Best Practices for Glass Primary Containers

Incoming Inspection

PDA Parenteral Drug Association

PDA TRAINING

Overview incoming inspection

1 Requirements for incoming inspection

2 How to set up in practice

3 What to consider or to avoid examples

4 Coordination process between packaging manufacturer & customer

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Part I

Requirements for Incoming Inspection

What is the use of packaging?
general remarks

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

Challenges in being up to date

- 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 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 (ophtalmica)

Legal Basis & regulatory Framework

- Directive 2001/83/EC
  - National law (Germany: AMG)
- EudraLex
- CFR
- Pharmacopoeia

Legally binding

- Scientific guidelines

Implementation rules

- ISO
- PQIR

Non binding

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.“

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

→ have appropriately detailed written procedures for any handling of components

→ Ensure traceability. Have a unique code identifyier for each lot in each shipment received and use it in your recordings of the disposition. Have the batch status assigned and identifyiable (i.e., quarantined, approved, or rejected).

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

D (1) *At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.*

D (3) *Containers and closures* shall *be tested for conformity with all appropriate written specifications.*

EU GMP Guideline Part 2, 7.3 Sampling and Testing of Incoming Production Materials

7.31 Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

Sampling, Defects and Acceptance Levels

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

Annex 8, SAMPLING OF STARTING AND PACKAGING MATERIALS

- test on **representative** samples
- have a **sampling plan** with statistically determined number of samples

In Practice

- Control Sample Unit (Tailgate samples) is important for evaluation of a batch
- Sampling often delegated to supplier
- The number of samples for incoming inspection depends on batch size and defined AQL

Sampling

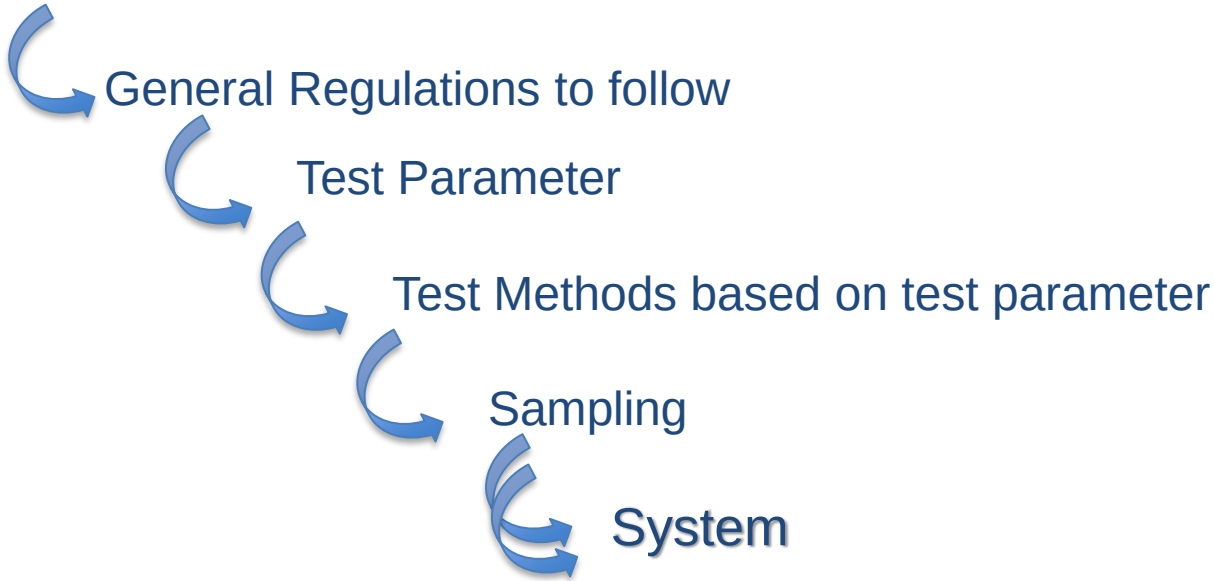
Sampling for Incoming Inspection
21CFR820.250 – Statistical Techniques

(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:

- Acceptance Criteria: Product- Patient- Profile



Requirements for Inspection- Acceptance criteria

ACCEPTANCE CRITERIA

… based on the intended use of the glass container

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

Requirements for Inspection - Testparameters

Test parameters	
Physical / chemical	Pharmacopoeia Regulations Standards
Microbiological	Pharmacopoeia Internal conditions
Dimensional	Technical drawings Engineering standards (i.e. ISOs) Product & process requirements
Visual Inspection by attributes	Product & process requirements PDA Technical Report 43 Defect Evaluation List

- Requirements from pharmacopeias, regulations and defect evaluation lists are important and can be used in general

- Specific requirements may need to be defined individually and mutually agreed with the supplier

- Supplier data complement or may replace incoming test parameter (risk-based approach)

- know your product
- know your process
- know what you get and what you need

… and than you know what to test

Chemical Testing

EP 3.2.1 Glass containers for pharmaceutical use
USP/NF Section <660> Type I Highly Resistant Borosilicate Glass

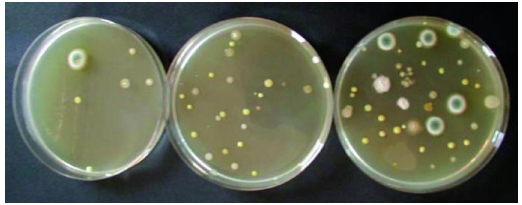
- Hydrolytic resistance
  - Glass grain
  - Surface glass test
- Arsenic release (containers for aqueous parenteral preparations only)
- Fill volume
- Spectral transmission (amber only)

Microbiological Testing

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

https://static.nationalgeographic.de/files/styles/image_3200/public/pfeilschwanzkrebs-im-labor-13565.jpg?w=1600&h=900

- Microbial Enumeration Test (MET)
  - Bioburden
  - according to Ph. Eur. 2.6.1; USP <71>, JP



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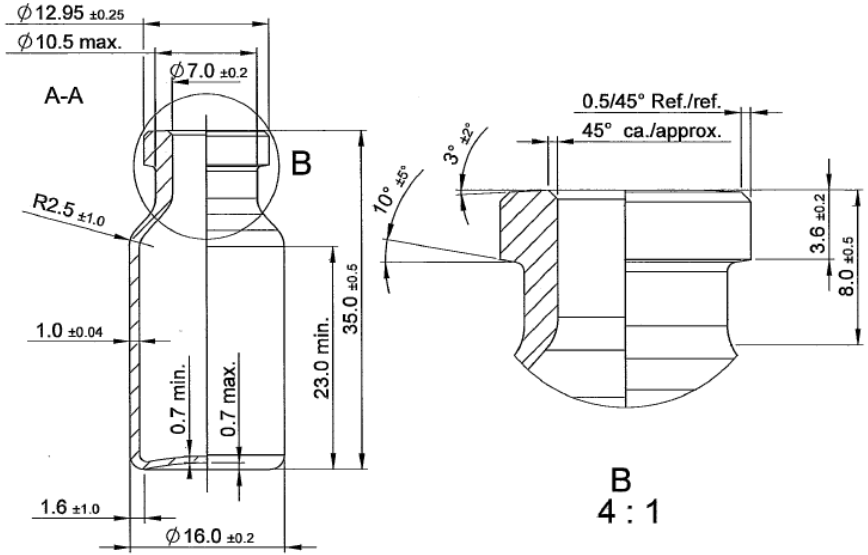
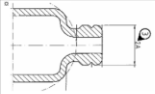
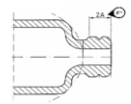
Dimensional Testing



Requirements for Inspection - Testparameters

- Example of an individual 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

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	cosmetic	6,5	Marks on head of cartridge		
Formmarken und narbige Erscheinungen > 1 mm² auf der Glaskörperaußen-oberfläche; Dichtigkeit nicht beeinträchtigt	*kosmetisch*	*6,5*	*Rattermarken am Konus*		
			Wrinkles on head of cartridge		
			Quetschfalten am Bördelkopf		

- Define the risk of individual parameter and acceptance level
- A joint risk assessment of packaging components with manufacturing can also increase the acceptance of incoming inspection activities!

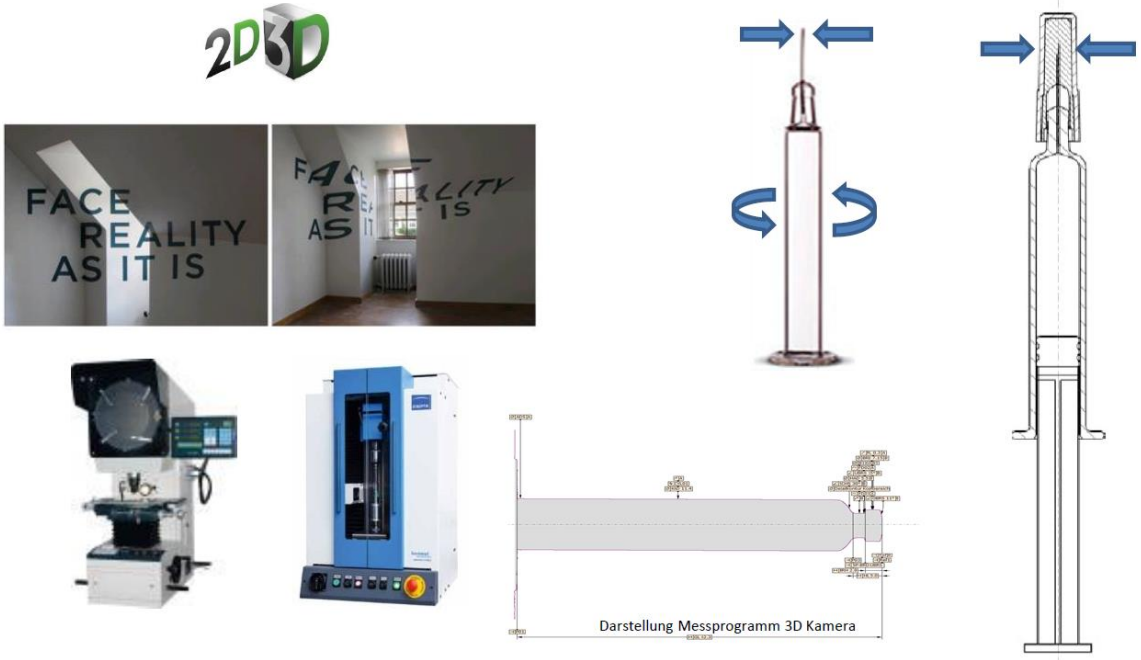
Requirements for Inspection - Testmethods

Requirements for inspection: Testmethods

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

Source: Juan Andres at ISPE/FDA/PQRI Quality Manufacturing Conference in Washington DC (2015)

Requirements for inspection: Testmethods

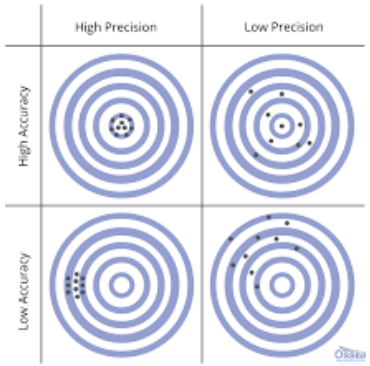


What is the correct method?

Requirements for inspection: Testmethods

Dimensional Testing - Equipments

- Gauge
- Caliper
- Micrometer caliper
- Profile projector (manual or electronically)
- Electronic camera measuring system



https://www.ossila.com/pages/accuracy-vs-precision

→The method is depending on Parameter & specification
→The method is depending on internal assessment and need

Requirements for inspection: Testmethods

Visual Inspection - by Attributes

- Special attention should be taken on visual nonconformities to align incoming inspection parameters with the relevant control units of the filling / inspection lines
- Defects are described and classified
- PDA Glass Task Force Technical Report 43
- Edito Cantor Defect Evaluation List

Attribute Classification- Guidance

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

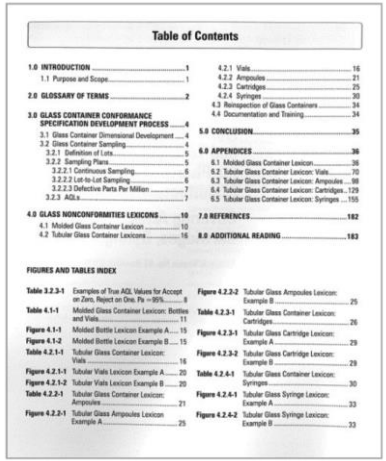
  CRITICAL - MAJOR - MINOR

to support a quality decision-making process

- The characteristics of these defects can vary,

→the acceptance level should be individually defined

- The sensitivity of camera control units should also be taken into consideration
- Defects may not be equally distributed across the batch manufacturing process (nested)



Glass Nonconformity Lexicon (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

Sampling, Defects and Acceptance Levels

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

AQL System per DIN ISO 2859

- 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

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

Losumfang (Lot Size)	Special Inspection Levels S 1	S 2	S 3	S 4	General Inspection Levels I	II	III
2 [illegible]	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

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

Kennbuchstabe für den Stichprobenumfang	Stichprobenumfang	Annehmbare Qualitätsgrenzlage, AQL, in Anteil fehlerhafter Einheiten in Prozent und Anzahl Fehler je 100 Einheiten (normale Prüfung)																									
		0,010	0,015	0,025	0,040	0,065	0,10	0,15	0,25	0,40	0,65	1,0	1,5	2,5	4,0	6,5	10	15	25	40	65	100	150	250	400	650	1 000
		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

Translation

- AQL 0.65 Level II
- Acceptance limit 10 - Rejection limit 11 defects

- 0.65% AQL Quality Statement:

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

Sampling is an important process

- Sampling is mostly delegated to supplier per contract
- Tailgate samples are pulled by the supplier during manufacturing
- 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
- verification of sampling by supplier audits & dual batch sampling

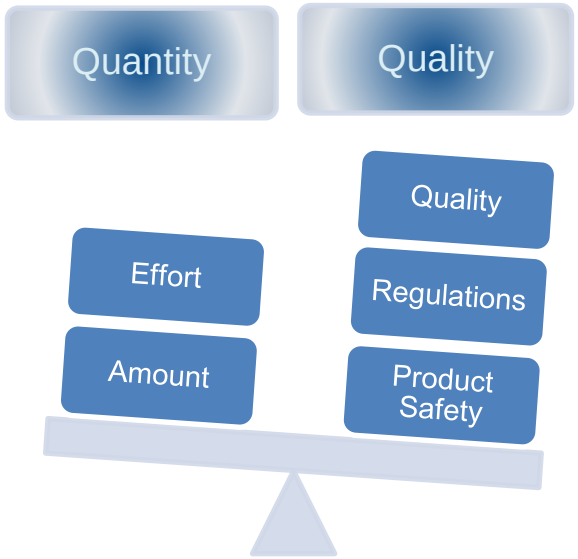
Requirement for Inspection: System in written and justified

	What	Why	how often?
	Suppliers certificate	is the basis	Every time
	Regulations / Norms	name the requirements (i.e.EP/USP)	at minumum as per certificate
	Attributes	Critical to quality (cracks,scratches) Market specific (JP)	may be risk based
	Chemical Analysis	Suitability	Full analysis „…appropriate interval…“ may be risk based
	Microbiological	Contamination control (i.e.parenterals)	
	Dimensions	are often based on (DIN)ISO Dossier relevant for container closure	may be risk based
	Functionals	Critical to quality, process, application	may be risk based

At your own discretion

Take-Home Message

- Know the regulations-
  - where is a degree of freedom, what is legally binding
- Have a good partnership with your supplier, you need him
  - the better you know him, the processes & control strategy behind the product you buy, you can justify to do less yourself
- Have a good partnership with the production- colleagues
  - hear what they need for a smooth process, involve them in the decisions what to test, it will be of benefit
- Have all this in written
  - Statistically based, scientifically sound
  - Justifiable
  - Standardized procedures



make the regulations your friend

End of Part I

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Part II

Incoming inspection how to set up in practice

Part II – how to set up in practice

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

What is the Specification?

„all appropriate written specification“

„Full analysis“

“Reliability of Certificates of Analysis”

All documents describing the material belong to the specification

- *Technical Drawing*
- *Material Characteristics (including Compliance bulletin,)*
- *Regulatory Requirements (e.g. Ph. Eur., USP, JP, ISOs)*
- *Test Parameter (including suppliers DEL)*
- *Certification of Parameter*

Index of a Packaging Material Specification (Example)

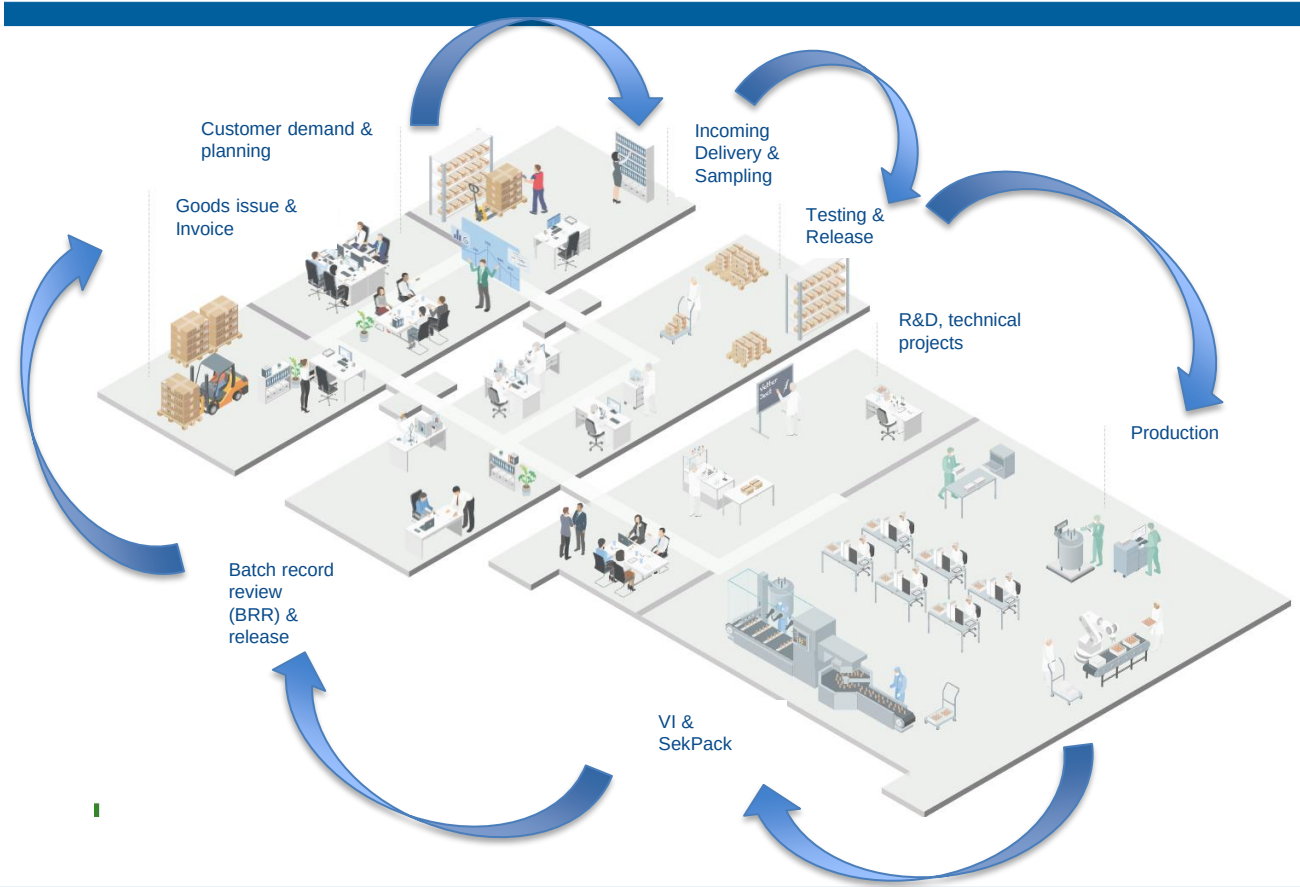
- 1. Material Specific Chapter – Technical Drawing
- 2. General Chapter
    - 2.1 Material & Design
    - 2.2 References & Standards
    - 2.3 Packaging Instructions
    - 2.4 Quality Acceptance Criteria
    - 2.5 Supplier control samples (sampling plan)
- 3. Characteristics / Specifications
    - 3.1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

Quality control needs Specifications

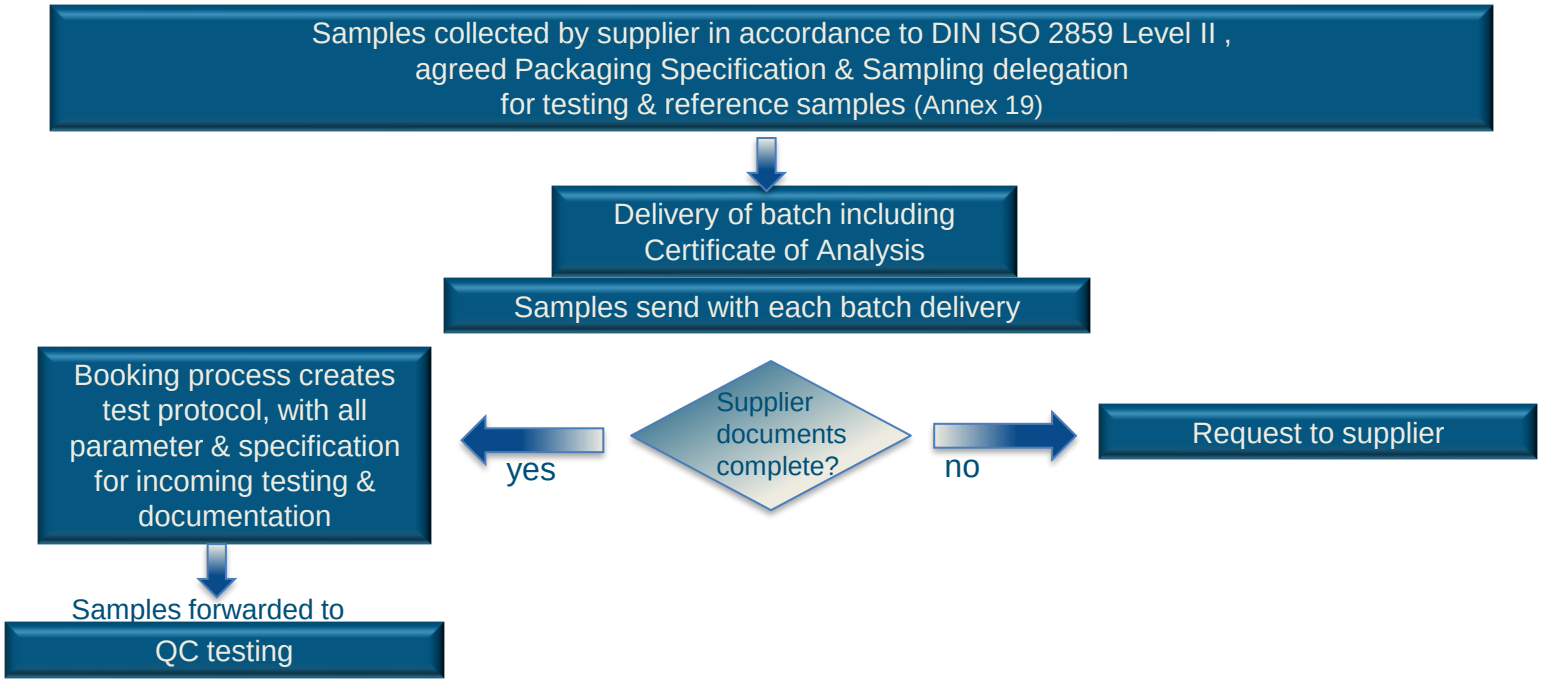
Batch testing / release is based on these documents

- It is recommended to agree on inspection methods upfront with supplier
- Visual Inspection (limit sample, defect catalogue)
- Specific methods not described in literature
- Method comparison
- Accuracy of measurement
- Sample defect catalogue

Contractual,
Specifications to be referenced in the Quality Agreement!



Batch & sample delivery

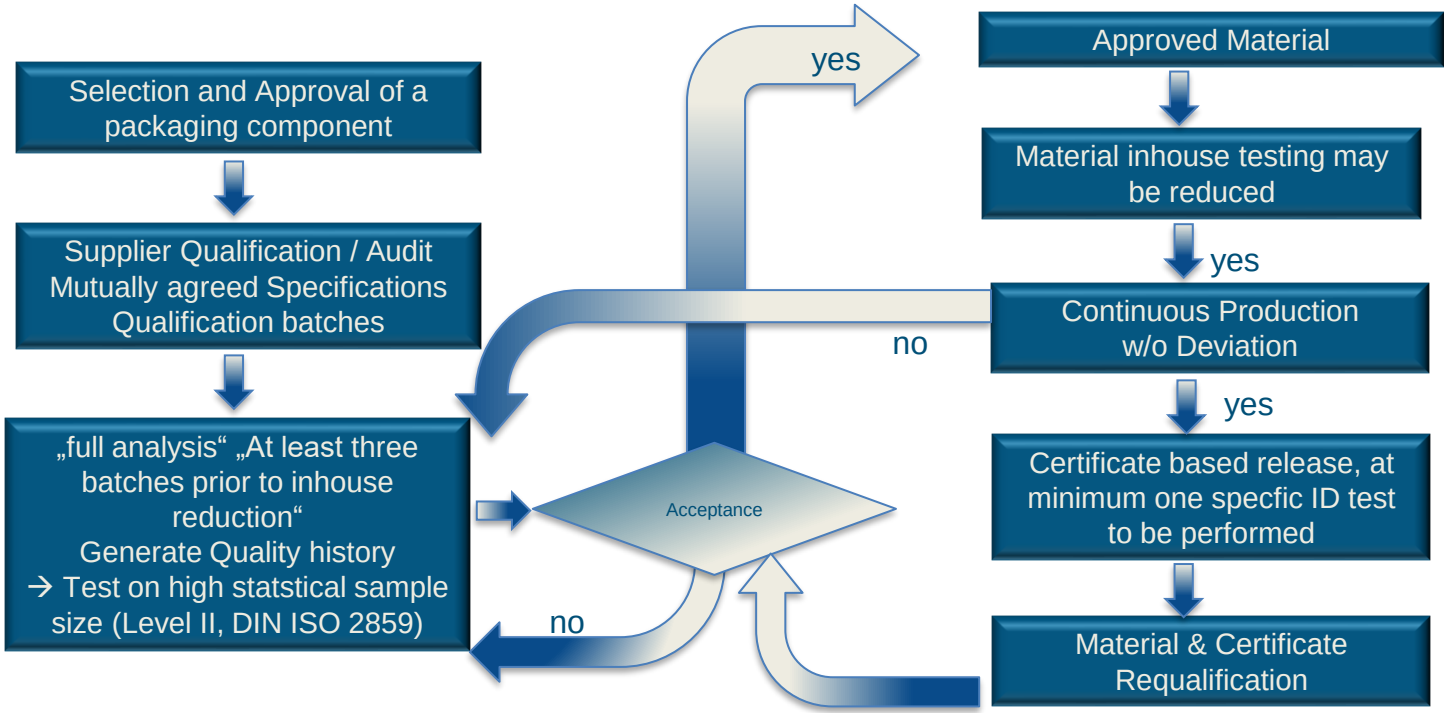


Warehouse controls at delivery

… to be checked at delivery

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

Material Approval Process



Performance of QC-testing

Suppliers certificate

Attributes

Chemical Analysis

Microbiological

Dimensions

Functionals

- EU GMP Part 2, 7.31
  - ➢ 3 batches full analysis prior to inhouse reduction
- CFR 211.84 d
  - ➢ shall be tested… lieu of such testing certificate may be accepted
  - ➢ at minimum Certificate & one specific ID-test
- Pre-defined testing schedule
- Regular requalification /verification of certificate data
- Depending on your needs, processes, CCS
- Justified in written

Certificate check

Content (examplarily)

- Product ID, name/number and description
- Specific dates – manufacturing, sterilisation, release
- Specific critical to quality criteria
- Statement of conformity
  reference to Specification, Pharmacopoeia, ISOs

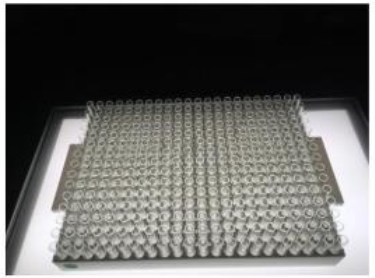
If CoA

- Criteria, specification, result, evaluation

- Signature by qualified personnal (Quality function)

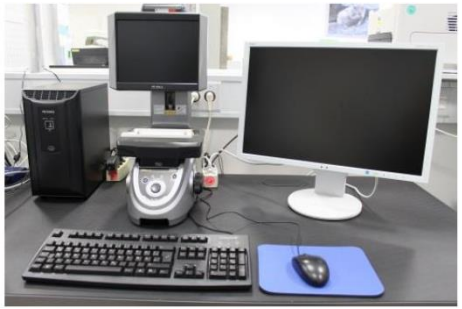
Visual Inspection by Attributes

- Light conditions
  - non specified, most applied: Ph. Eur. Method 2.9.20 Particulate Contamination: Visible Particles
  - Distance to (naked eye)
  - Light box/black white background
- Documentation of inspection results
  - Reporting of individual inspection criteria
  - One generic (sum) criteria, combined with a defect catalogue and the corresponding AQL
    - if deviating to supplier, complaints may be challenging



Dimensional testing

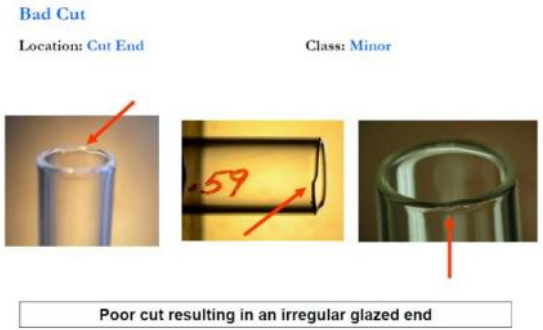
- Gauges & manual devices vs electronic camera systems

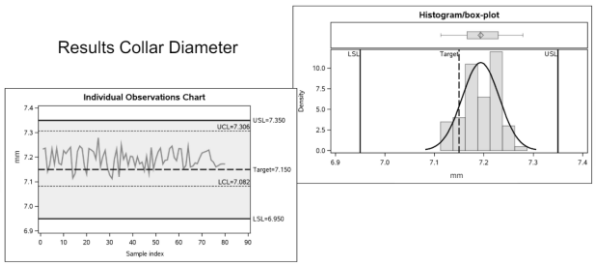


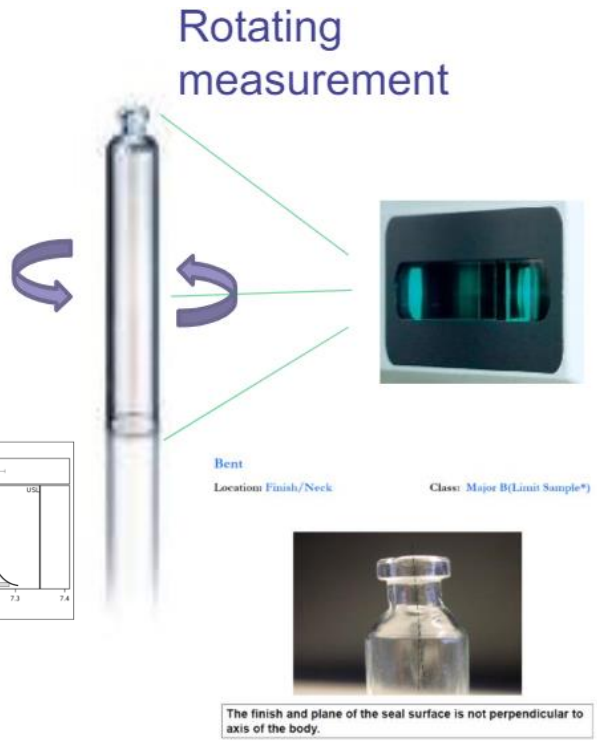
…depends on specification and assessment of accuracy needed

Dimensional testing

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





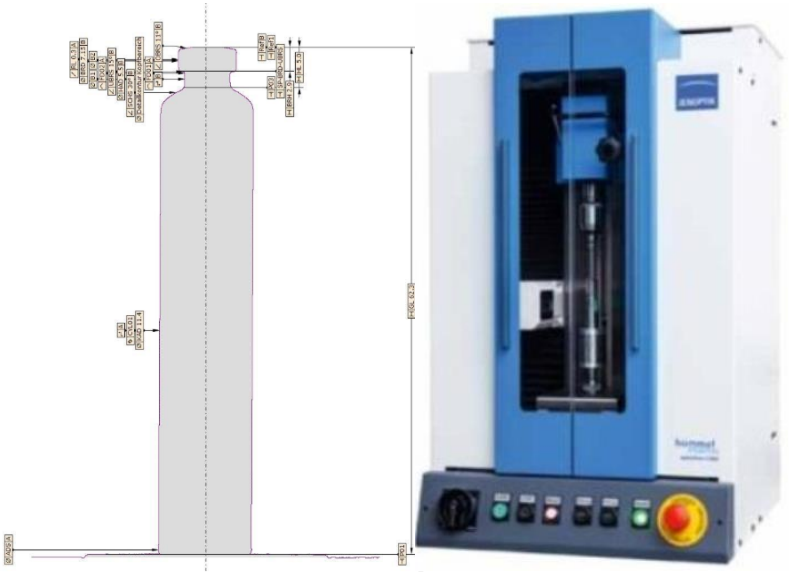


Challenges in semi-automatic methods

How to set the method programm

- needs knowledge
- may be crucial to be aligned with supplier

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



Documentation

Supplier documentation

- Delivery note
- Certificate
- Specifications
- Test Protocol

Test performance

- valid SOPs
- Released Test Methods
- Agreed Specifications
- Released Test Plan

Inspection documentation

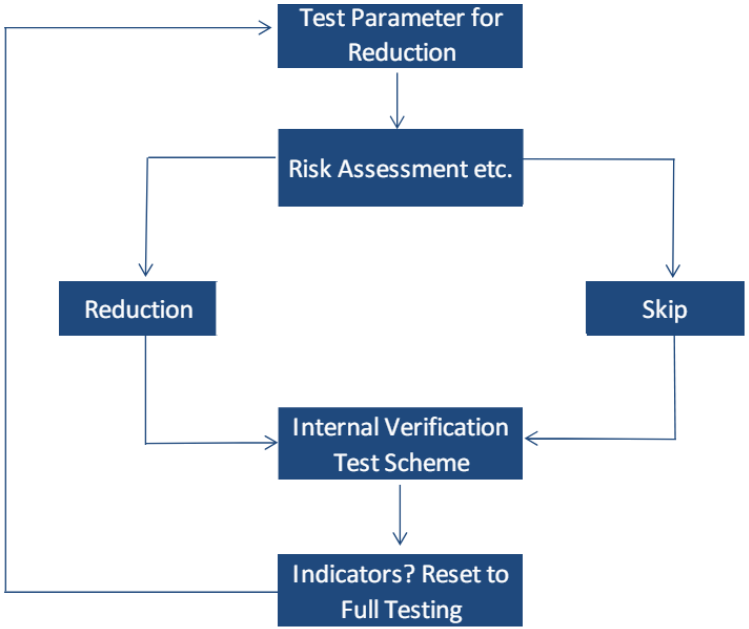
- Raw data & Results via test protocols and log books
  - Visual
  - Dimensional
  - functional
  - Chemical/ Microbial
- Equipment performance- SST and Audit trail
- Evaluation
- ALCOA

Risk based incoming inspection system

- Test at minimum 3 batches according to all appropriate written specification
- Build a quality history (material & supplier)
- Allowed to apply **reduced testing**
- Close loop to findings and deviation in production
- Have a flexible loop back to batchwise testing

- Prerequisite for reduced testing
  - Quality History
  - Quality Management System
  - Verified Supplier Certificate
- Risk Analysis in written to evaluate potential impact
  - Reduction of individual test parameter
  - Supplier results disclosed on CoA
  - Determination of verification strategy
  - SKIP-Lot testing

Example of a reduced testing scheme



End of Part II

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Part III

Inspection of glass

Challenges – to avoid and to consider

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Distribution of Defects

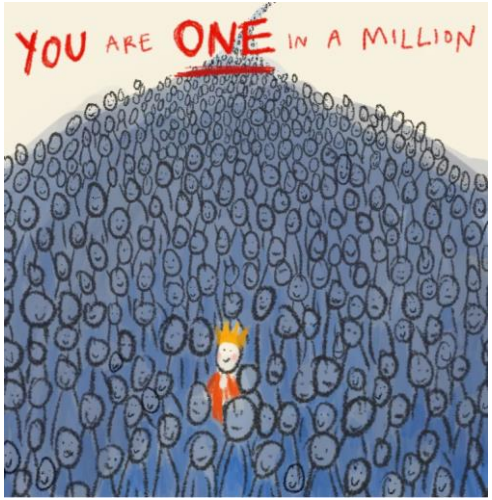
- Defects / Imperfections are not always distributed across the entire batch

  → Tailgates need to be representative to catch the standard distributed ones

- Rare or nested defects may not be detected during incoming control

  →need a control loop from production → QC → supplier

- Glass forming process variability controlled by IPC & control cameras

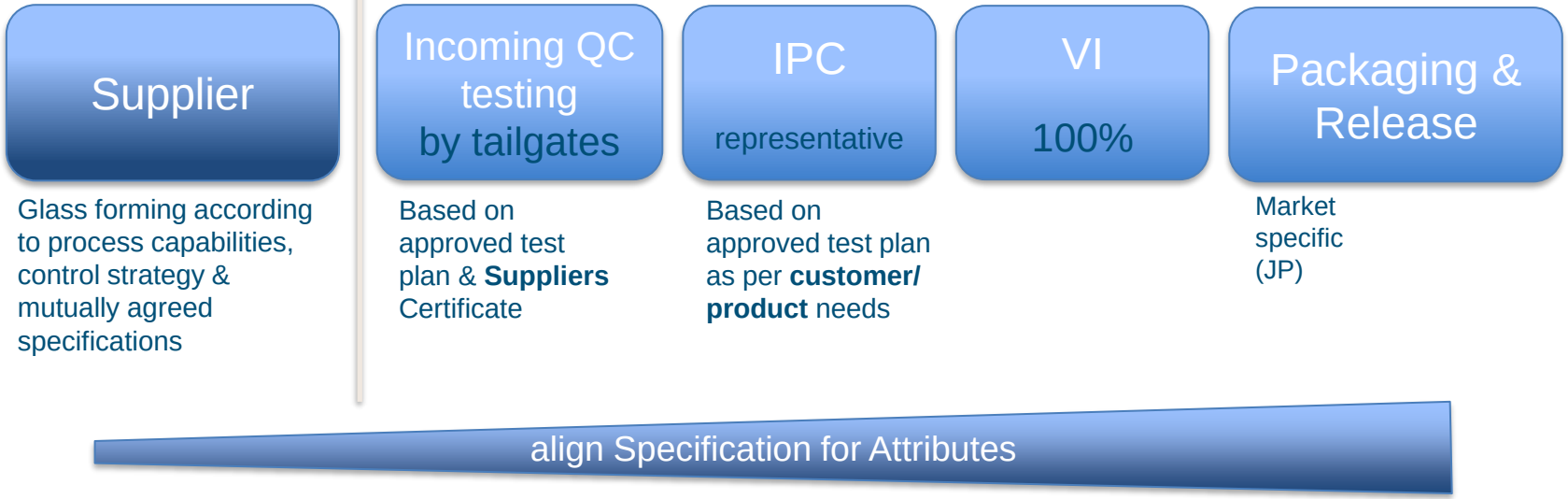


https://poetandpainter.co.uk/cdn/shop/products/FP3009OneInaMillion_1200x1200.jpg?v=1638884379

Control strategy

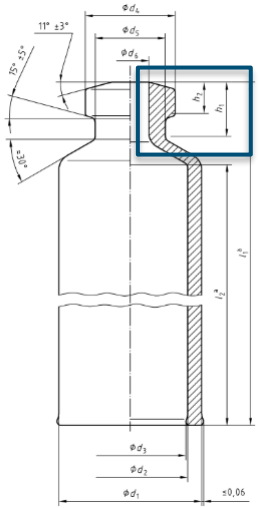
Specifications and controls need to be harmonized

Does the end-product specification fit to the components specification?



Glass forming brings some variance

- Glass container for the pharmaceutical industry are standardized, by ISOs



Maße in mm
Dimensions in mm

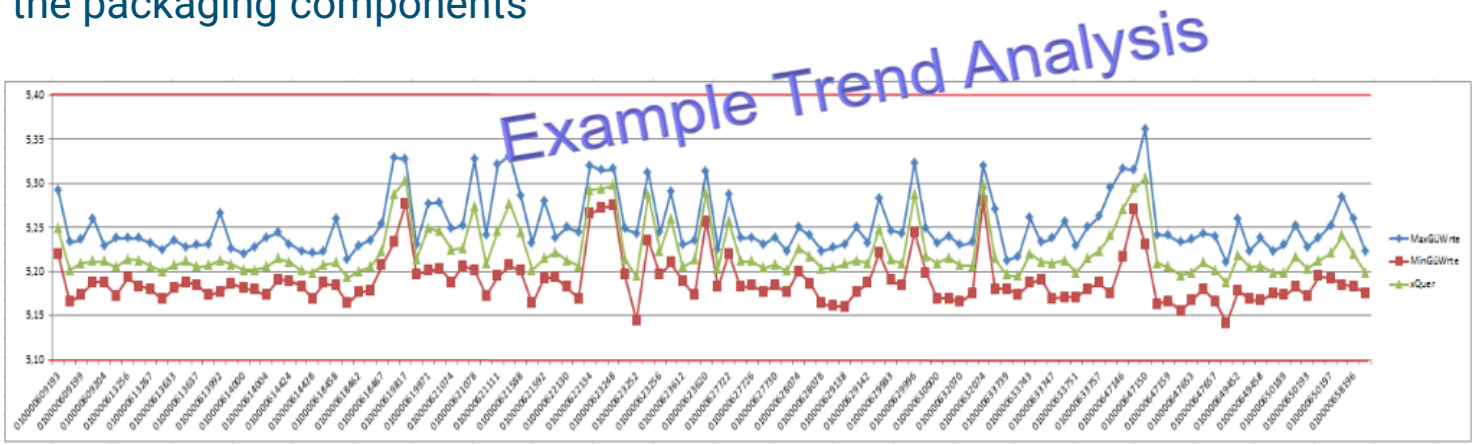
d_1	Grenz-abm. tol. ±	d_2	Grenz-abm. tol. ±	d_3 min.	d_4	Grenz-abm. tol. ±	d_5	Grenz-abm. tol. ±	d_6	Grenz-abm. tol. ±	h_1	Grenz-abm. tol. ±	h_2	Grenz-abm. tol. ±
8,65	0,1	6,85	0,1	6,55	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,85	0,1	8,65	0,1	8,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,95	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

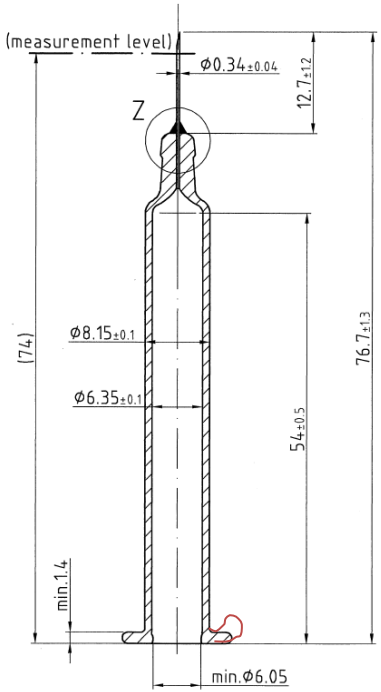
- these standards might lead to uneccaptable variances of certain dimensions especially for fast running lines, depending on format

Continuous monitoring

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



Glass forming and breakage risk



- as per the technical drawing dimensions seem fixed and straight
- free forming might lead to variances
- variances might impact testing and lead to breakage in production or latest within devices at the patient

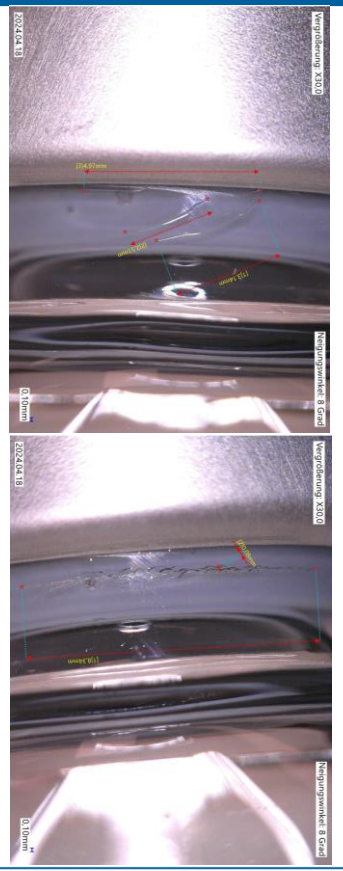
- Single sided breakage event at incoming is a defect or not?

→ what is the specification and method agreed?

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
- Processing will have an impact

- How to investigate?

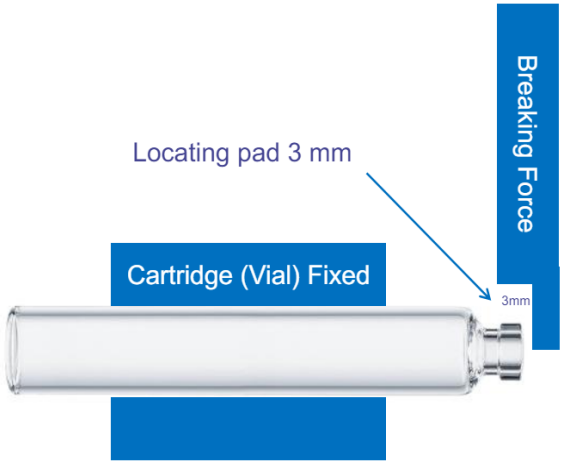


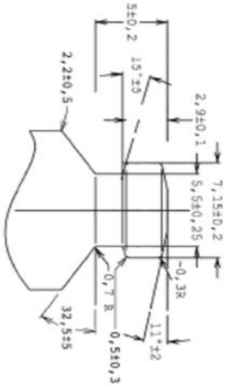
Glass strength, forming and breakage risk

Functional test at incoming control, ISO based

- Breakage test for cone strenght
- Finger flange breakage
  - might give hints on underestimated forming issues

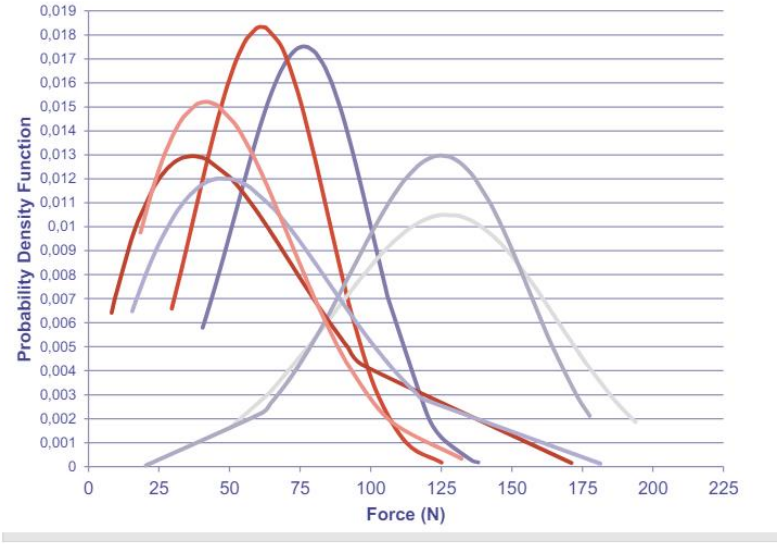
- Investigational tests





Mimic the process or application

Glas stability testing –stopper mouth



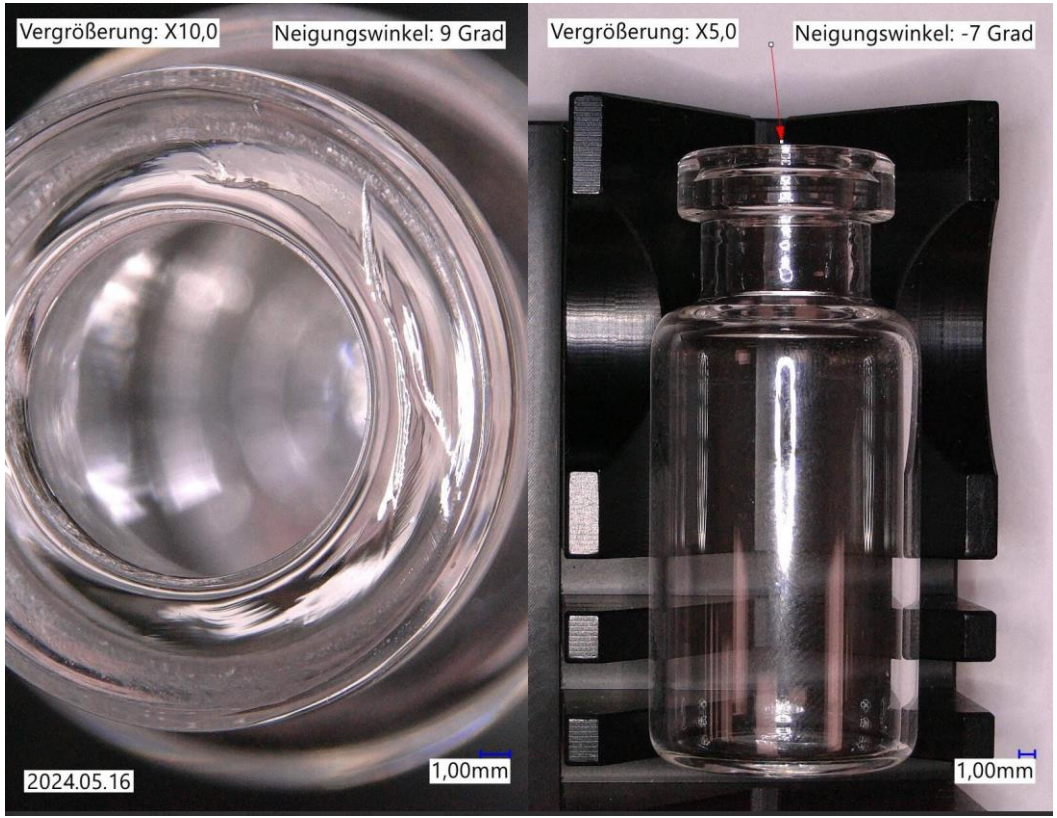
- Check for suitability of component
  - In the process (R&D)
  - For application
- Try to specify test with your supplier (already described Method, ISO?)

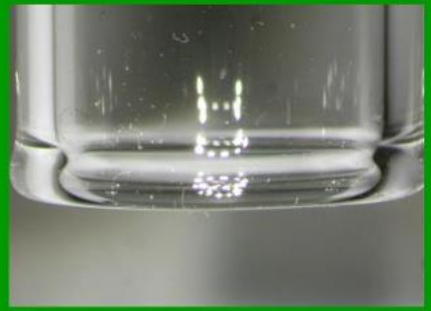
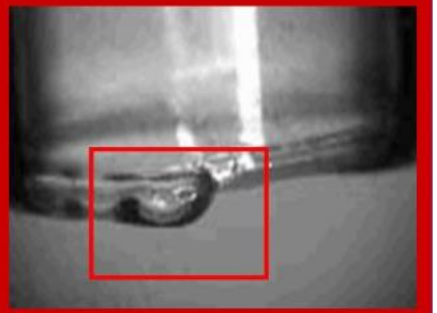
Attribute Defect pictures and differentiation

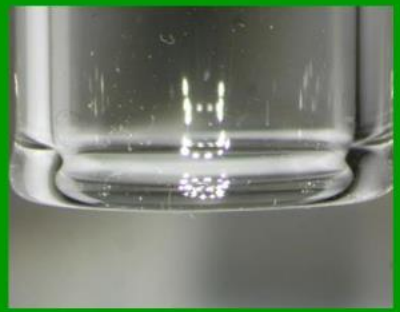
Definition of Defects

- Can be quite subjective for visual parameter
- The one`s mutually agreeing on the defects and descriptions might not be the ones applying it in daily work
- Make sure everybody knows what is meant

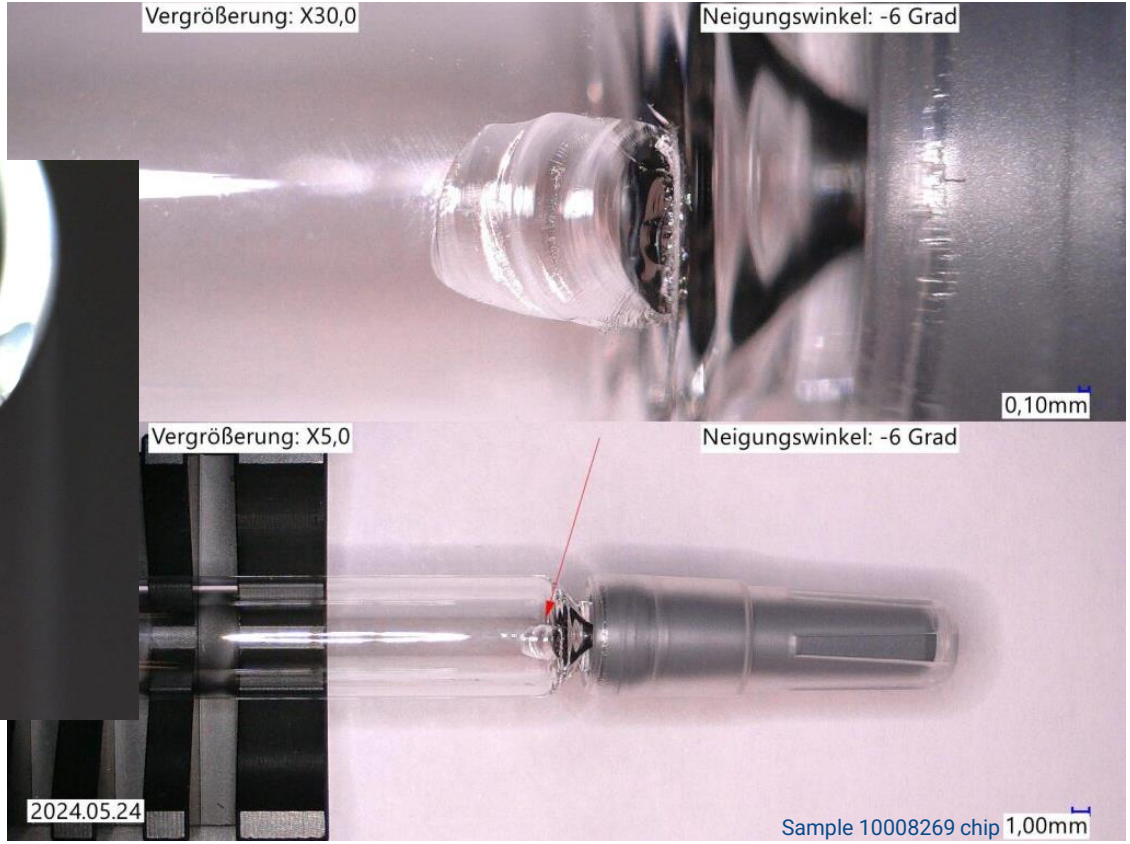
Description of Defect	Acceptable	Poor Quality
Pressure / Tool Marks	 Faint tool marks - process related	 Tool marks with potential functional impact

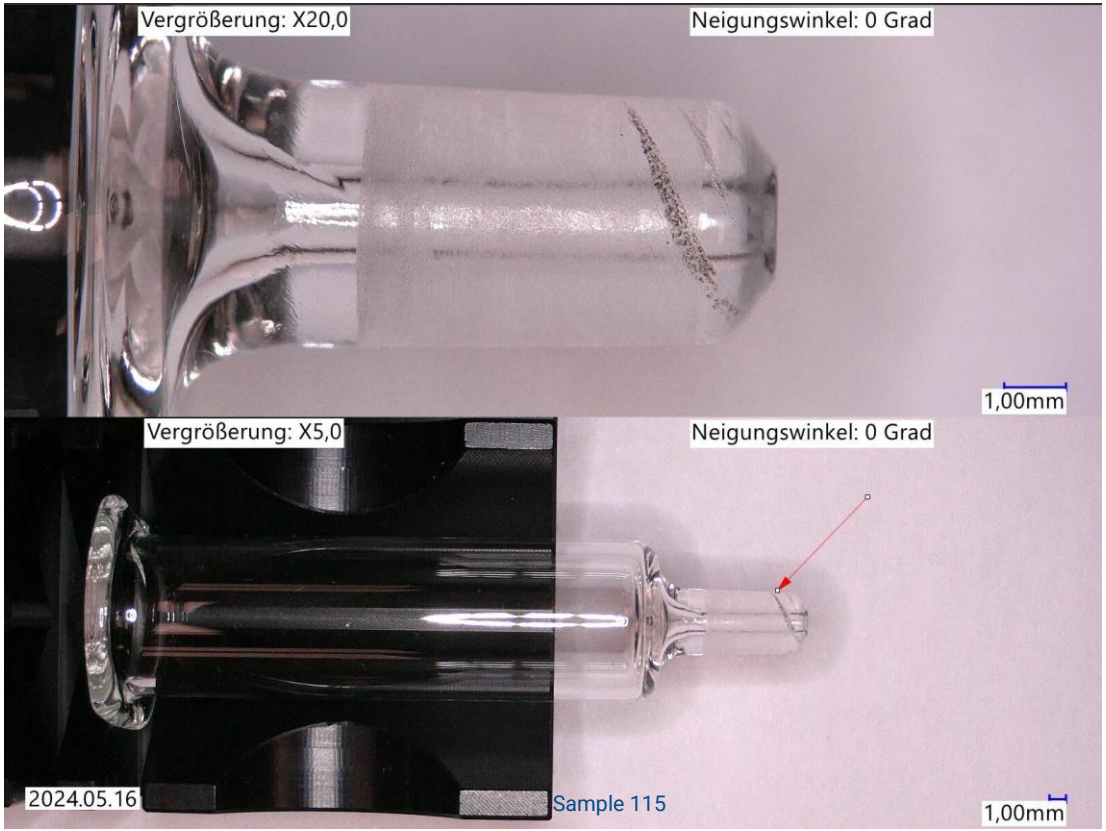


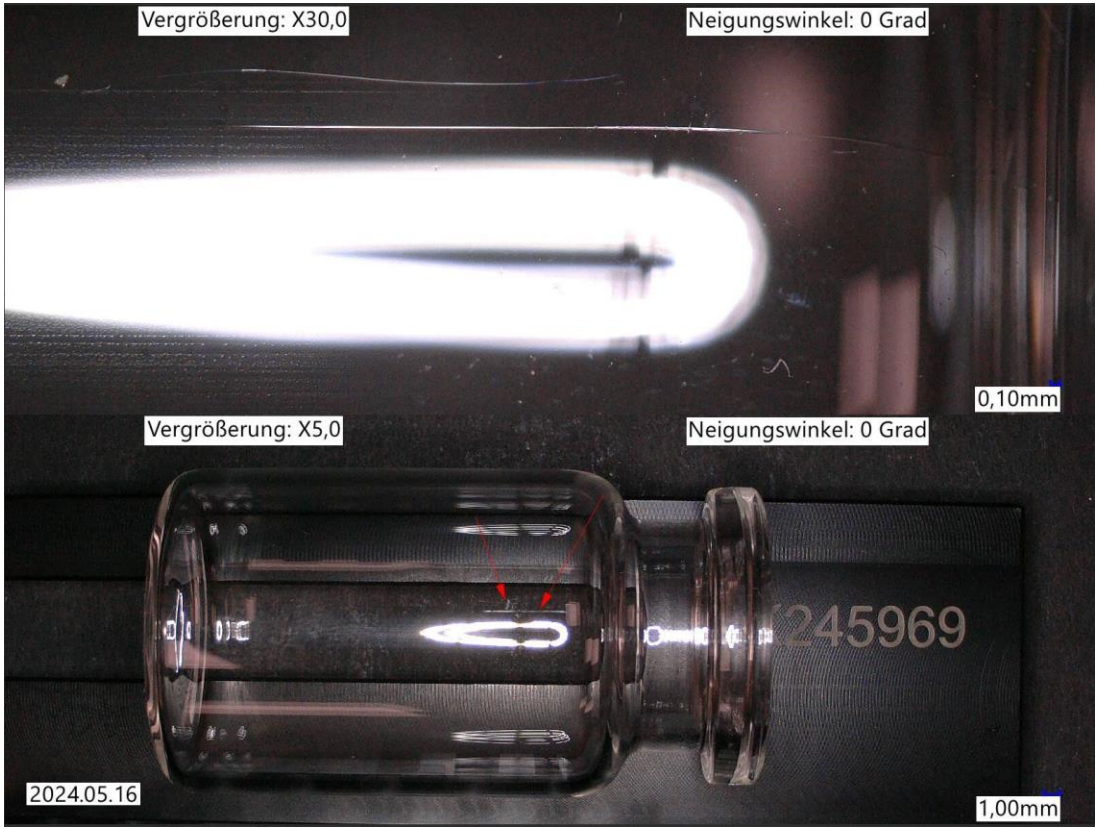
Description of Defect	Acceptable	Poor Quality
Deformed or damaged cartridges, function / processing impacted		 Melting ring deformed

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

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







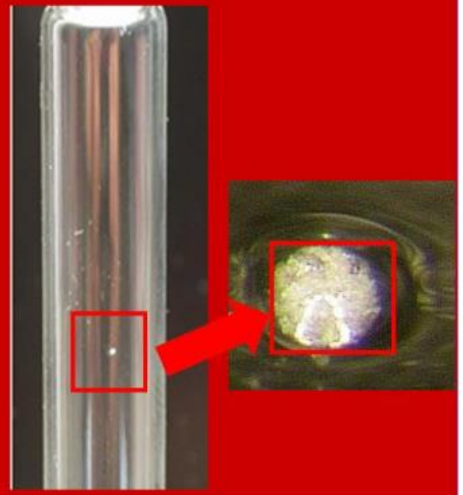
Crack or Airline??

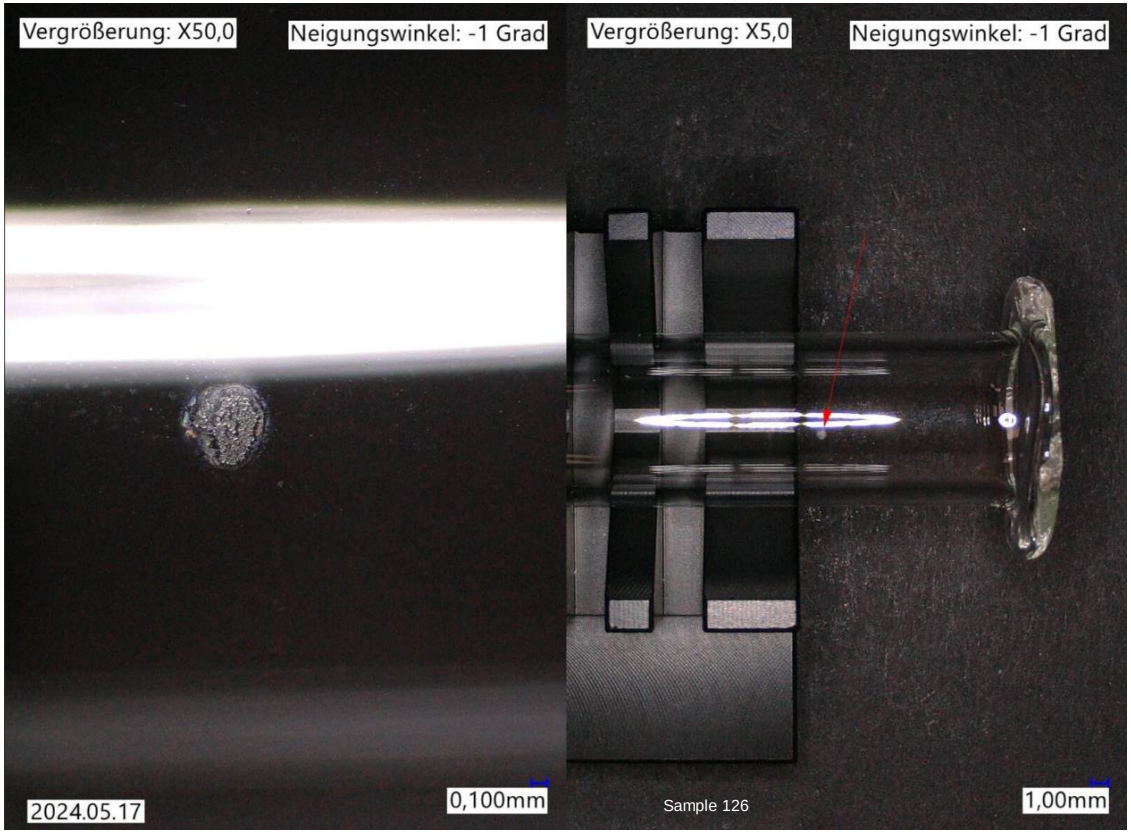
If Airline: open or closed?

Description of Defect	Acceptable	Poor Quality
Deformed cartridge Container closure impacted		

Container closure integrity impacted?

Batch impact or singular event?

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



- bruise

End of part III

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Part IV

coordination manufacturer ←→customer

Quality management system

Drug Product manufacturer produce according to cGMP

Suppliers do not …?

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.

Supplier Approval Process

Selection and Approval of a Supplier for packaging components

↓

Supplier Qualification / Audit
Mutually agreed Specifications
Incl. Production, Control strategy, Distribution, Sampling, Methods, QMS

↓

Successful Audit
Issuance of Quality Agreement
allow for sourcing from this supplier

→

Generate Quality history

↑

Approved Supplier
(for this material)
Approve Material

↑

Continuous Supplier Quality/ Relations Management,
i.e. by KPI/ MbO,
Complaint & Change Management, technical visits,
Joint activities by multiple departments

→

Contractually agreed, regular (risk based) Requalification of Supplier

…Is not a one-way road

mutual & fair feedback and open discussion
open doors…

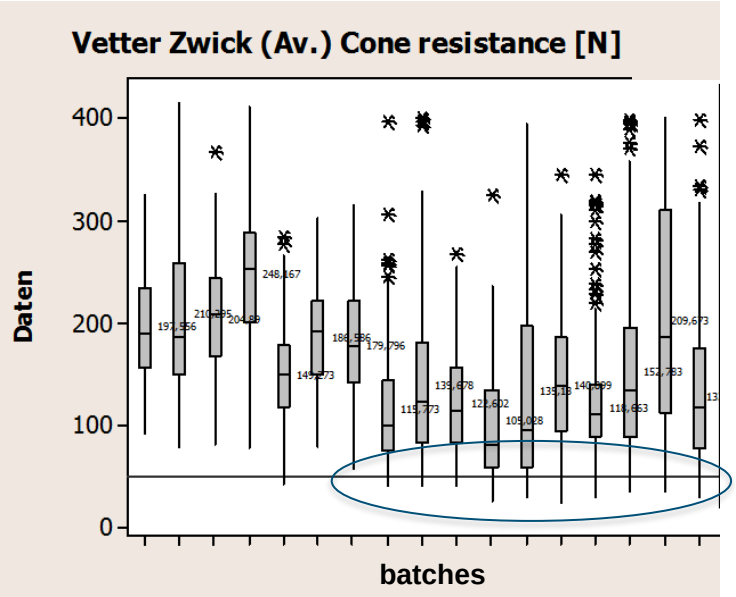
Case study I

Cone breakage at incoming

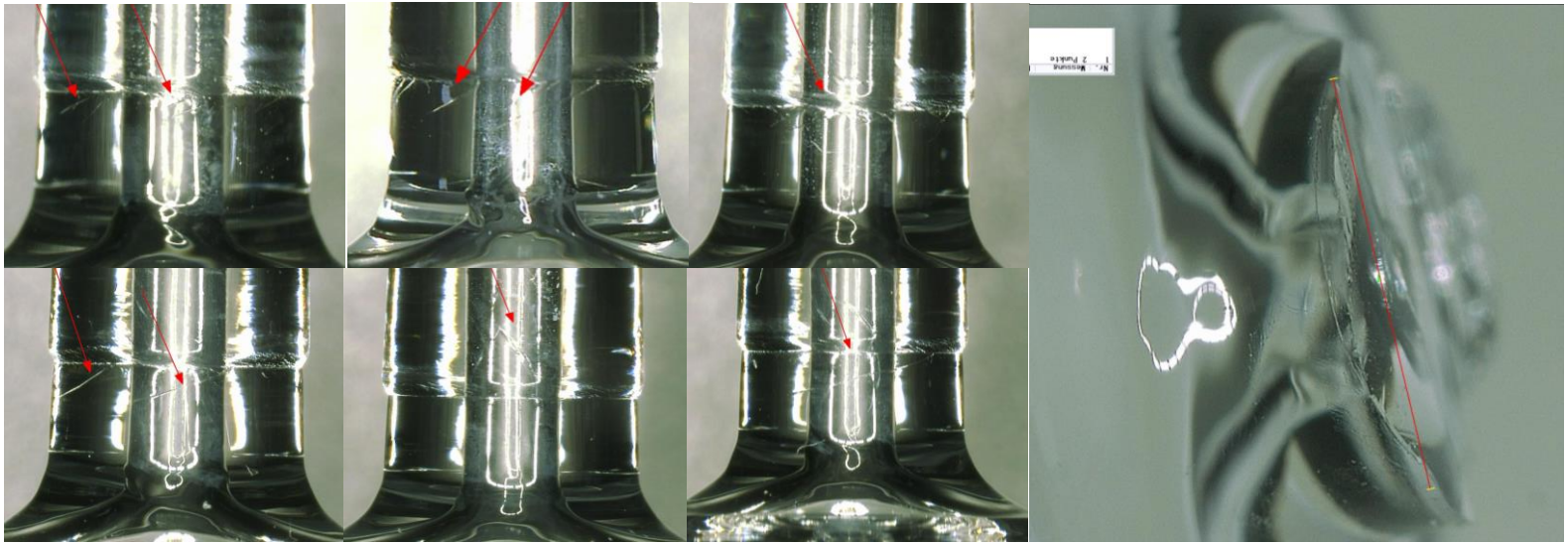
- Series of batches measured OOS
- Suppliers` data were borderline but ok

→Methods not aligned?

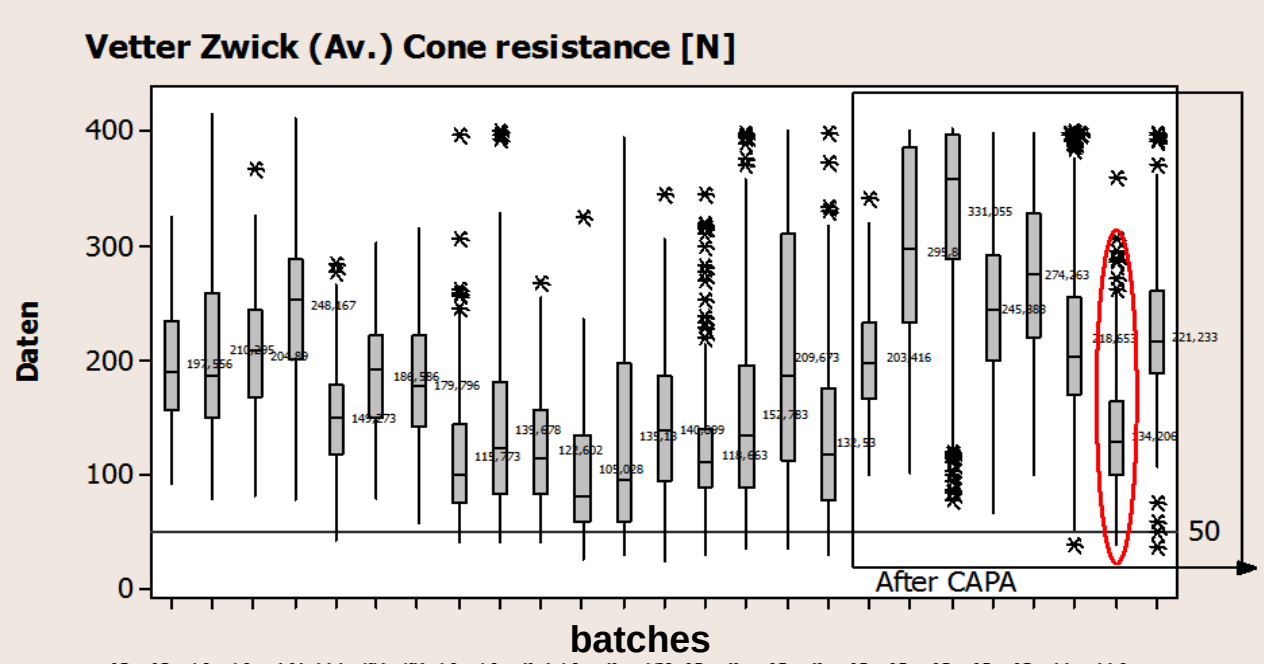
→ Deep method & equipment investigation startet



Root cause investigation



- Breakage at the scar

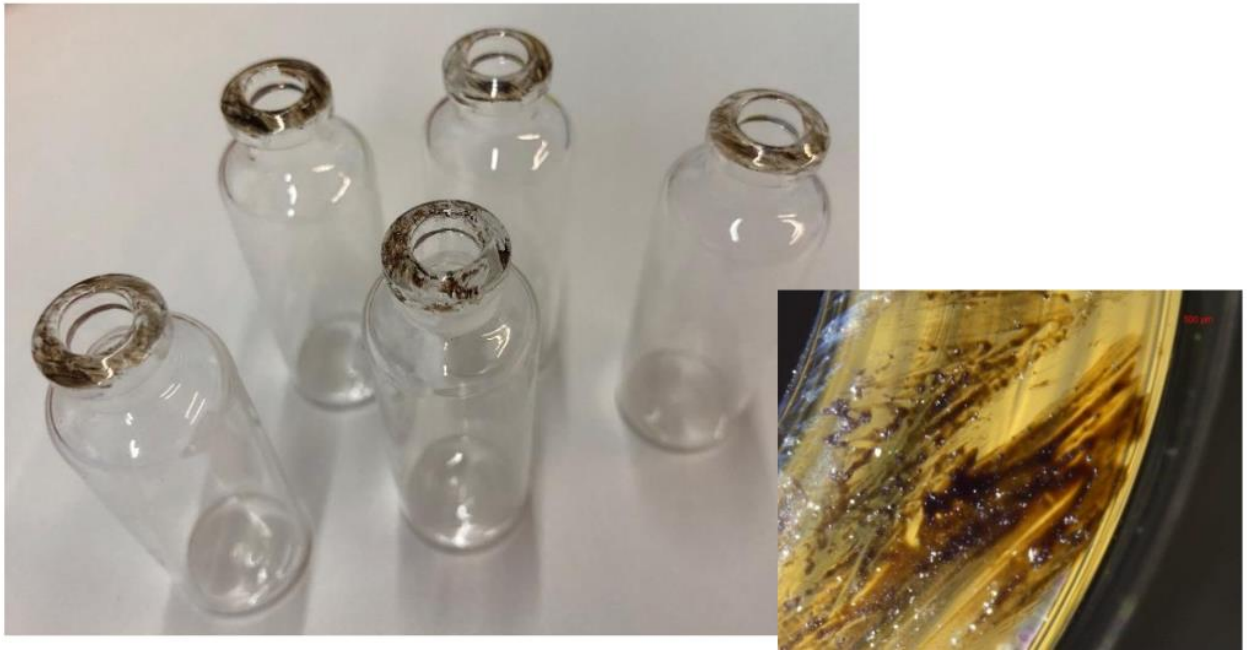


Case I Root cause Analysis

- Method & Equipment investigation showed unexplainable offset
- CAPA implementation show improvements
- no full consolidation as now line-differences at supplier were revealed
- 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

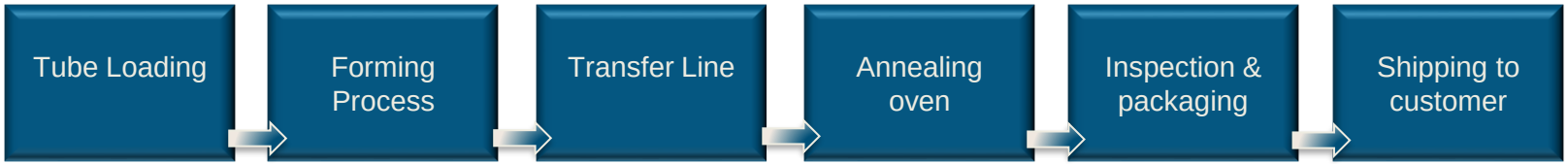
→ Partnership with supplier is an important factor for resolution of this type of issues

Case Study II:
vial collar with brown contamination after sterilisation



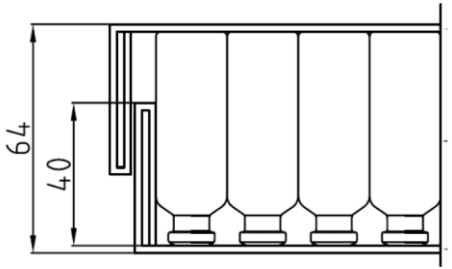
Investigations

Suppliers` Process Analysis
Potential for Contamination?



by tube → not likely
while forming → would get obvious earlier
transfer → no contact (only) to collar
annealing oven → no contact only to collar
Inspection & Packaging → …?
Shipping → …?

Root cause analysis



Case I
- Investigation **inconclusive**
- Most probable root cause: oil contamination from the polypropylene box

Similar defect pattern at another company
- Investigation with clear root cause found
- Foil residues from the packaging were melted on the collar
- After heat tunnel sterilisation burned to brown residues

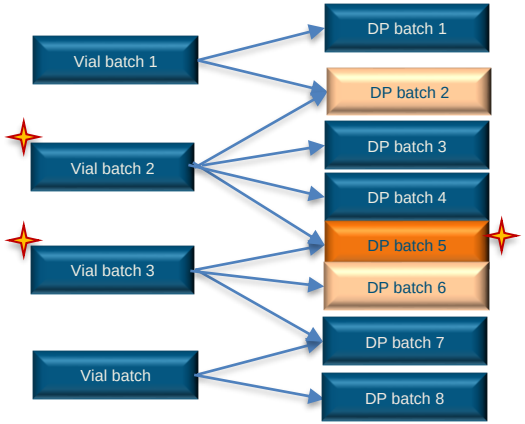
→ What looks similar must not be the same
→ Close interaction needed with any party involved in the process …

Case study III

Finding at least in Drug Products final visual inspection

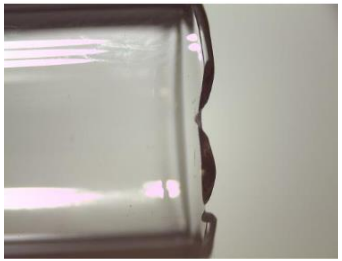
- Containment and Drug Product impact may be high, but unclear
- Systemic and nested defects may contribute

- Shared investigation needed for the combined processes



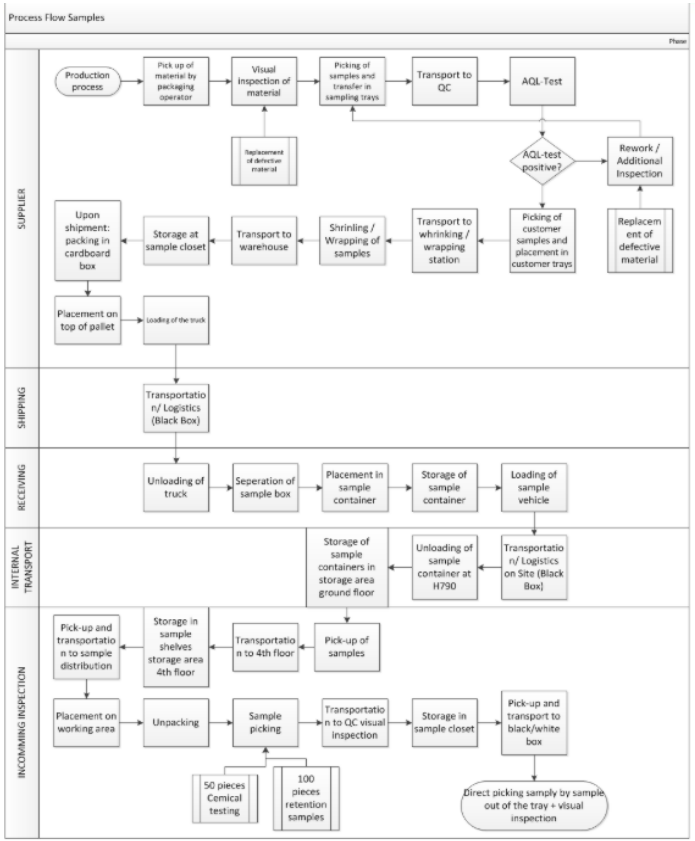
Case Study IV Tailgates

Batches rejected due to increasing high defect rate: chipped glazing

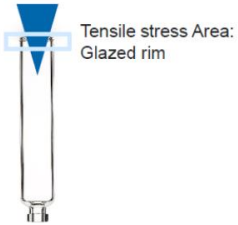


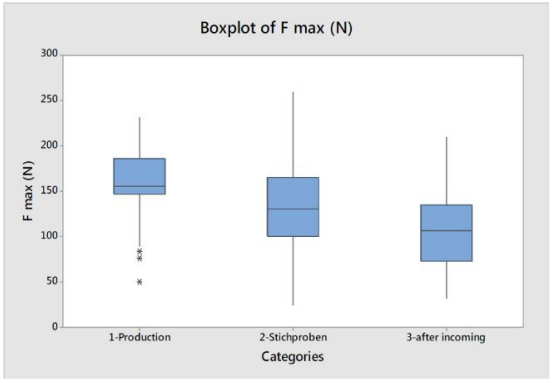
Resorting did reveal
0.000 - 0.002 % of defects in the batches

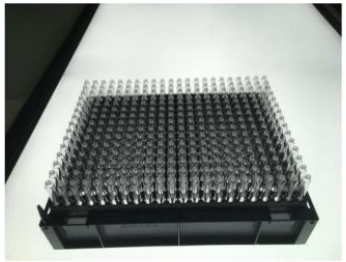
→No general batch quality issue
→Representativeness of tailgates?!



Investigational studies & Improvements







- Single root cause could not be identified
- Several contributing factors have been identified and related improvements implemented at both parties

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Thank you

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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