Glass Handling
Best Practices for Glass Primary Containers

PDA Training Course, Mainz, October 9th/10th 2019

Dr. Karl Siemoneit
Head of Quality Supplier Management
Sanofi Site Frankfurt Insulin

- Course Overview

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

Incoming Inspection of Glass Primary Packaging Material

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

Incoming Inspection of Glass Primary Packaging Material

- General Remarks
  - Quality requirements for primary glass container for drug product filling are continously increasing
  - Fast running filling lines require smooth supply of packaging components
  - Supply of packaging 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

Requirements for Inspection

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

Requirements for Inspection

- 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.*

Requirements for Inspection

- 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. ..*

Requirements for Inspection

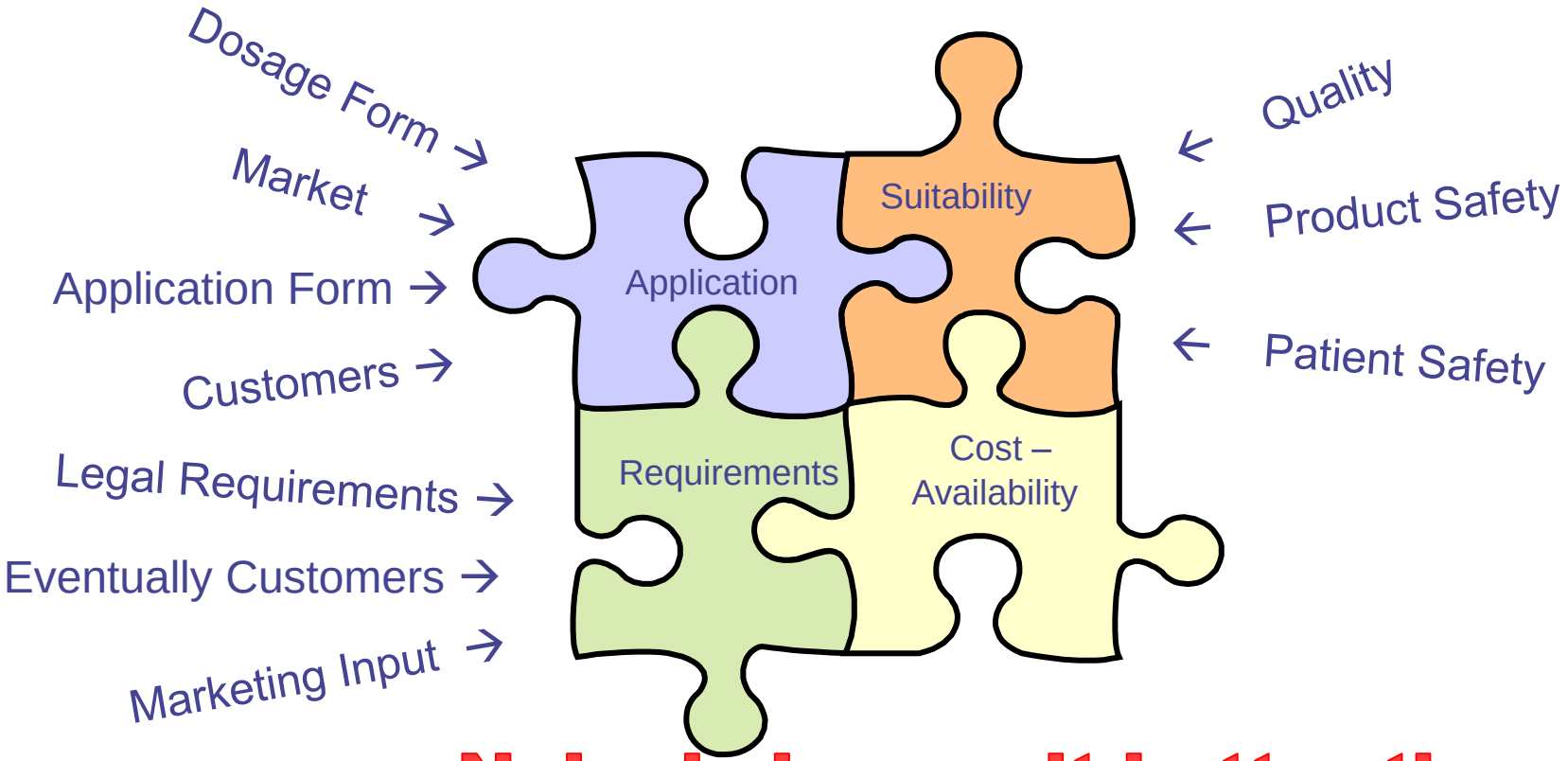
- Specifications / Acceptance Criteria
  - What are acceptance criteria?
  - Who specifies these criteria?
- Test Parameter
  - Definition of test parameter
- Test Methods
  - Identification of methods based on test parameter

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

ACCEPTANCE CRITERIA



Nobody knows it better than you !

TEST PARAMETER

… can be defined based on Acceptance Criteria

• Physical / Chemical	Pharmacopeia Regulations Standards
• Microbiological	Pharmacopeia Internal conditions
• Dimensional	Technical drawings Engineering standards Product & process requirements
• Visual - Inspection by attributes	Product & process requirements PDA Technical Report 43 Defect Evaluation List

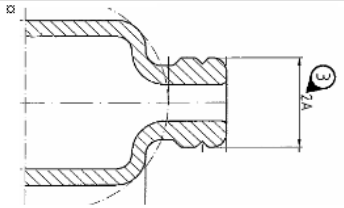
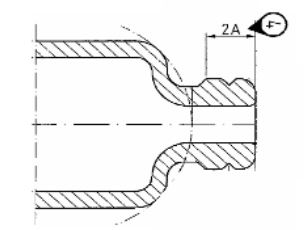
Requirements for Inspection

- 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!

Requirements for Inspection

- Example of an individual risk based defect categorization

Maß· Nr.¤	Technical Drawing	Nomen-clature	Risk prod technical	Classification
3¤		Flange (Collar) Outside Diameter	☐·1¶ ☒·2A¶ ☐·2B¶ ☐·3¤	Potential Impact on Container Closure Integrity
4¤		Flange (Collar) Height	☐·1¶ ☒·2A¶ ☐·2B¶ ☐·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!

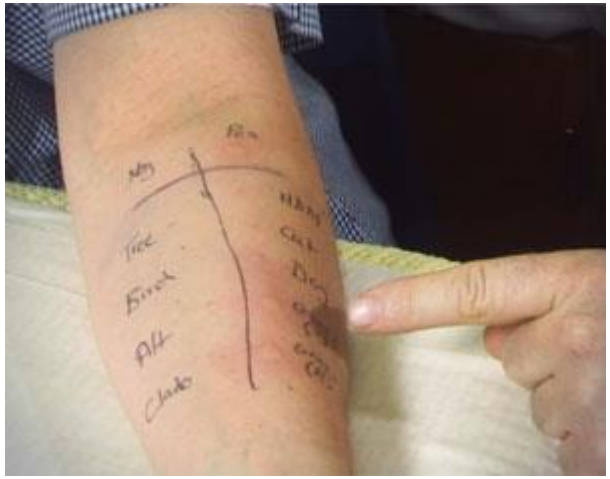
Requirements for Inspection

Description Fehlerbeschreibung	Category / Kategorie	AQL-Level	EXAMPLES / BEISPIELE Comment / Bemerkung	Defect sample / Schlechtmuster	Sample according to specification / Gutmuster
Form burrs and scars > 1 mm² on the outer surface of the glass barrel; closure integrity not impaired *Formmarken und narbige Erscheinungen > 1 mm² auf der Glaskörperaußen-oberfläche; Dichtigkeit nicht beeinträchtigt*	cosmetic ***kosmetisch***	6.5 *6,5*	Marks on head of cartridge *Rattermarken am Konus*		
			Wrinkles on head of cartridge *Quetschfalten am Bördelkopf*		

Define the risk of the individual parameter and acceptance level!

Requirements for Inspection

- **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)?
  - 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

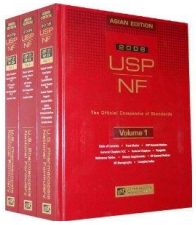
    Type III glass soda-lime; moderate chemical durability; for tubing and moulding; high thermal expansion; non suitable for injectable liquids; variously coloured.

- 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)**



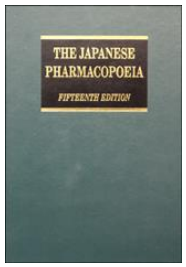
Relevant European Pharmacopeia Testing

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

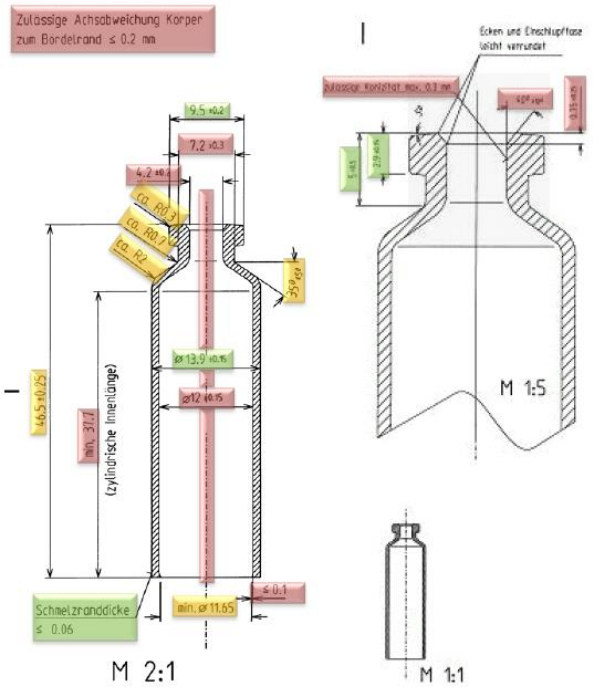
Endotoxin- / Bioburden- Testing

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

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

Requirements for Inspection

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



Requirements for Inspection

- 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 List

Requirements for Inspection

- 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

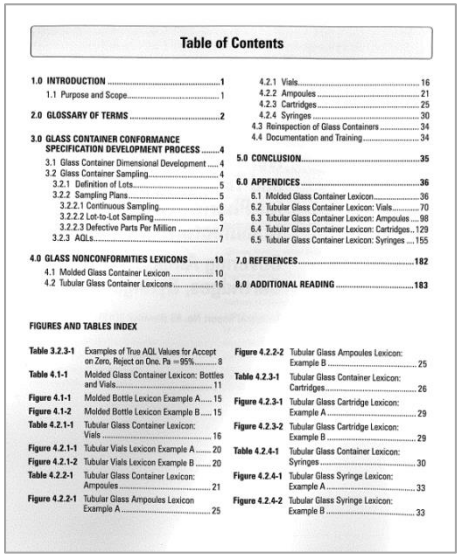
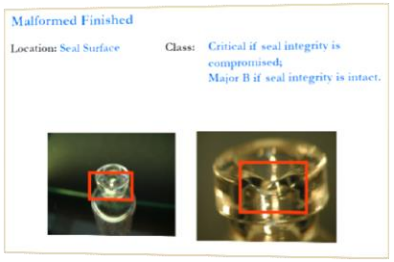


Table of Contents

FIGURES AND TABLES INDEX



Excerpt TR 43 PDA Glass Task Force

Glass Nonconformity Lexicons (PDA TR 43)

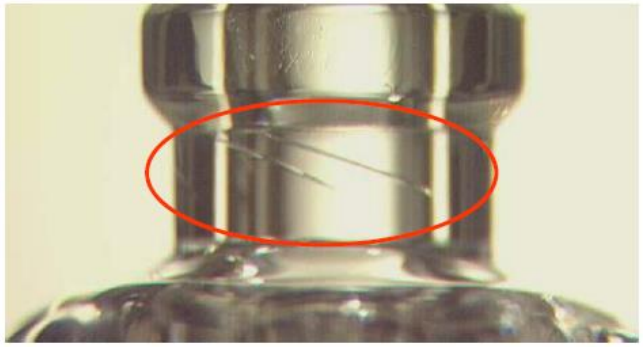
CRITICAL	*A Nonconformity that is likely to result in personal injury or potential hazard to the patient (including defects that compromises the integity of the container.*
MAJOR A	*… leading to serious impairments e.g. a malfuction that makes the packaging unusable*
MAJOR B	*Impairments of a lesser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

Requirements for Inspection

- 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.”

Requirements for Inspection

- 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 a normal statistical distribution

Requirements for Inspection

- Defects and Acceptance Levels
  - The control sample unit (Tailgate samples) 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 AQL
  - The AQL represents the percentage of defects routinely accepted

Requirements for Inspection

- 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
Lot Size		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	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

Requirements for Inspection

- 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)**

Kenn-buch-stabe für den Stich-proben-umfang	Stich-proben-umfang	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
A	2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	⇩	0 1	↓	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31
B	3	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45
C	5	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑
D	8	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑
E	13	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑	↑
F	20	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑
G	32	↓	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑
H	50	↓	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑
J	80	↓	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑
K	125	↓	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
L	200	↓	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
M	315	↓	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
N	500	↓	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
P	800	↓	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Q	1 250	0 1	⇧	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
R	2 000	⇧	↑	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

⇩ - 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 - Rückweisezahl

Excerpt DIN ISO 2859

Requirements for Inspection

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

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

Requirements for Inspection

- In most cases Tailgate 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

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

How to do it in practice

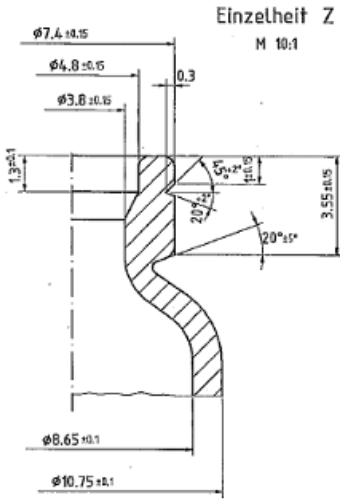
- Content
  - Specification
  - Sampling
  - Sample size
  - Equipment, Tools
  - Documentation
  - Supplier Certification

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*

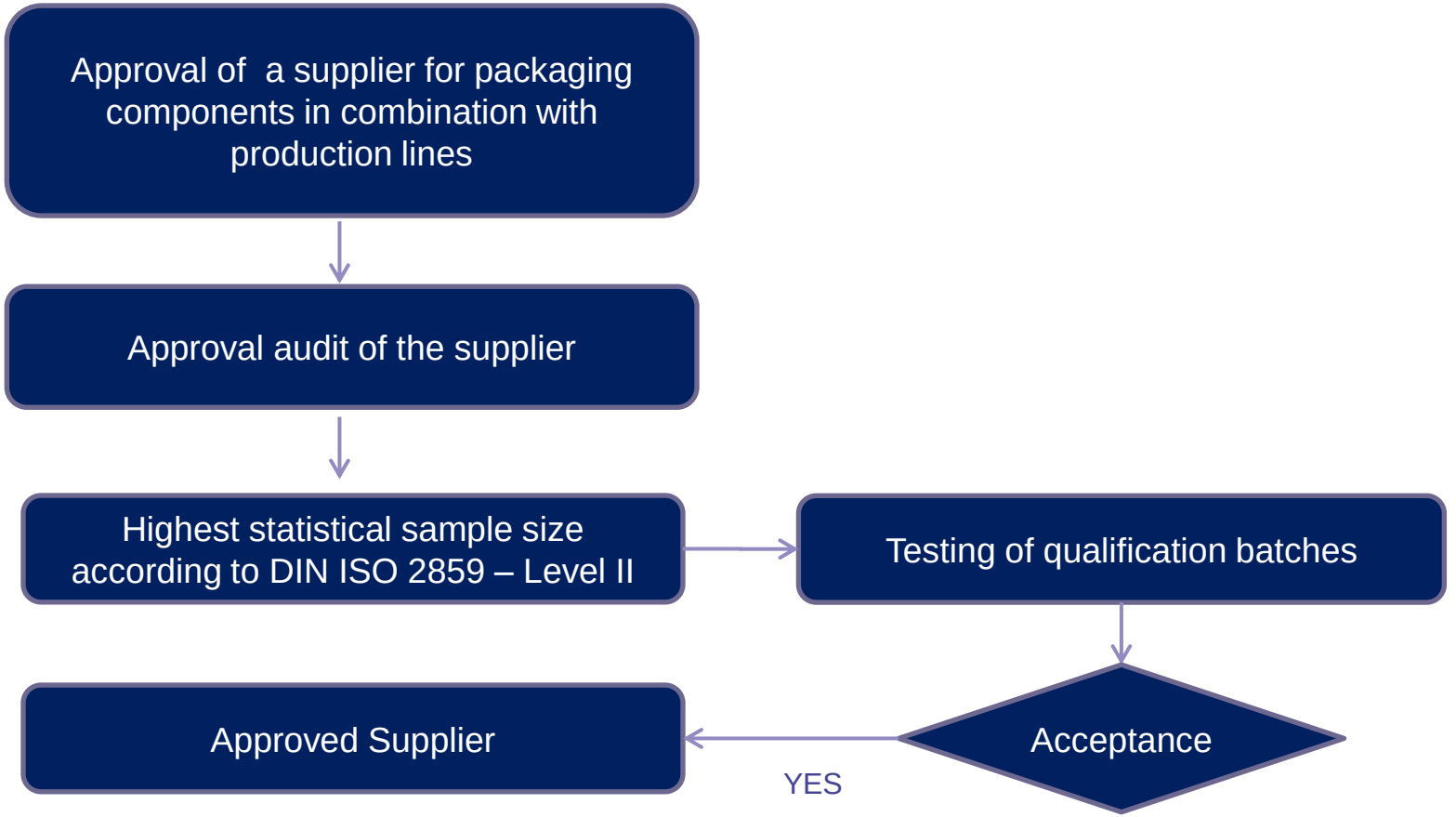


Specifications (EU-GMP; Kap. 4)

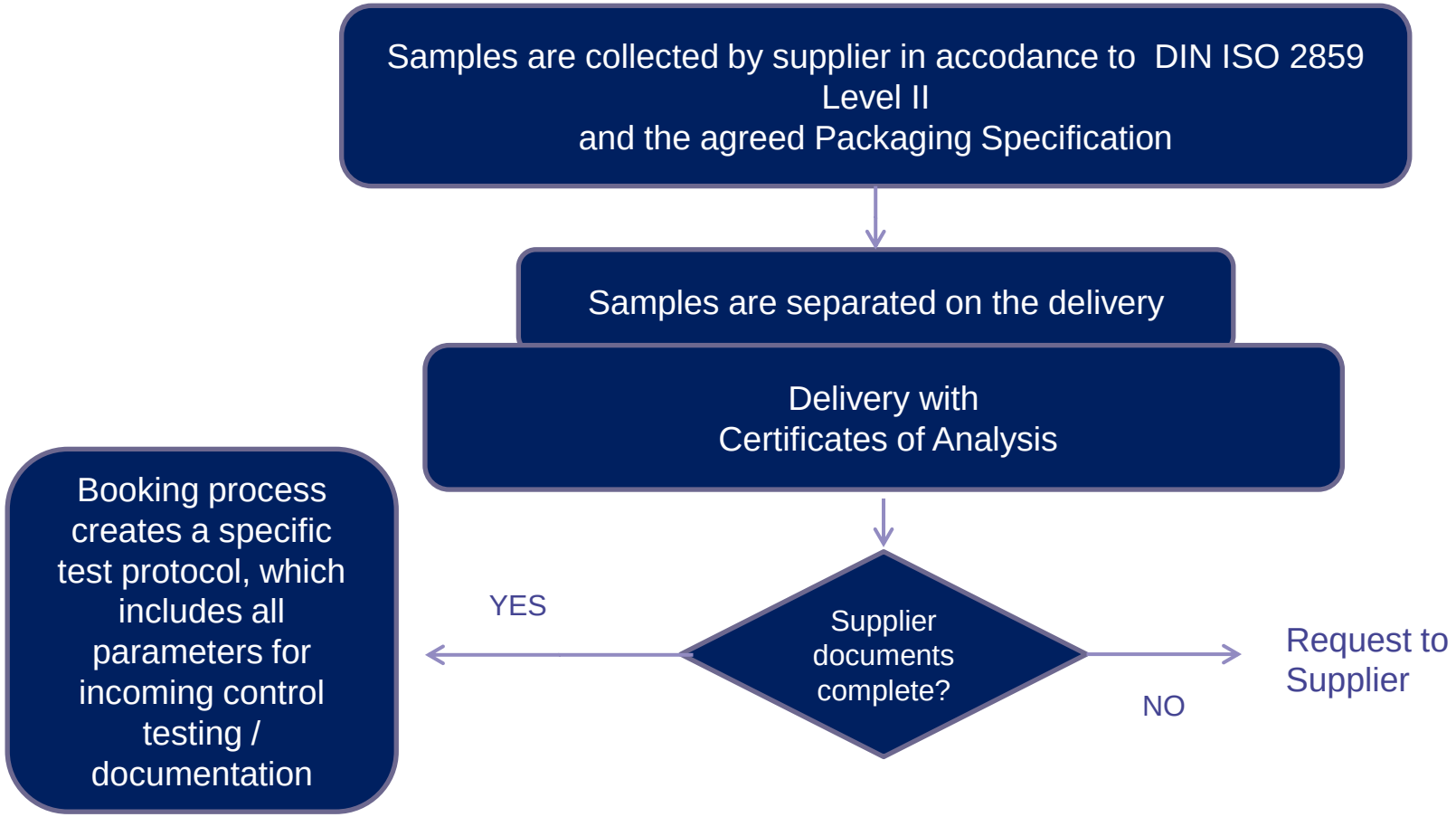
- Batch testing / release is based on these documents
- It is recommended to agreed on inspection methods upfront with supplier
  - Visual Inspection (visual devices)
  - Specific methods not described in literature
  - Method comparison
  - Accuracy of measurement

Quality Agreement!

Supplier Approval Process



Tailgate Samples with each Delivery



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 anually

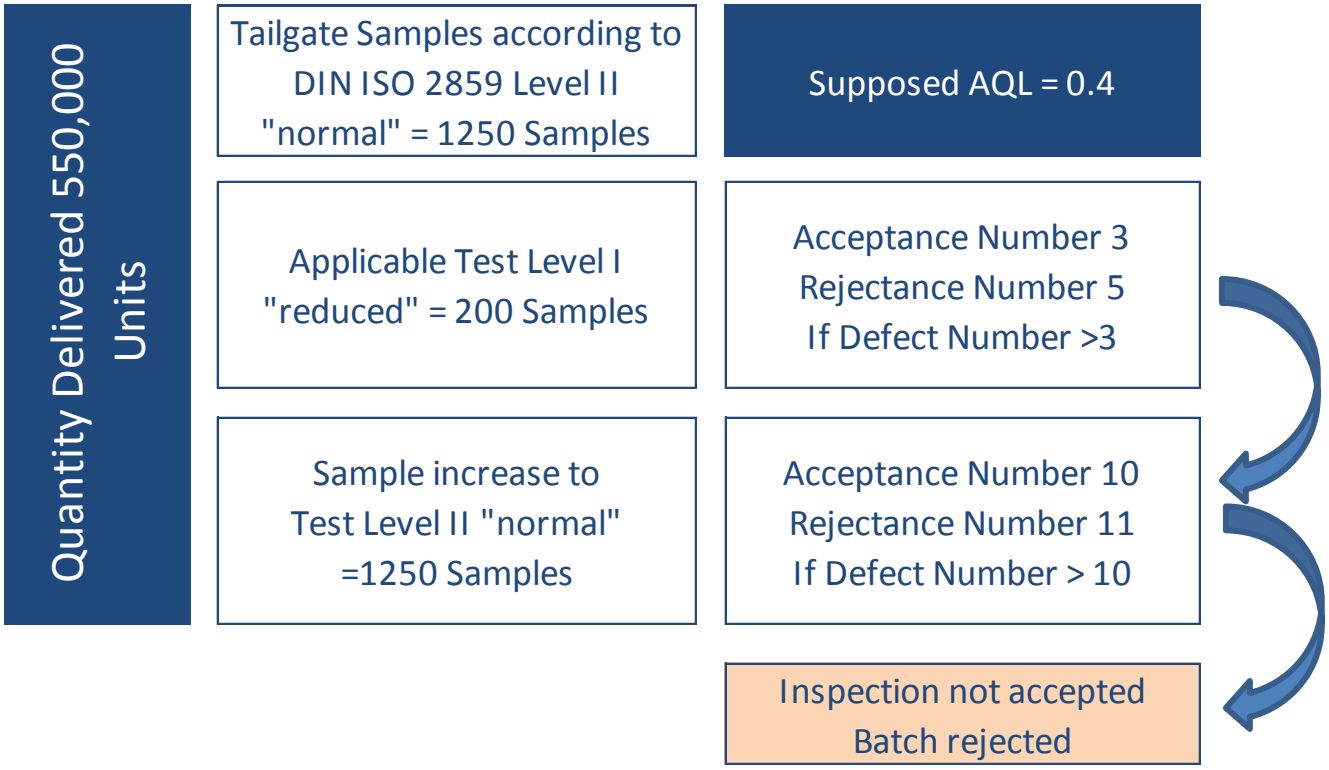
3.3 Specific Criteria e.g. micobial testing

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 (manufacturing site)

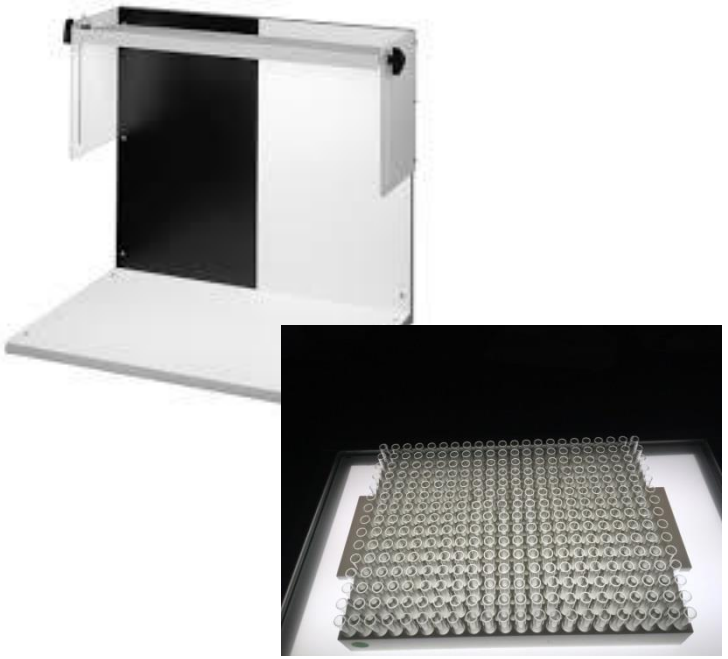
Example of an two phase inspection approach (by attributes)



Visual Inspection

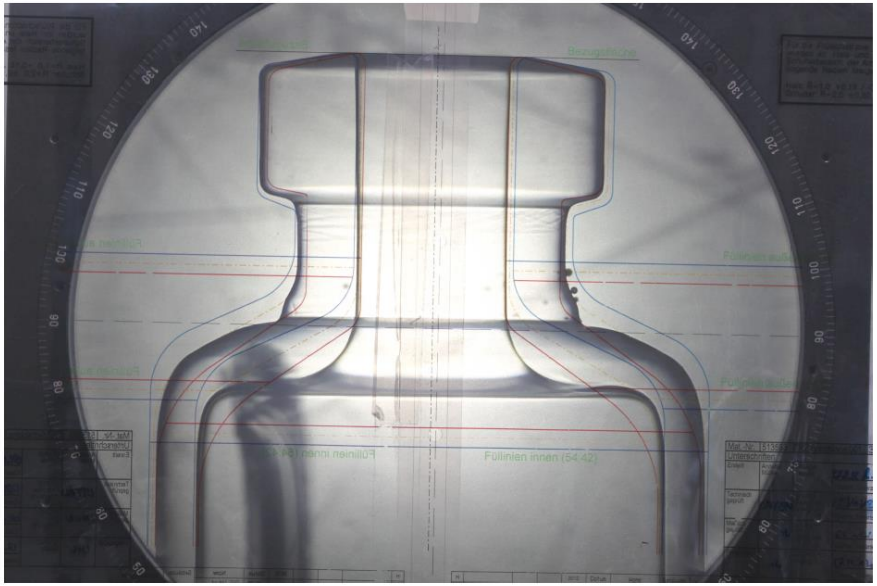
- In order to standarize the inspection it can be helpful to use the method described in Ph. Eur. Method 2.9.20. Particulate Contamination: Visible Particles. Terms and conditions are defined.

  - ➢Intensity of light
  - ➢Period under review
  - ➢Viewing background



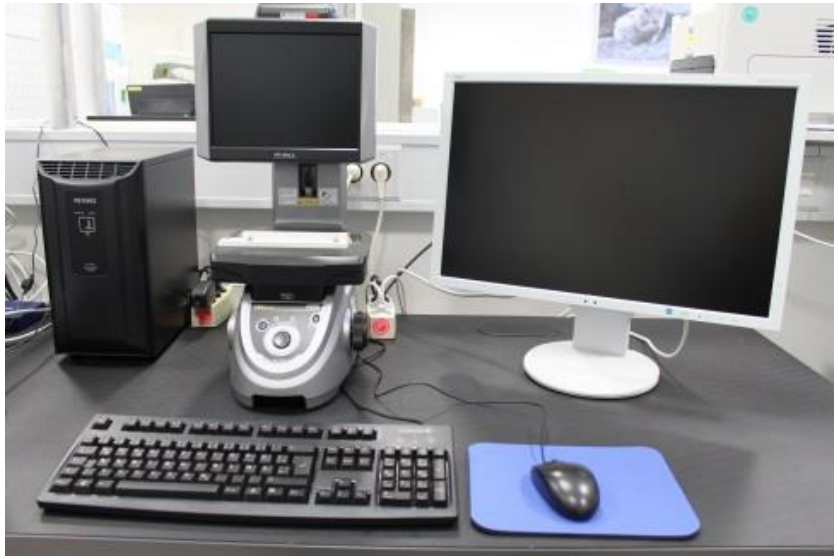
Dimensional Inspection

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



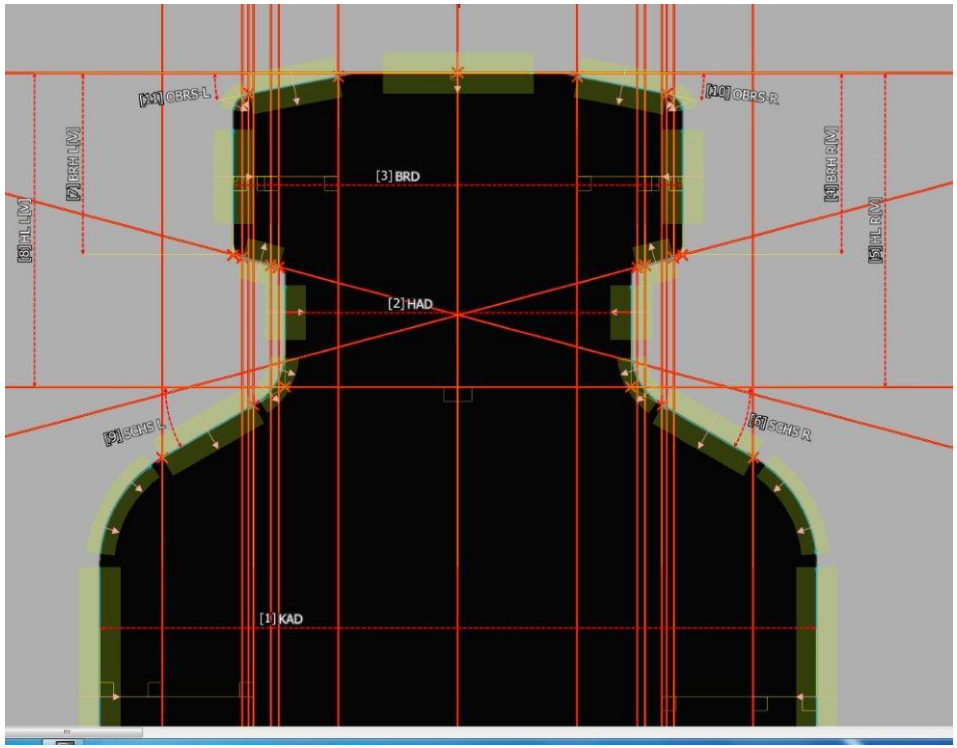
Dimensional Inspection

- Manual measuring devices or electronic camera systems

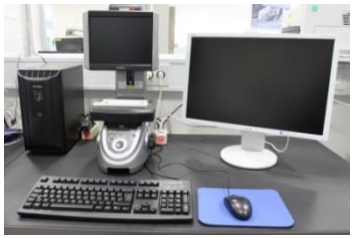


Dimensional Inspection

- Set up of a camera system: Reference lines and intercept points to be defined

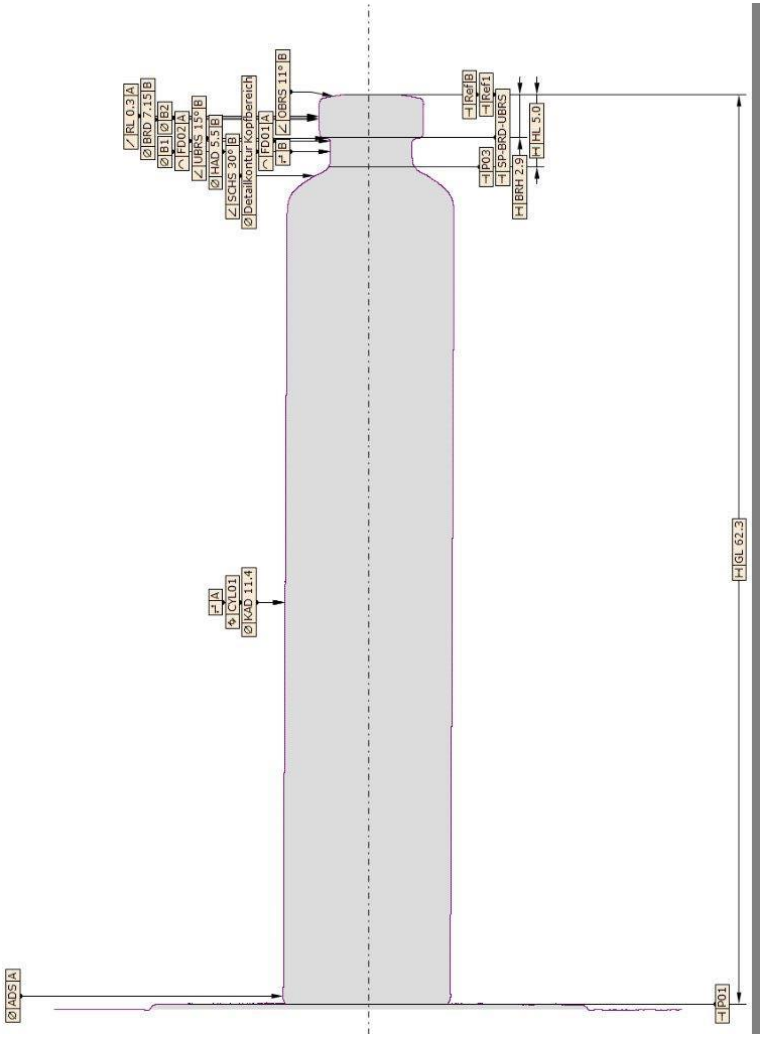


Dimensional Inspection



Dimensional Inspection

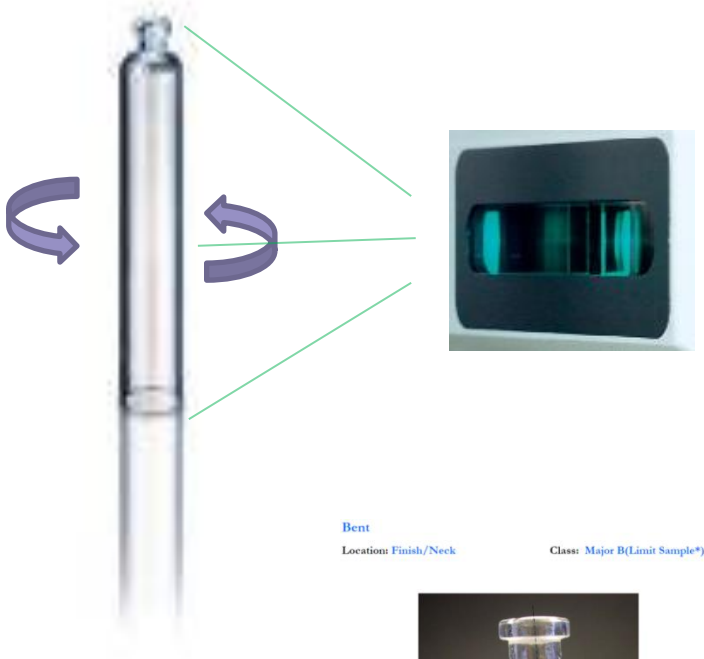
Unit of measurement	Characteristics
mm	Glazing ring diameter
mm	Body diameter
mm	Neck diameter
mm	Flange diameter
mm	Flange height
mm	Neck height
mm	Total lenght
°	Upper locking ring angle
°	Lower locking ring angle
°	Shoulder angle
mm	Excentricity

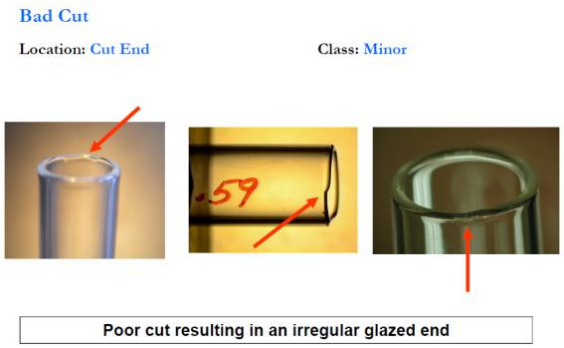


Dimensional Inspection

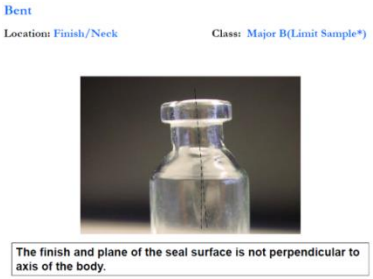
- Three-dimensional rotation-symetric results
- Contact-free measurement
- Evaluation of multiple parameter of complex bodies

Rotating measurement





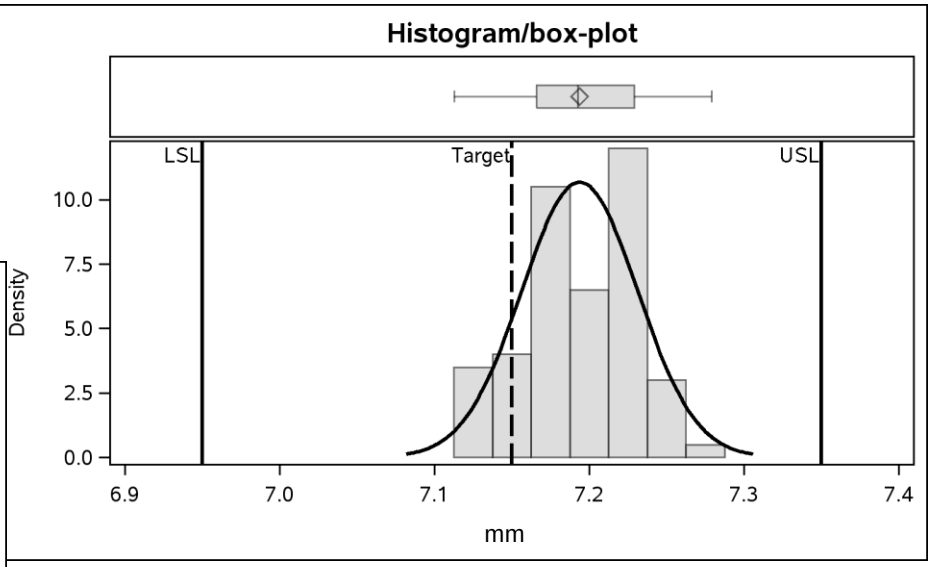
Poor cut resulting in an irregular glazed end

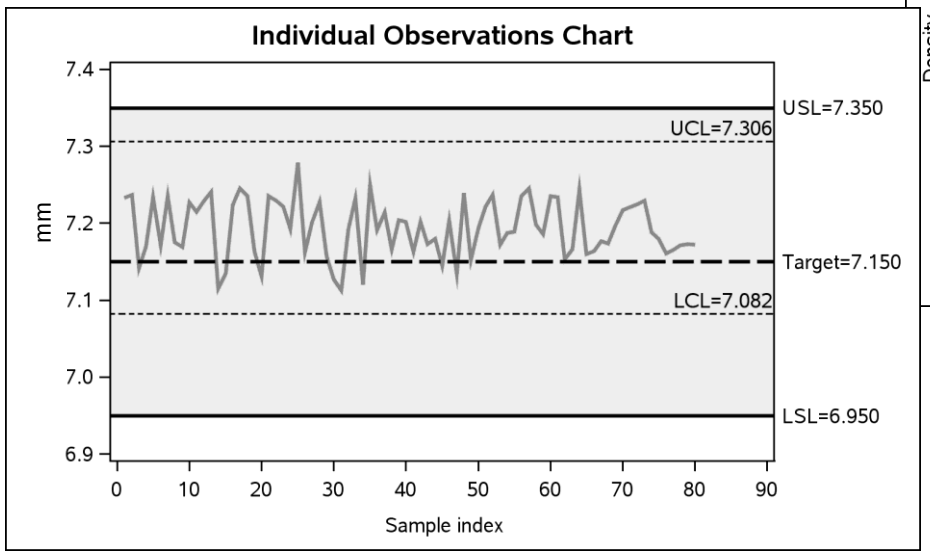


The finish and plane of the seal surface is not perpendicular to axis of the body.

Dimensional Inspection

Results Collar Diameter





- Documents relevant for batch release
  - Supplier documentation
    - Certificate
    - Specifications
    - Test Protocol
    - Delivery slip
  - Inspection documentation
    - Dimensional Test Results
    - Chemical Test Results
    - Visual Inspection Results
    - Test Protocols
    - Log Books

Test Methods
Standard Operating Procedures
Specifications

End of Part 2

- Overview

1 Requirements for incoming inspection

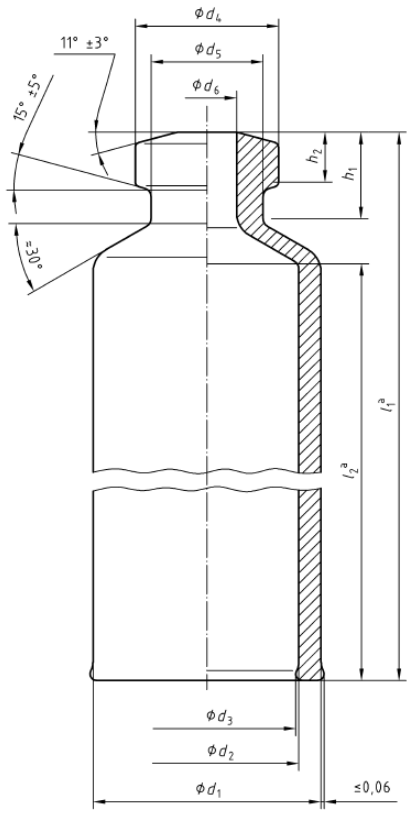
2 How to do it in practice

3 **What to consider or to avoid (examples)**

4 Coordination process between packaging manufacturer and customer

What to consider or to avoid (examples)

- 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 min.	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. ±
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

What to consider or to avoid (examples)

- 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 ± 0,20 mm to ± 0,50mm depending on the format!

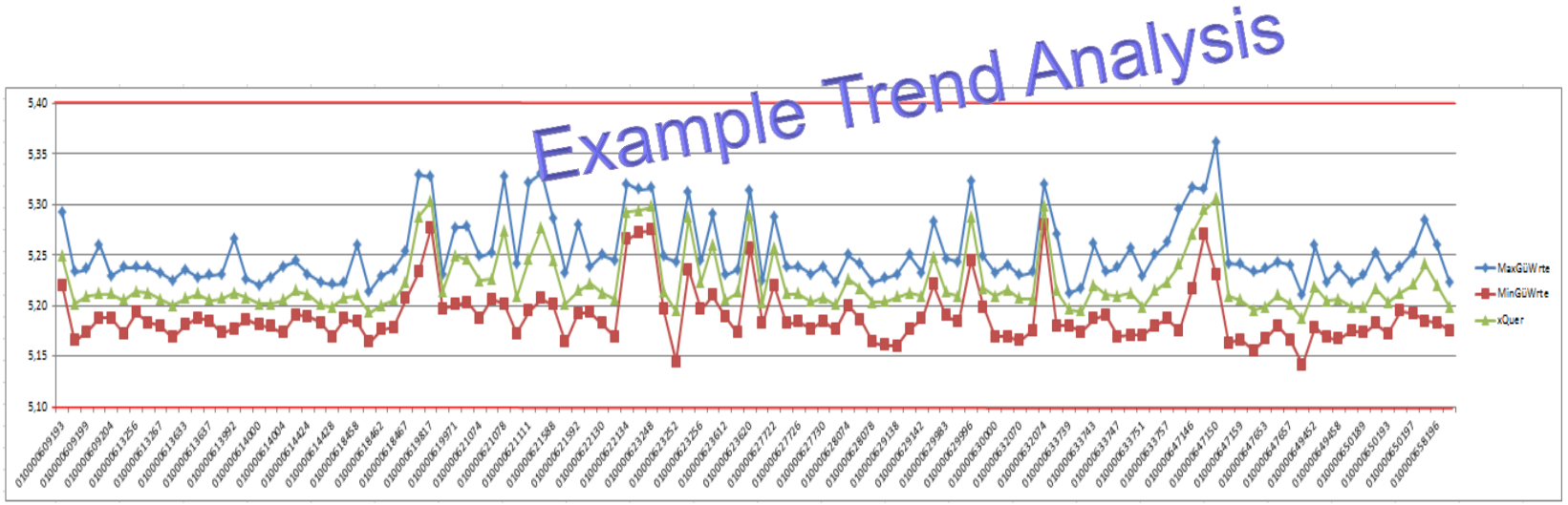
Maße in mm
Dimensions in mm

d_1	Grenz-abm. tol. ±	d_2	Grenz-abm. tol. ±	d_3 min.	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. ±
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

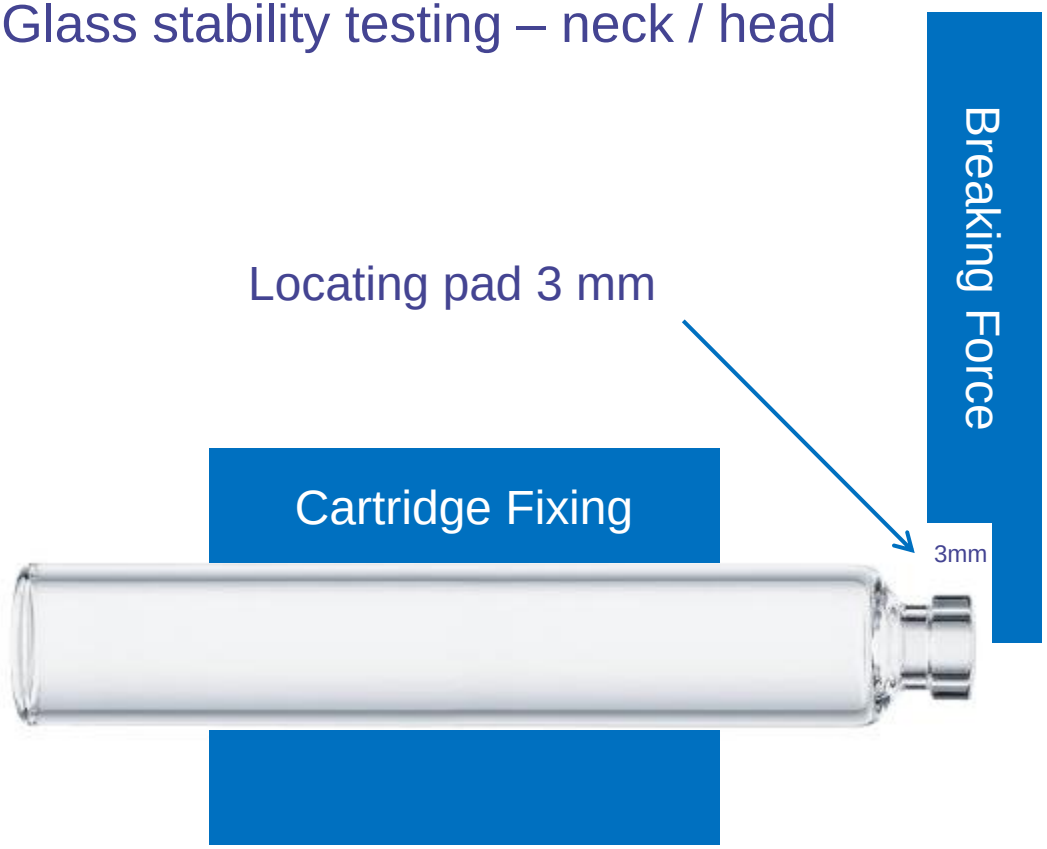
What to consider or to avoid (examples)

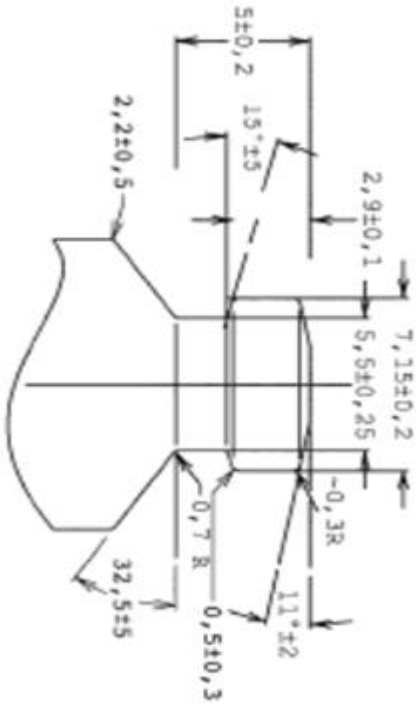
- It can be important to know and understand the characteristics of the container of individual suppliers and their forming lines
- Monitoring of critical dimensional characteristics can give a good understanding of the packaging components



- 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

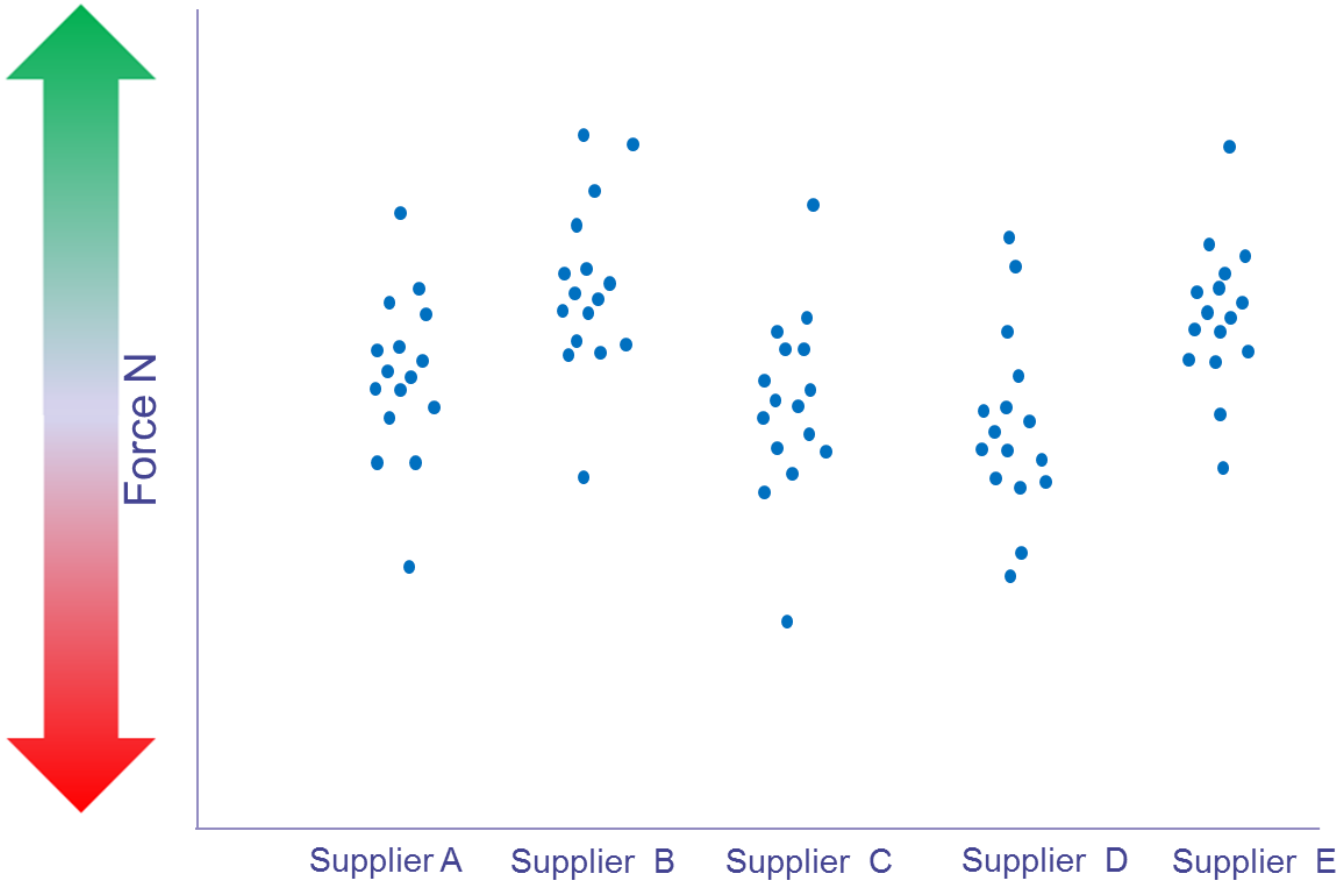
- Glass stability testing – neck / head





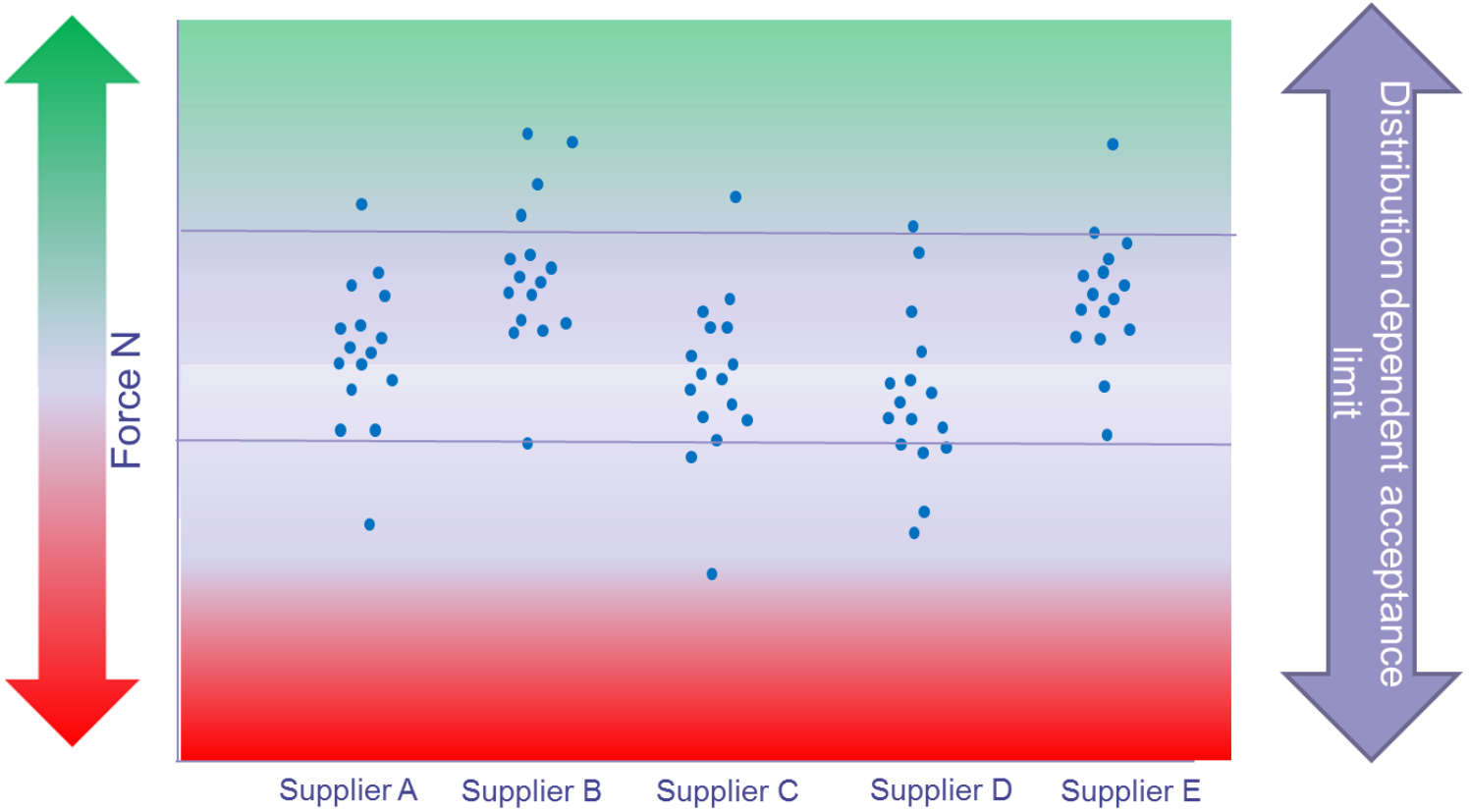
What to consider or to avoid (examples)

- Glass stability testing results



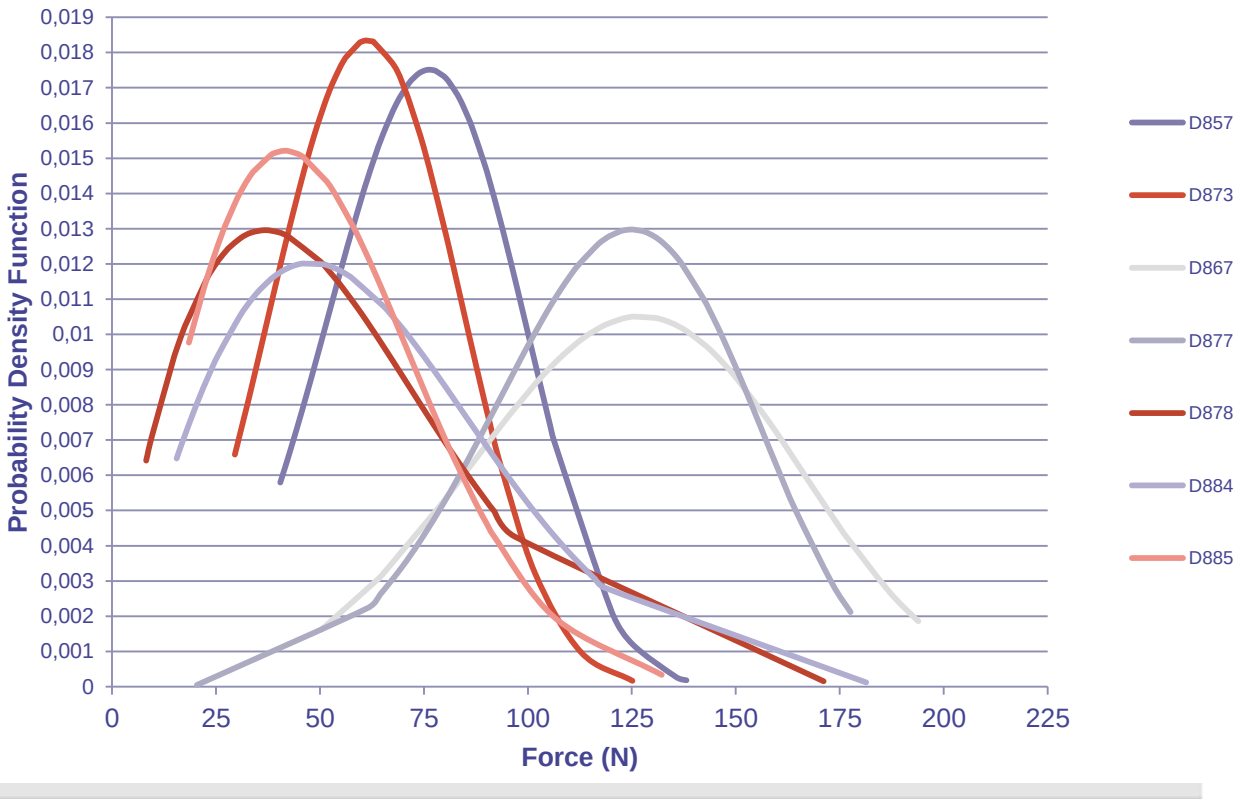
What to consider or to avoid (examples)

- Glass stability testing results



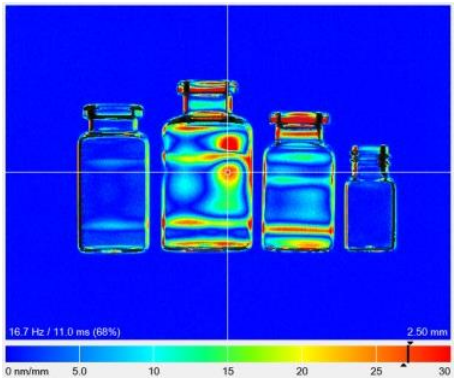
What to consider or to avoid (examples)

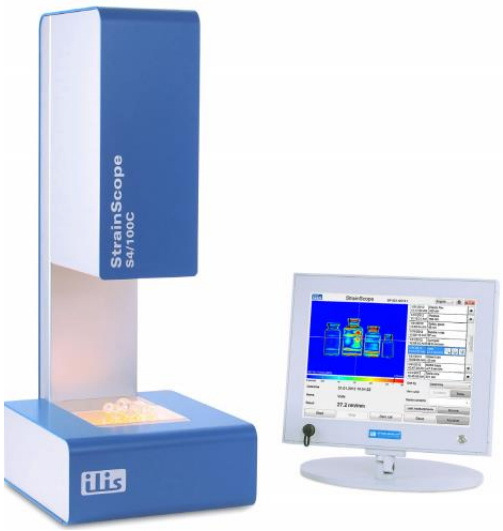
- Glass stability testing – stopper mouth



What to consider or to avoid (examples)

- Identification of residual stress

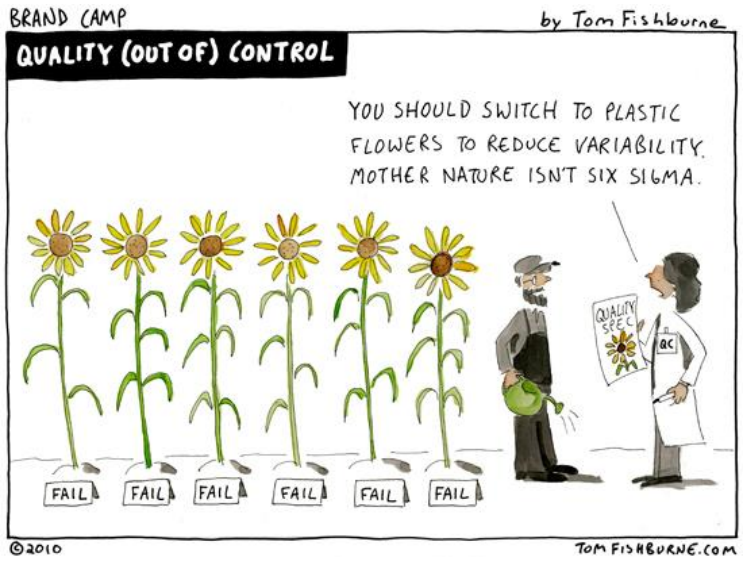




StrainScope S4 – ilis

- GMP compatible photograpic documentation
- Fast multiple sample testing

- Defects and Imperfections
  - Defects / Imperfections not always distributed across the entire batch
  - Rare or nested defects may not be detected during incoming control

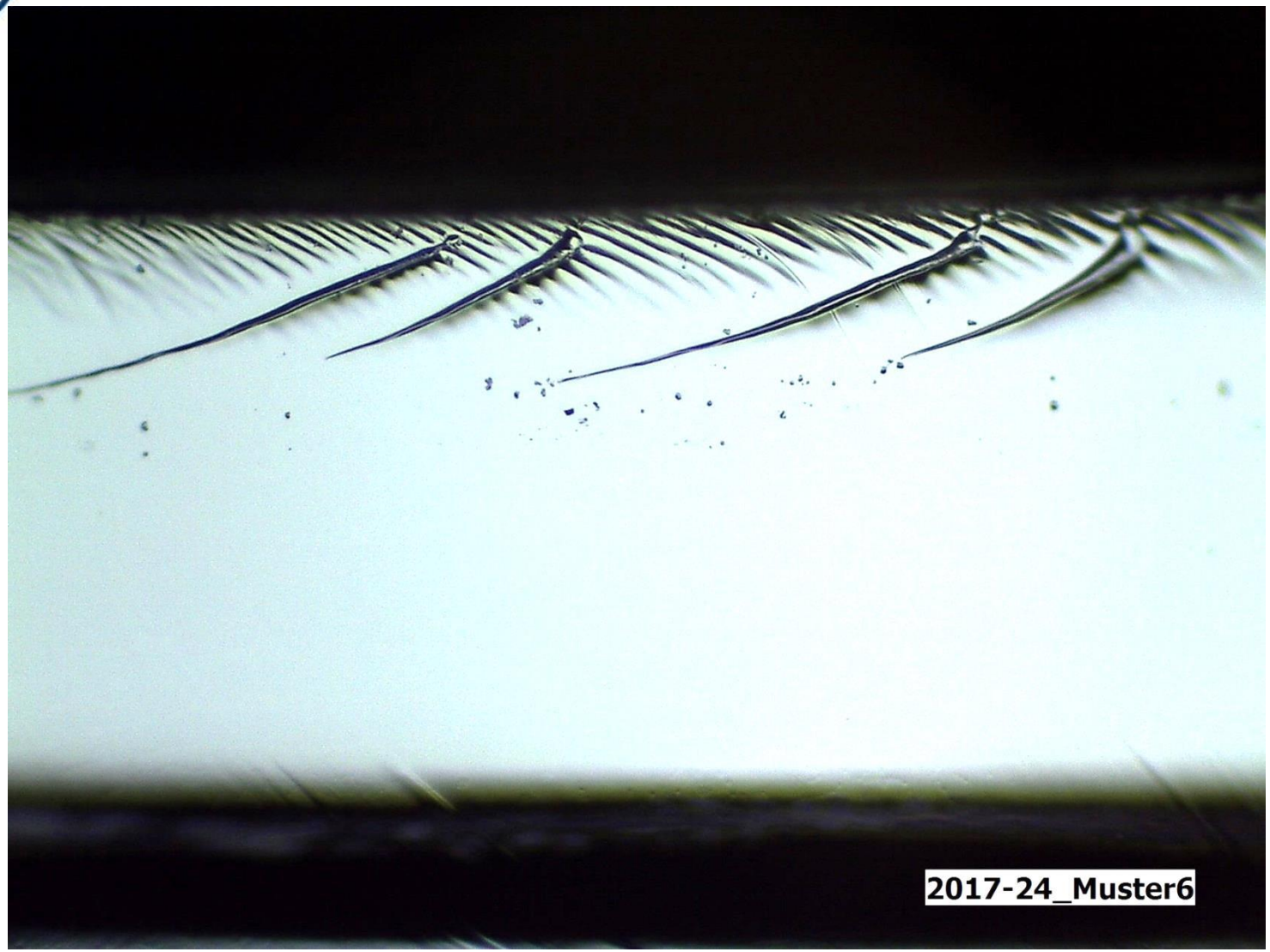


What to consider or to avoid (examples)

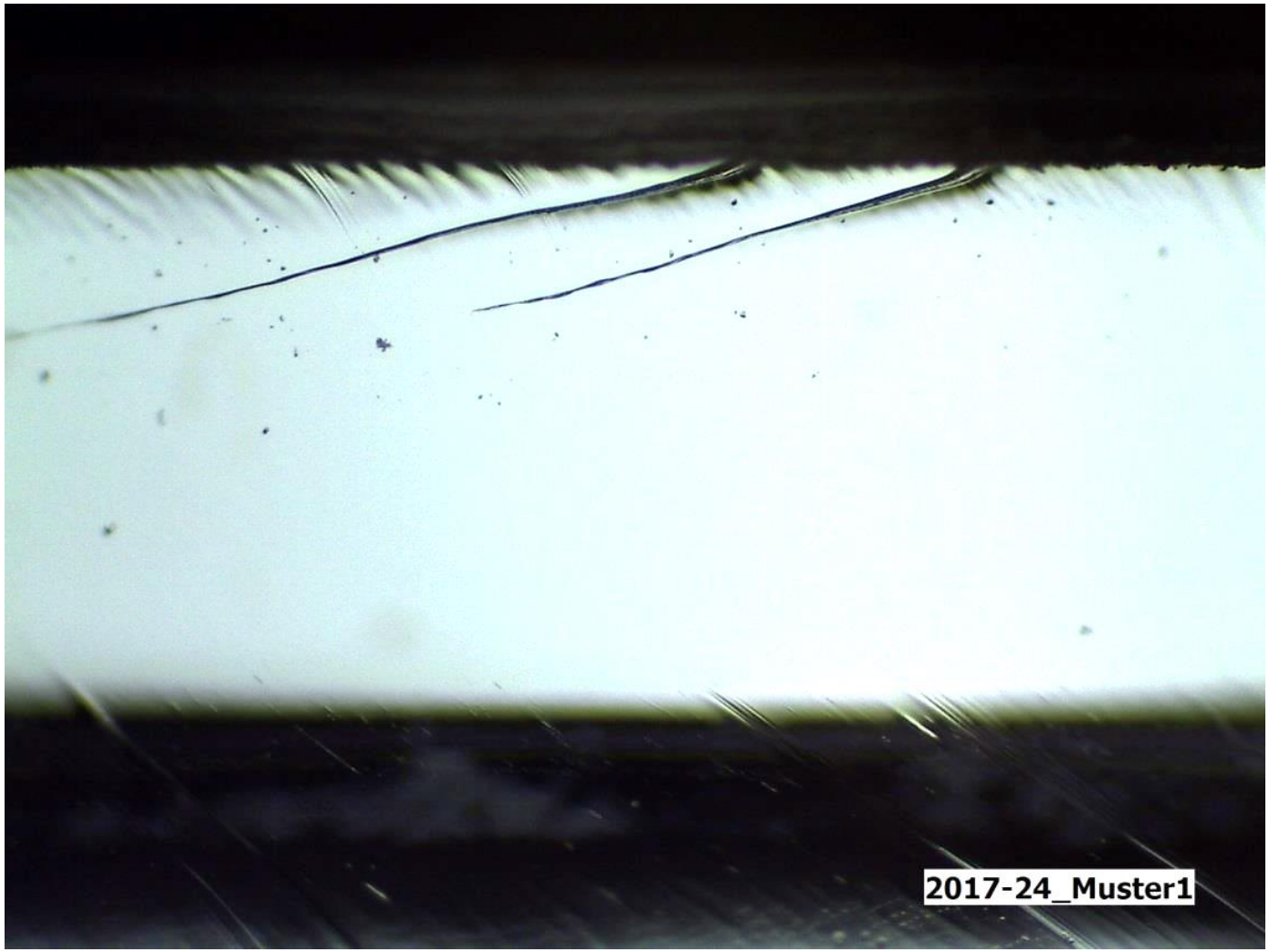
Description of Defect	Acceptable	Poor Quality
Pressure / Tool Marks	 Faint tool marks - process related	 Tool marks with potential functional impact

What to consider or to avoid (examples)

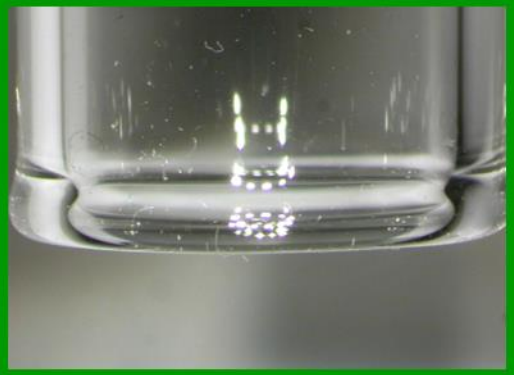
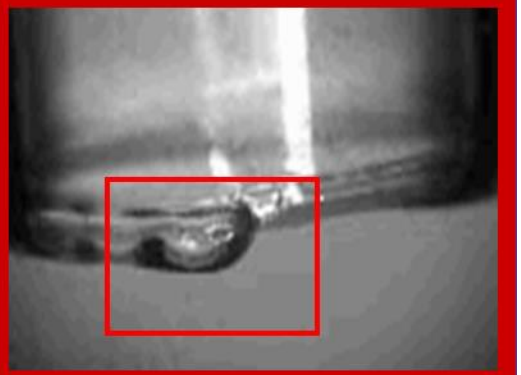
What to consider or to avoid (examples)



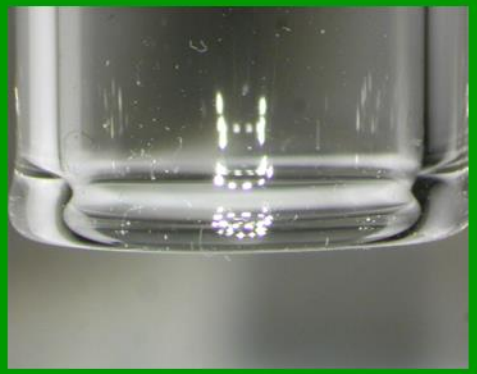
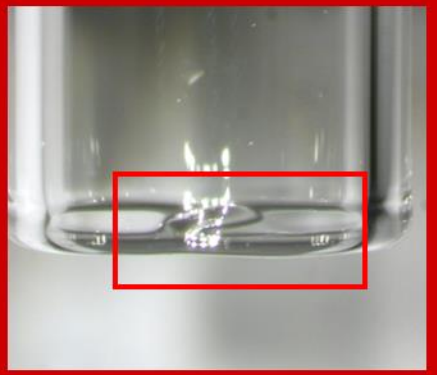
What to consider or to avoid (examples)



What to consider or to avoid (examples)

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

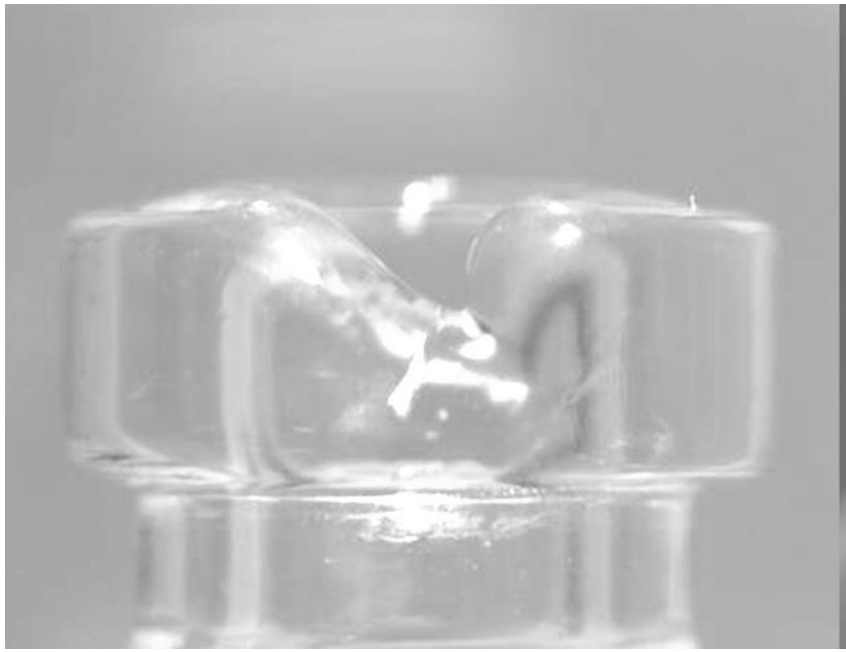
What to consider or to avoid (examples)

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

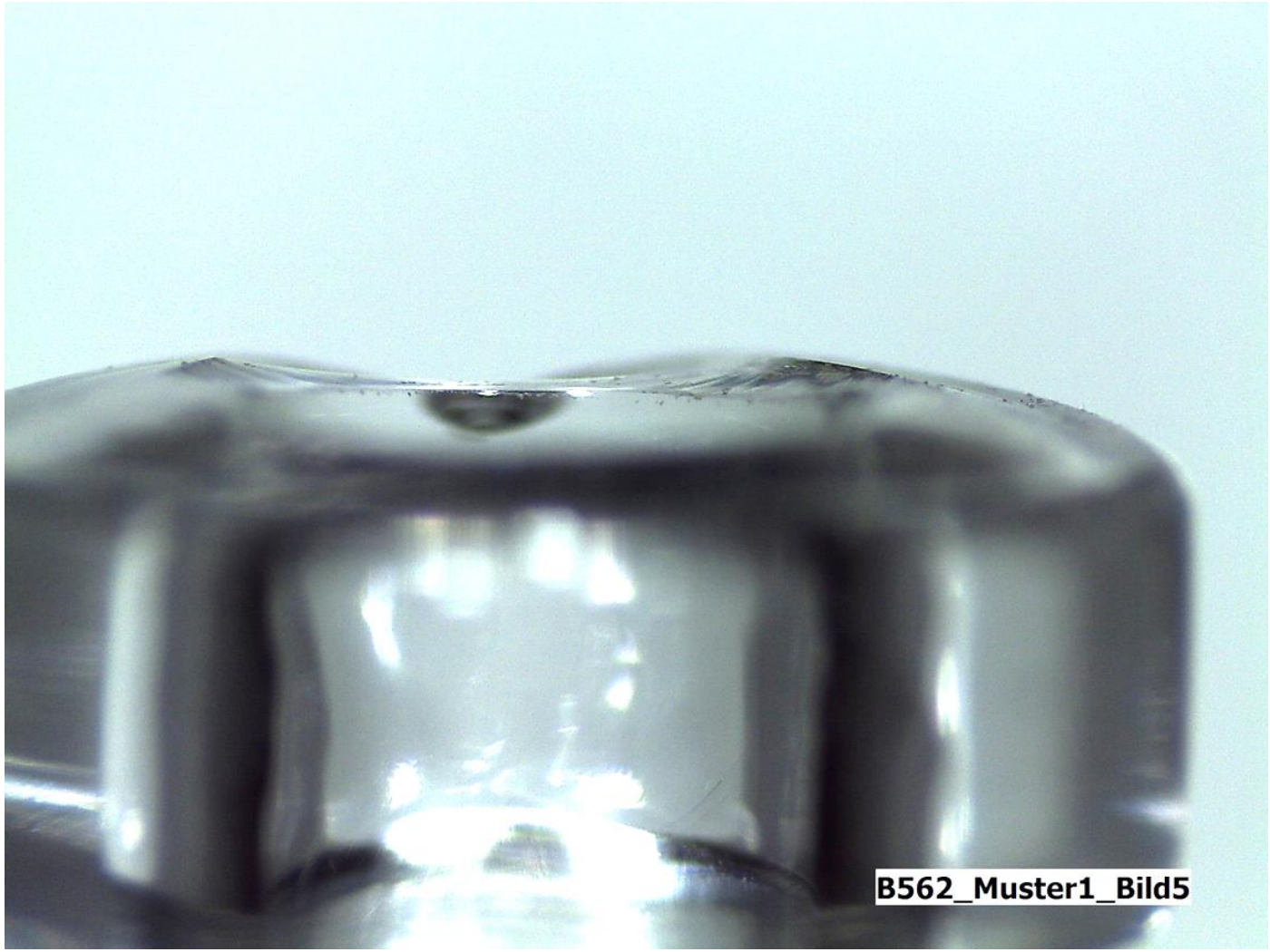
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Deformed cartridge Container closure impacted		

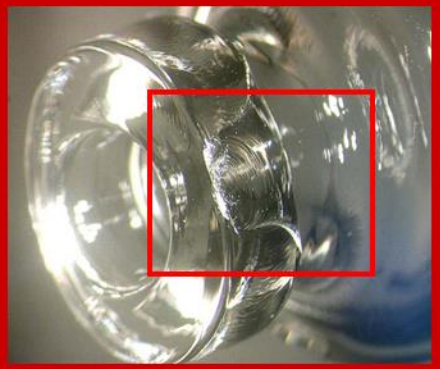
What to consider or to avoid (examples)



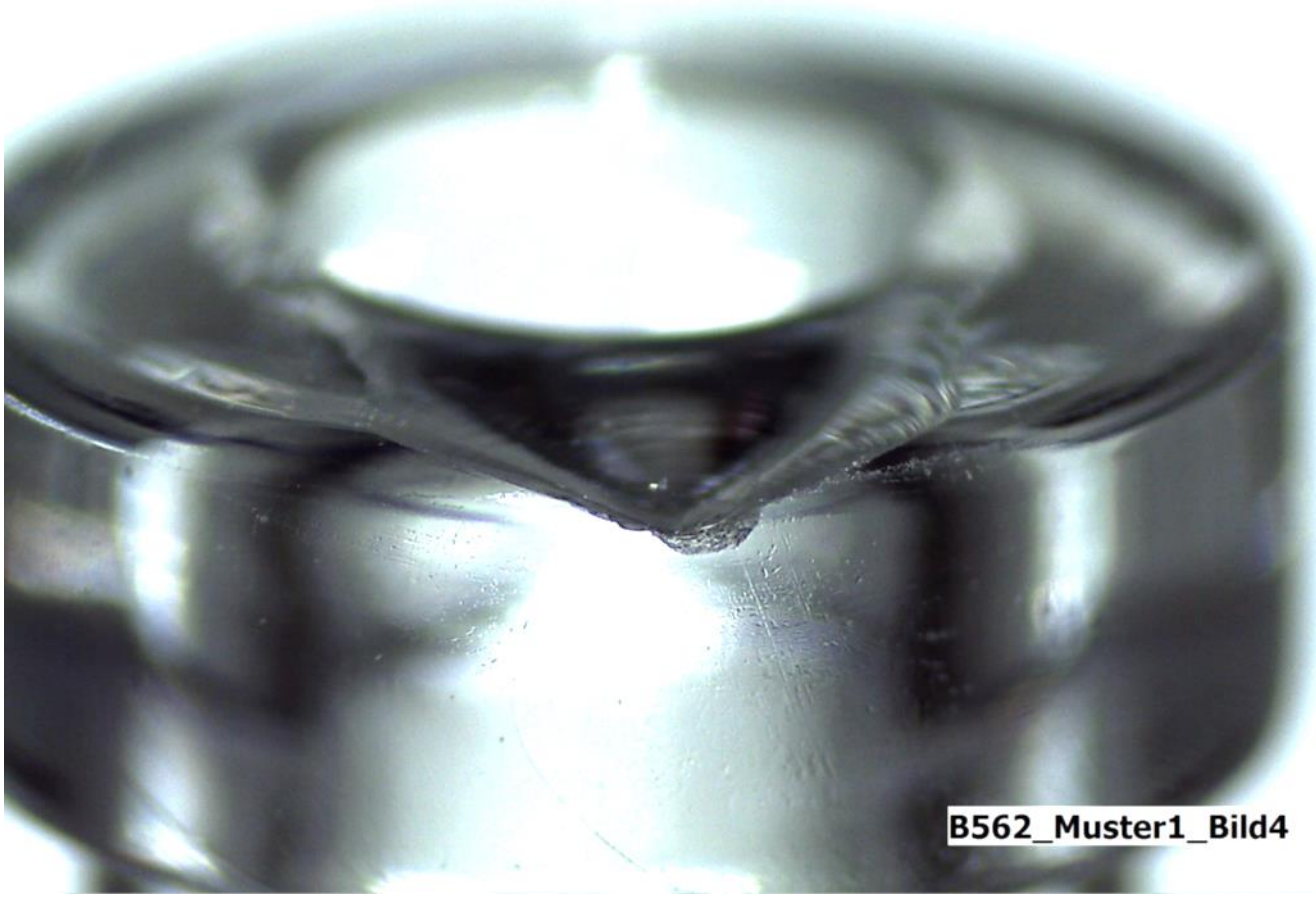
What to consider or to avoid (examples)



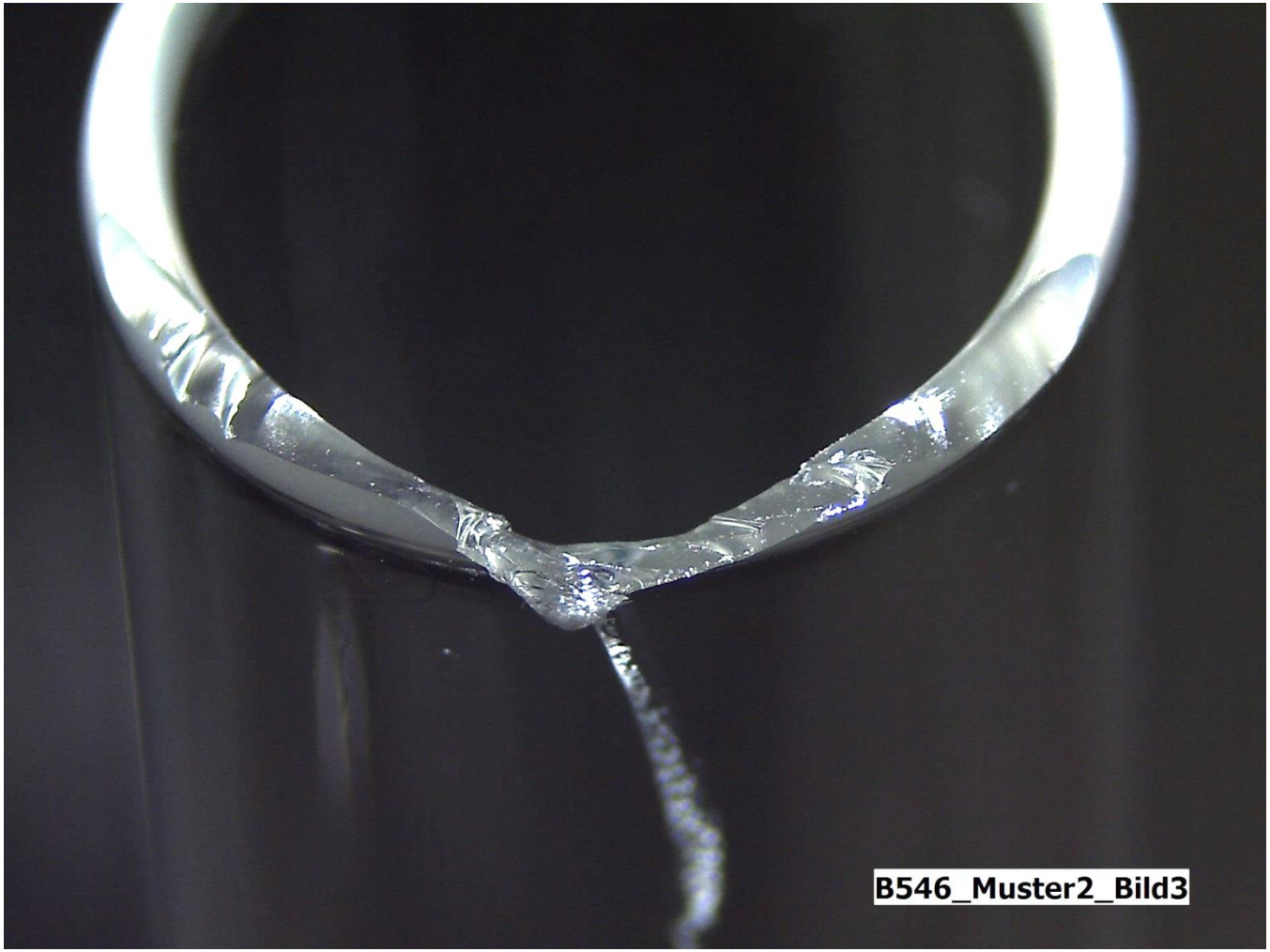
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Chipped glass (Cracks)		

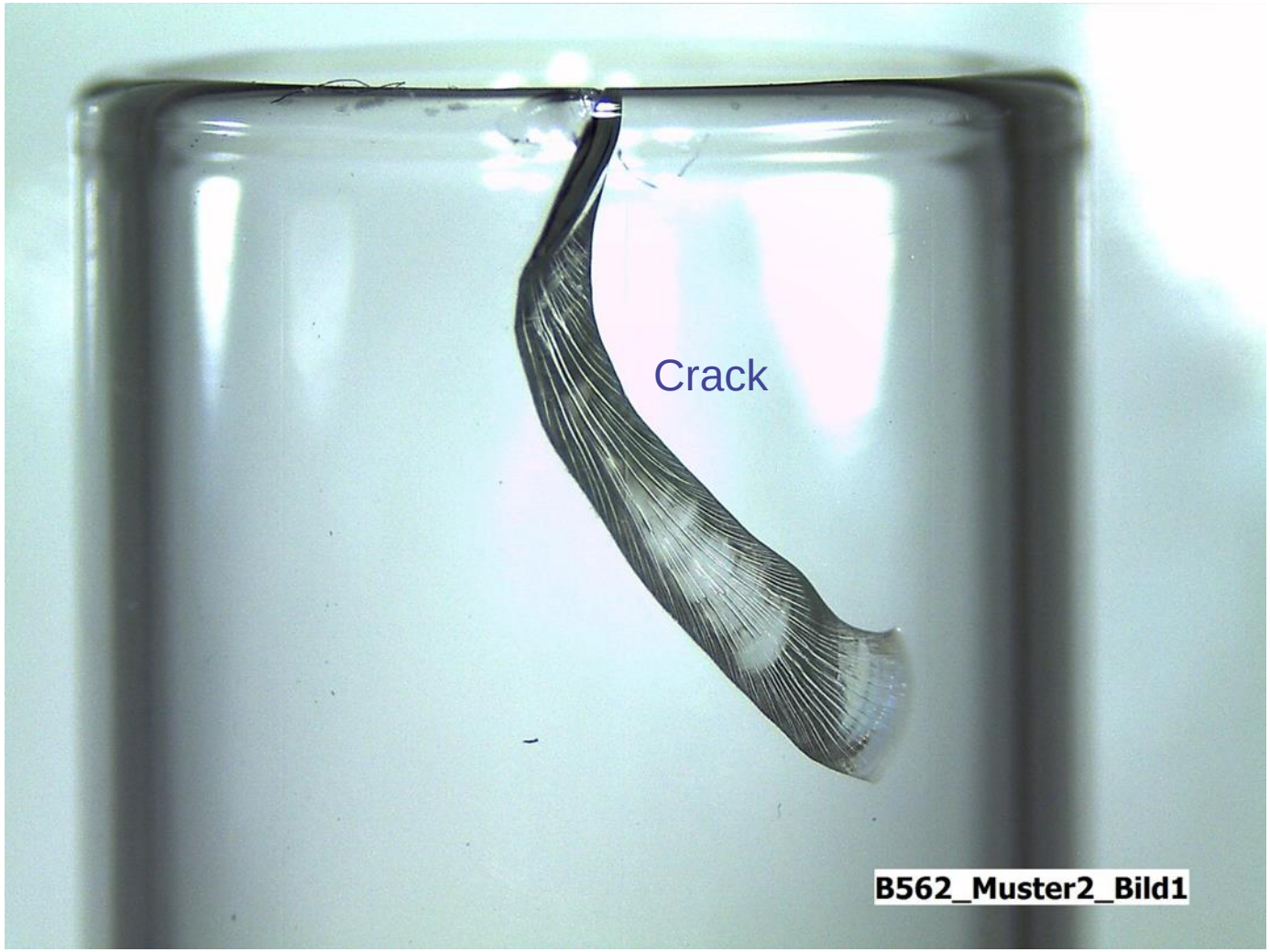
What to consider or to avoid (examples)



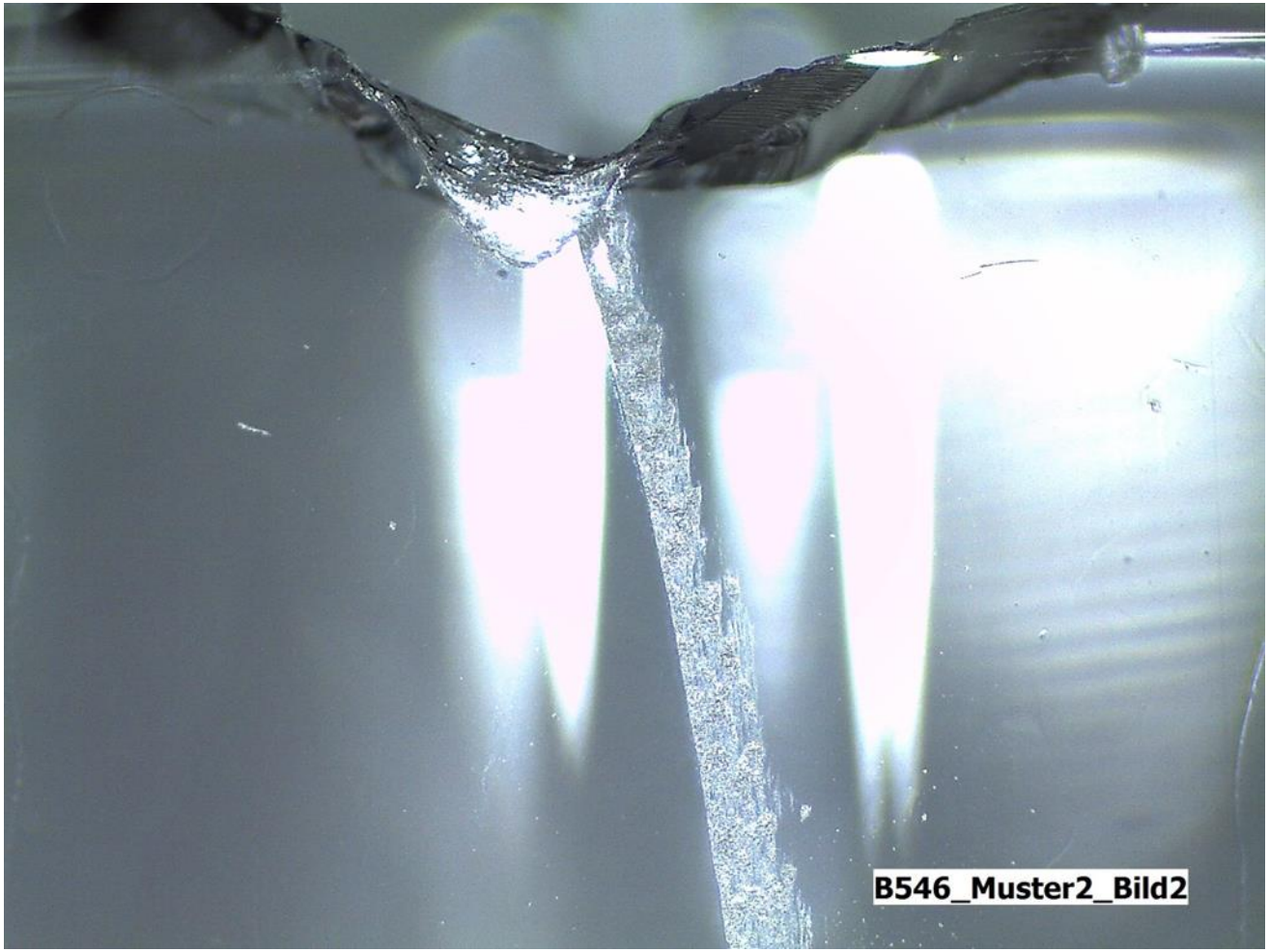
What to consider or to avoid (examples)



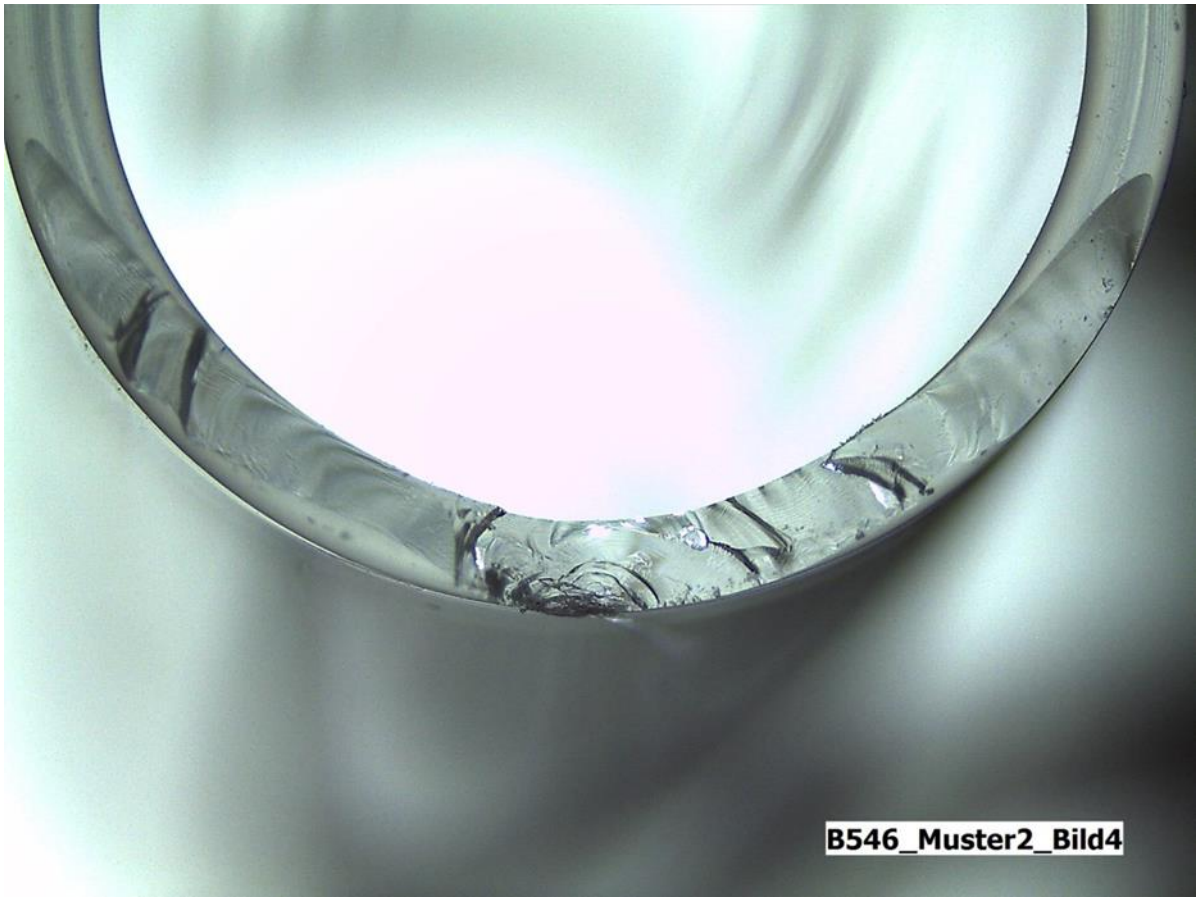
What to consider or to avoid (examples)



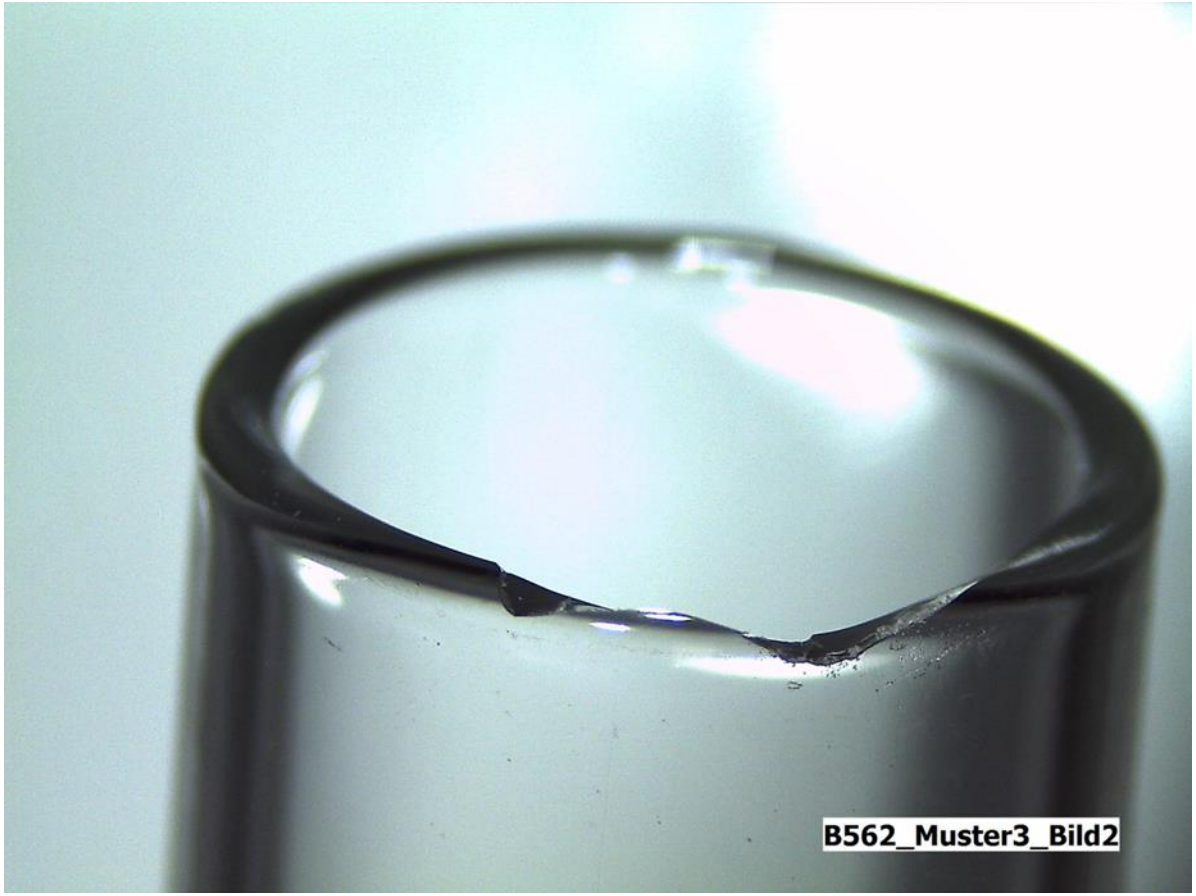
What to consider or to avoid (examples)



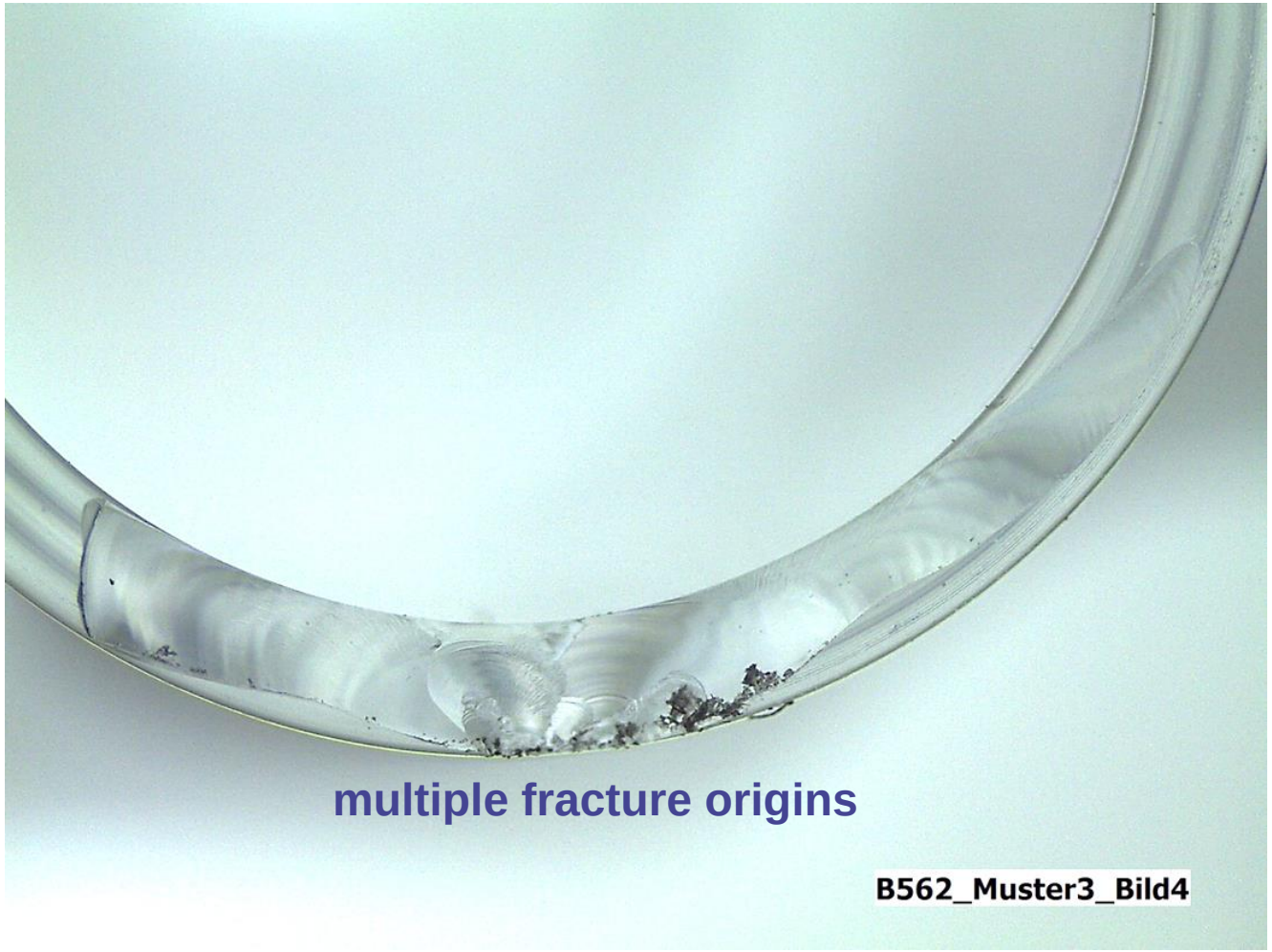
What to consider or to avoid (examples)



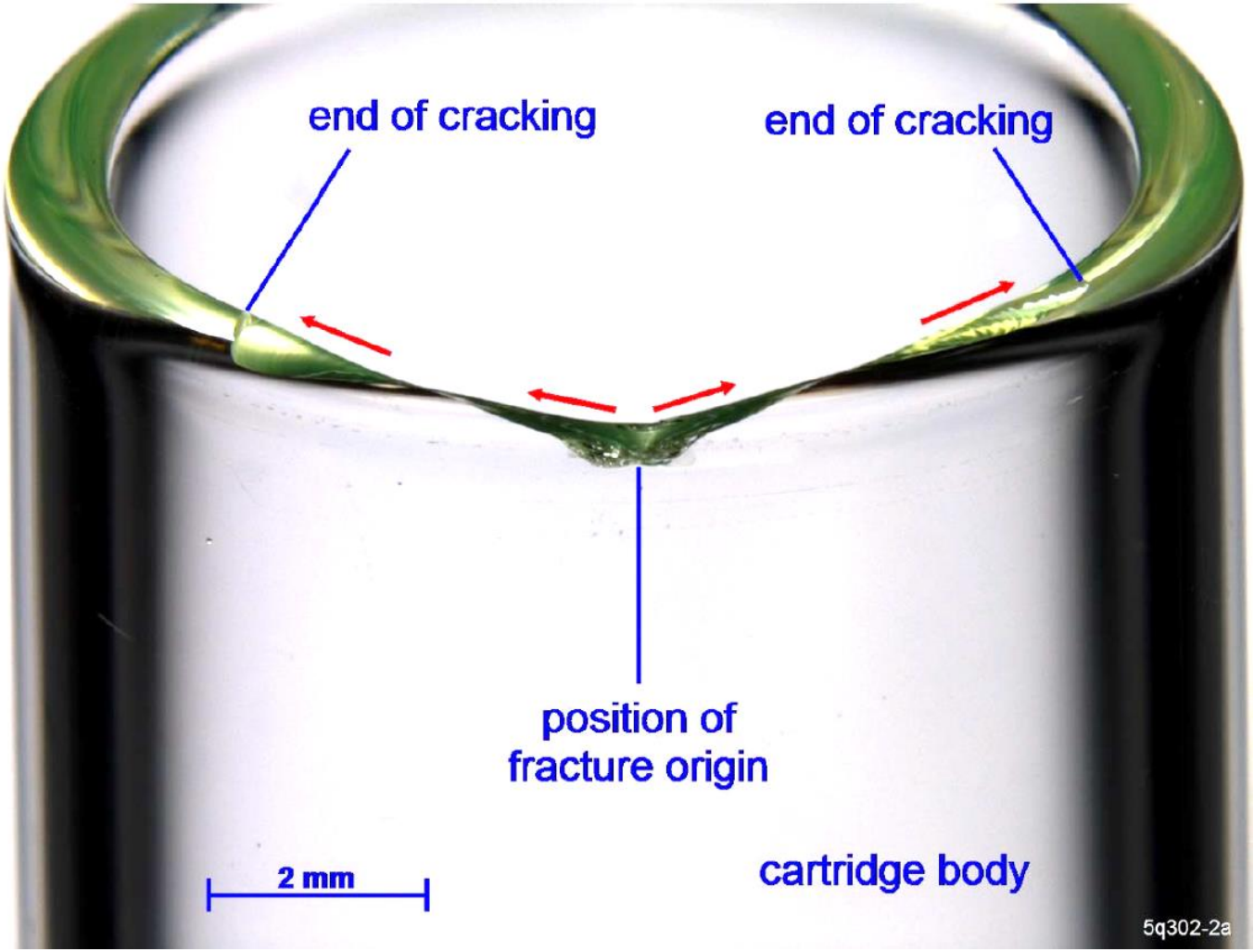
What to consider or to avoid (examples)



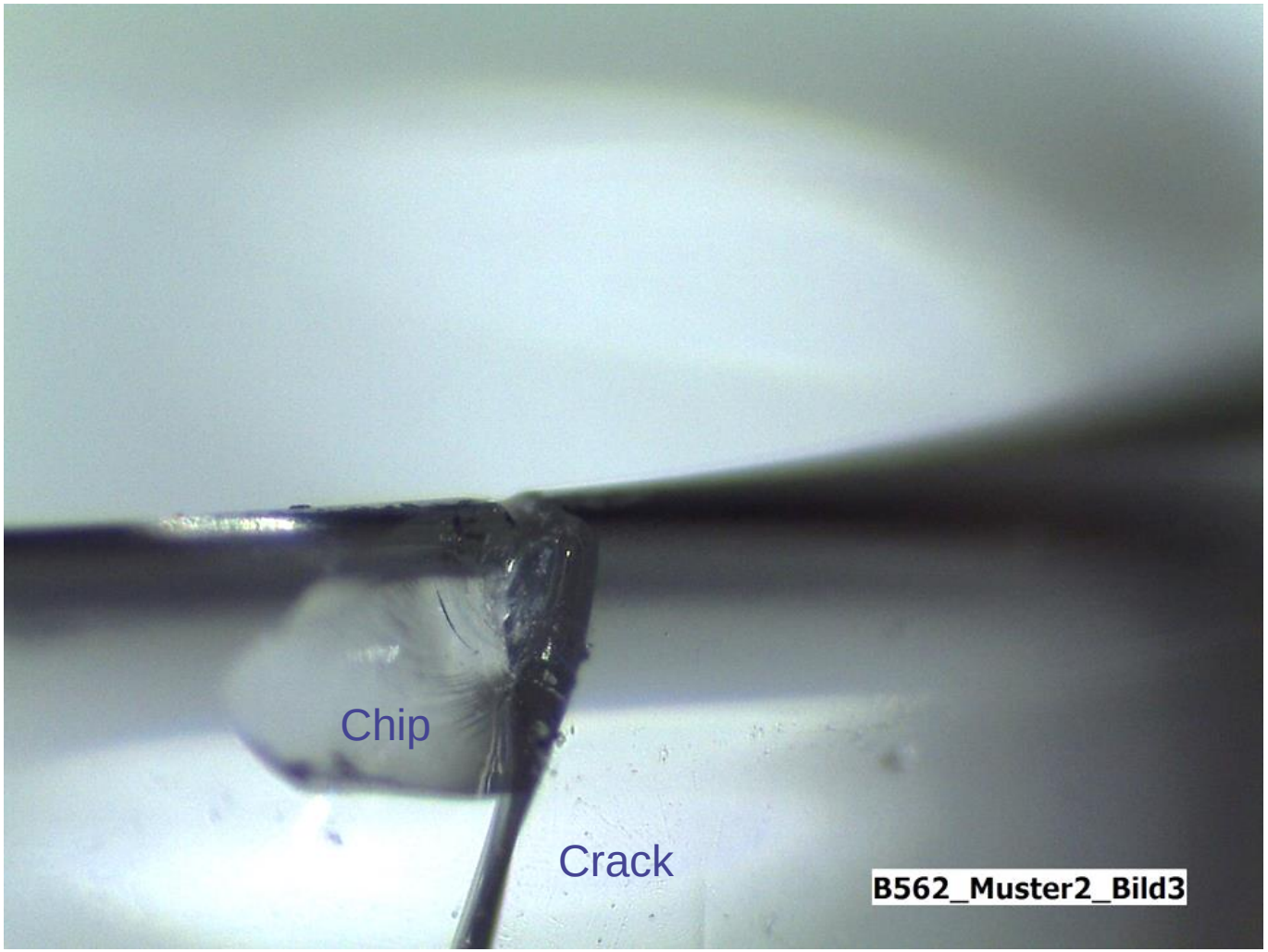
What to consider or to avoid (examples)



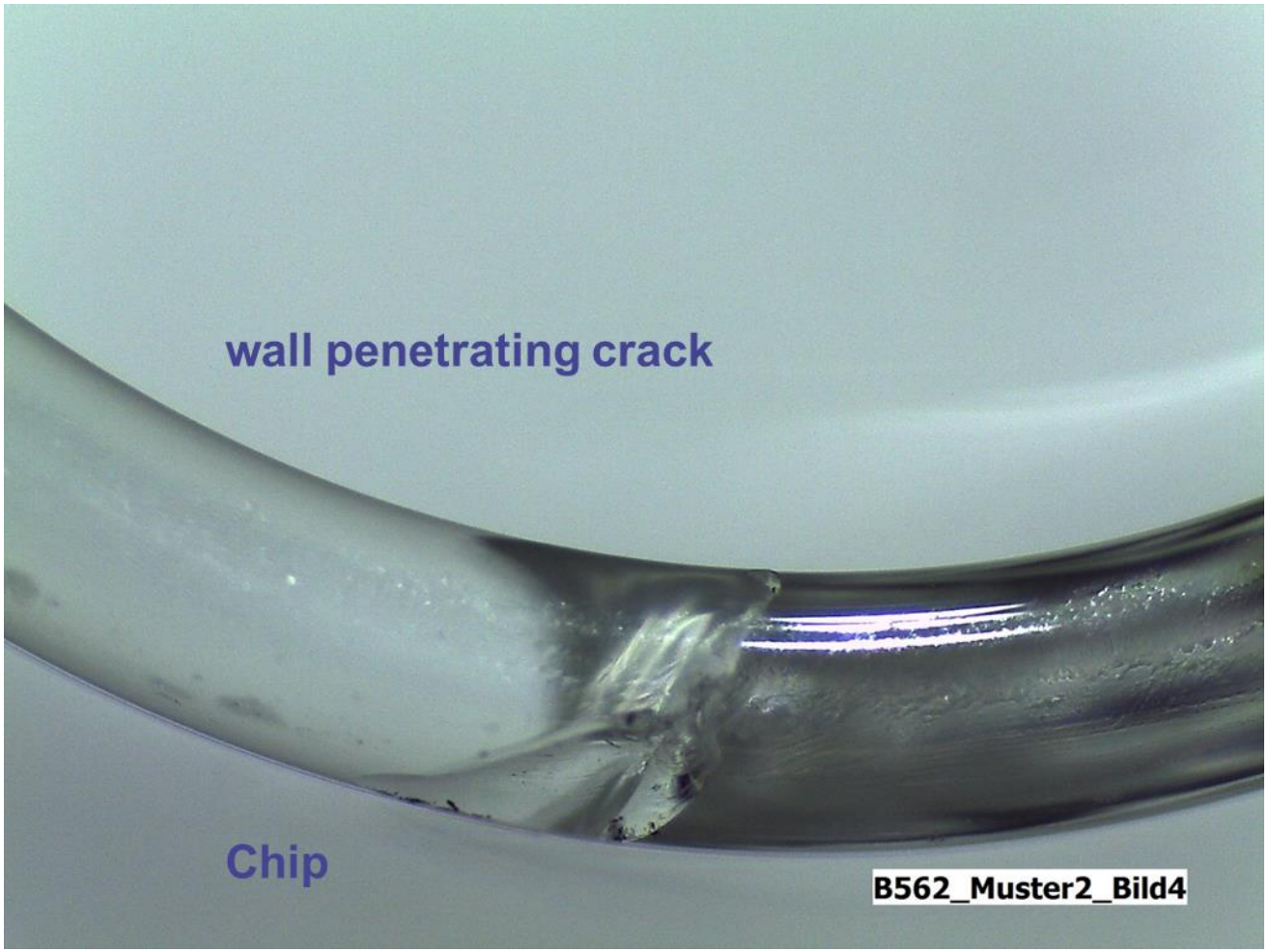
What to consider or to avoid (examples)



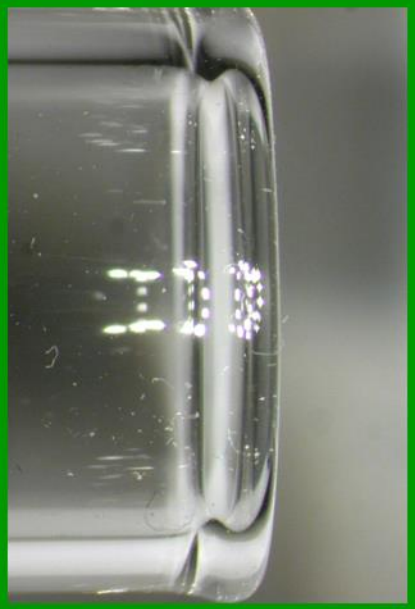
What to consider or to avoid (examples)



What to consider or to avoid (examples)



What to consider or to avoid (examples)

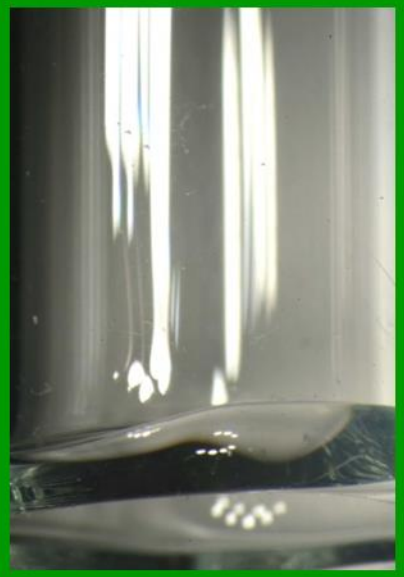
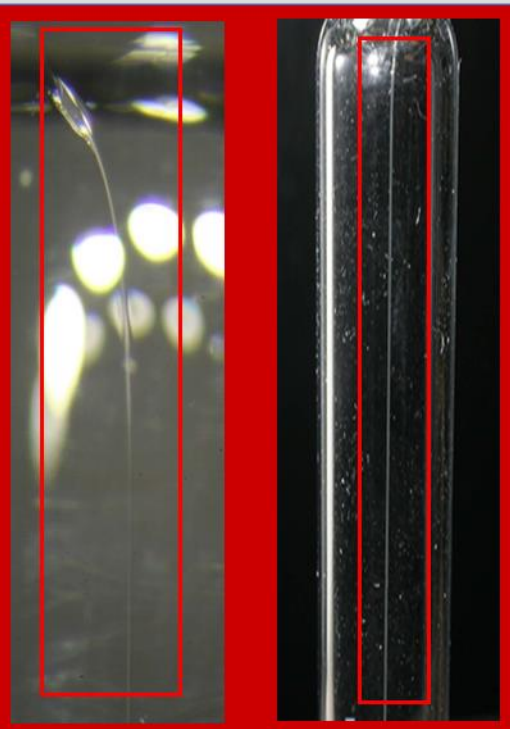
Description of Defect	Acceptable	Poor Quality
Partially or not molded cartridges function / processing impacted		

What to consider or to avoid (examples)

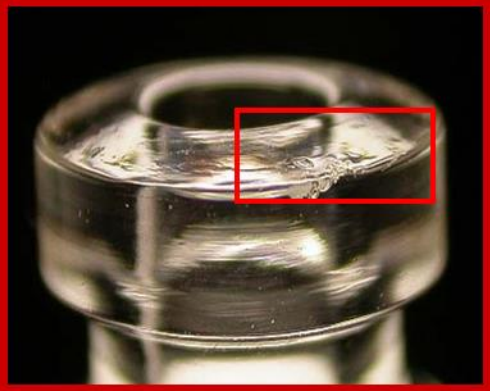
Description of Defect	Acceptable	Poor Quality
Scratches / air lines outer surface		 Kratzer oder Luftlinien 

What to consider or to avoid (examples)

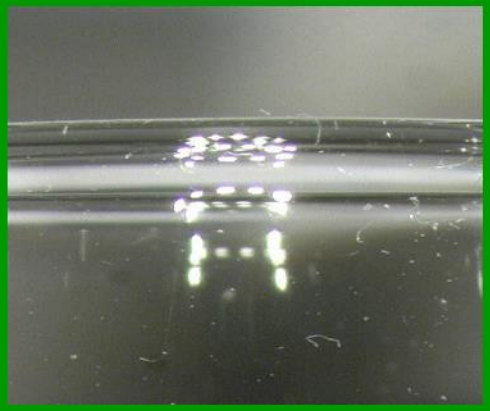
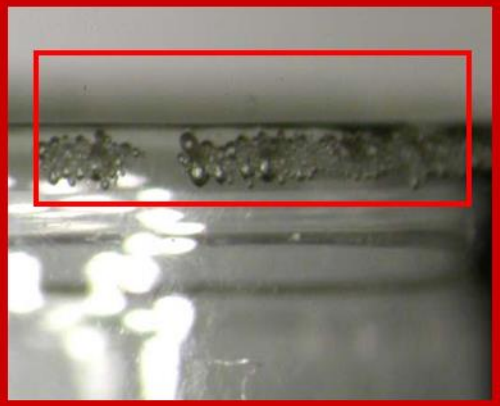
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Closed air lines		

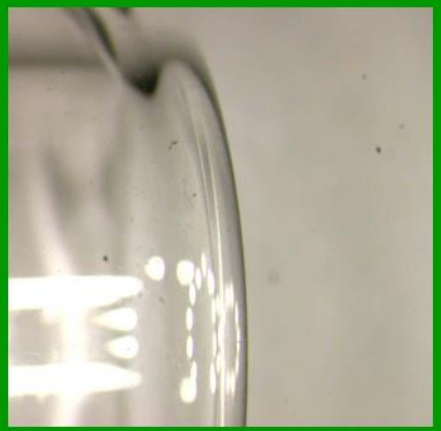
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Air bubbles		

What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Air bubbles		

What to consider or to avoid (examples)

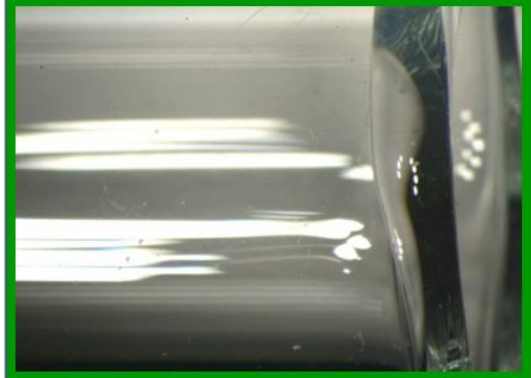
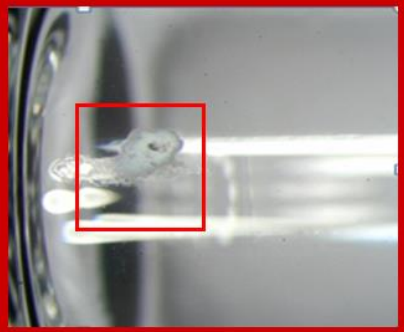
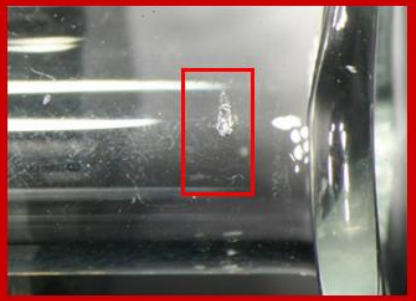
Description of Defect	Acceptable	Poor Quality
Contamination inside, not easy removable (not embedded)		 Abrasion

What to consider or to avoid (examples)

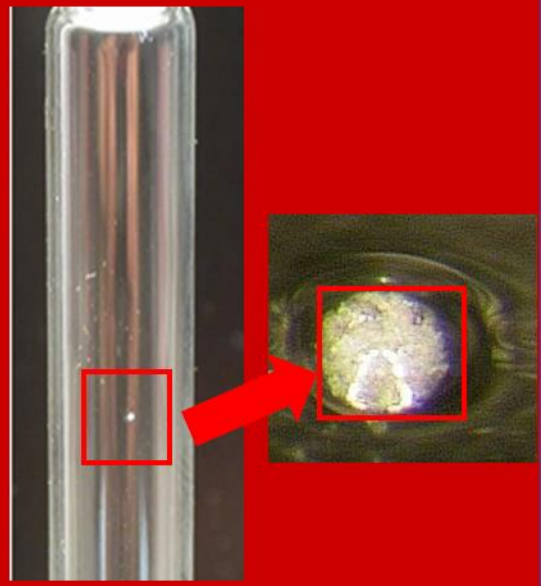
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Contamination outside or embedded not removable		 

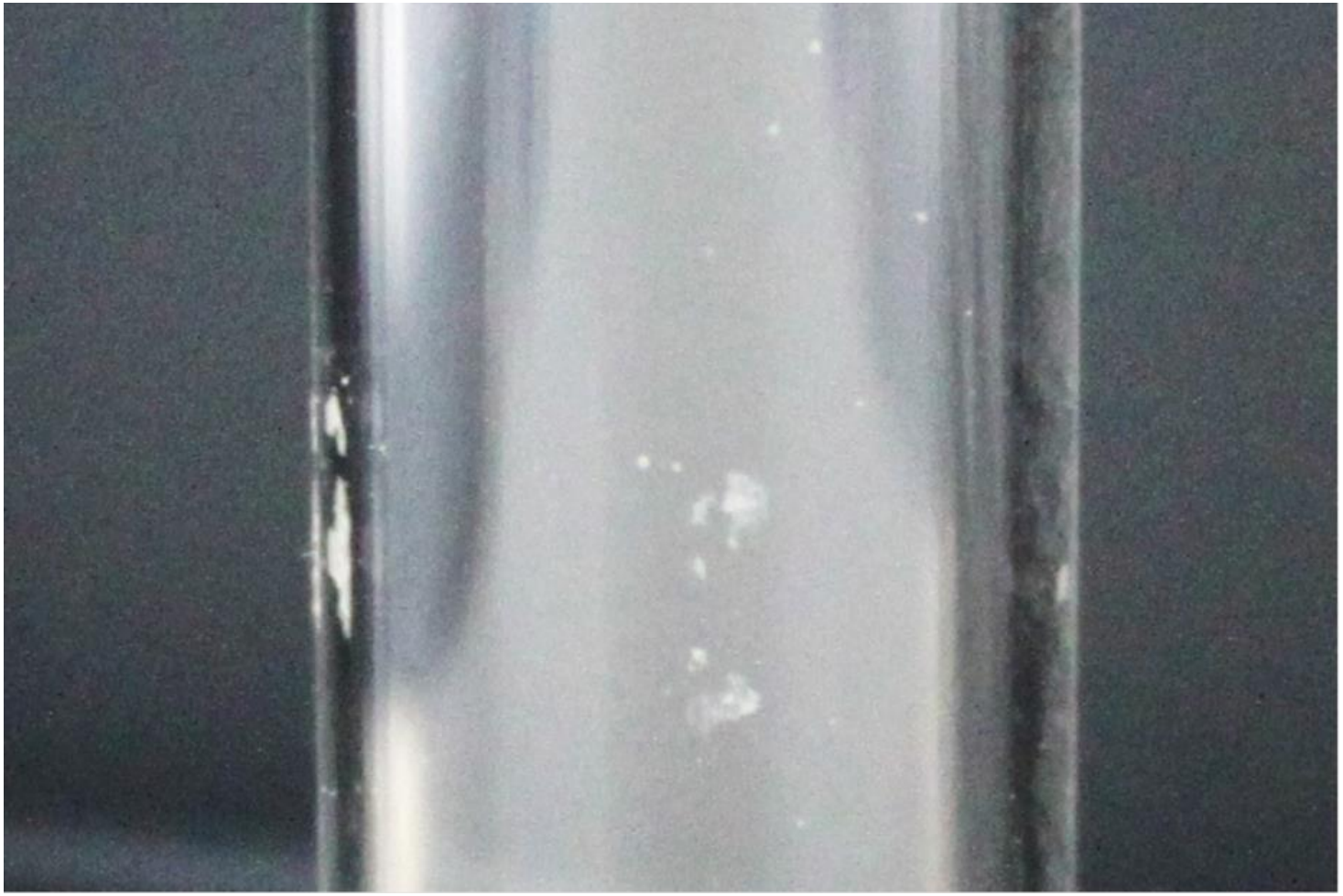
What to consider or to avoid (examples)

Description of Defect	Acceptable	Poor Quality
Visible baked glass grit / chips On the glass surface		 angesinterter Glasgries 

What to consider or to avoid (examples)

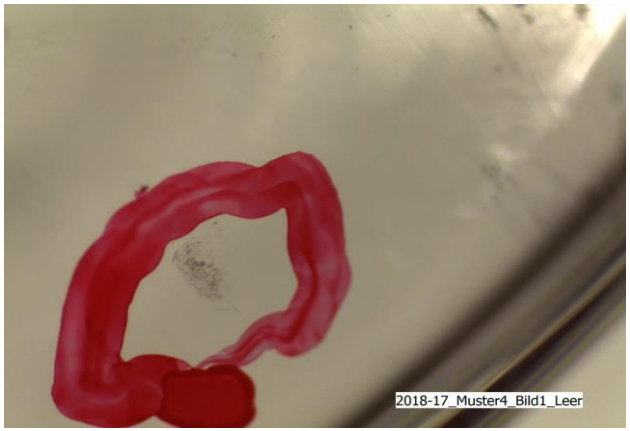
Description of Defect	Acceptable	Poor Quality
Visible baked glass grit / chips On the glass surface		

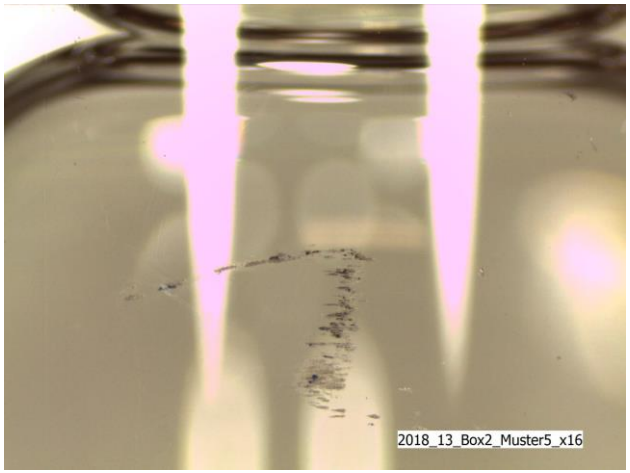
What to consider or to avoid (examples)

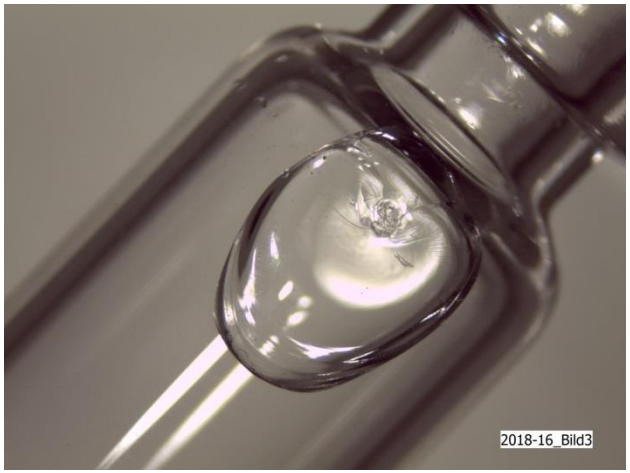


What to consider or to avoid (examples)

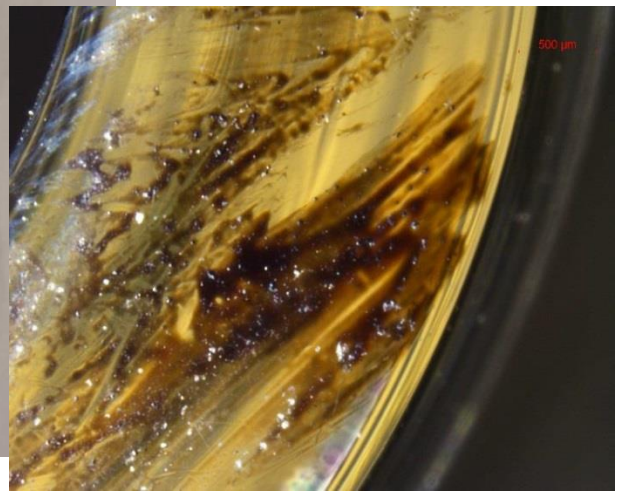
- Defects from filling operations







Vial collar with contamination



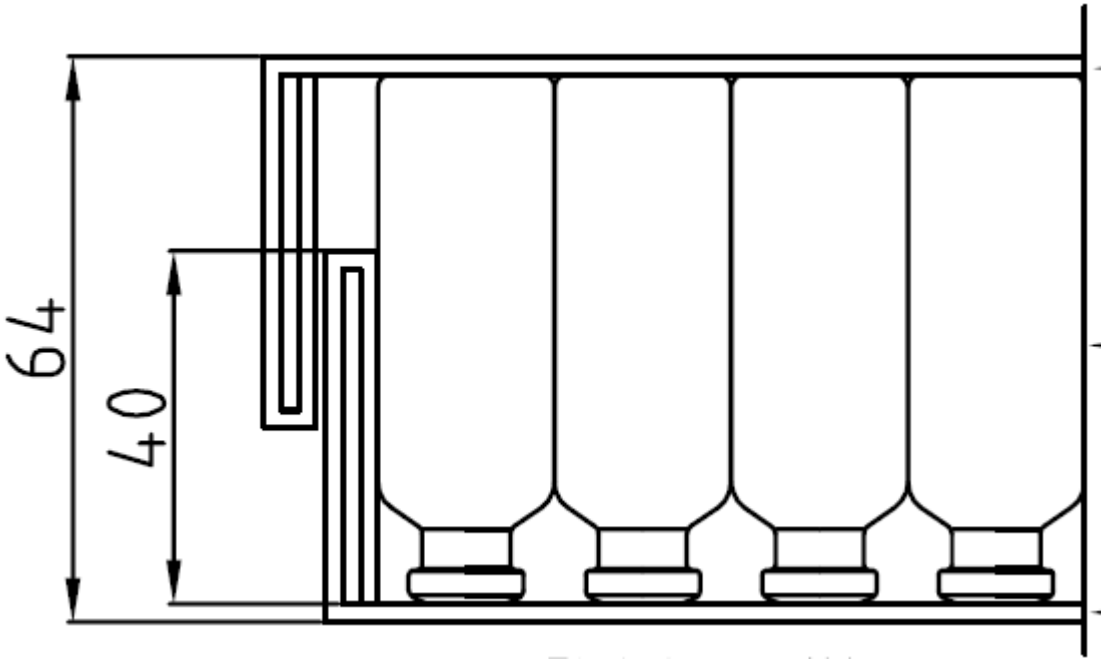
Vial collar with contamination

- Identified after heat sterilization

- Supplier Investigation

Vial collar with contamination

- Investgation inconclusive
- Potential Root cause



What to consider or to avoid (examples)

- 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

What to consider or to avoid (examples)

- 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

What to consider or to avoid (examples)

- 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 fullfilled 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 appropiate intervals*

Note: The same applies to packaging materials

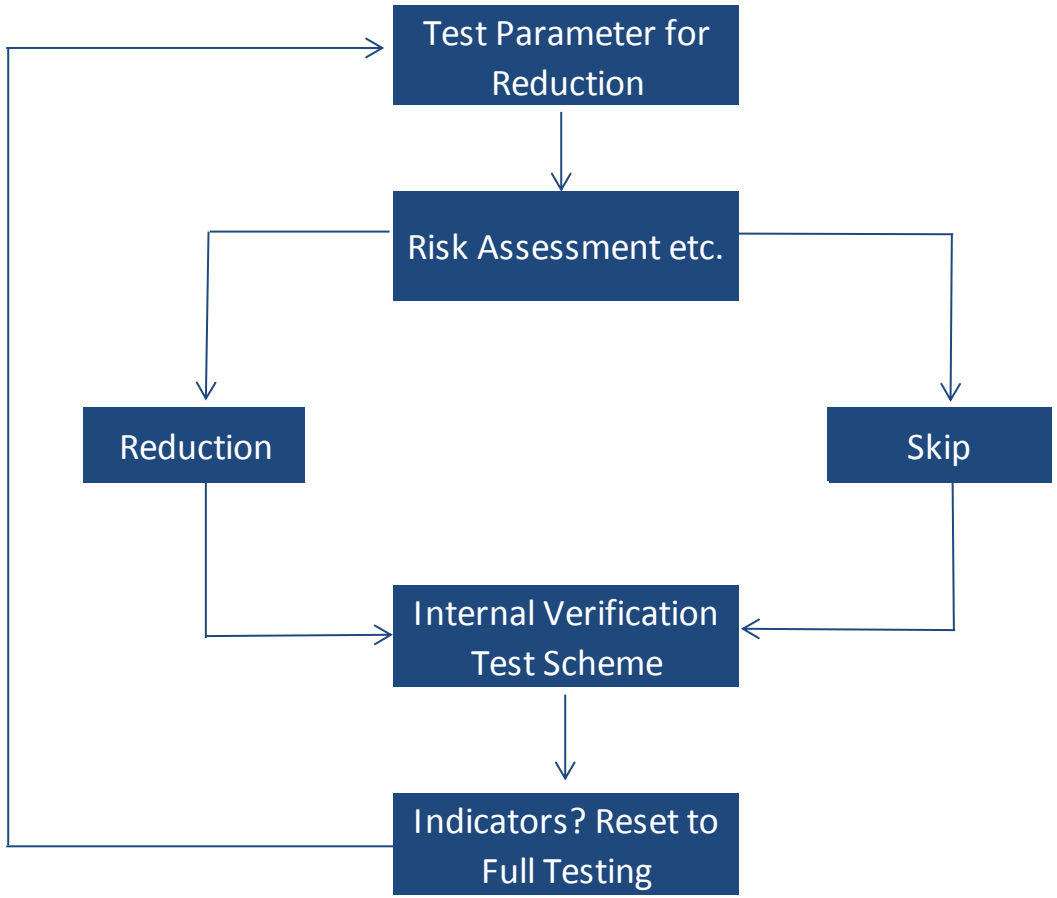
What to consider or to avoid (examples)

- 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 containters/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

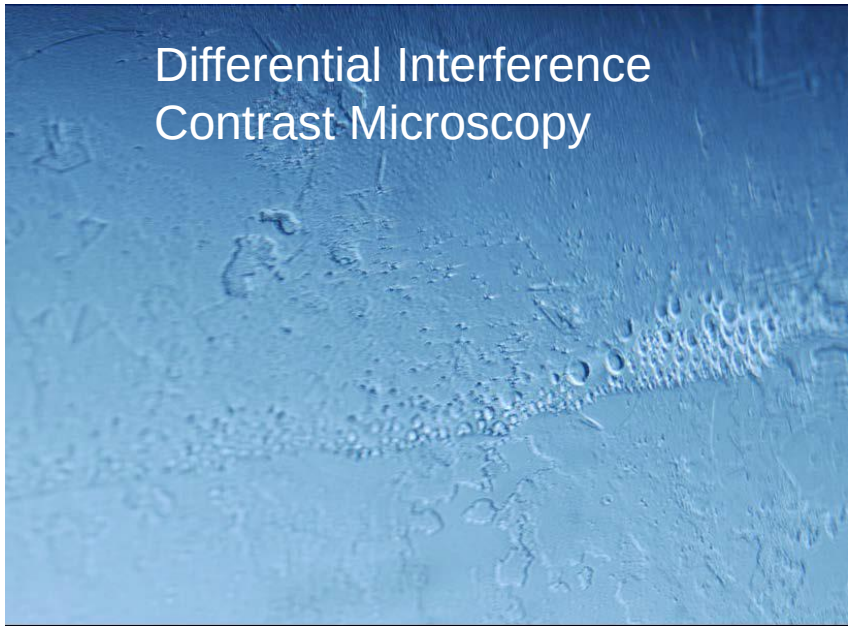
Reference and Retention Samples

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



What to consider or to avoid (examples)

- Delamination Risk

		Risk factor
Primary Packaging (PP)	Type I without or Silicone	1
	Type II with treatment	10
	pH	
Product Formulation (PF)	Buffer (B)	
	Ionic Strength (IS)	
	Complexing Agent (CA)	
	pH </= 7	1
	pH > 7 & </=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**

Coordination process between packaging manufacturer and customer

- Selection and Qualification of Supplier
  - Pre-qualification (questionaire, information, due diligence visit)
  - Negotiate contract(s)
  - Supplier audit
  - Agree upon specifications (sampling)
  - Quality Agreement
    - Mandatory if data from CoAs are accepted for incomming 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

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

Coordination process between packaging manufacturer and customer

- 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

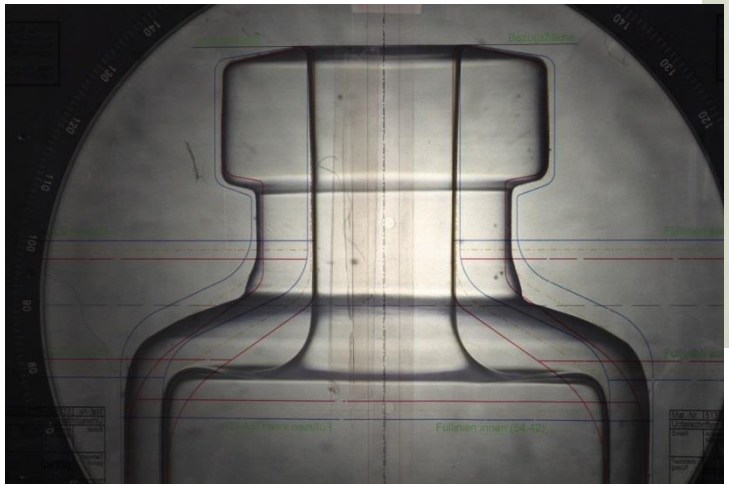
- The ISO 15378 standard enables the supplier to comply with legal requirements for pharmaceutical and medical device primary packaging materials
- The standard integrates the requirements of ISO 9001 as well as GMP prinziples, a regulatory requirement for the pharmaceutical and medical device industries 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.
- The standard delineates GMP principles and specifies Quality Management System requirements applicable to primary packaging materials.

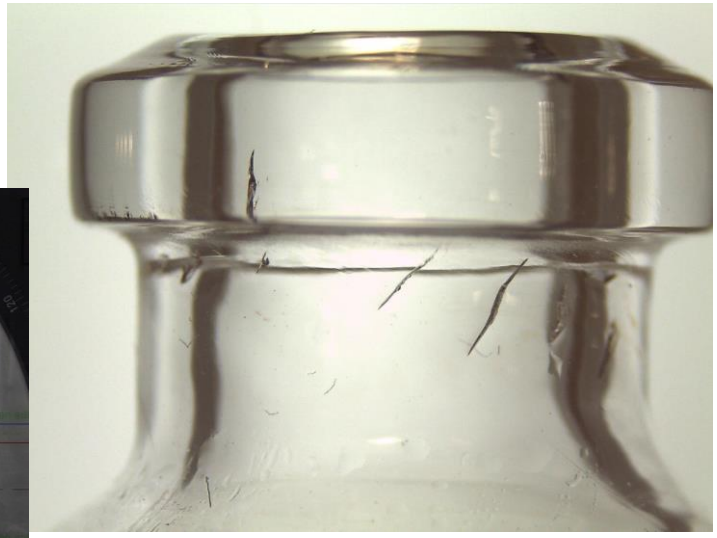
Coordination process between packaging manufacturer and customer

- 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 e.g. Japan

Coordination process between packaging manufacturer and customer

- 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



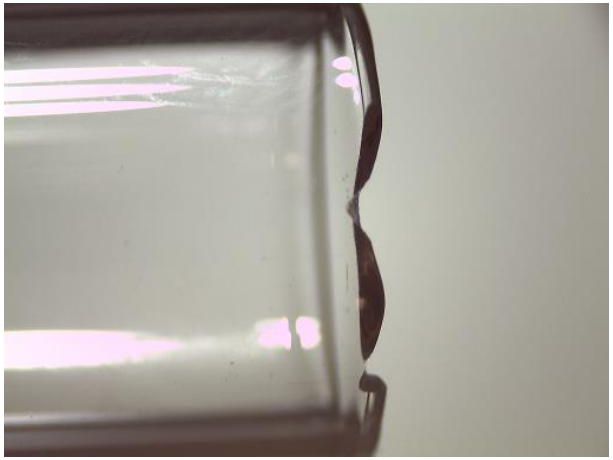


Coordination process between packaging manufacturer and customer

- 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 (supplier) certificate before processing
  - Documentation: recording of inspection data in suitable achives
  - Reference Samples

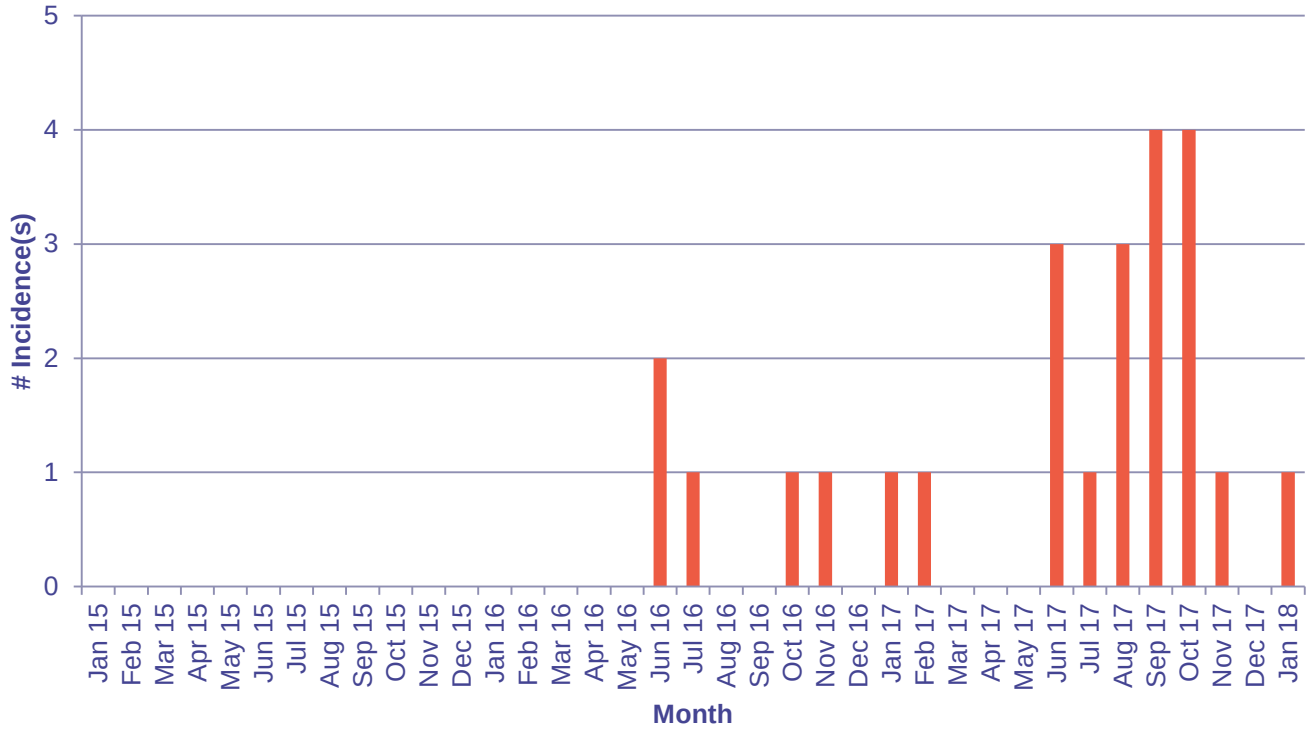
- Case Study

Glass chippings at the glazing end



Incoming Inspection of Primary Packaging Material

- Incidences during incoming inspection



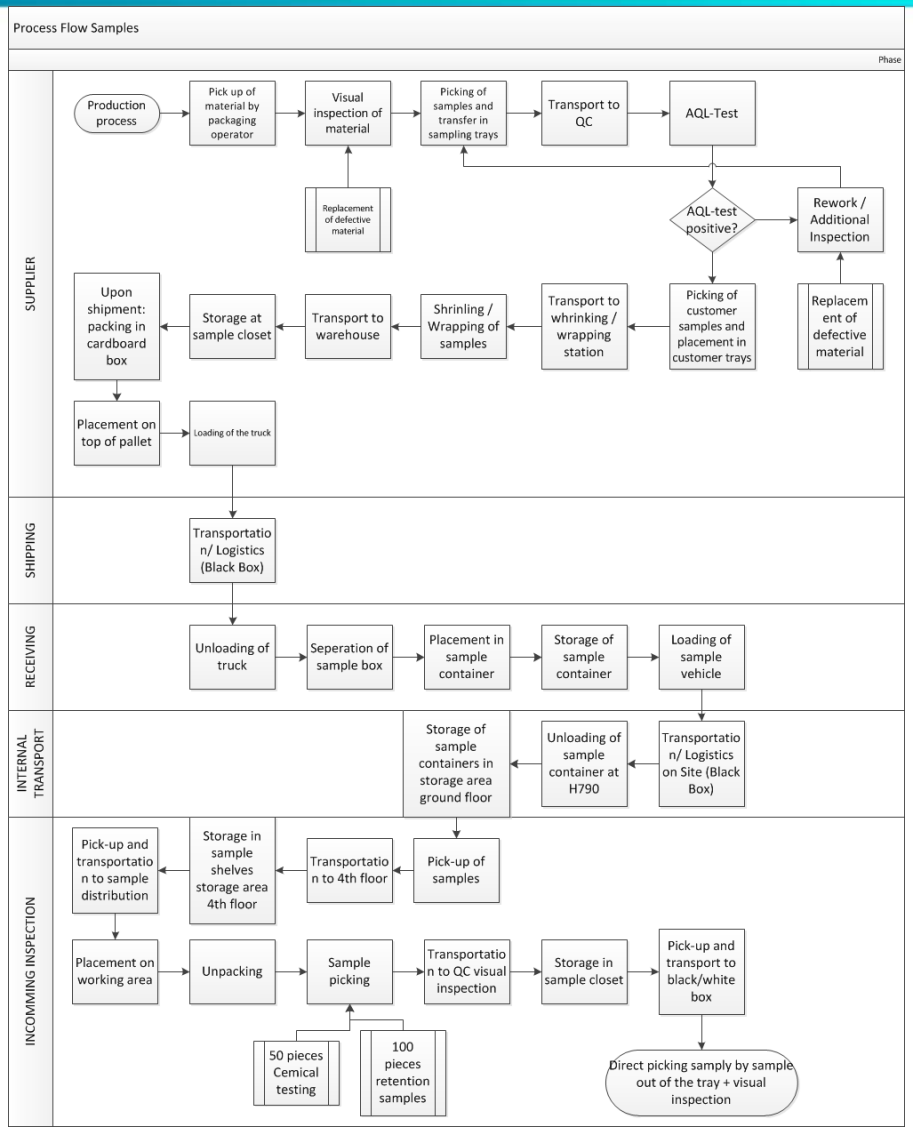
Incoming Inspection of Primary Packaging Material

- 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 %

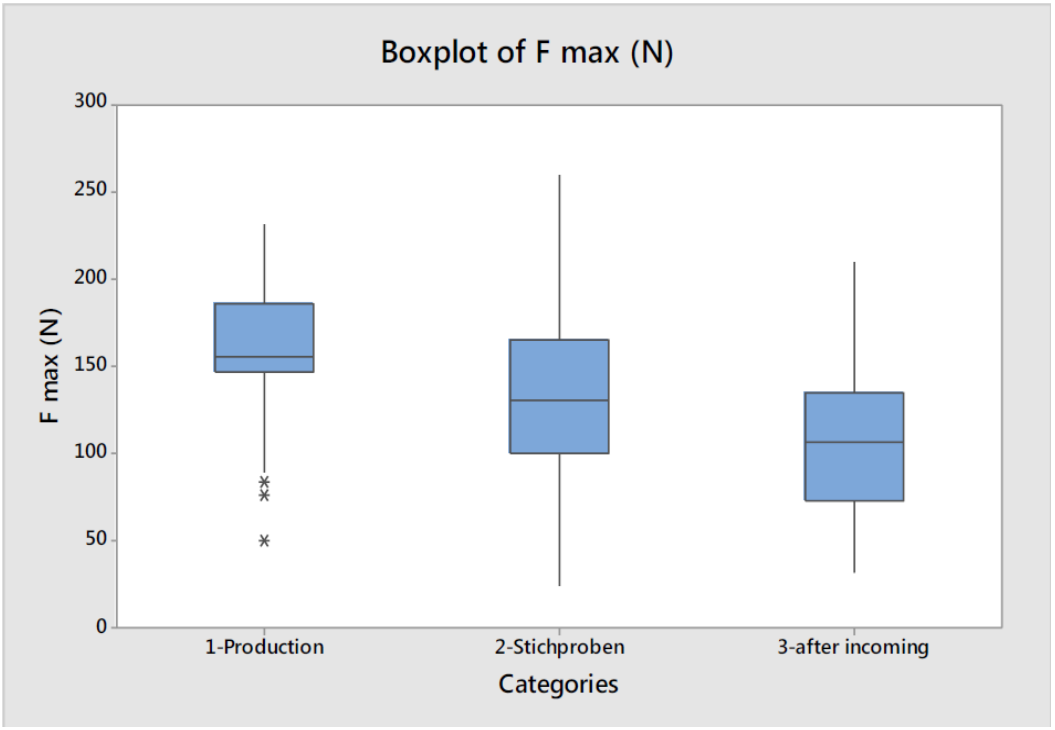
Incoming Inspection of Primary Packaging Material

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



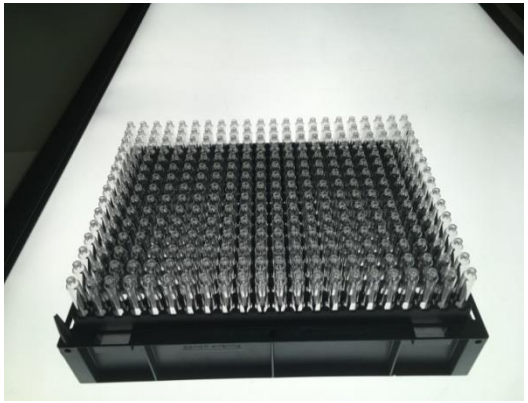
- Investigation of glass stability pre-/ post-shipment

Tensile stress Area:
Glazed rim



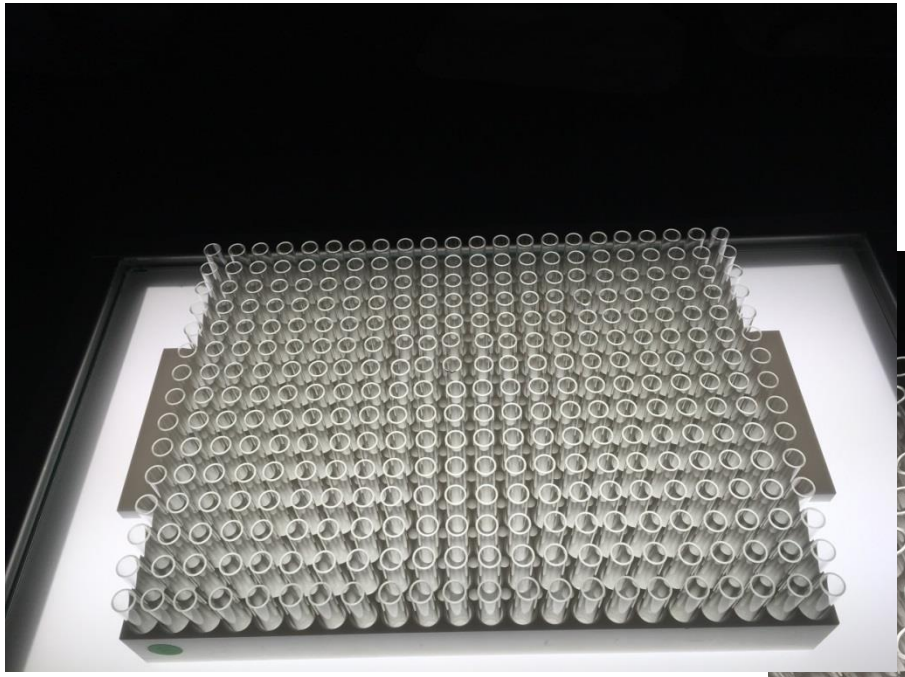
Incoming Inspection of Primary Packaging Material

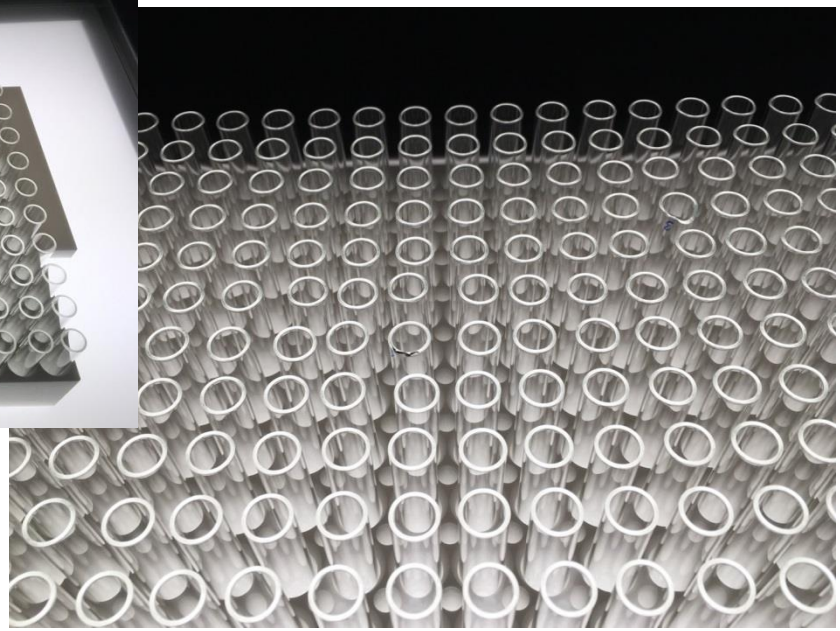
- Improvement potential identified for processing of Tailgate samples



Incoming Inspection of Primary Packaging Material

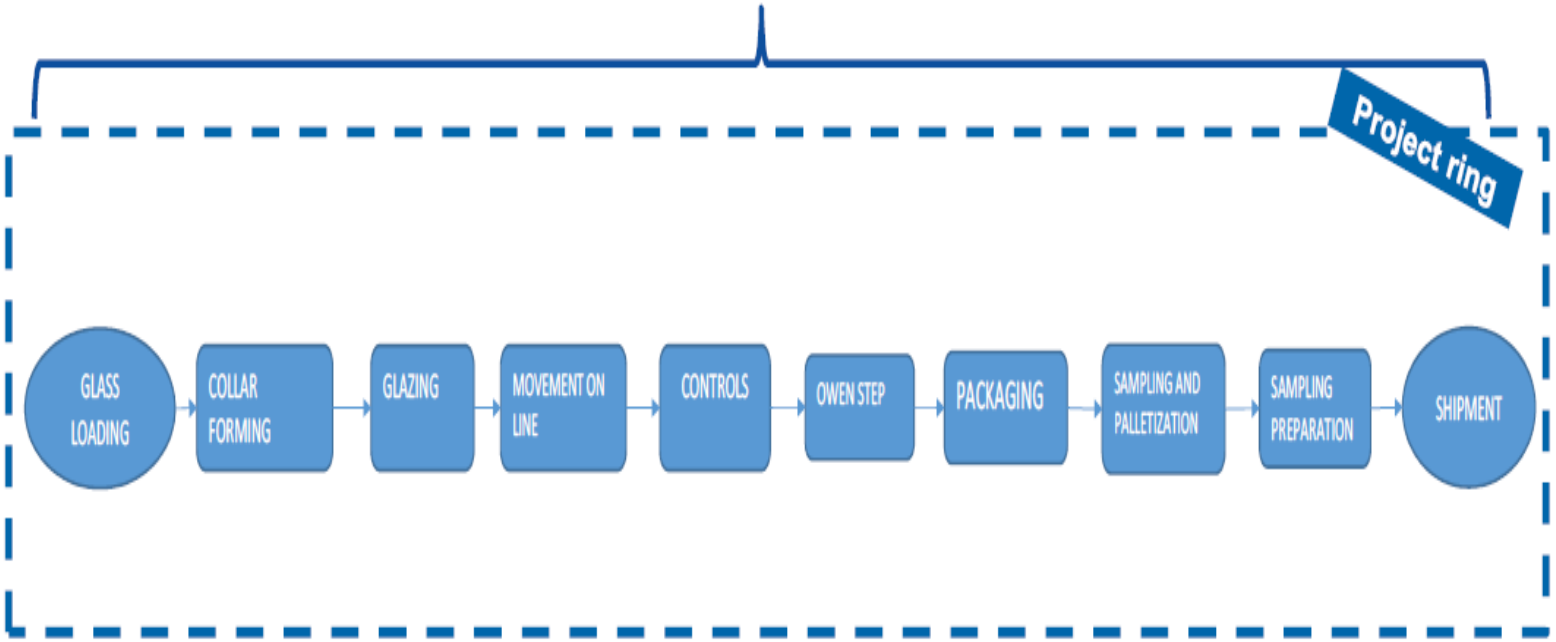
- Improvement potential visual inspection (light box)





Incoming Inspection of Primary Packaging Material

- 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

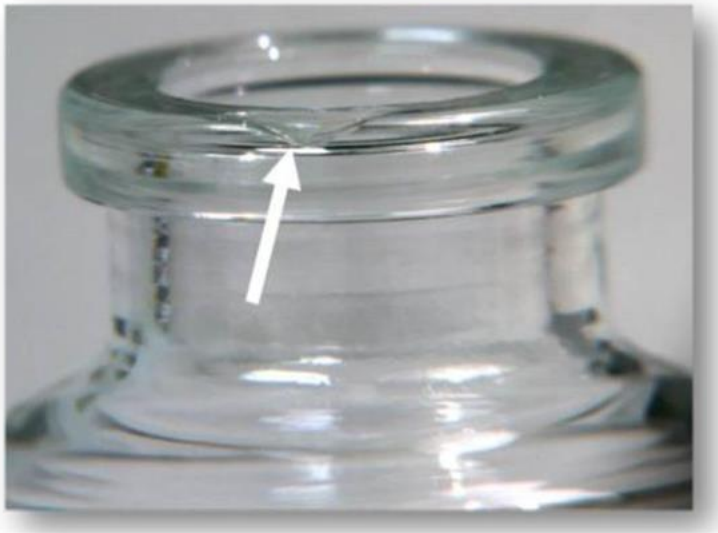
Incoming Inspection of Primary Packaging Material

- 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

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.

- CHIPS

- 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

Thank You!

Incoming Inspection of Primary Packaging Material

- 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