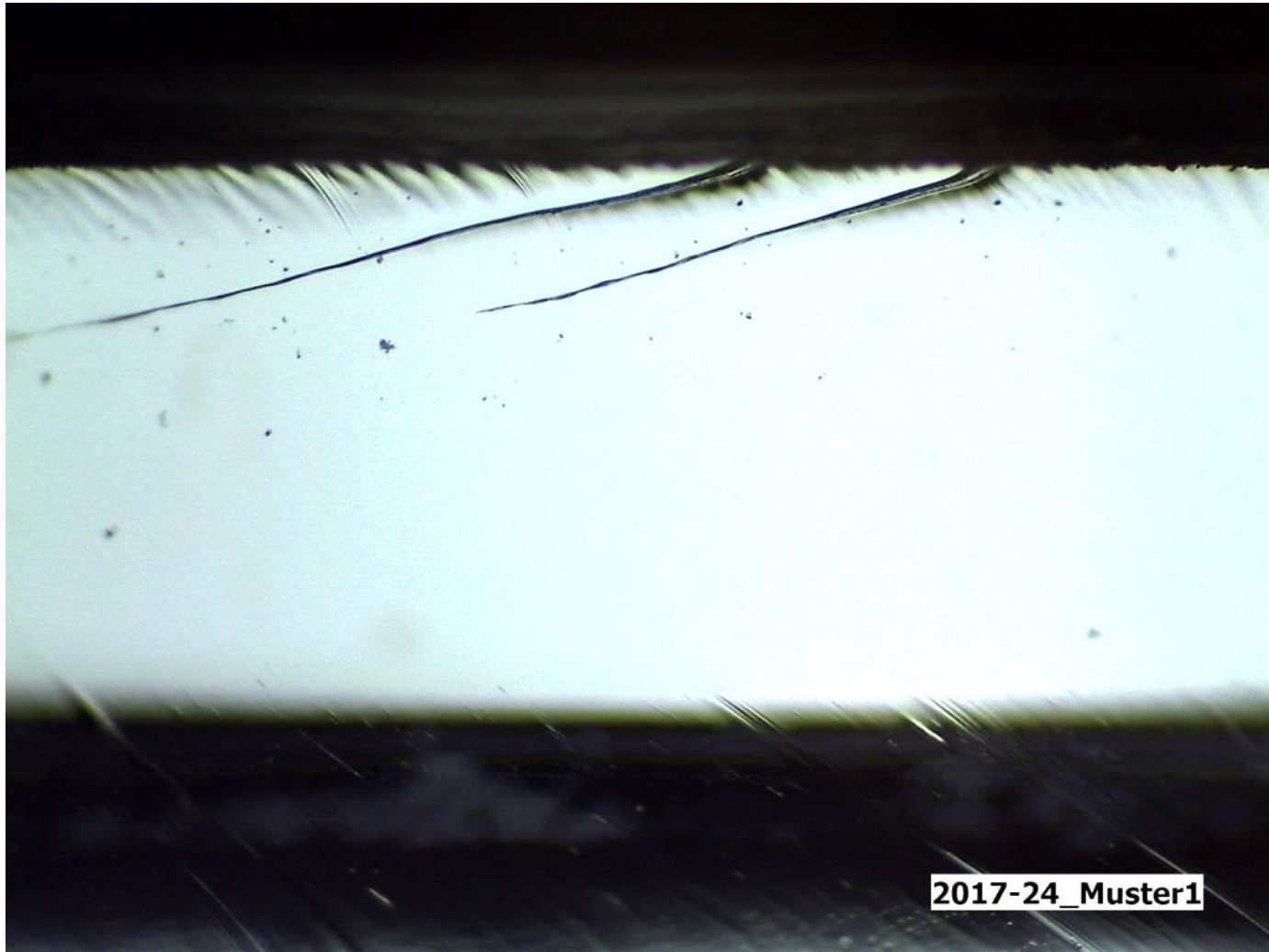
- Defects and Imperfections
 - Examples
 - Defects / Imperfections not always distributed across the entire batch
 - **Nested defects**
 - **Rare defects**

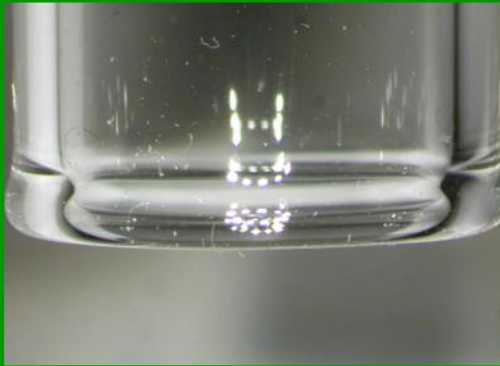
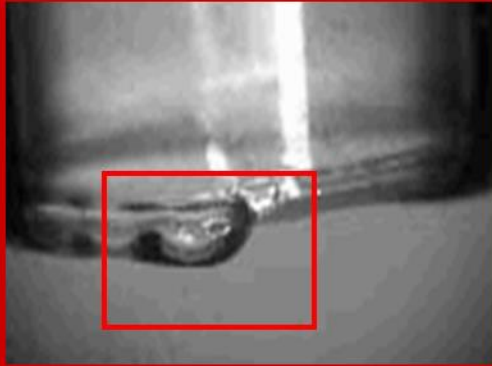
Description of Defect	Acceptable	Poor Quality
<p>Pressure / Tool Marks</p>	 <p>Faint tool marks - process related</p>	 <p>Tool marks with potential functional impact</p>

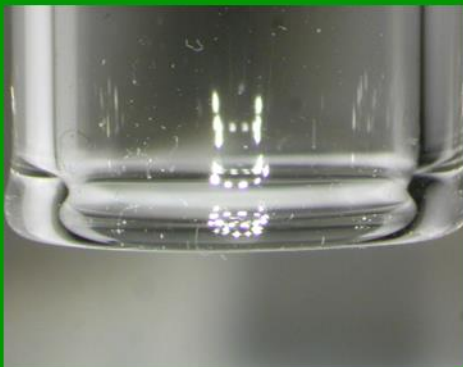







2017-24_Muster6



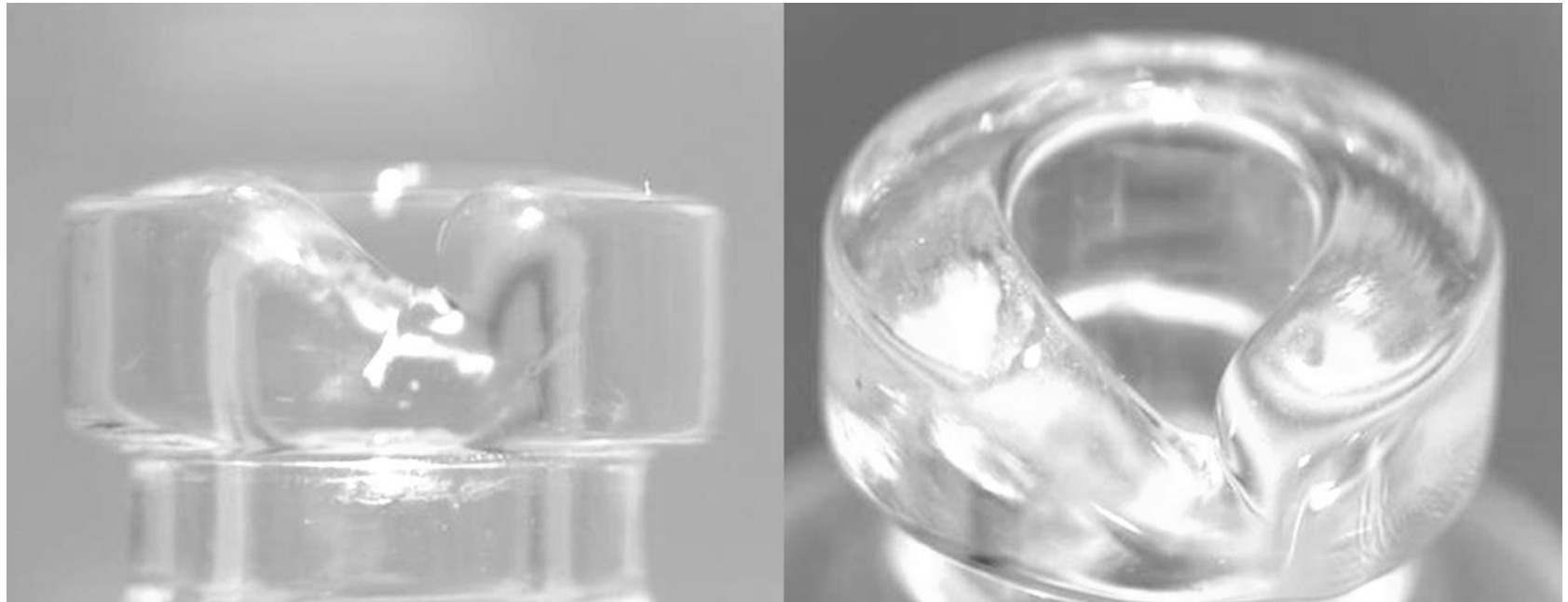
Description of Defect	Acceptable	Poor Quality
<p>Deformed or damaged cartridges, function / processing impacted</p>		 <p>Melting ring deformed</p>

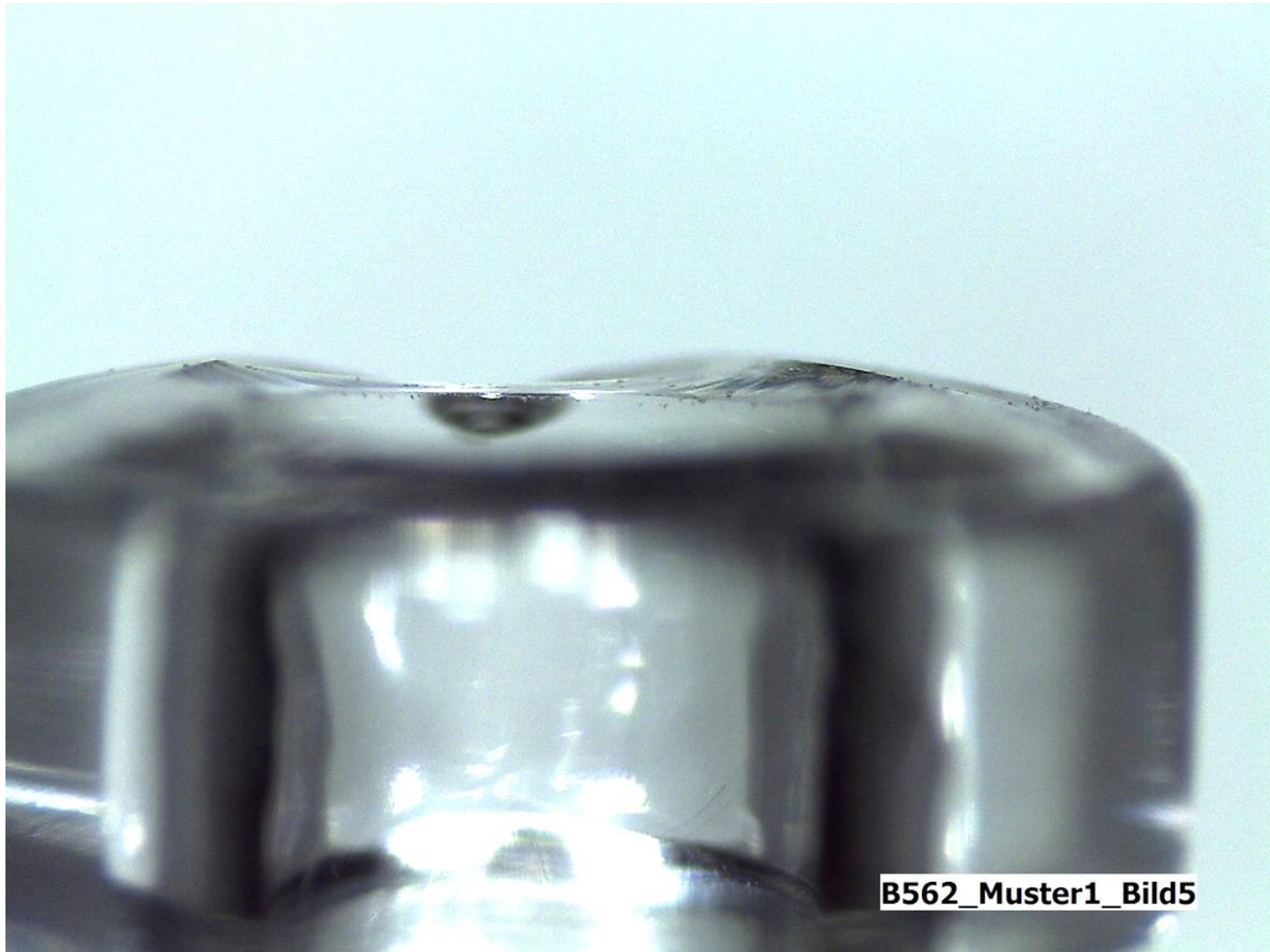
Description of Defect	Acceptable	Poor Quality
<p>Deformed or damaged cartridges, function / processing NOT impacted</p>		 <p>Molding ring slightly deformed</p>

Description of Defect	Acceptable	Poor Quality
<p>Deformed cartridge Container closure impacted</p>		


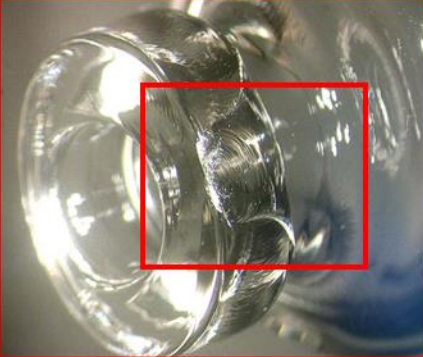


B562_Muster1_Bild4

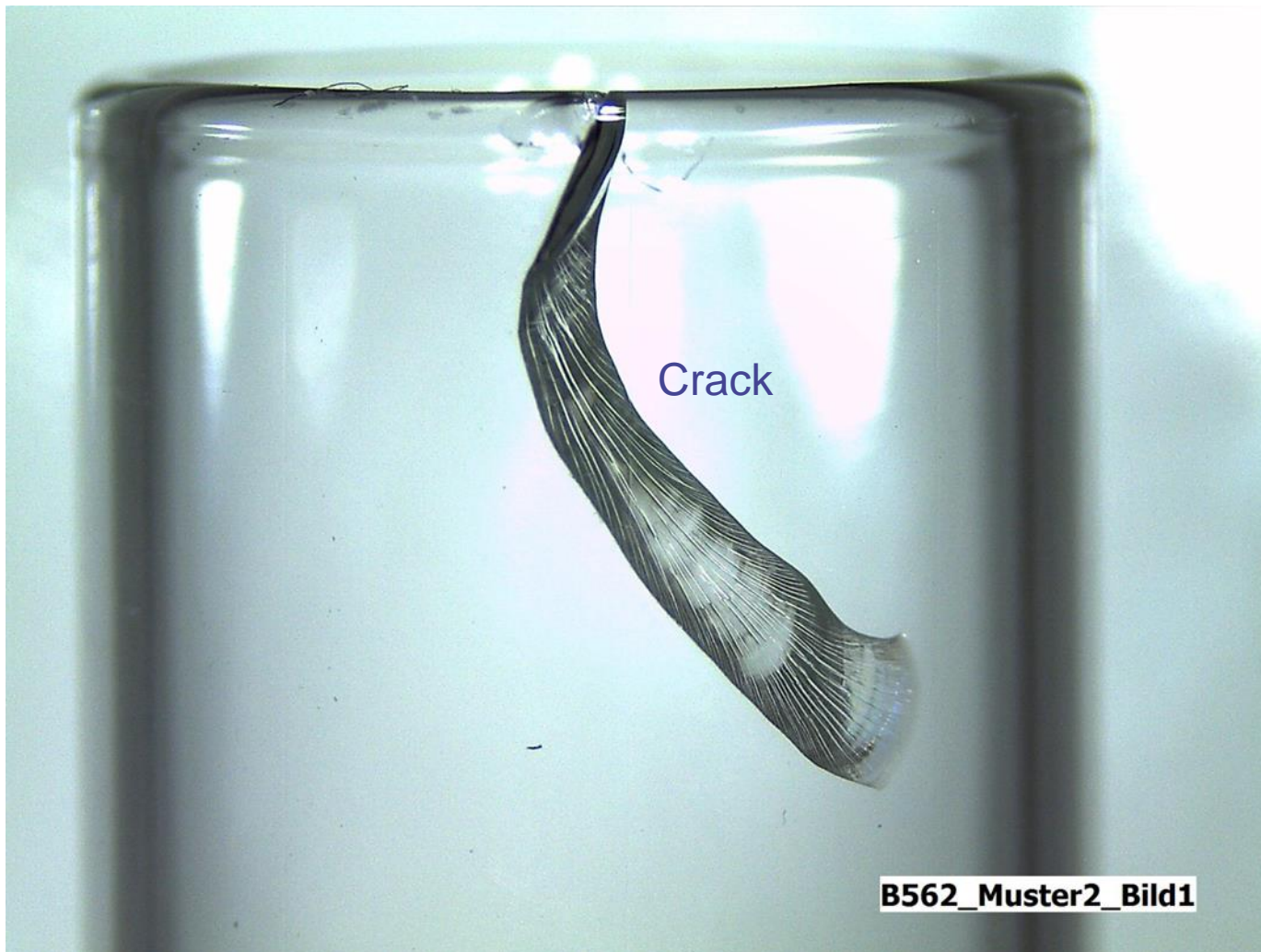




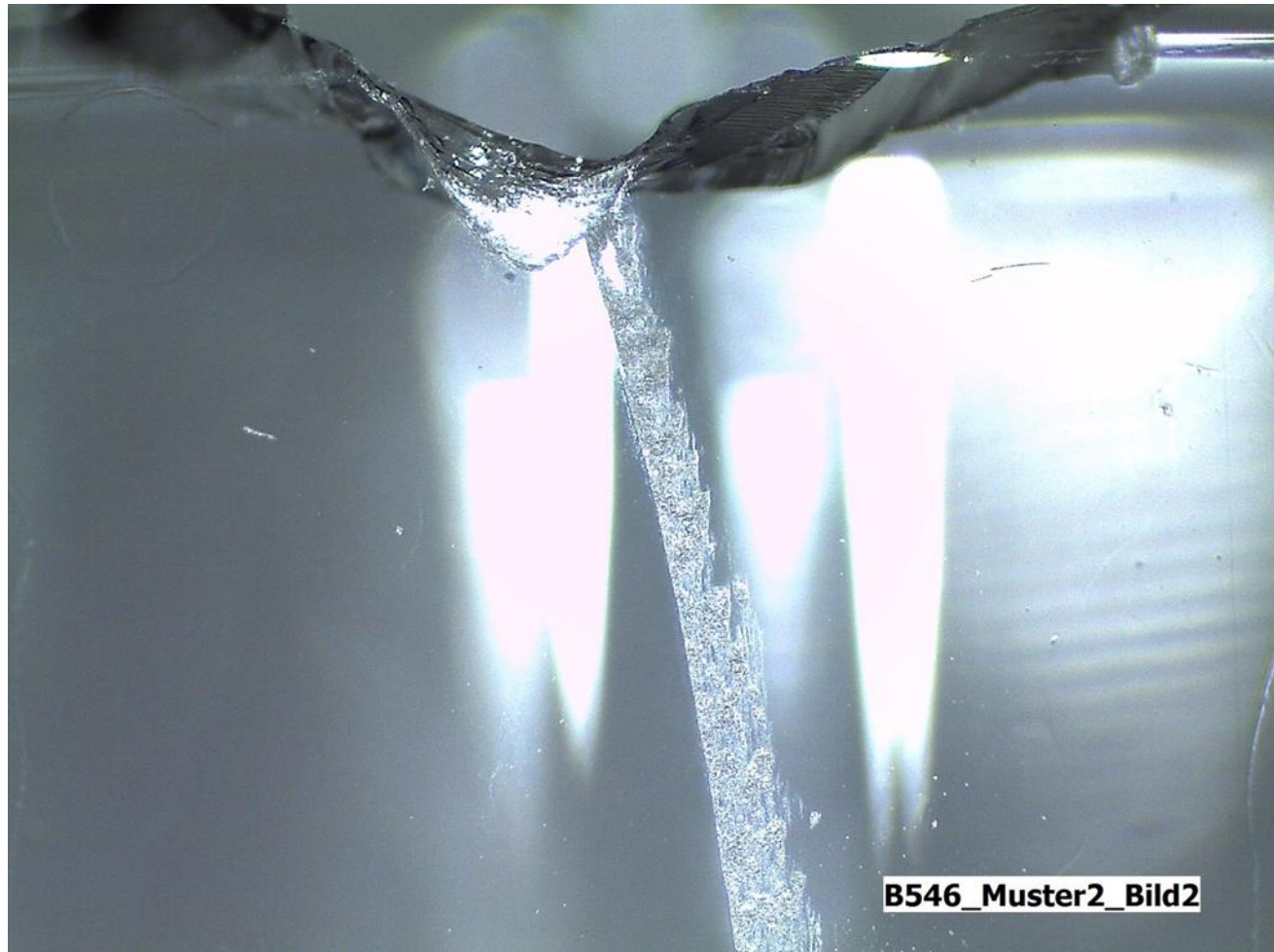
B562_Muster1_Bild5

Description of Defect	Acceptable	Poor Quality
<p>Chipped glass (Cracks)</p>	 A clear glass vial with a smooth, rounded stopper, set against a green background. The glass is clean and free of any visible defects.	 A clear glass vial with a rounded stopper, set against a red background. A red rectangular box highlights a significant chip and crack on the glass surface.

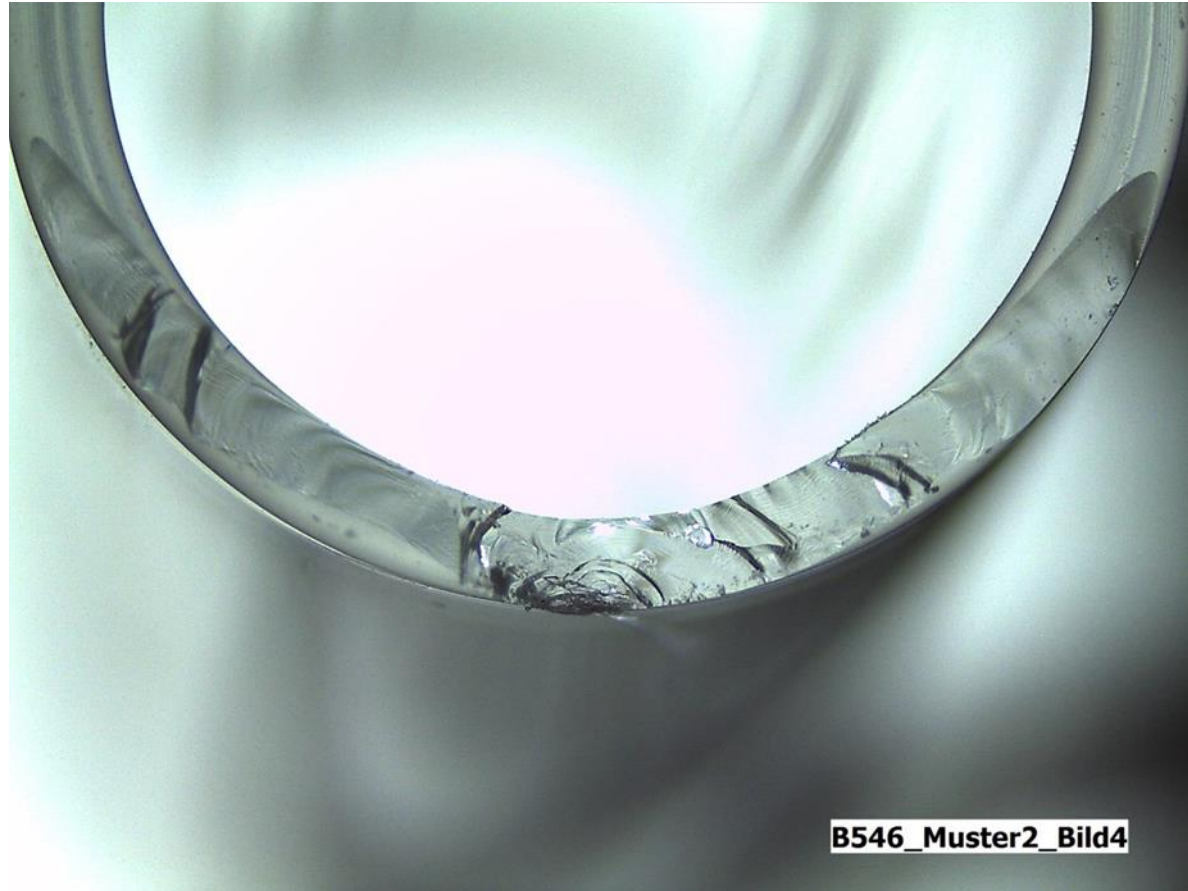




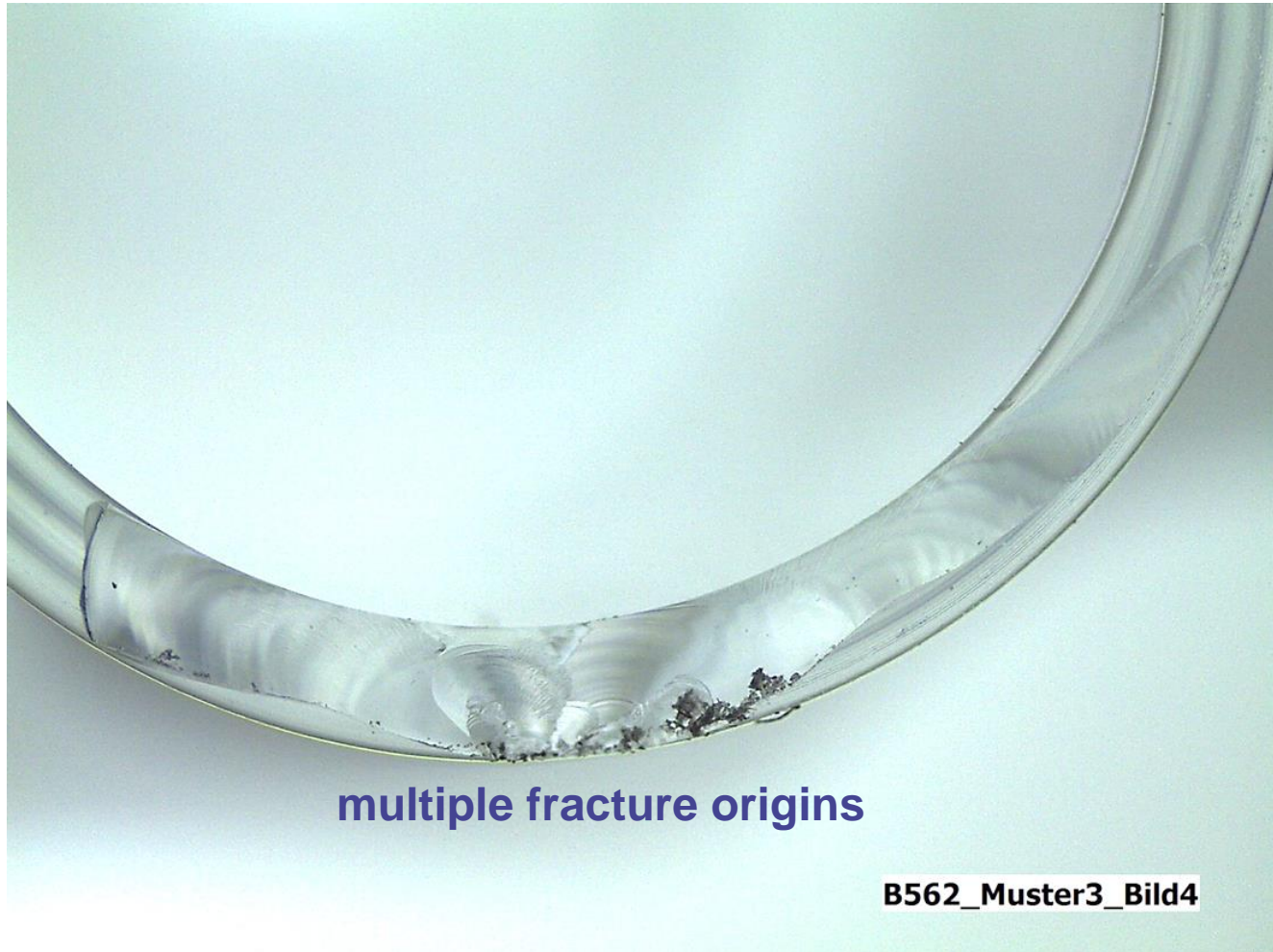
What to consider or to avoid (examples)



What to consider or to avoid (examples)



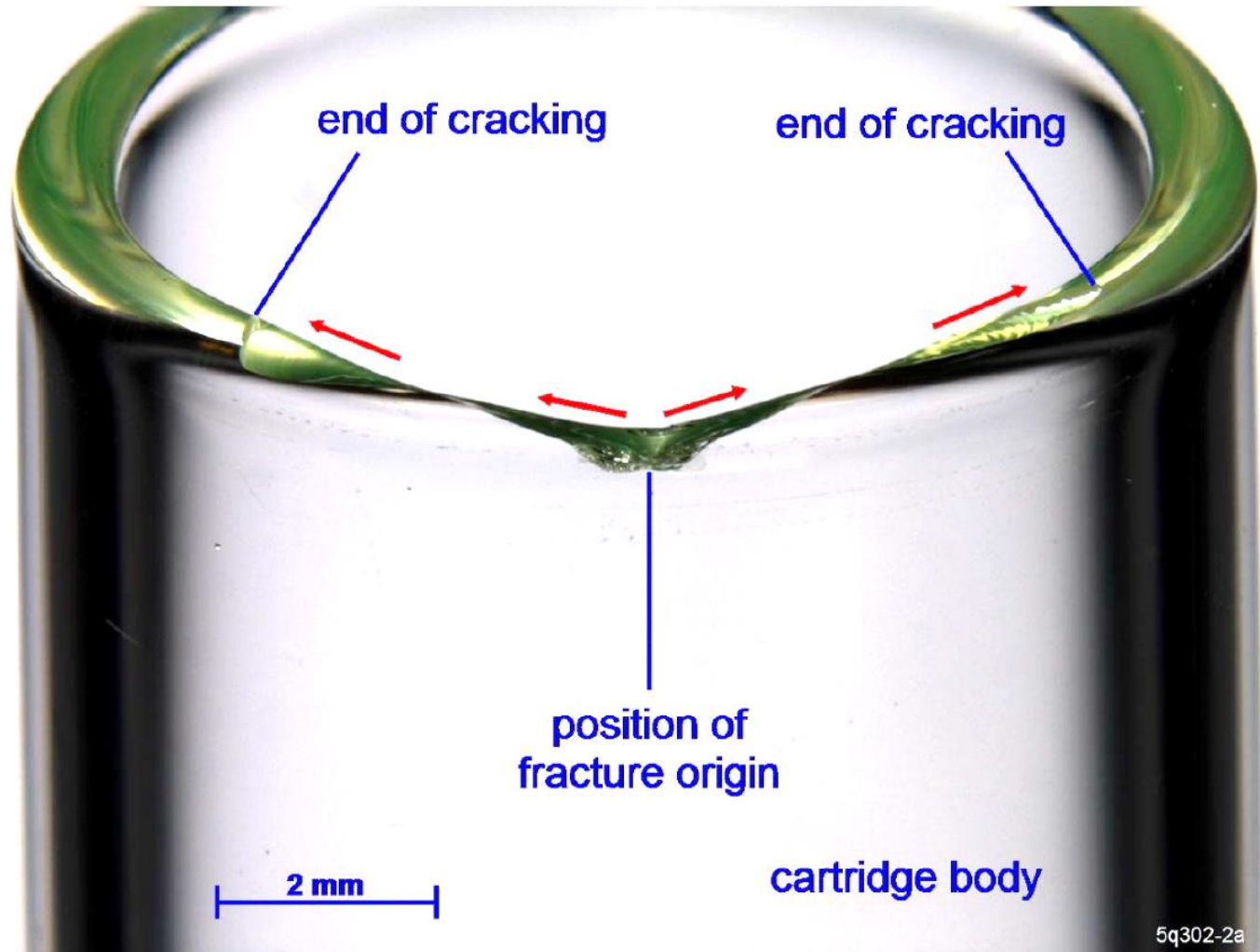




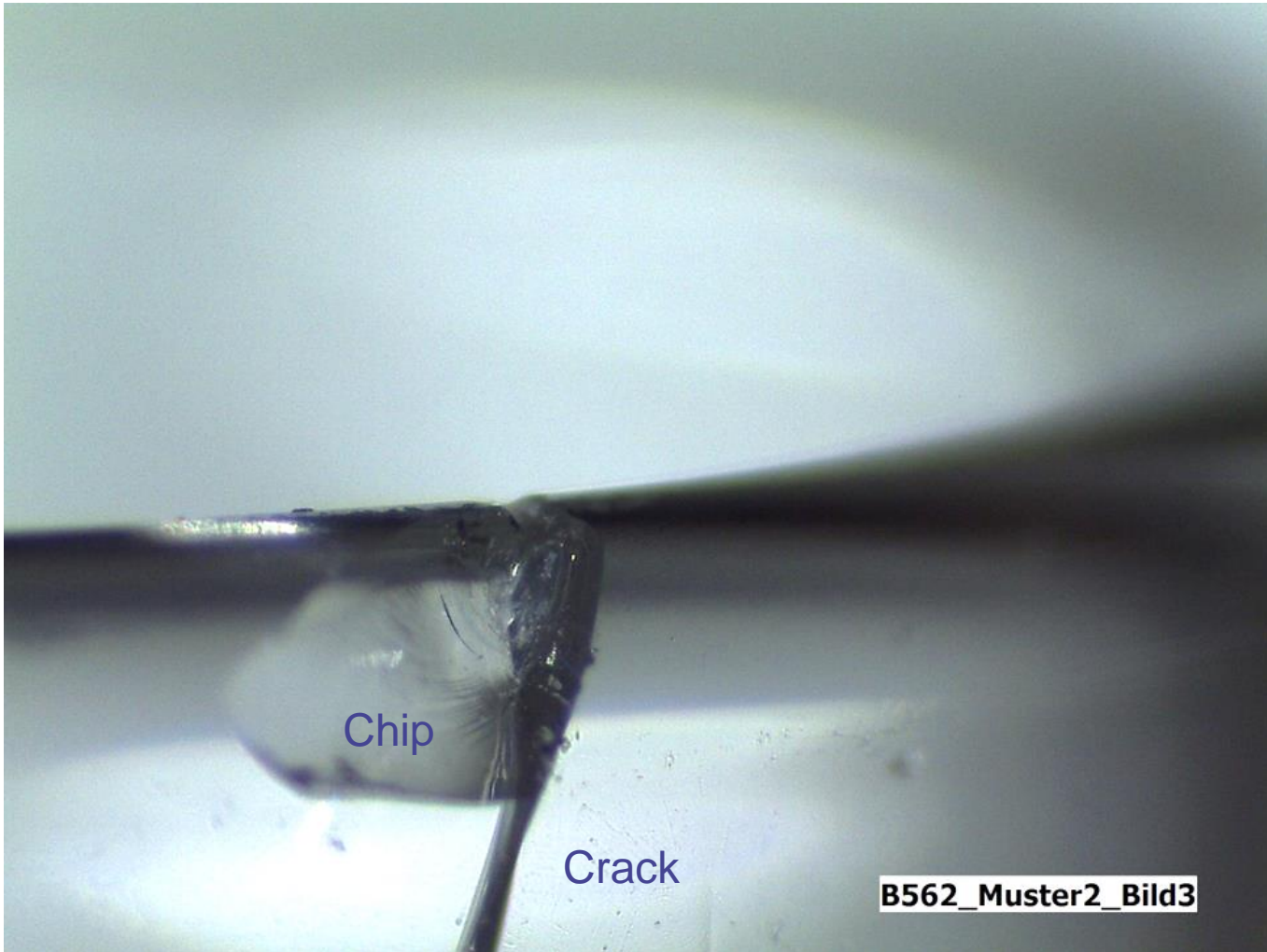
multiple fracture origins

B562_Muster3_Bild4

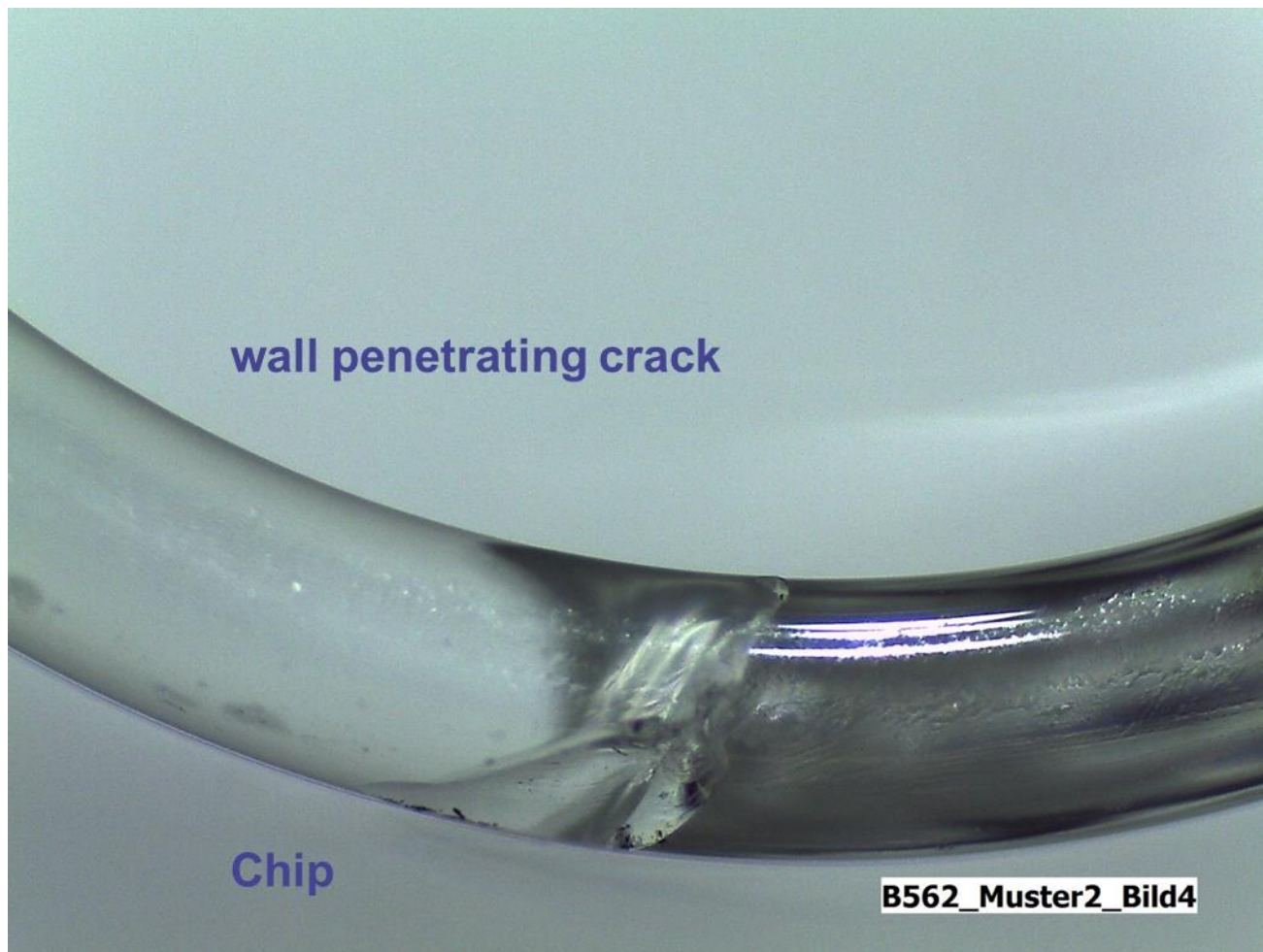
What to consider or to avoid (examples)

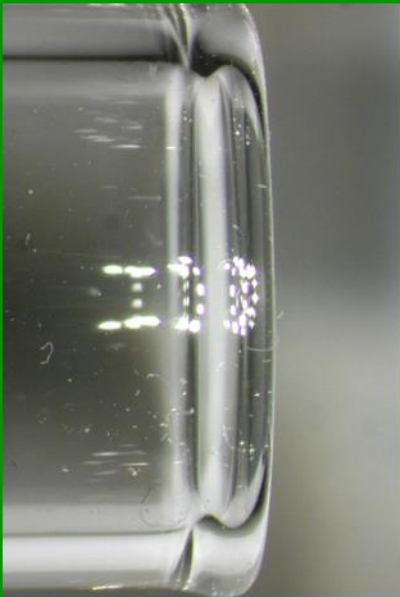





What to consider or to avoid (examples)

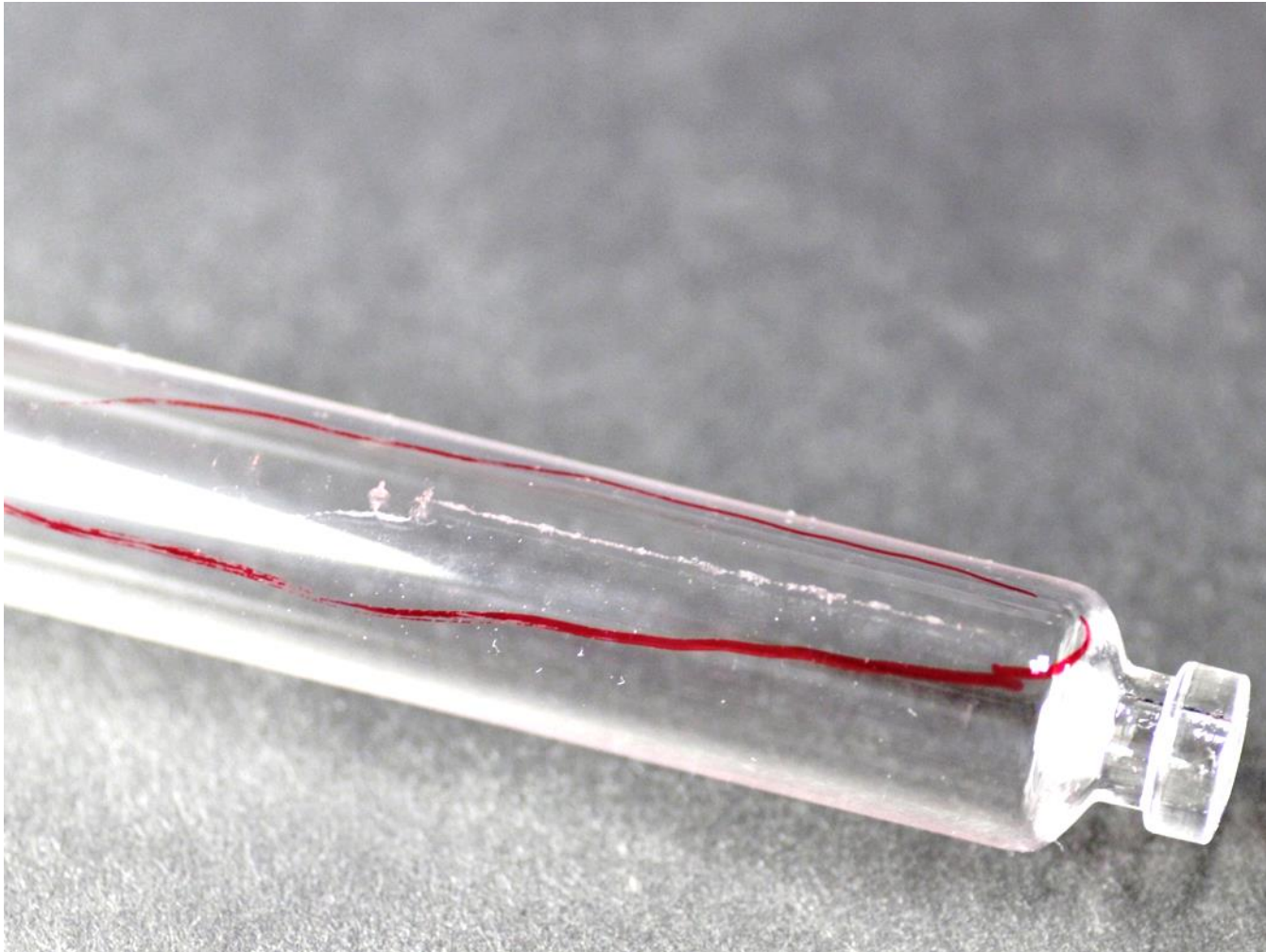


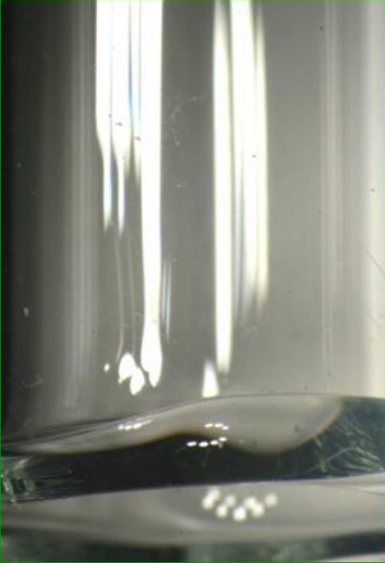
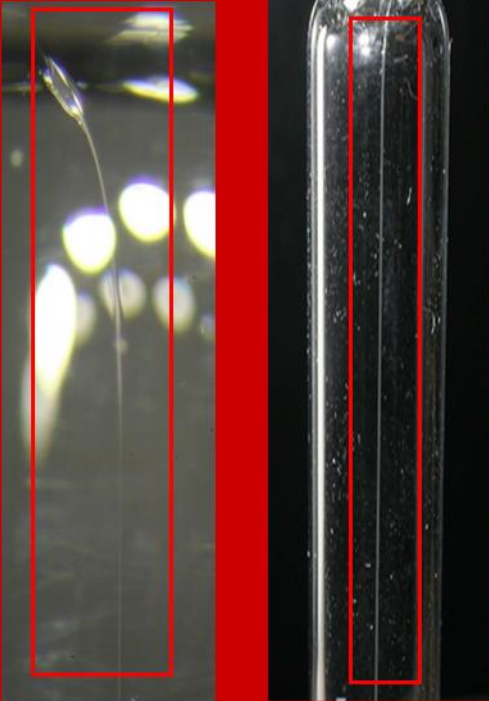
What to consider or to avoid (examples)


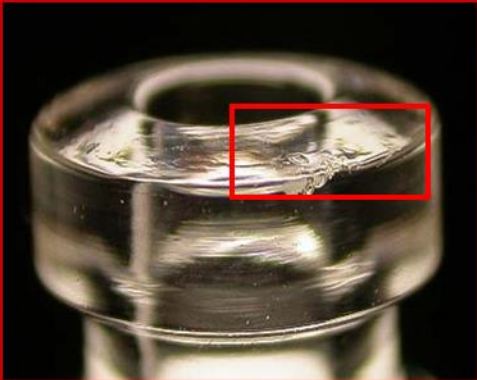


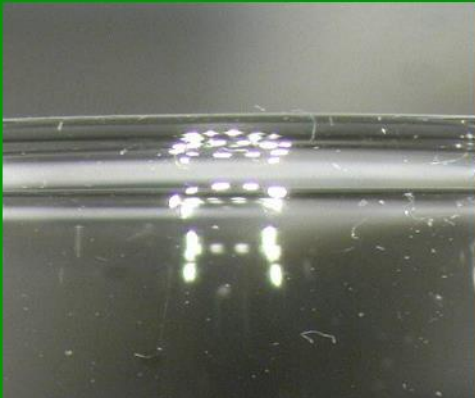
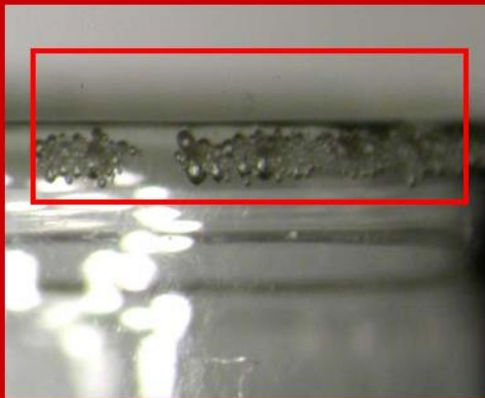
Description of Defect	Acceptable	Poor Quality
<p>Partially or not molded cartridges function / processing impacted</p>		

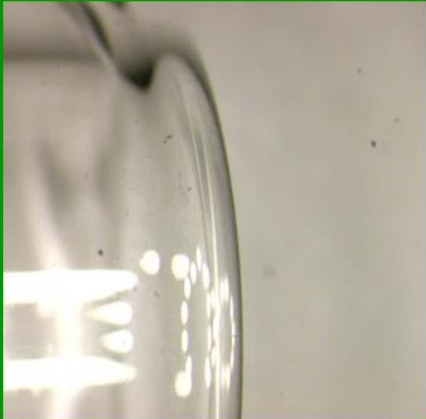

Description of Defect	Acceptable	Poor Quality
<p>Scratches / air lines outer surface</p>		 <p>Kratzer oder Luftlinien</p>






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

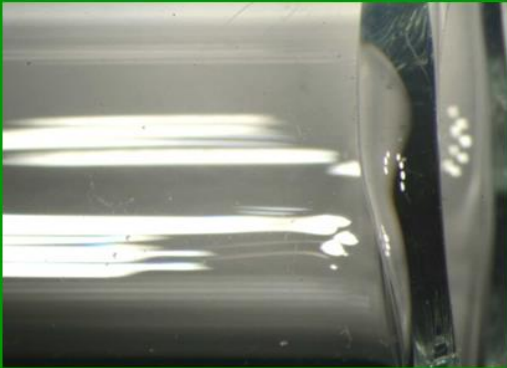
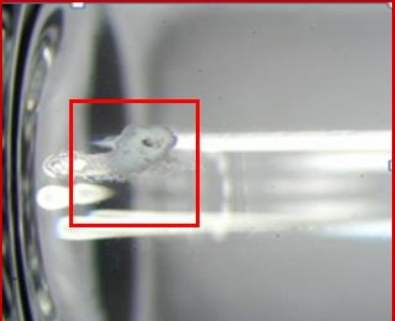
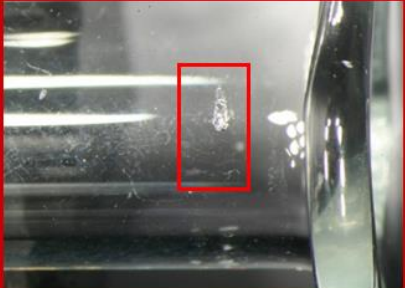
Description of Defect	Acceptable	Poor Quality
Air bubbles	 A clear glass vial stopper with a smooth, rounded top and no visible defects.	 A clear glass vial stopper with a red rectangular box highlighting a small, irregular air bubble trapped on the top surface.

Description of Defect	Acceptable	Poor Quality
Air bubbles		

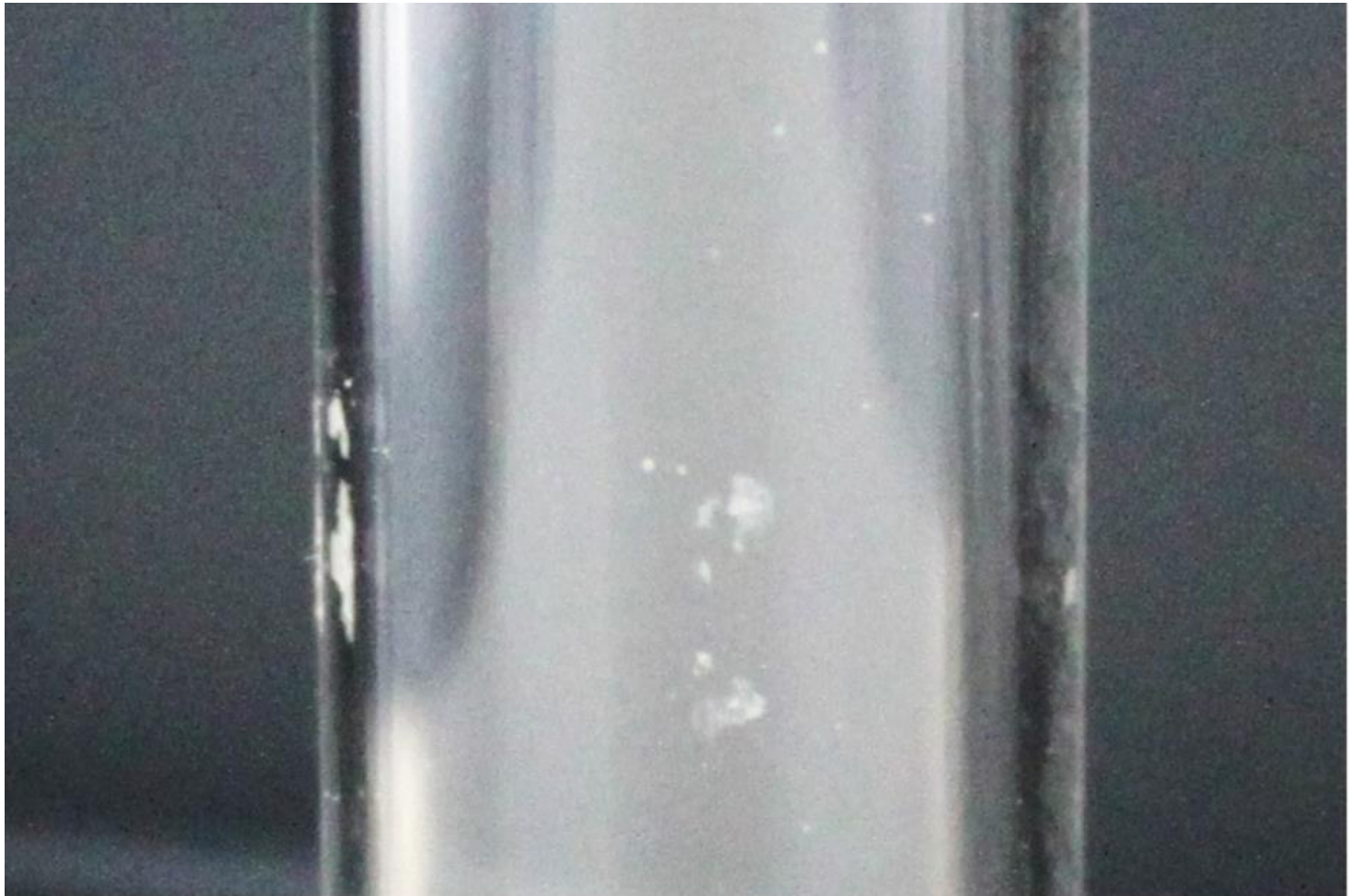
Description of Defect	Acceptable	Poor Quality
<p>Contamination inside, not easy removable (not embedded)</p>		 <p>Abrasion</p>



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>angesinterter Glasgries</p> 

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



- Reduced Testing – Supplier Certification
 - Prerequisite for reduced testing
 - ⇒ **Quality History**
 - ⇒ **Established Quality Management System at Supplier**
 - 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
 - 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*

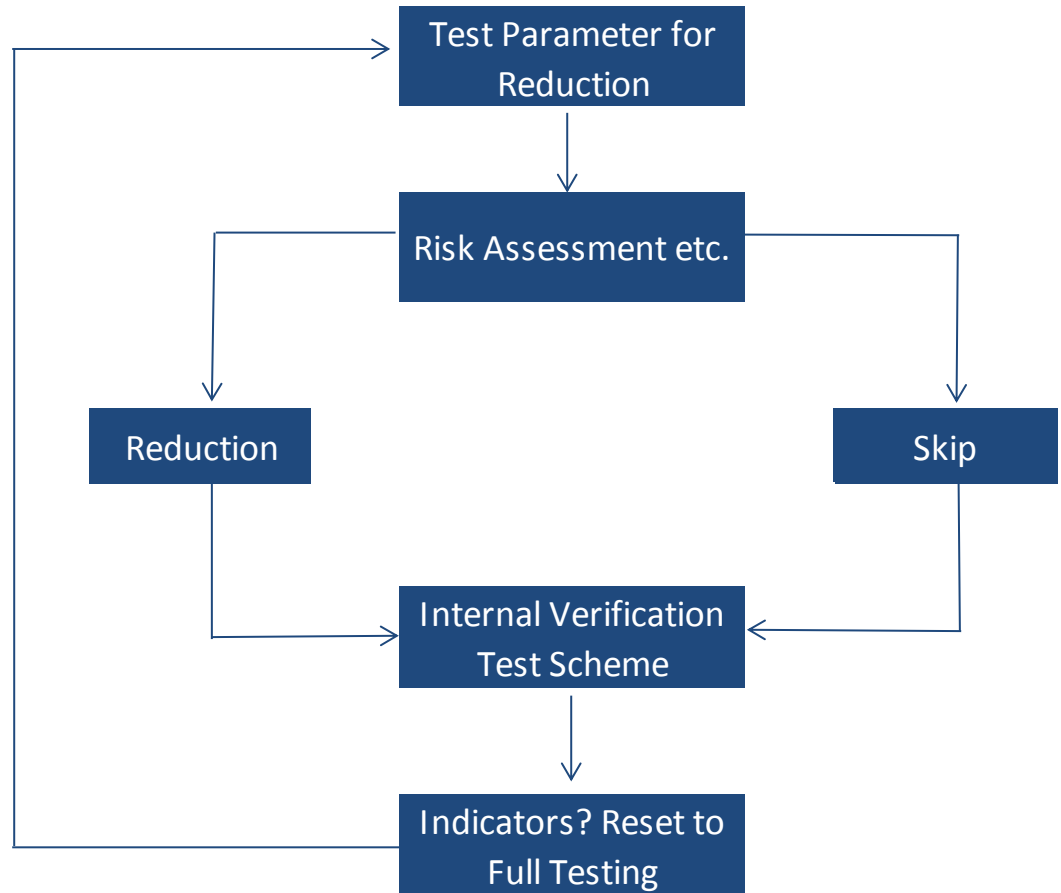
Note: The same applies to packaging materials

- 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

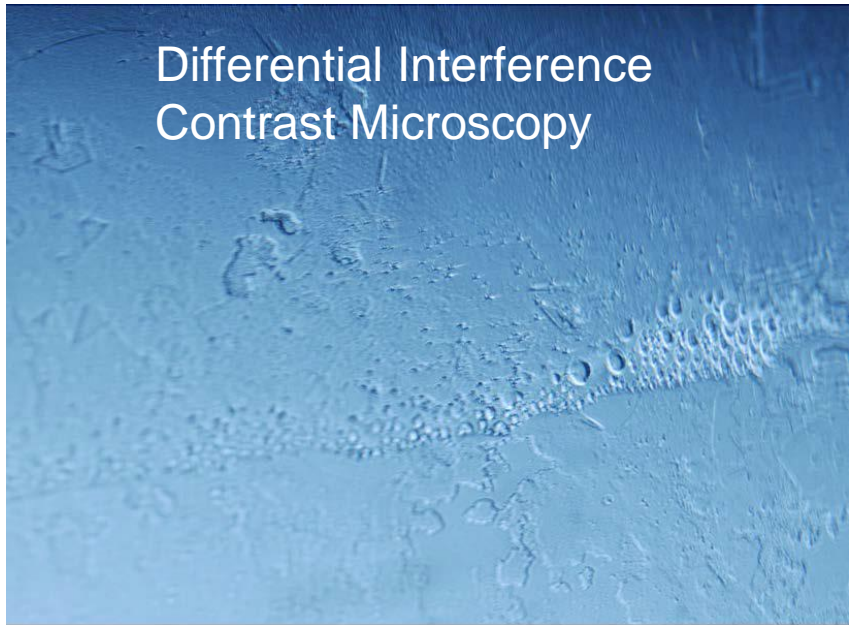
Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.

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

● Risk of Delamination

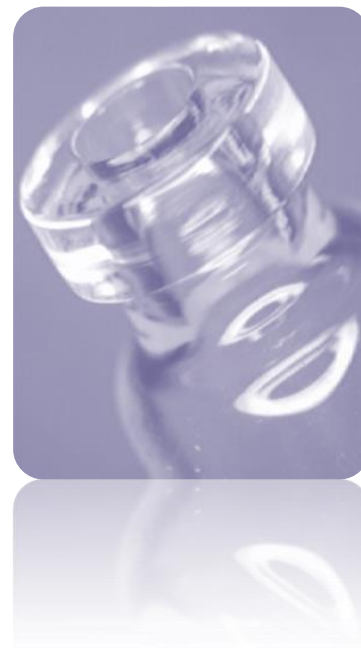
- The phenomenon gained attention of pharmaceutical industry in 2010 as a result of products recalled from the market (vials).
- An advisory was published by the FDA informing drug manufacturers of the phenomenon and the conditions associated with elevated risk of delamination.
<http://www.fda.gov/drugs/drugsafety/ucm248490.htm>
- 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.

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



- Overview

- 1 Requirements (from pharmacopoeias) regarding 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-qualify (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**
 - **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.**

- **Monitoring of Supplier**
 - **Supplier Management System (Supplier relationship management)**
 - **Classification**
 - **Assessment**
 - **Monitoring and Trend Performance**
 - **Complaint Management**
 - **Supplier Information**

- **Supplier Management**

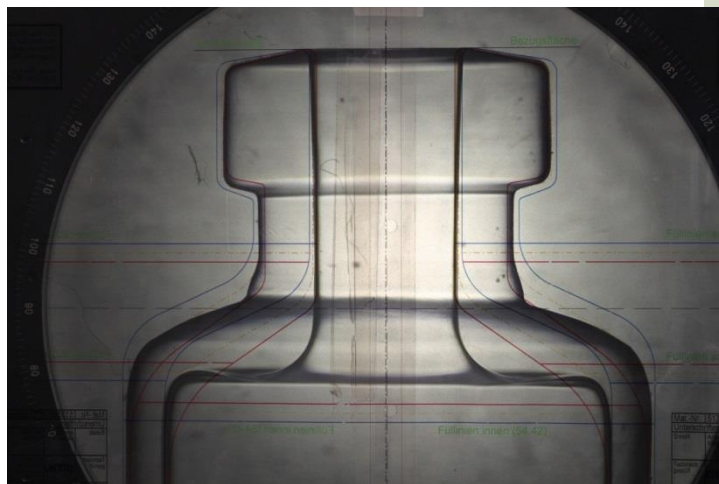
- Specification Documents (contractual)
- Quality Agreements
- Supplier Audits
 - **ISO 15378:2017 (en) Quality Management System for Medicinal Packaging Material Supplier**

ISO 15378 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. The standard delineates GMP principles and specifies Quality Management System requirements applicable to primary packaging materials.

- The ISO 15378 standard enables the supplier to comply with legal requirements for pharmaceutical and medical device primary packaging materials. ISO 15378 integrates the requirements of ISO 9001 as well as GMP, 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, and ensure product efficacy and shelf life.

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

- 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**



- Supplier
 - In-process control: inspection during processing
 - Final inspection: inspection of finished product
 - Reference Samples

- Pharmaceutical Manufacturer
 - Receiving inspection: Inspection for quality-determining parameters
and/or the manufacturer's certificate before processing
 - 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, Editio Cantor Verlag für 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