



Particle Characterization and Identification

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483 Observations

Root cause, particle characterization

*Investigation regarding the metal particulate contamination in lots was inadequateThe atypical contamination found in these lots was metal, however, the batches were not rejected. Additionally, there was **no investigation** conducted to determine the cause of the black metal particulates found in these lots*

*You have **not established a characterization** for particulate matter for all your products as corrective action promised in your response to previous deficiencies.*



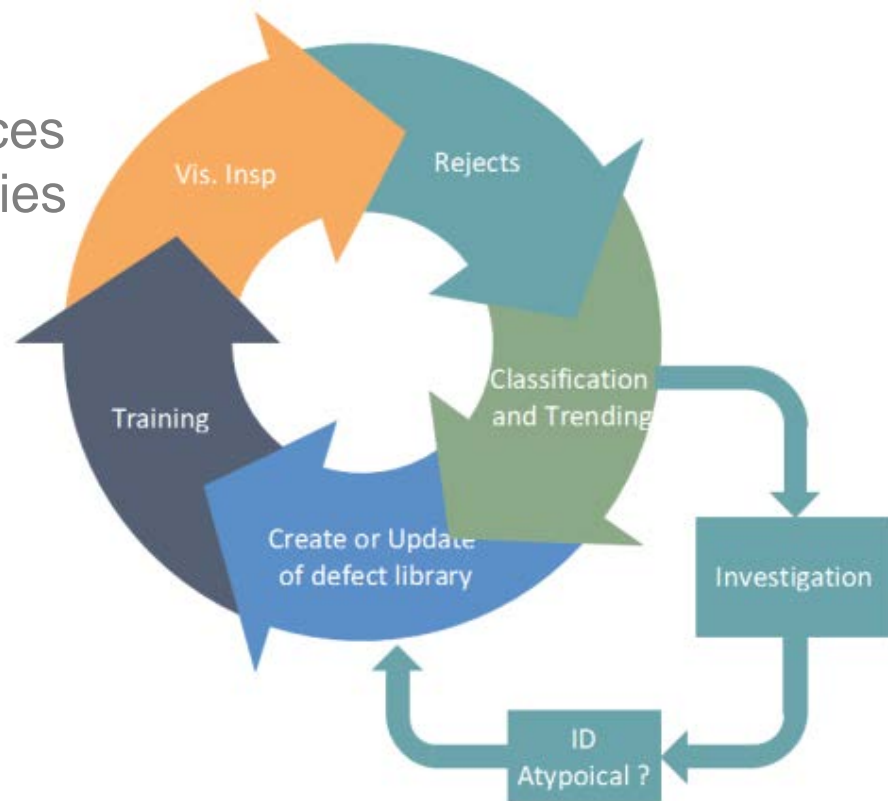
Reasons for Particle ID

1. Classification and Trending
2. Root cause analysis
3. Manufacturing Process
Continuous Process Improvement



Visual Inspection Lifecycle

- Use the Trending Data from Reject Characterization and Monitoring
- Review the various particulate sources for Process Improvement opportunities
- Focus on the most predominant particle types
- Repeat the Cycle of Monitoring, Trending, Corrective actions and follow-up Monitoring





Classification and Trending



Quality Control Methods

Particulate Characterization/ID Levels

Level One: Visual classification (in-Situ)

- Nondestructive, as seen during manual inspection
- Light, dark, sinking, floating, color, shape, etc.



Level Two: Macroscopic and Microscopic

- Rapid characterization to specific material categories
- Metallic, glass, rubber, plastic, fiber (natural or synthetic), silicone lubricant, inherent particles, etc.



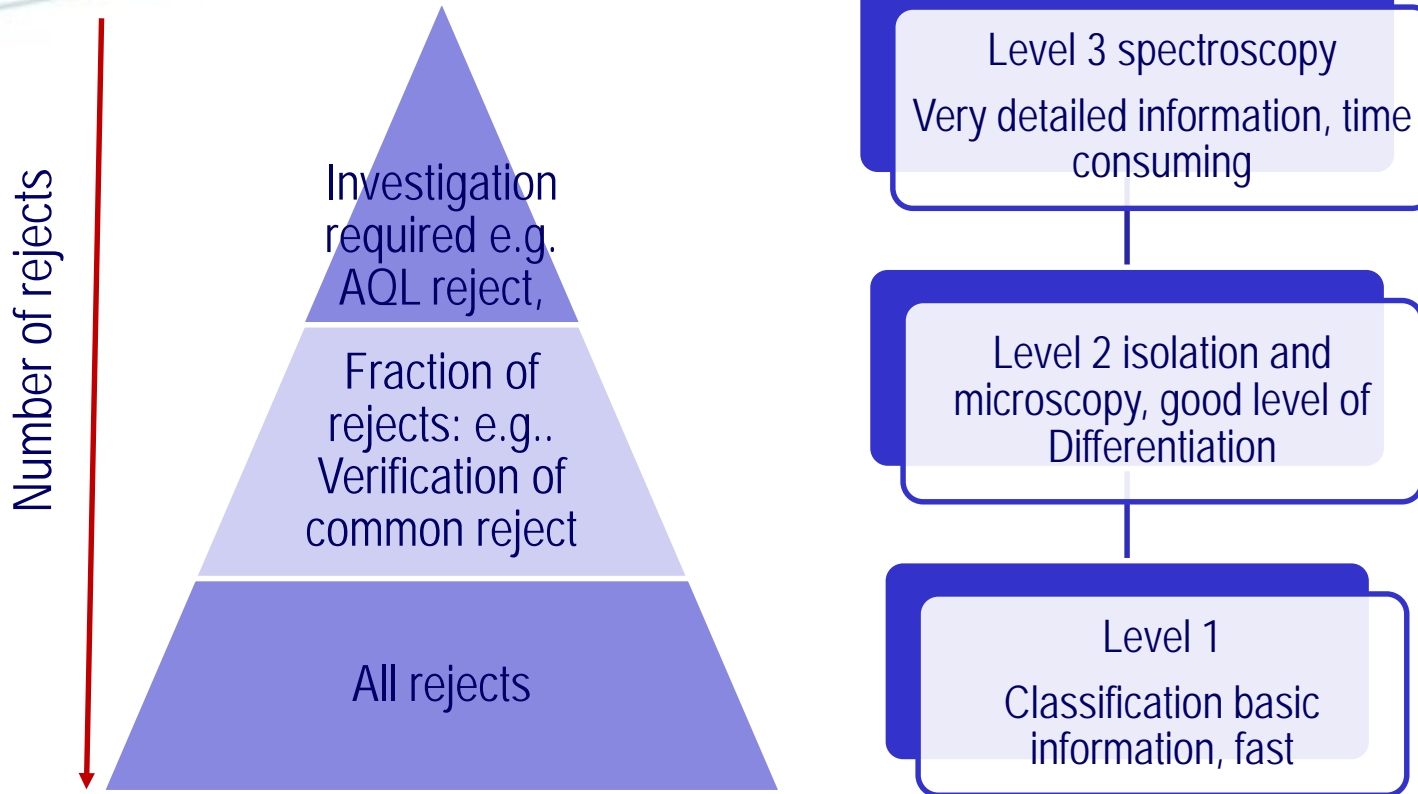
Level Three: Spectroscopic or other fingerprint ID

- FTIR, Raman, Elemental, Mass Spec, etc.

Roy Cherris Visual Inspection Forum 2013, Bethesda



When do I need which kind of information ?





Comparison of Characterization Level

Level		Cost	time/particle
1	light microscopy	Invest: 2T€ €	15 min
2	Isolation, Polarized Light microscopy	Invest: 60 T€	30 min
3	SEM / Raman/ IR	Invest: 70 T€ (IR), 150 T€ (Raman), 180 T€ (SEM)	30 min



Classification Level 1

1. Classification is based on basic observations
Defined by trajectory, shape, density
2. Classification could be done by a
experienced operator probably trained for
special tools
3. Reason to go on with level 2 characterization
could be statistics, uncertainty about nature
of the particle





Categories / Attributes

Categories

Category		Category	
Glass-Like	[]	Polymeric-like	[]
Metallic-like	[]	Dark Particle	[]
Fiber-like	[]	Light Particle	[]

Attributes for further description

Shape	Colour	Location	Density	Size
Spherical	Light	Body	Floater	
Irregular	Dark	Bottom	Fixed	
Elongated	Transparent	Shoulder		



Microscopic investigation – Level 2

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Level 1 characterization groups e.g. dark particle, light particles, fiber-like might be sampled by a basic universal sampling plan like $\sqrt{N+1}$

Isolation is required for further investigation

Clean area mandatory:

- clean room, clean bench, ultra cleaned glassware, requires trained personnel

Various tools for isolation:

- Capillary, tungsten needles, filtration

Microscope helps to give further details:

- Rubber, metal, synthetic vs natural fiber, crystal shape, color

After isolation particle can be easily transferred to level three



PLM – Level 2 characterization




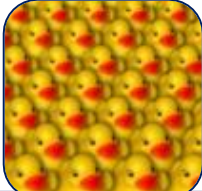

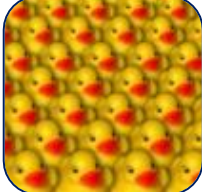





Microscopic information – Level 2

Incident Light	Select	Transmitted Light	Select
Clear	[]	Transparent	[]
Opaque	[]	Opaque	[]
Reflective	[]	Crystalline	[]
Physical	Select	Crossed Polars	Select
Crystalline	[]	Isotropic	[]
Shaving	[]	Anisotropic	[]
Resilient	[]	Pseudo-Birefringence	[]
Shard	[]	Isotropic Rod	[]
Size Length (um)		Uniform fiber	[]
Size Width (um)		Irregular frayed fiber	[]

Level II Category	Select	Level II Category	Select
Glass	[]	Polymeric	[]
Metallic	[]	Rubber Stopper	[]
Fiber	[]	Semi-Solid - Silicone	[]
Fiber - Natural	[]	Possible Inherent API	[]
Fiber - Synthetic	[]	Possible Extrinsic	[]

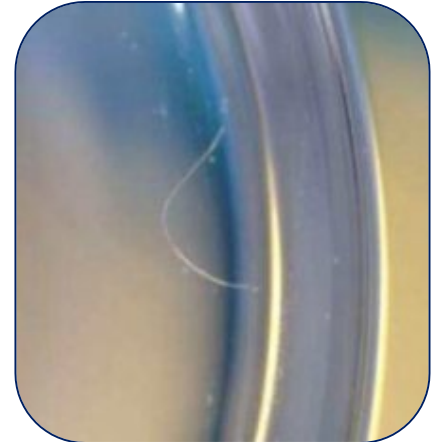
method	meaning		time/particle
PLM (polarized light microscopy)	color + shape e.g.: black fibres		1-5 min
SEM/EDS analysis	> 5µm Elements	 	20-180 min
IR – microscopy	> 50 µm Structure	 	20-180 min
RAMAN - microscopy	> 0.5 µm Structure	 	20-180 min



Fiber – Level 1

Category	Select
Glass-Like	[]
Metallic-like	[]
Fiber-like	[x]

Category	Select
Polymeric-like	[]
Dark Particle	[]
Light Particle	[x]

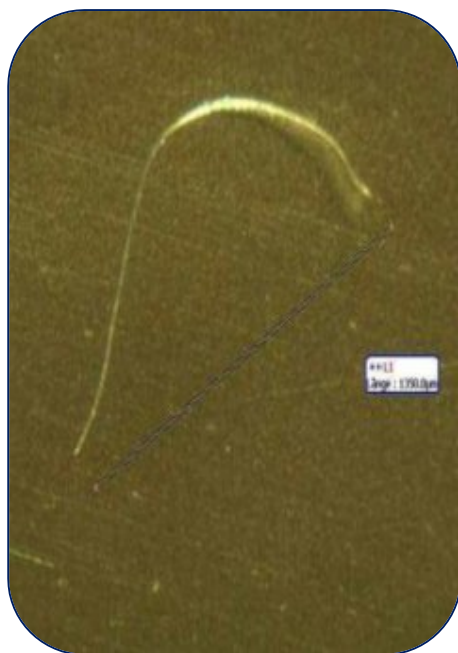


- Fibers can be easily classified. Might be sufficient for trending
- Further classification of fibers can be preformed in situ with an inverted microscope due to morphology and texture

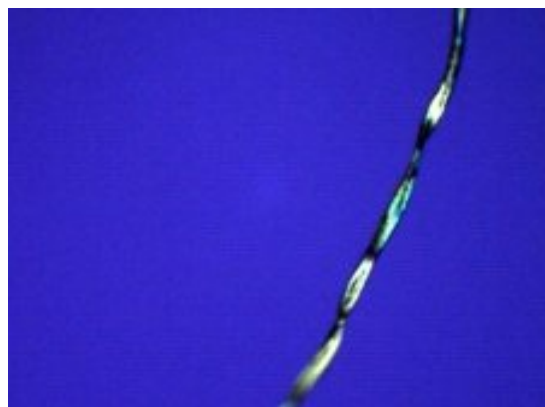


Fiber-Level 2: Isolation Microscopy₁₆

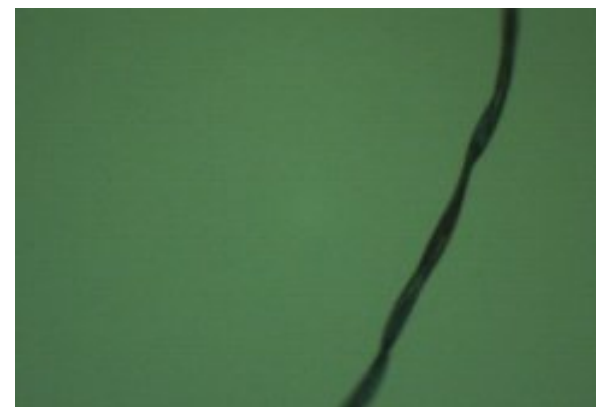
- Microscopy of isolated fiber gives further information (cotton, protein based fiber, synthetic)
- Spectroscopy can give a very specific fingerprint for root cause or kind if synthetic fiber



Level 2



Level 2



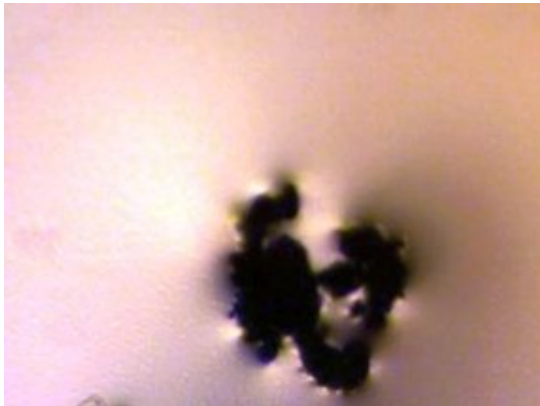
Level 1



Metal particle Level 1 and Level 2

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- Characterized density and reflectivity
- Sufficient for trending
- Hard to observe while swirling
- Usually easy to find at the bottom



Level 1



Level 2



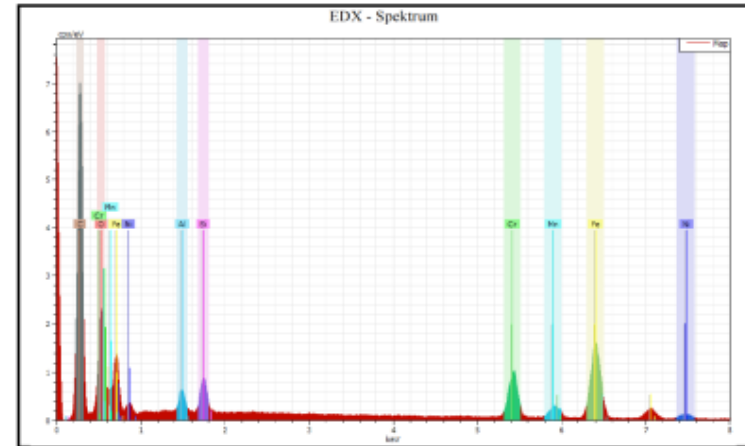
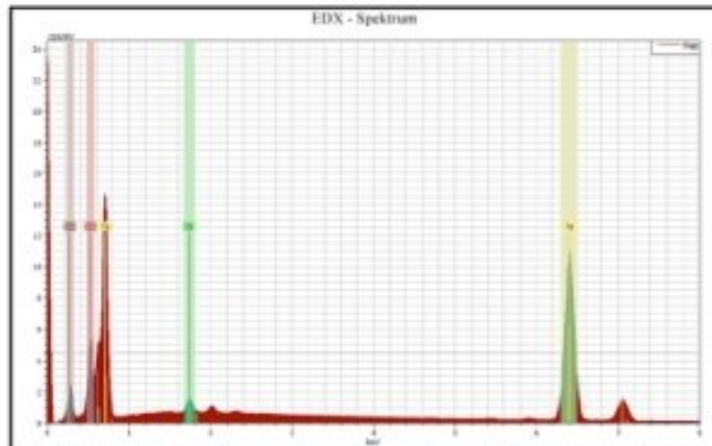
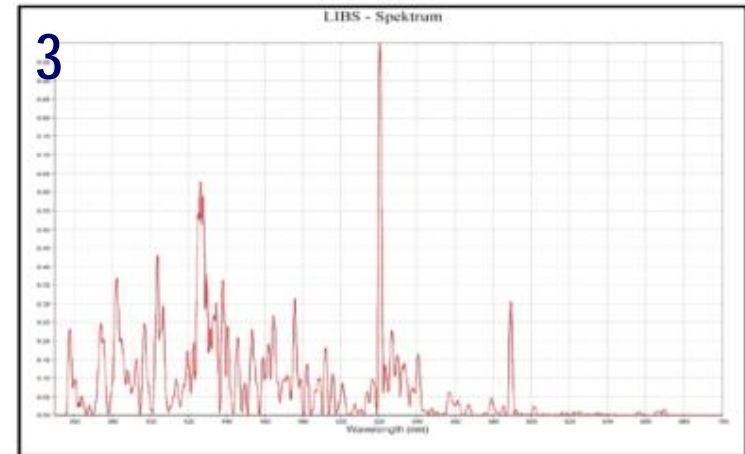
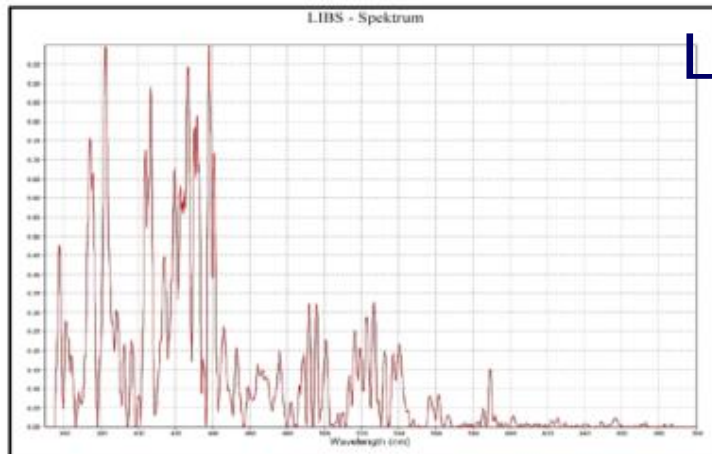
Level 2



Spectroscopy on metals – Level 3

Spectroscopy gives more detailed information on the kind of steel e.g. low alloyed vs high alloyed steel which might be needed for root cause investigation

Level 3



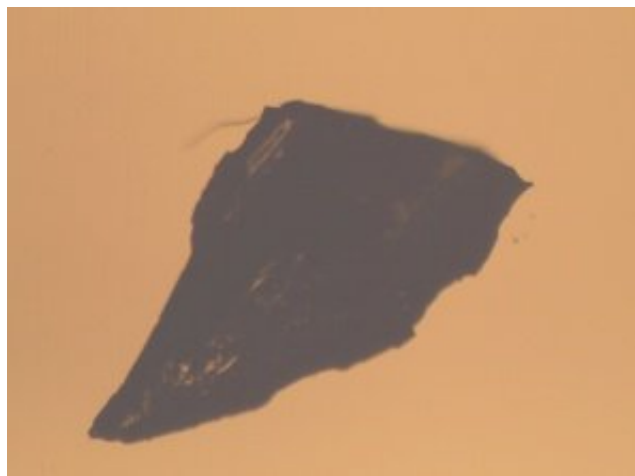
Element	Fe	C	O	Si
nor. [Gew-%]	73.8	13.0	12.1	1.0

Element	C	Fe	O	Cr	Ni	Si	Mn	Al
nor. [Gew-%]	41,2	26,4	15,4	9,2	2,9	2,1	2,0	0,9

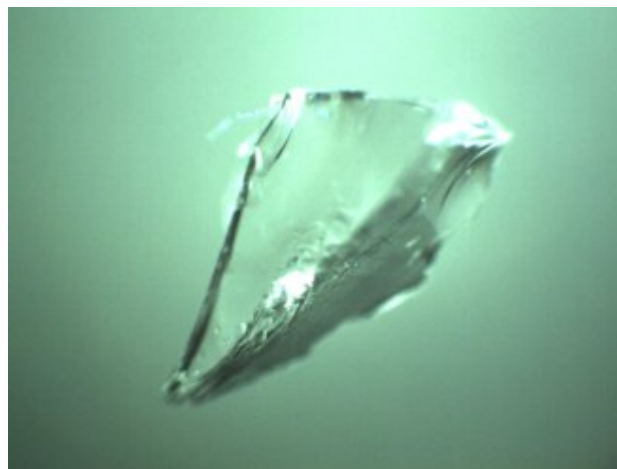


Glass particle - Level 1 and Level 2

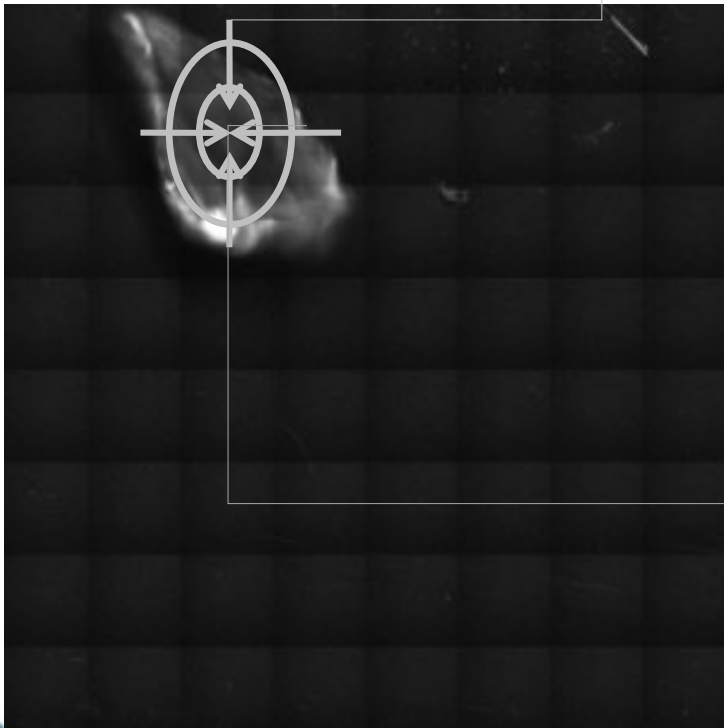
- Glass has a very characteristic shape which is sufficient for classification
- Further characterization for root cause investigation: element specific methods e.g. SEM or LIBS favorable



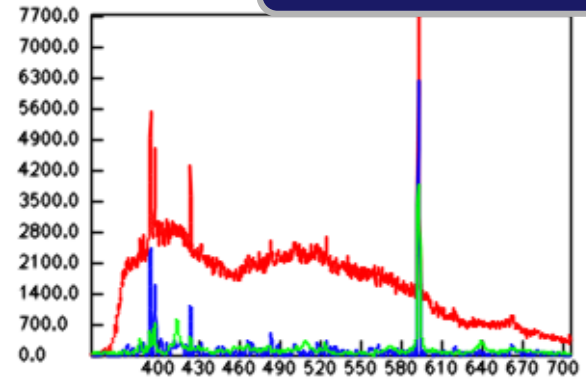
Level 1



Level 2

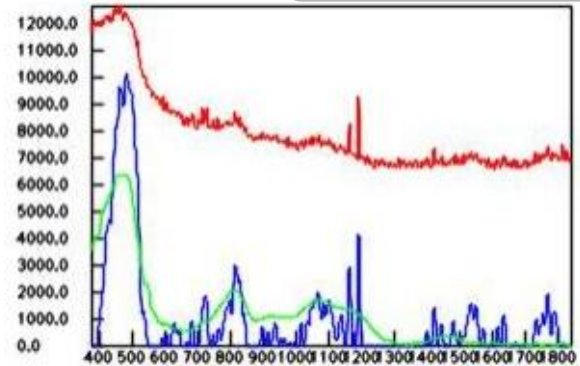


LIBS



Si, Na, Al (Fiolax)

Raman

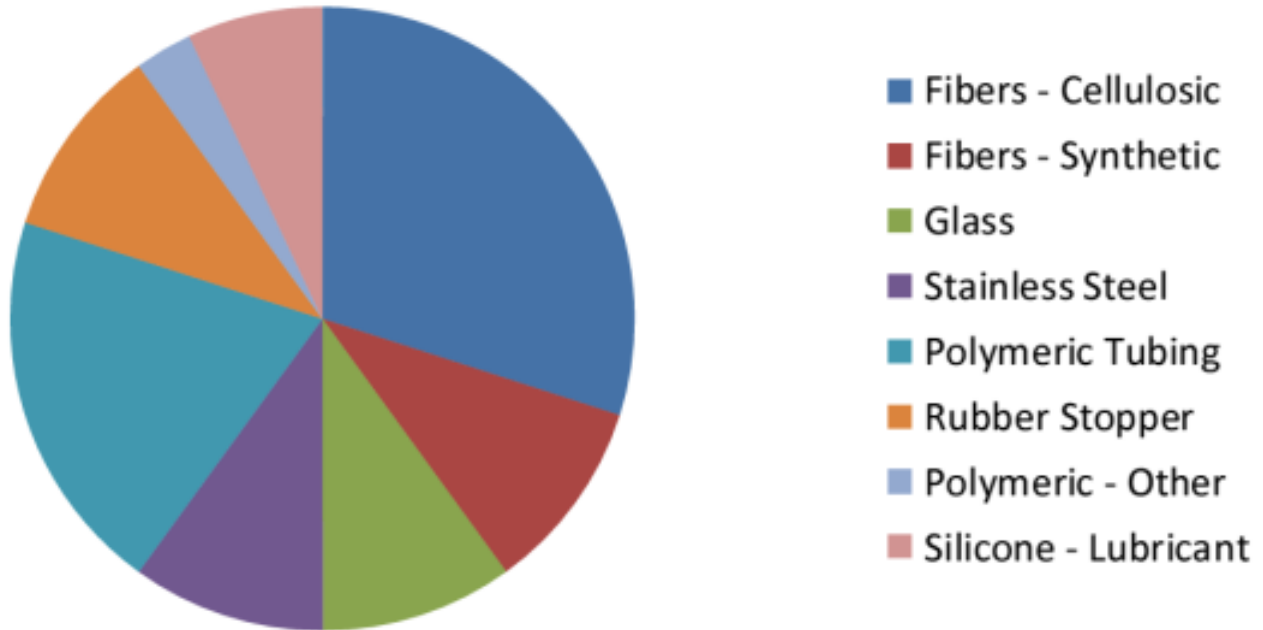


Glass



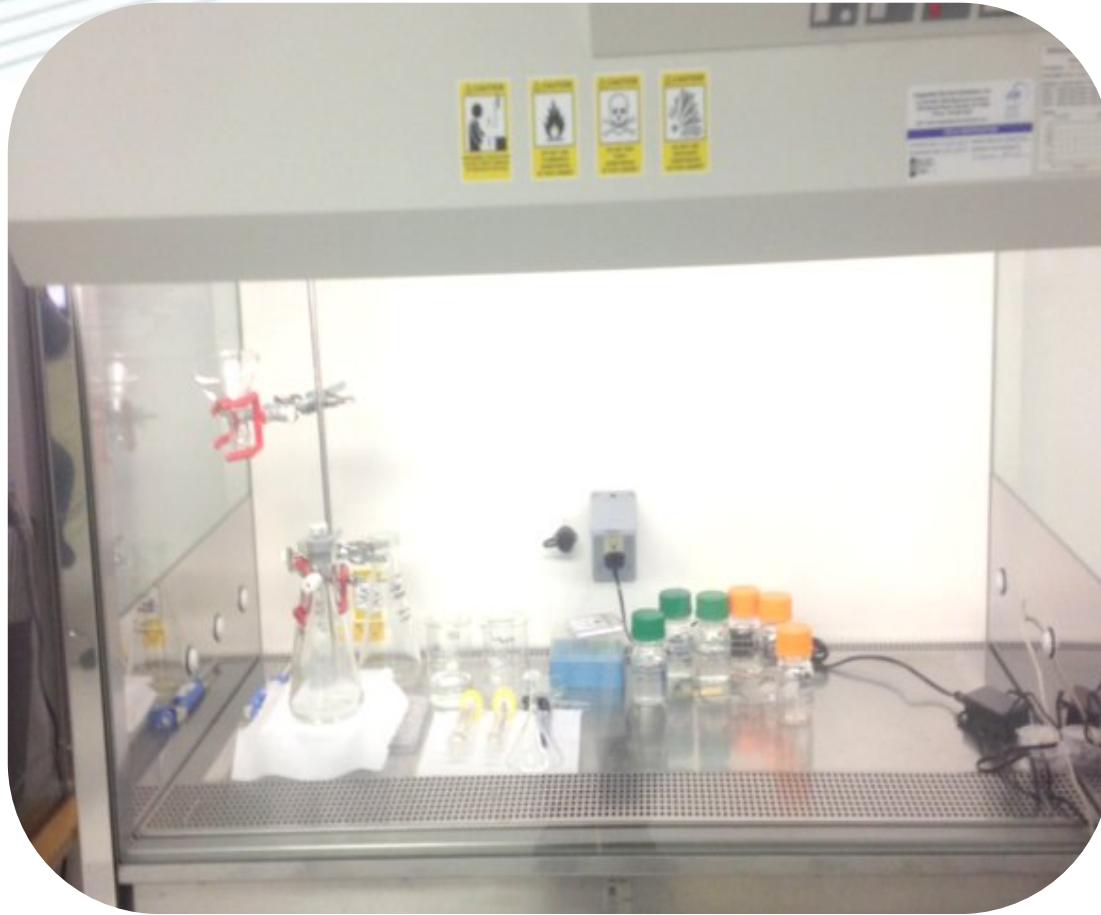
Trending

Level Two Visible Particle ID Trending



A scientist with short brown hair and glasses, wearing a white lab coat, is seated at a desk in a laboratory. He is looking intently at a computer monitor while his right hand rests on a mouse. To his left is a large, professional-grade microscope with a silver lampshade. The background is a plain white wall with a red and white geometric design. The text "Particle Isolation" is overlaid in red on the image.

Particle Isolation



Isolation



Environmental Considerations

- Class 100 clean bench is essential
- „Ball-park“ clean rooms would be beneficial
- Cleaning is essential and system suitability tests (blanks) have to be taken
- Training and control is essential
- Benches, coats, sleeves, microscopes, equipment and water should be clean and non-shedding



Isolation

Remove the particle from the matrix

Filtration or capillary / pipette

Put the particles on a suitable substrate:

Needles and tools

Avoid cross contamination

Cleaning / clean bench

Clean Media



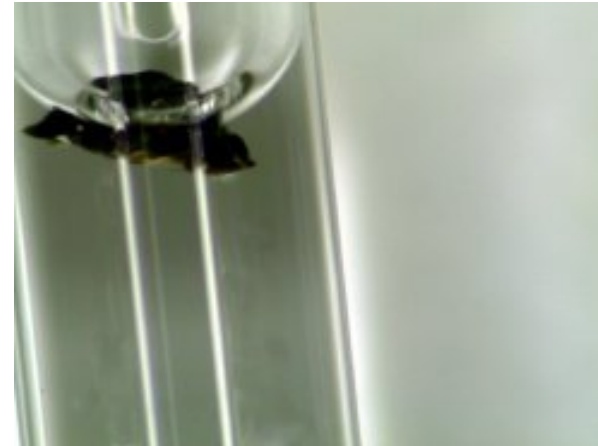


Isolation and transportation

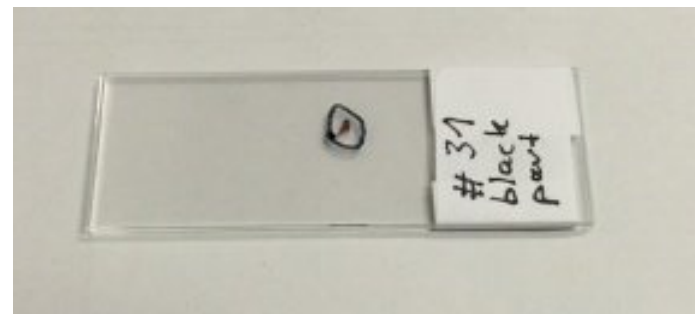
Capillary trapping



Tungsten needles for particle picking



Sending particles to a lab between 2 slides





Filtration / Particle Isolation



- Low blanks
- Cleanroom or LF
- Experienced staff
- Consider the right filter material



A scientist with short brown hair and glasses, wearing a white lab coat, is seated at a desk in a laboratory. He is looking intently at a computer monitor while his right hand rests on a mouse. To his left is a large, black and white microscope. A modern, silver desk lamp is positioned above the microscope. The background is a plain white wall with a red and white geometric design. The text "Particle Sources" is overlaid in red on the image.

Particle Sources



Inherent

Particulate made entirely of components of the formulated product, arising from the product itself. These particulates are related to the product formulation: API

Intrinsic

Particulate related to the production process of components of the formulated product, arising from the product itself. Processing Equipment, Primary Package, Active and other ingredients

Extrinsic (Foreign)

Environmental Contaminants
insect parts, hair, fibers, paint, rust



Sources for particulate matter ?

- personnel



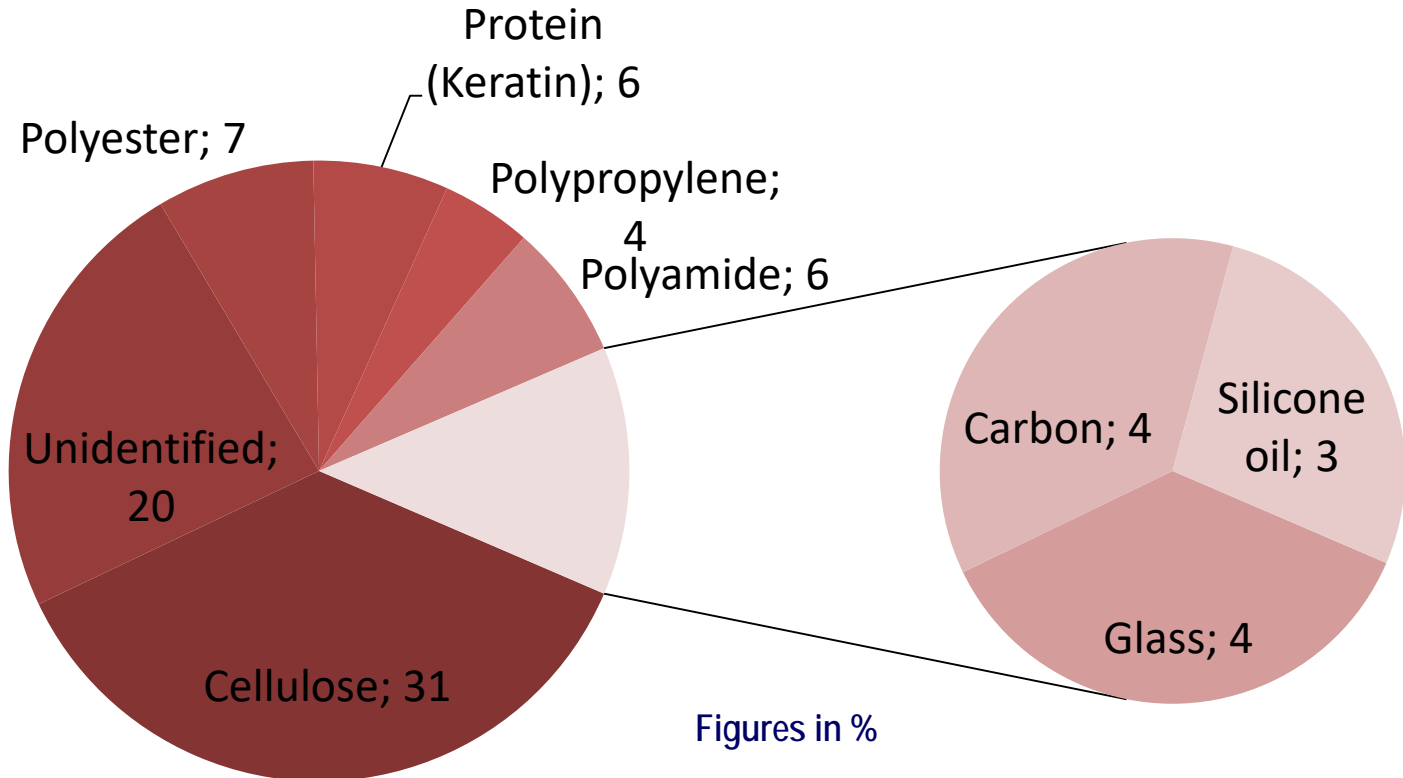
- Garnement
- Water
- container



- Process / Production Equipment e.g.: rubber
- Cleaning process

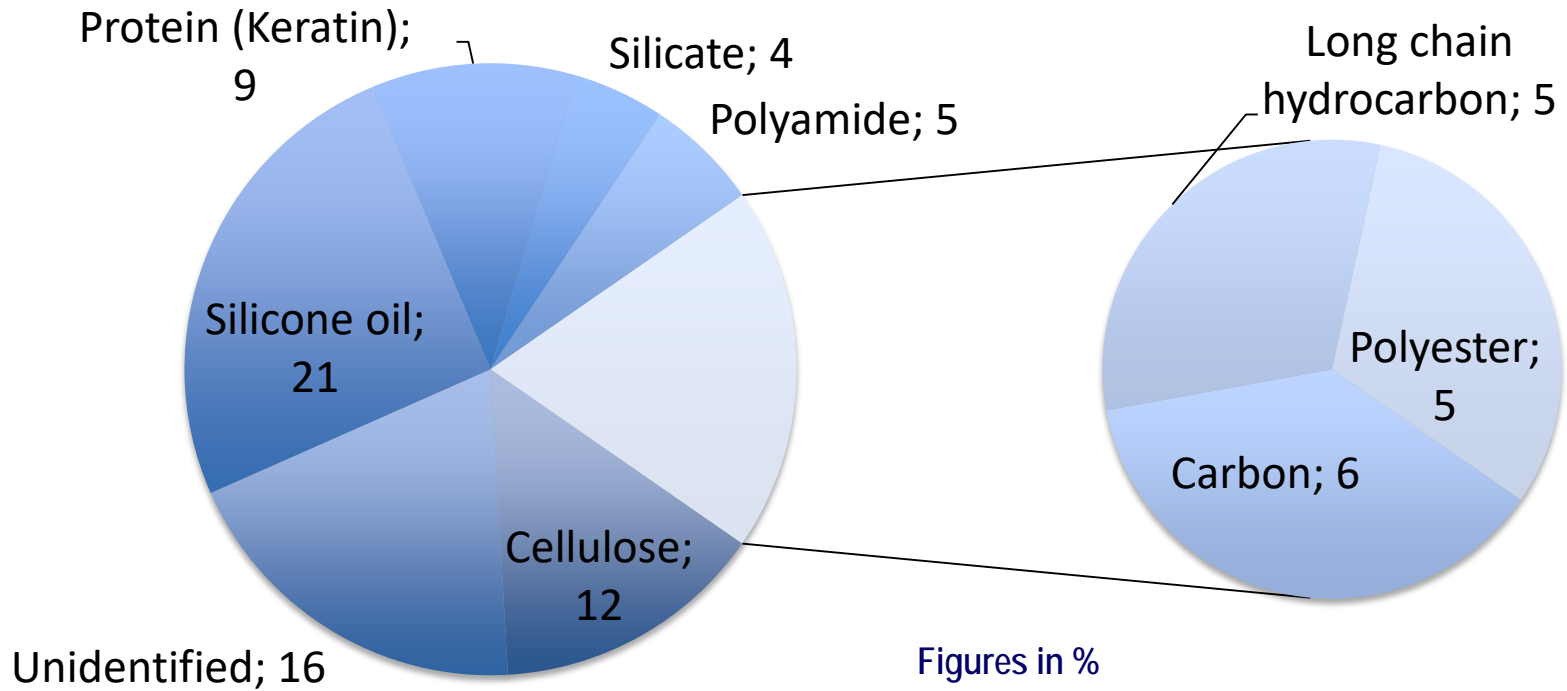


Visible



Cellulose, Polyester and Protein/Polyamide particles are major contributions to particulate contamination.

Sub-visible



Silicone oil, Protein, Cellulose particles are the most often found contaminants

Top Ten in more detail

- Cellulose: mostly fibres
 - source: clothes, **towels**, wipers, autoclave paper



- Longchain hydrocarbon
 - source: rubber (stopper), PE (bottles)



Top Ten in more detail

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- Glass: fibres and particles
 - Source: Primary packaging
 - But also glassfibers and hollow glass fibres (filter material)
- Carbon: particles
 - Usually black particles contain high content of carbon:
 - Sealings rubber material filled with carbon
 - Burned material

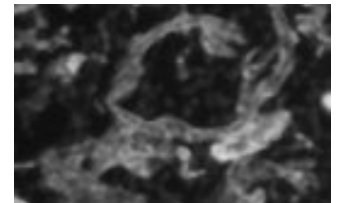




Top Ten in more detail

35

- Polyester: fibres and particles
 - Source: Cleanroom clothes and defect filter
- Protein: mostly flakes
 - Source human dust, protein particles from protein solution
- Silicone oil: compact particles
 - Source: sealings, siliconisation

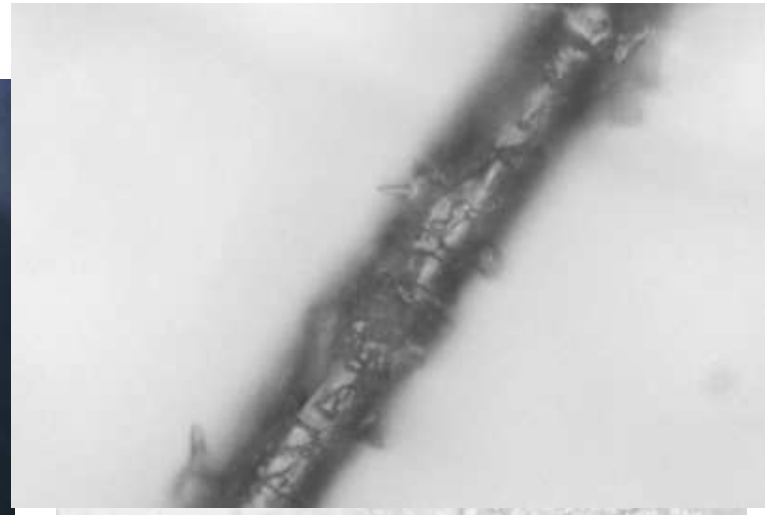




Plunger/stopper related defects

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- White or black spots on/between lips
 - Foreign material trapped between plunger and glass wall Glass bits
 - Rubber chunks
 - Fibres
 - Hair

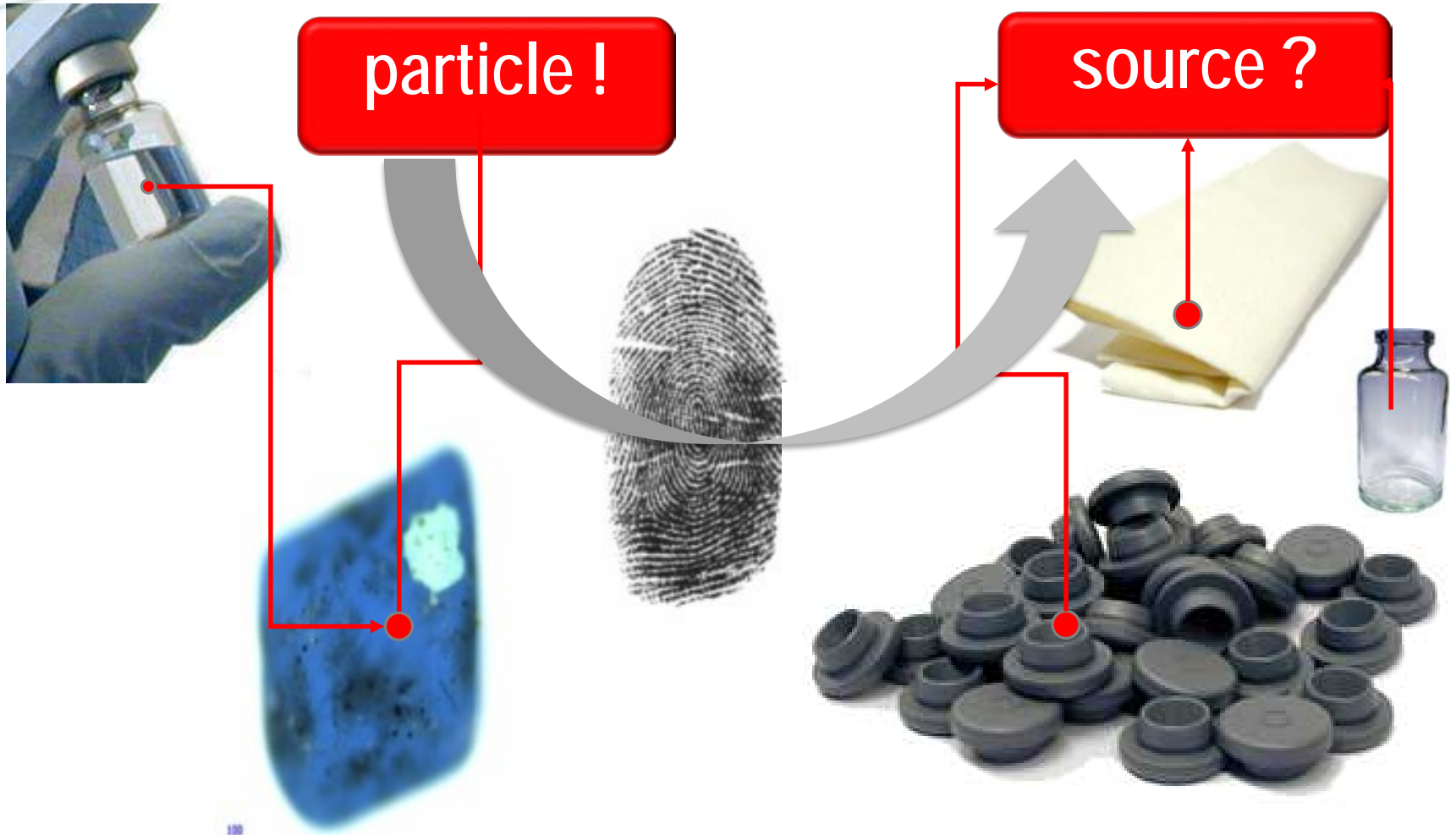


A scientist with short brown hair and glasses, wearing a white lab coat, is seated at a desk in a laboratory. He is looking intently at a computer monitor. In the foreground, a large, modern microscope is visible, with a silver lampshade above it. The desk also holds a keyboard and a mouse. The background is a plain white wall with a red and white geometric design.

Examples



Root cause analysis



100



Particle defect investigation

1. Documentation of the defect → in-situ (in the closed container)
2. Filtration and documentation of the sample on the membrane filter
3. Documentation of the analysis and the identification of the reject by Raman spectroscopy
4. Identification of sub-visible to gather further information
5. Verification of the findings (particle observed by visible inspection) with FT-IR or LIBS, EDX

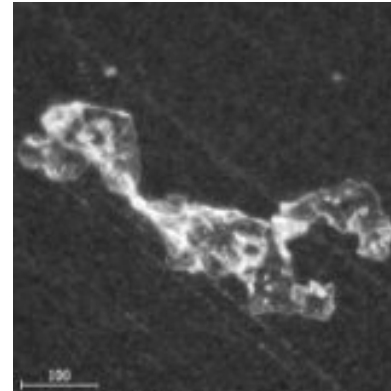
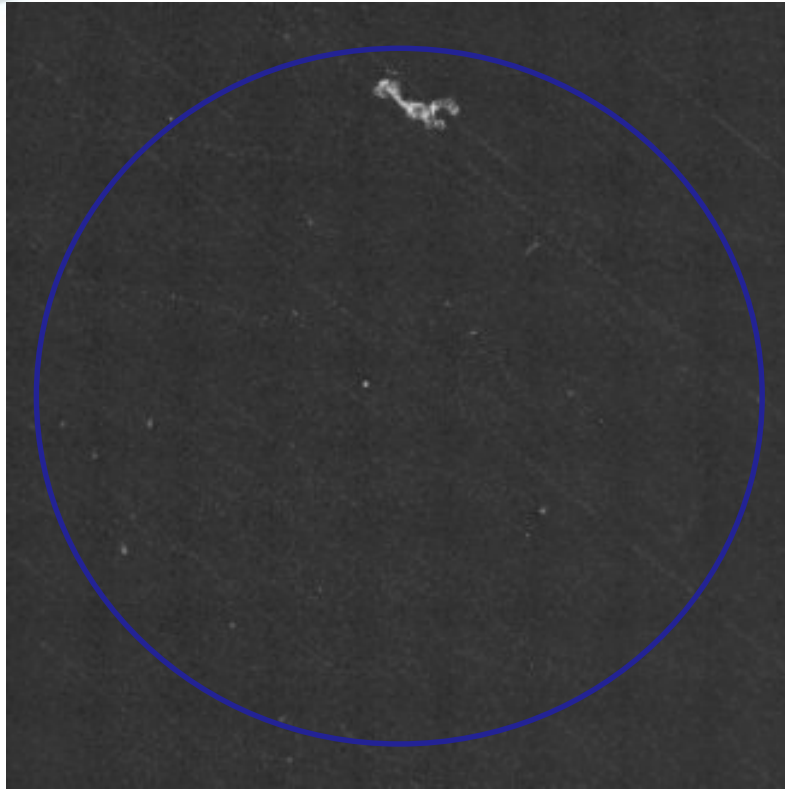


1. Particle in the vial

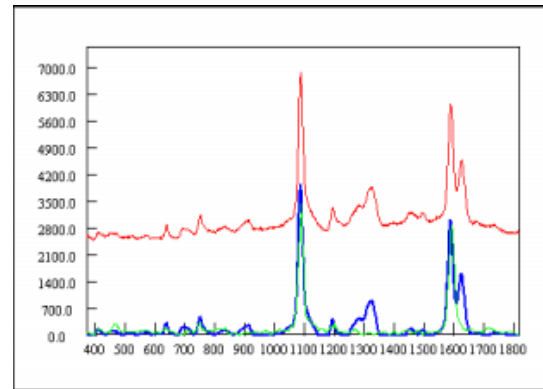




3. Particle Imaging + raman.ID



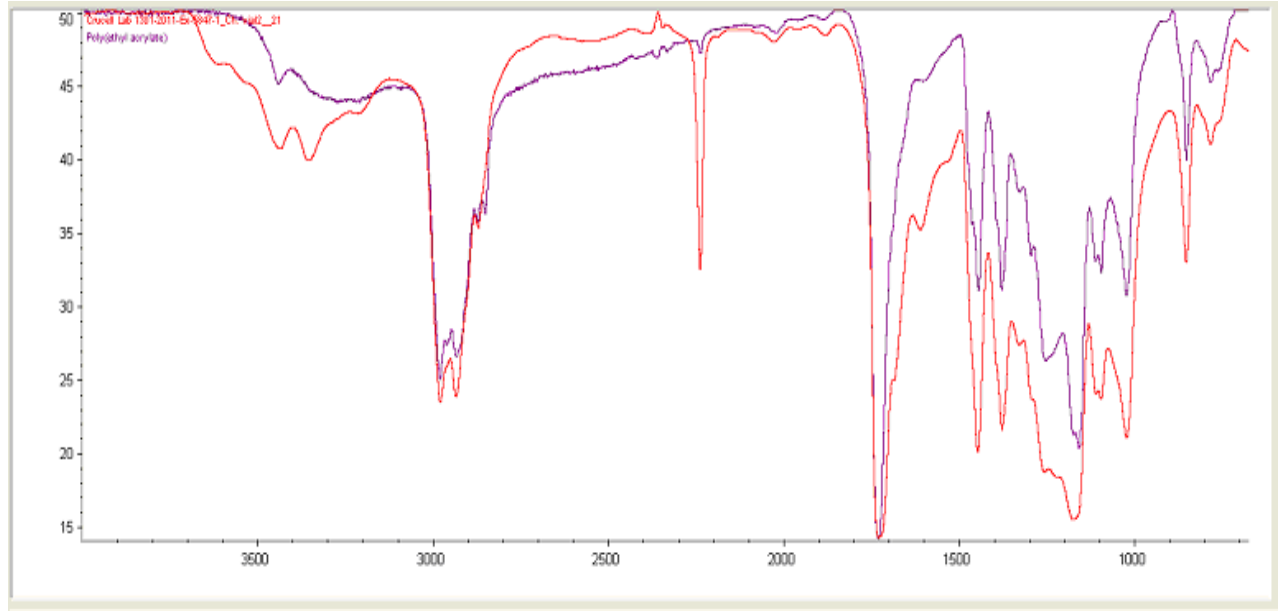
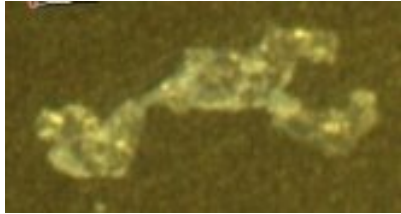
L=505.0 μm
w=202.6 μm
E=2.49
R=0.3071



Raman.ID: Polyethylene-terephthalate, PET
Rank: 887



4. Verification FT-IR → PET



Polyethylene Terephthalate, PET
76.16% matching

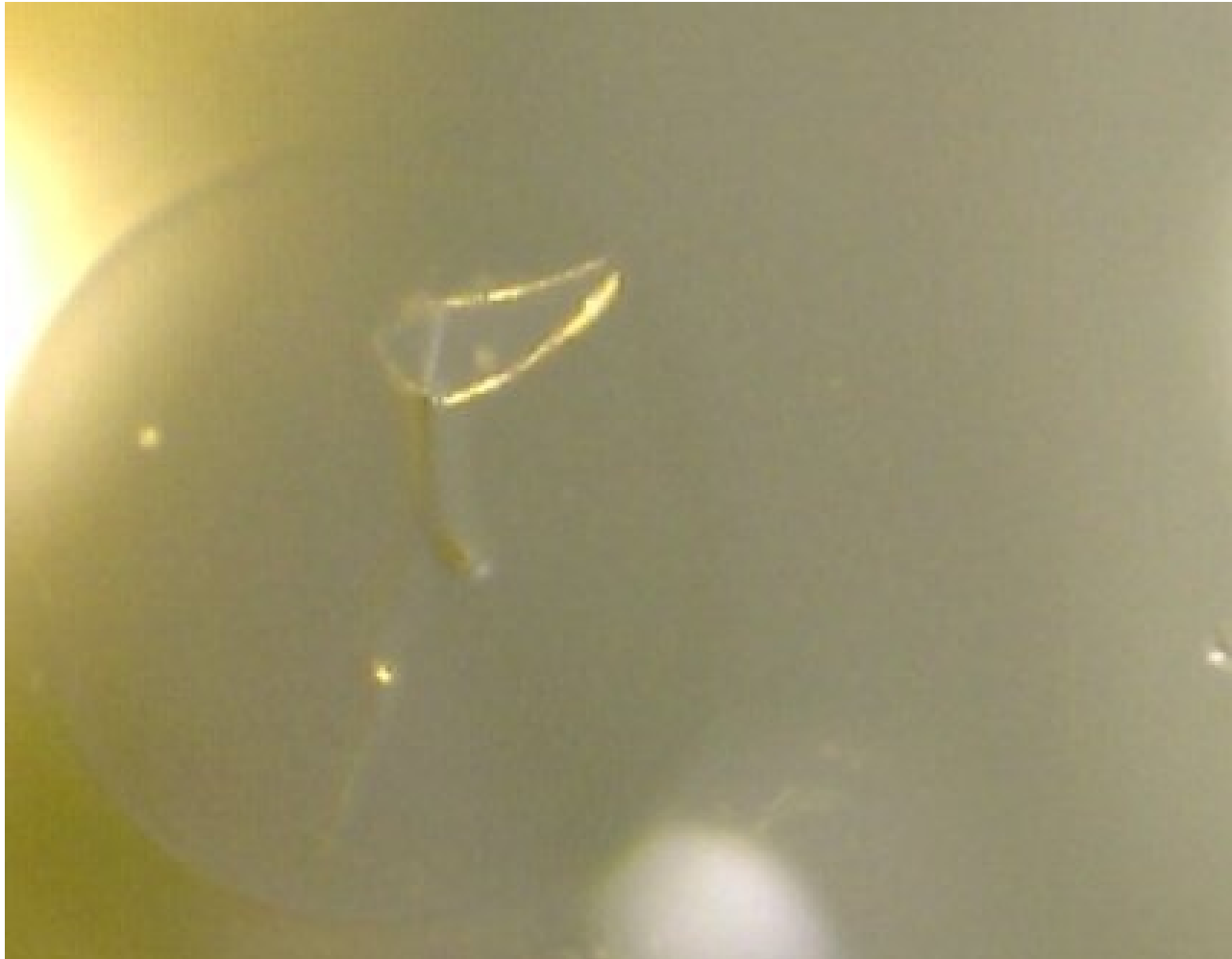


5. Particle (subvisible) Raman spectroscopy

Size and Substance Distribution of Measured Particles					
Substance	Number	Size Distribution [μm]			
-	-	2-5	5-10	10-25	25->50
PET	1	0	0	0	1
Rubber plug	1	0	0	0	1
Cellulose	1	0	0	1	0
Tween 80	1	0	0	1	0
Polyamide	2	0	0	12	0
Analysed particles	6	0	0	14	2
All particles	541	463	60	14	4

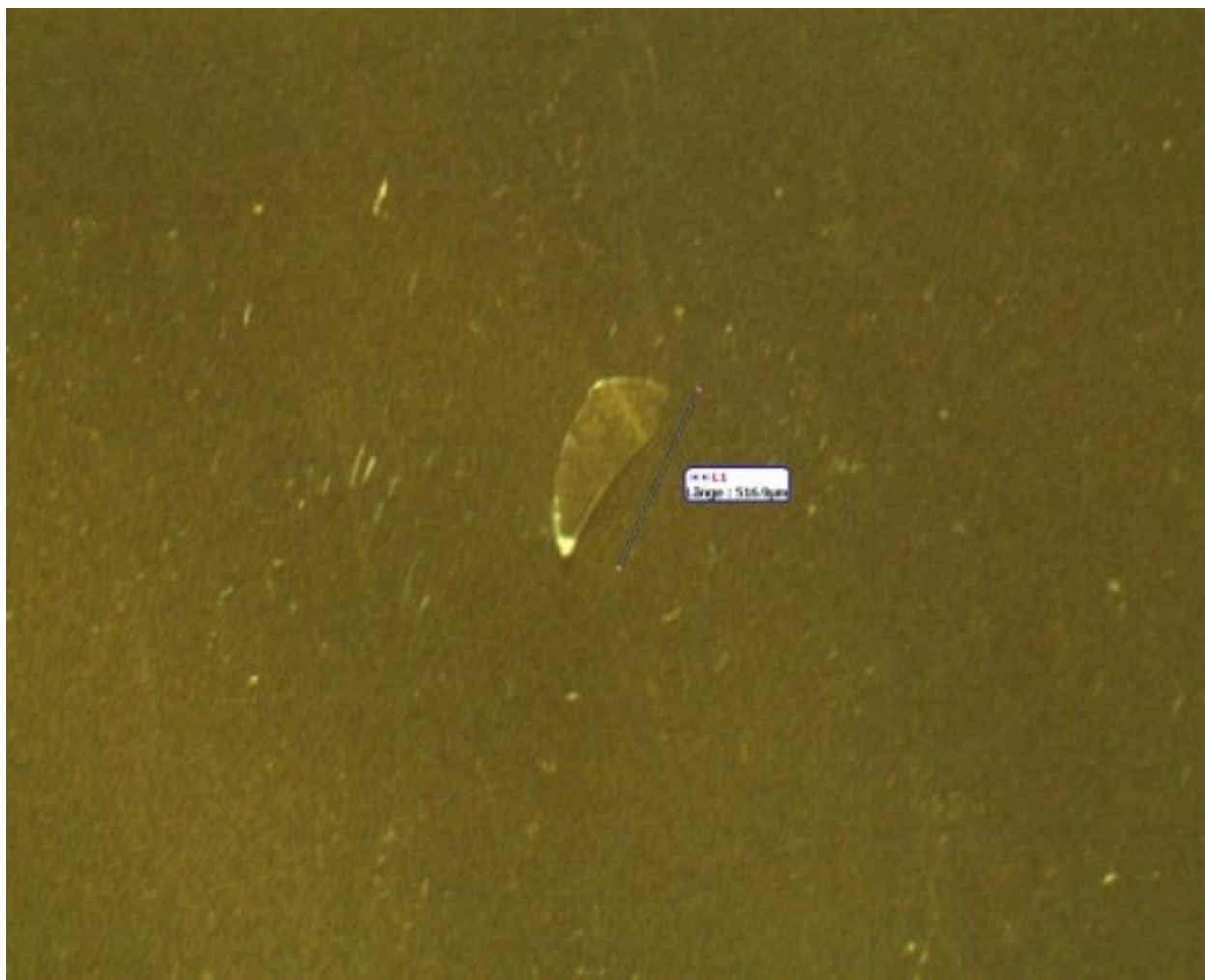


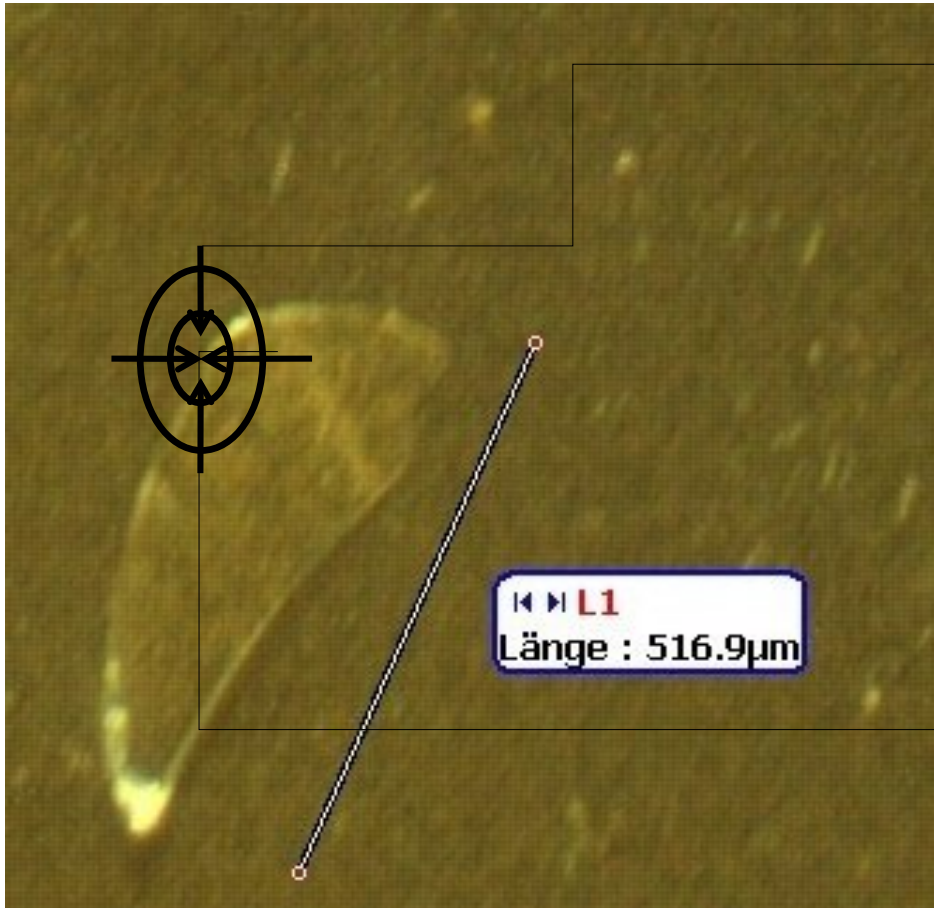
Visible Inspection: Particle Defect Reject II



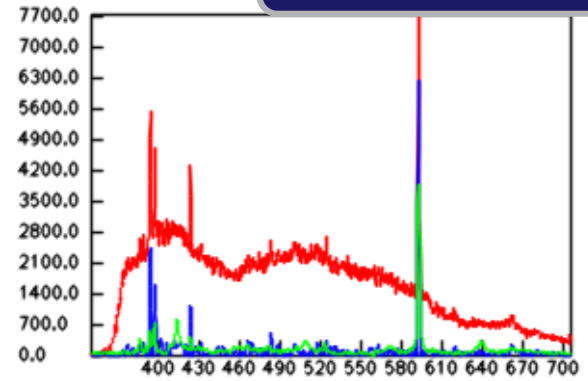


Sample prep. + Documentation



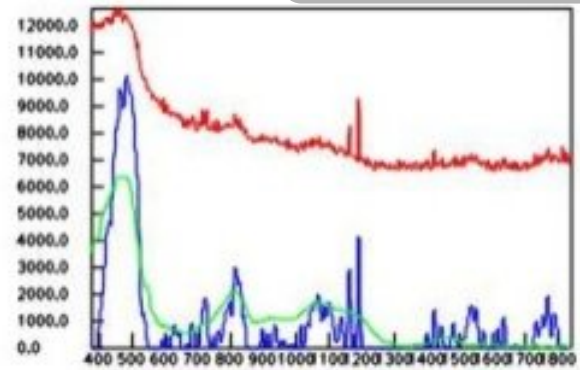


metal.ID



Si, Na, Al (Fiolax)

raman.ID



Glass



Report II - Summary

1. The largest Particle we observed in the vial (516 μm) was identified by means of Raman as well as FT-IR spectroscopy as glass.
2. This finding was also confirmed by LIBS Laser induced breakdown spectroscopy. The particle matched with Fiolax (Al is a marker).



CELLULOSE SOURCE

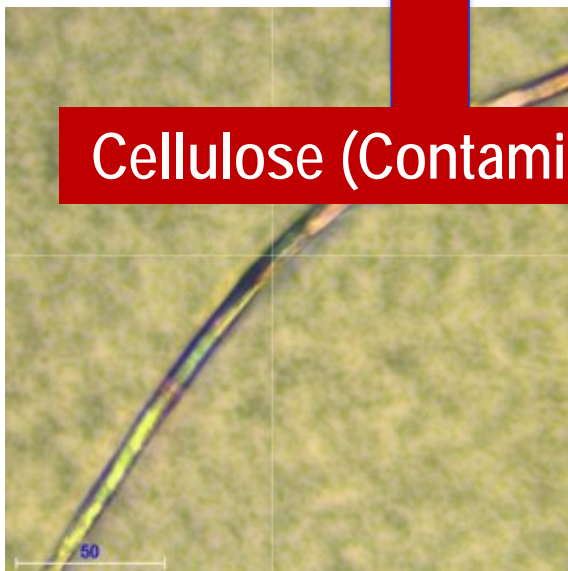
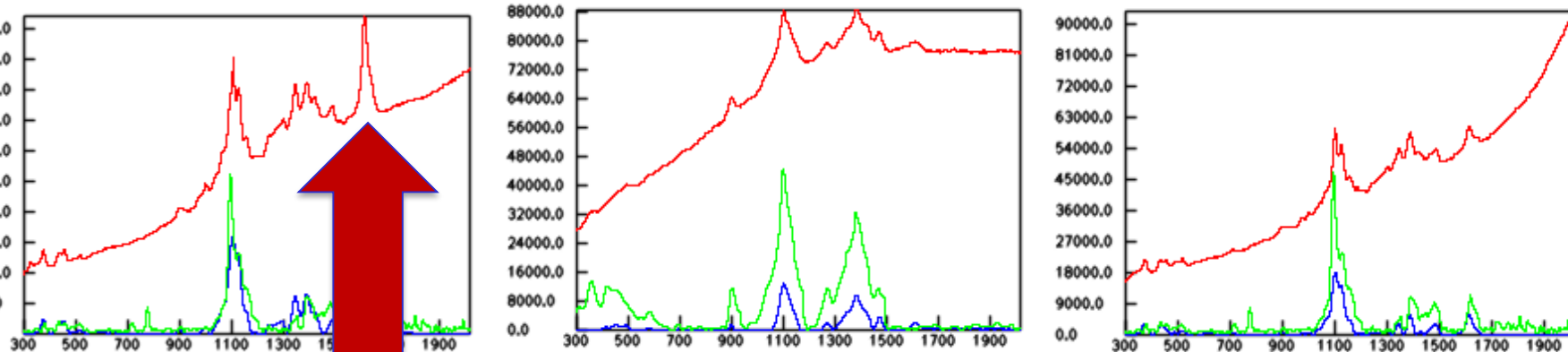


Example Cellulose Source

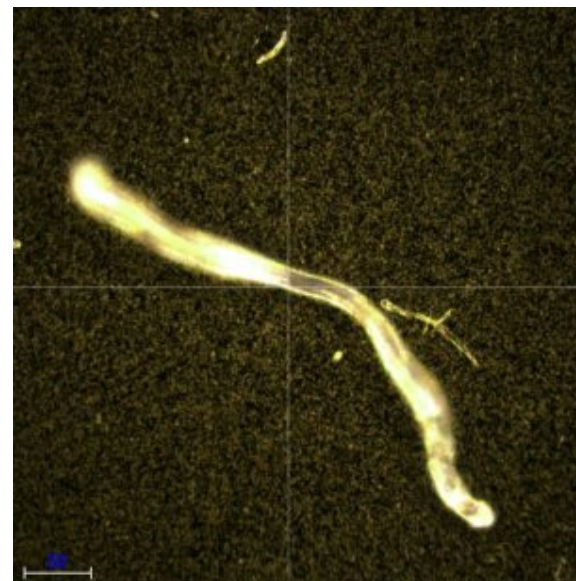
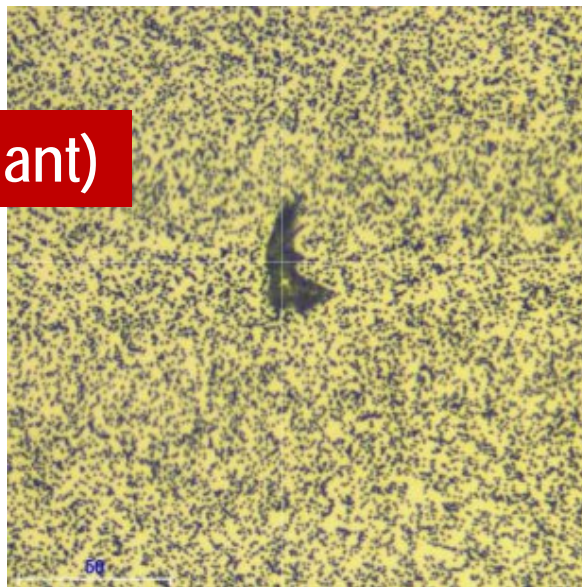
1. 4 batches failed in a row
2. 3 samples of each of the failed batches and one of the good batches were investigated
3. Soon it became clear that the problem was cellulose related....



Several cellulose fibers were found



Cellulose (Contaminant)





Samples from the filling were taken

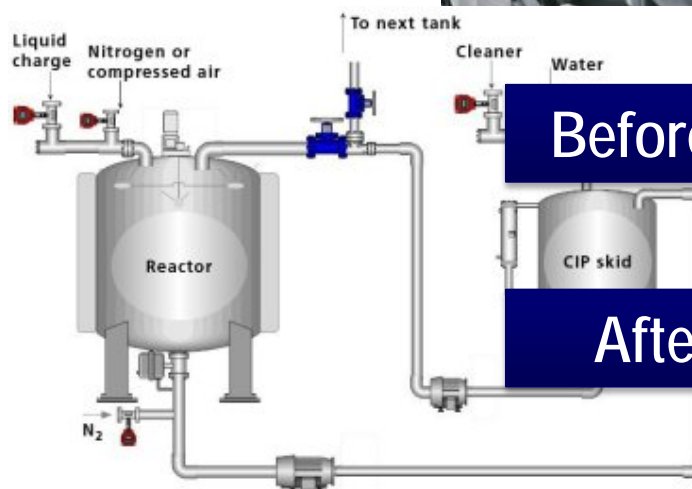
Before Tubing Rinse Sample

After Tubing Rinse Sample



Before CIP Rinse Sample

After CIP Rinse Sample



Stopper Sample





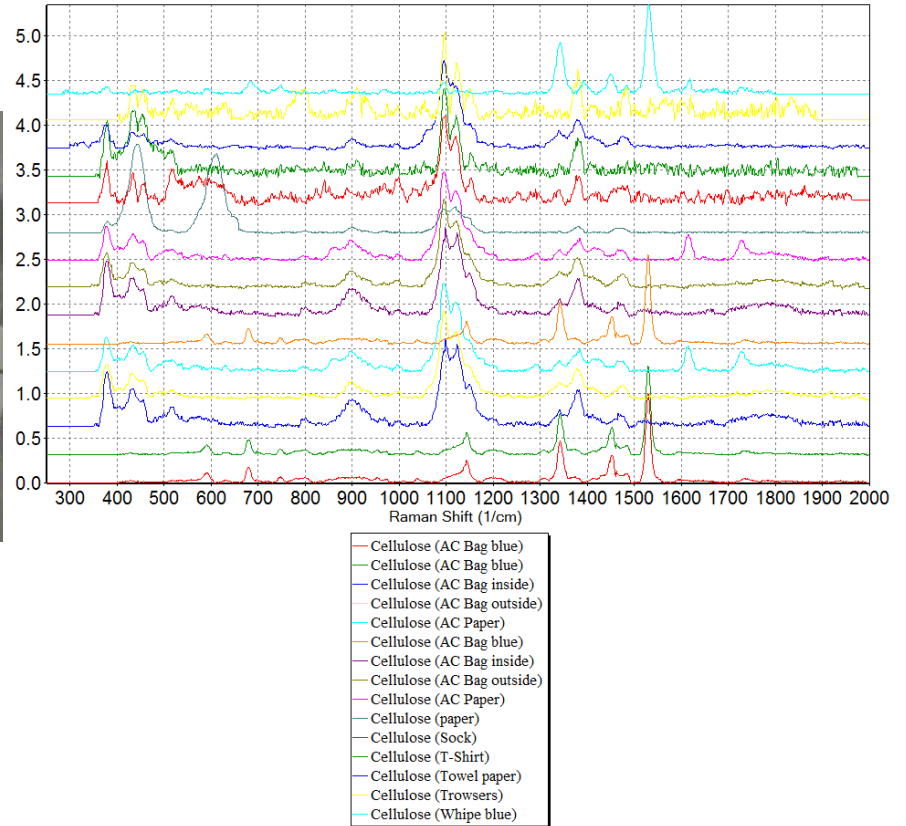
Samples from the process were taken





Database with filling line related materials was built

1.



No Cellulose (Contaminant) !



Tube rinse result

Size and Substance Distribution of Measured Particles

Substance	Number	Size Distribution [μm]				
		≥ 5	≥ 10	≥ 25	≥ 50	≥ 100
-	-					
Cellulose (AC Bag blue)	5	0	0	0	1	4
Cellulose w. Polyester (Papertowel II)	1	0	0	0	1	0
Ethyl Cellulose	1	0	0	0	0	1
Cellulose (AC Bag inside)	19	0	0	0	6	13
Pigment, Indian Yellow	1	0	0	0	0	1
Other Particles	143	0	0	5	38	100
beta-Carotene	50	0	0	3	19	28
Skipped particles	2283	889	808	432	137	17
All particles	2503	889	808	440	202	164



No Cellulose (Contaminant) !



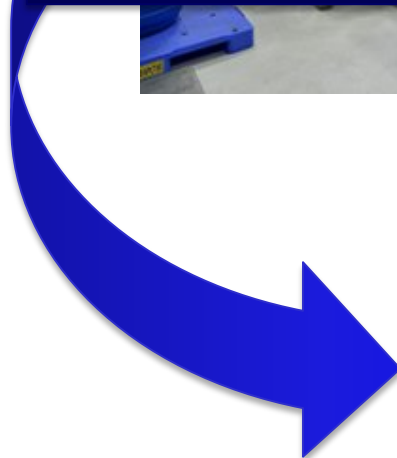
Closer look into the API production (site in Italy)



Tank A Sample

Tank B Sample

Tank C Sample



Substance	Number	Size Distribution [µm]				
		>=5	>=10	>=25	>=50	>=100
-	-	>=5	>=10	>=25	>=50	>=100
Cellulose (AC Bag blue)	1	0	0	0	1	0
Labcoat	1	0	0	1	0	0
Fluorescence	1	0	0	1	0	0
Carbon	4	0	0	3	1	0
Cellulose	1	0	0	0	1	0
Indanthrene Blue	1	0	0	1	0	0
Cellulose (Contaminant)	31	0	0	8	18	5
Pigment, Indian Yellow	3	0	0	3	0	0
Polysulfone	5	0	0	1	2	2
Cellulose (Towel paper)	5	0	0	5	0	0
Other Particles	28	0	0	22	1	5
Skipped particles	1716	1353	362	1	0	0
All particles	1797	1353	362	46	24	12

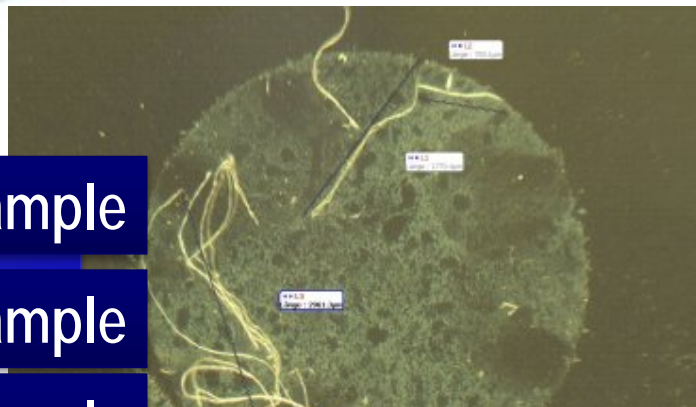


Samples from API tanks and tubings showed this type of fiber.

Tank A Sample

Tank B Sample

Tank C Sample

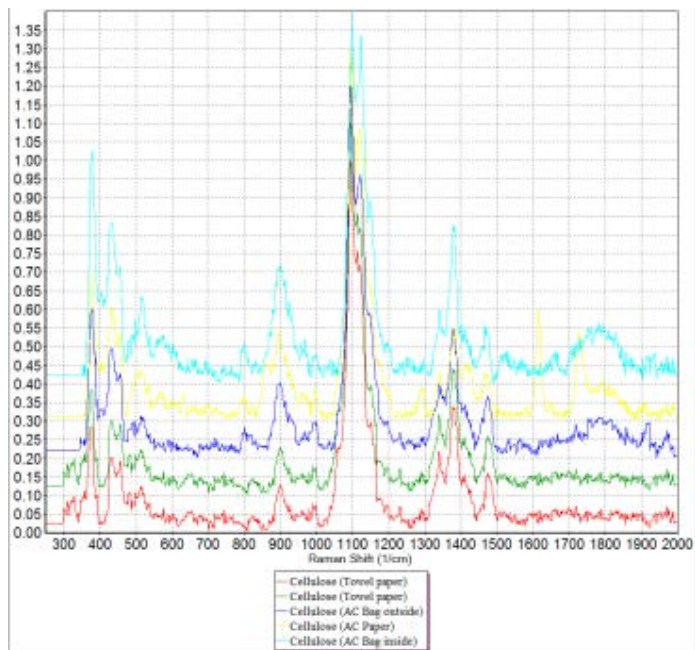


Size and Substance Distribution of Measured Particles

Substance	Number	Size Distribution [µm]				
		>=5	>=10	>=25	>=50	>=100
-	-	>=5	>=10	>=25	>=50	>=100
Cellulose (AC Bag blue)	1	0	0	0	1	0
Labcoat	1	0	0	1	0	0
Fluorescence	1	0	0	1	0	0
Carbon	4	0	0	3	1	0
Cellulose	1	0	0	0	1	0
Indanthrene Blue	1	0	0	1	0	0
Cellulose (Contaminant)	31	0	0	8	18	5
Pigment, Indian Yellow	3	0	0	3	0	0
Polysulfone	5	0	0	1	2	2
Cellulose (Towel paper)	5	0	0	5	0	0
Other Particles	28	0	0	22	1	5
Skipped particles	1716	1353	362	1	0	0
All particles	1797	1353	362	46	24	12



Update of the library with towels used in API production



Cellulose (Contaminant)



Conclusion Cellulose Example

1. One special type of cellulose could be identified by the typical peak @ 1600
2. Database was built with suspect cellulose samples used in production
3. These Cellulose (contamination) fibers were found in smaller concentration in CIP rinses no fibers ...were found in the process prior to filling!
4. Samples from API tanks and tubings showed this type of fiber.

→ API manufacturer used paper towels and introduced cellulose into the process



Know Your Particles!

Control Your Packaging Material

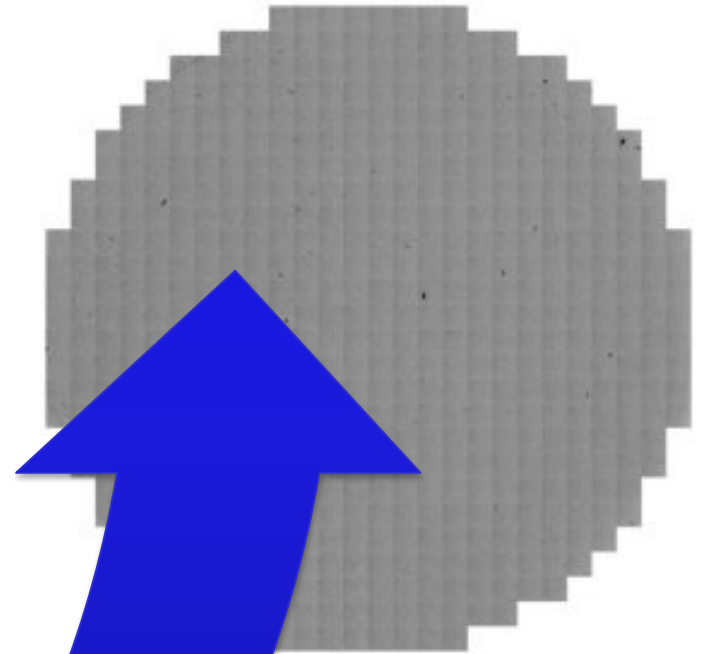
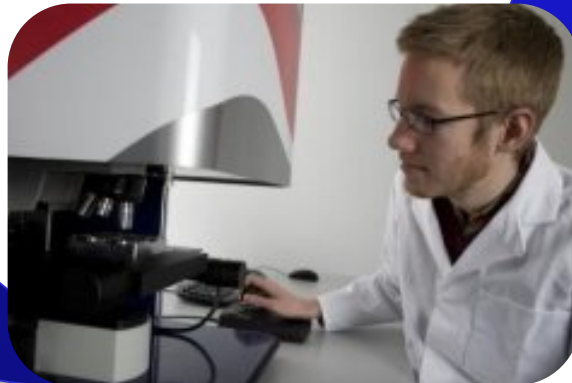
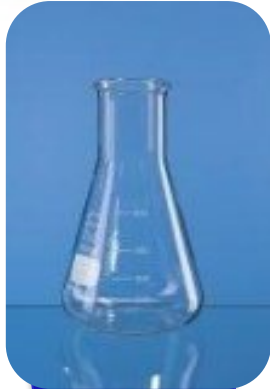
Plunger

Silicone

Syringe (Glass)



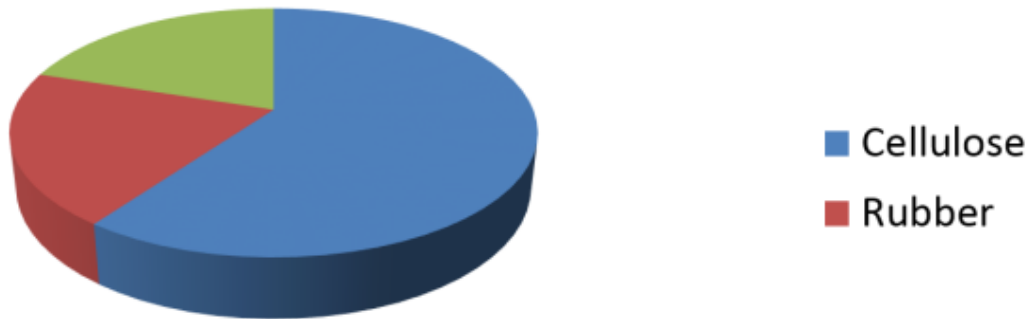
ISO 8871-3





Fibers and particles on rubber

- 10 stoppers contaminated with fiber
Cleaning following ISO 8871
- 51 particles > 50 μm found

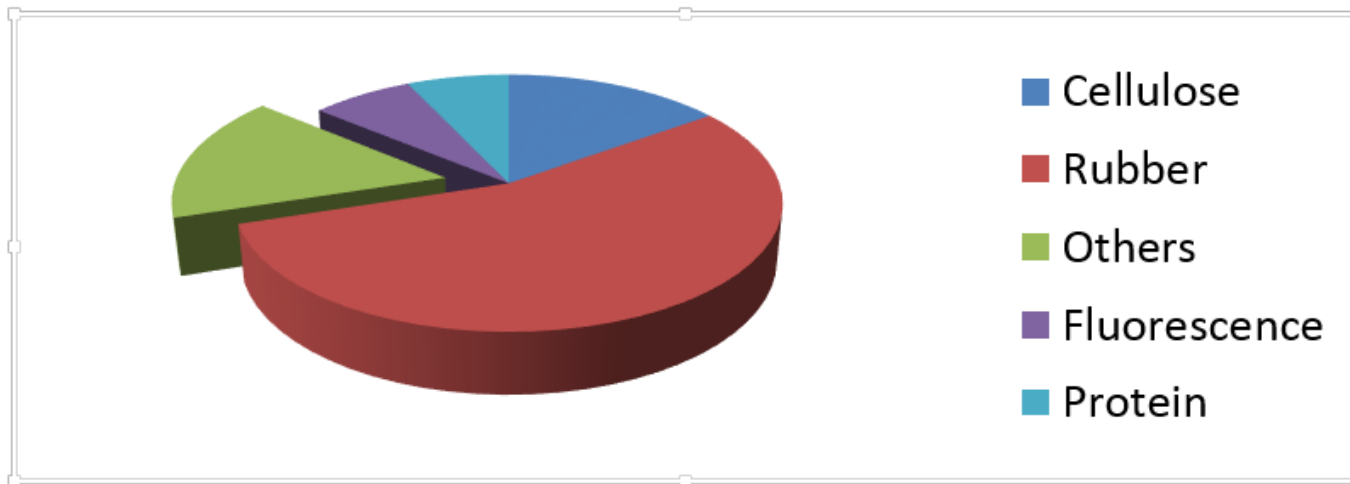


Large scattering in particle number and composition can be observed in one batch and different bags



Fibers and particles on rubber

- 10 stoppers contaminated with particles Cleaning following ISO 8871
- 144 particles found $> 50 \mu\text{m}$

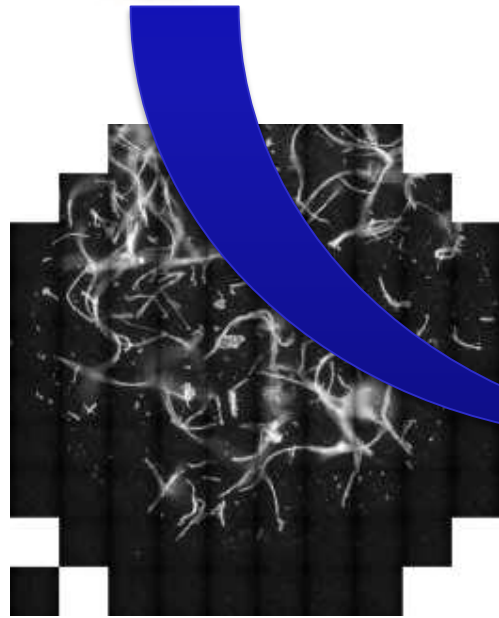




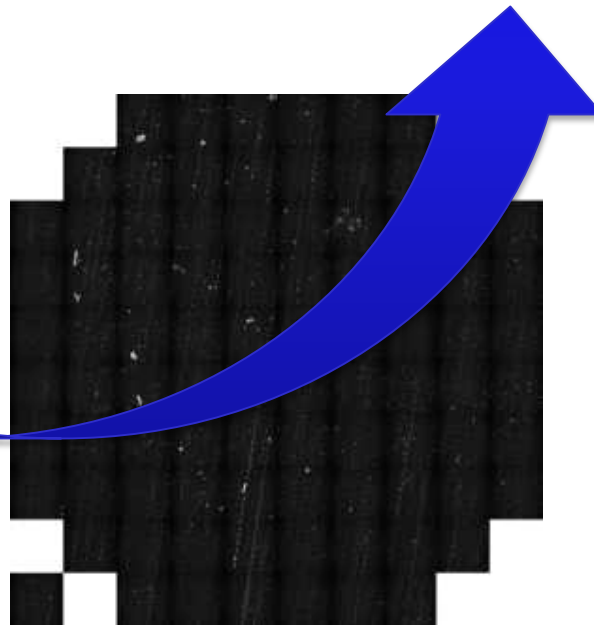
Bags



Stopper Bags have an impact or reflect stopper quality



Fibres collected from one bag; 375 particles > 25 μm

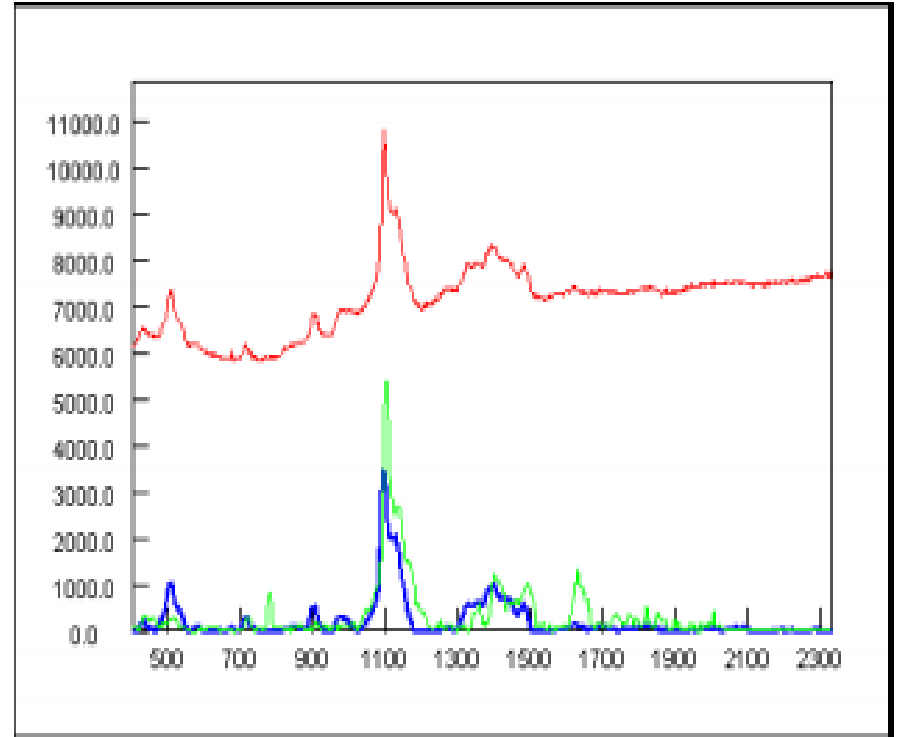


Fibres collected from one bag; 45 particles > 25 μm

Test Procedure:
Bag rinsed with 250 ml water / SDS, filtration, counting



Fiber → Paper



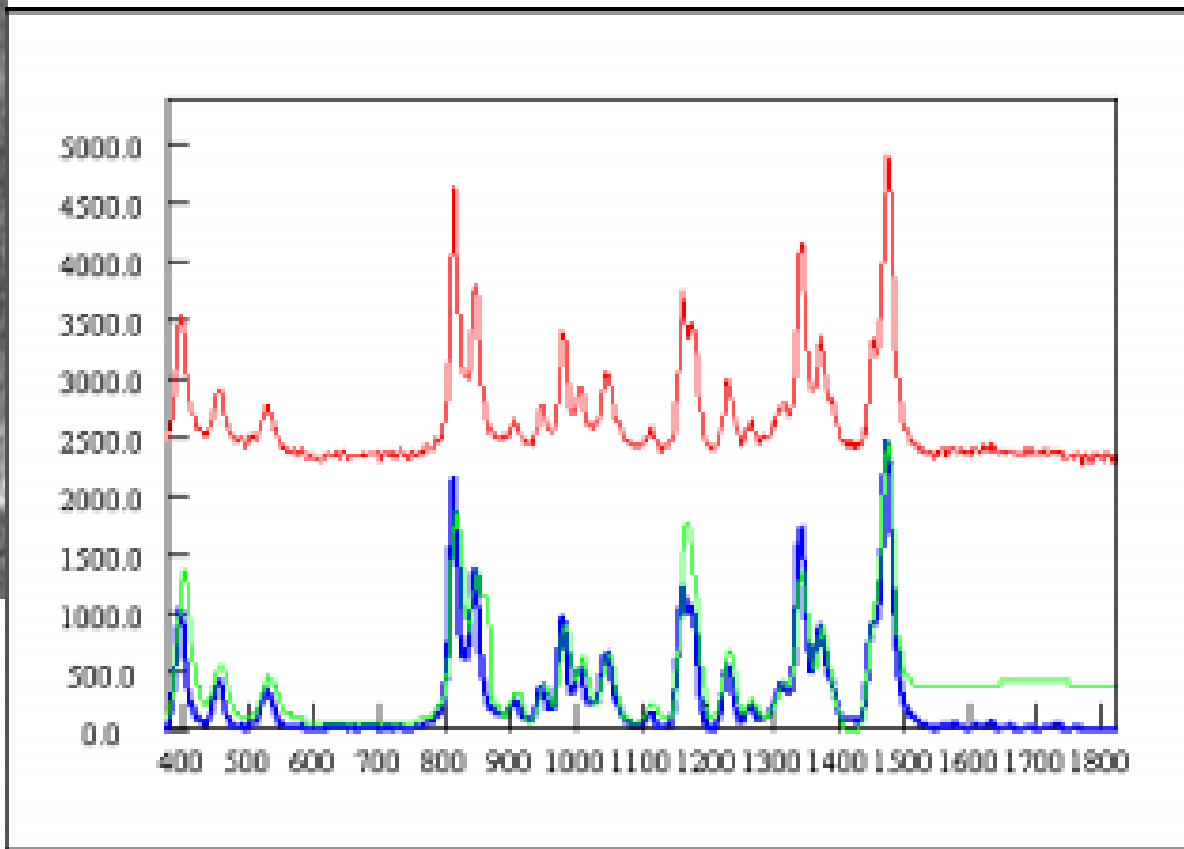
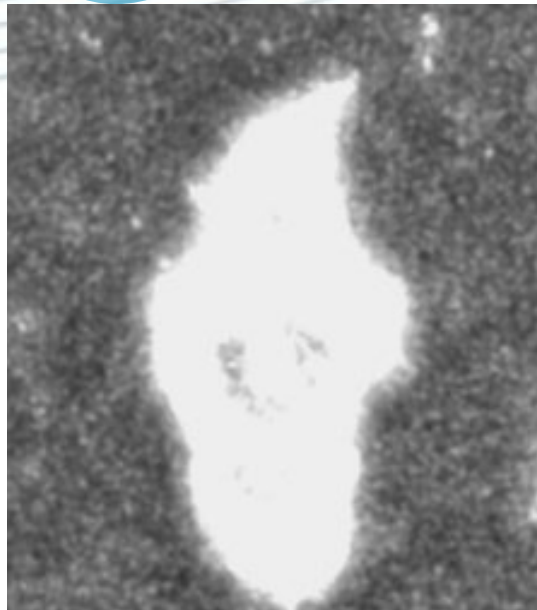
RESULT: Cellulose [Paper]

RANK: 882, S/N: 39.2

14.02. Particle: (x,y): 3485.6, 869.5 Length: 30.6, Class: 4, L/W: 2.3,



Particles → Rubber

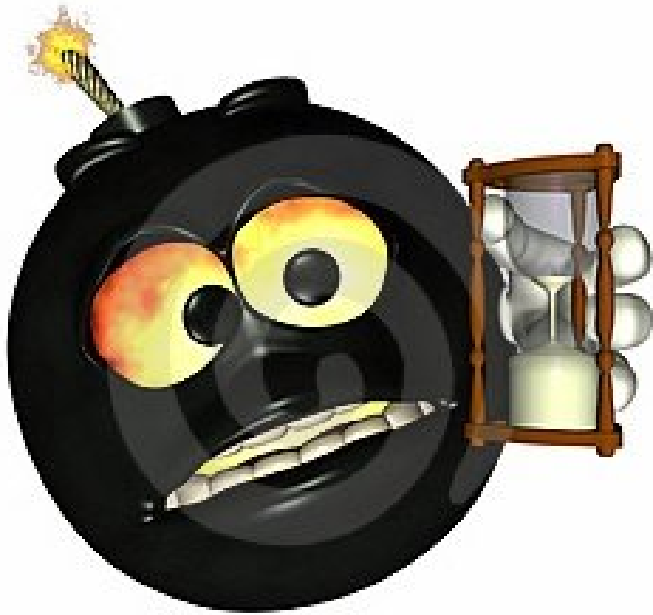


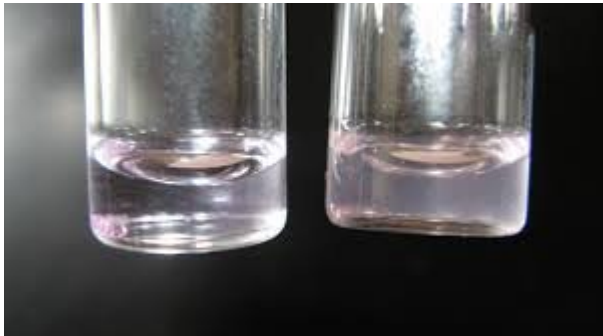
RESULT: Rubber, RANK: 974, S/N: 30.3



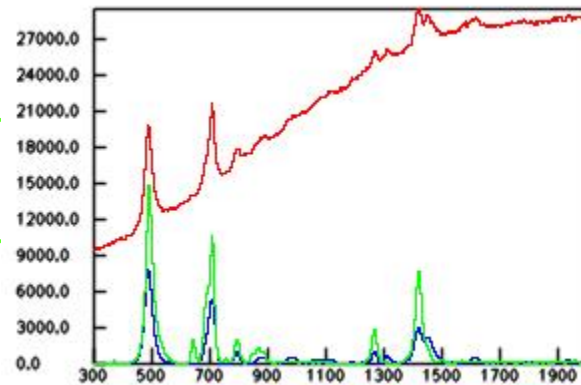
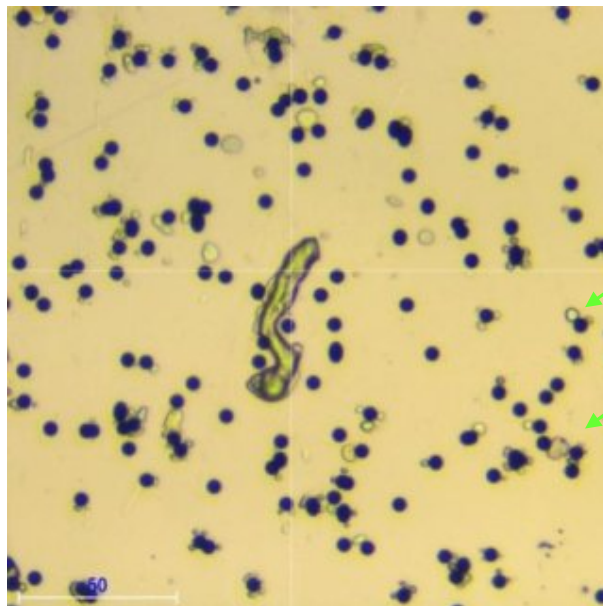
Time bombs

- 1: Increase of rejects with time
2. Chemical reactions taking some time
 - Silicone oil on stoppers: Agglomeration of Proteins
 - Coatings
 - Glass delamination



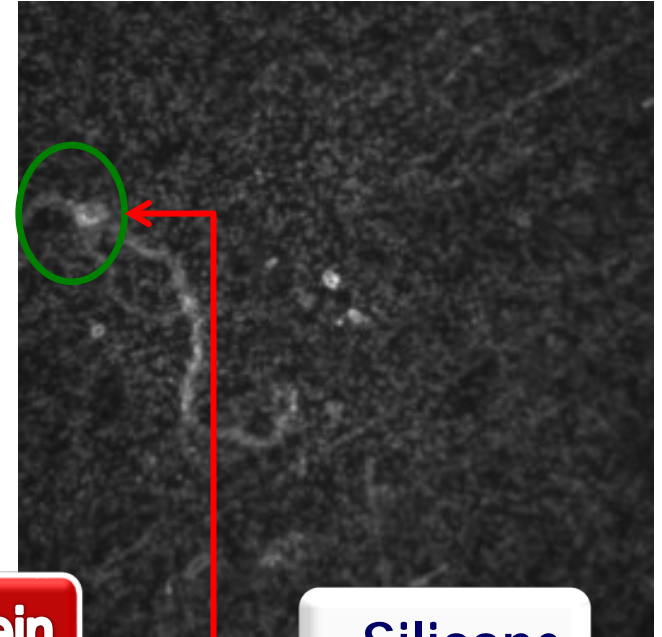
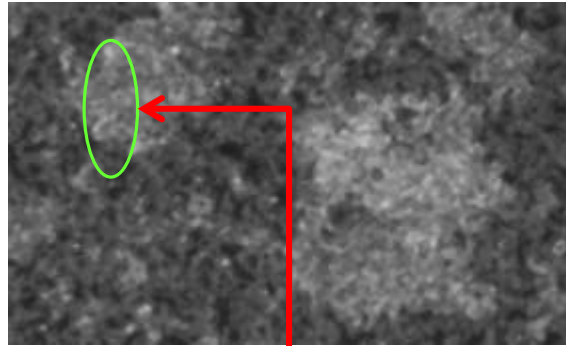
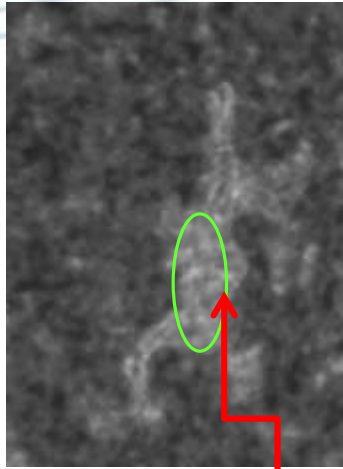


Observation of haziness and aggregates in a new a new batch after slight process change





Protein and Silicone

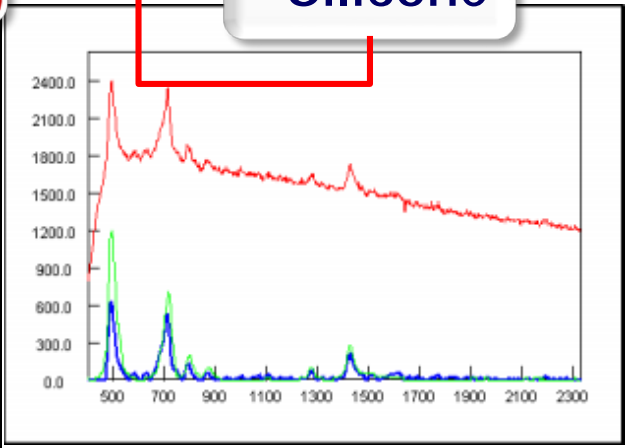
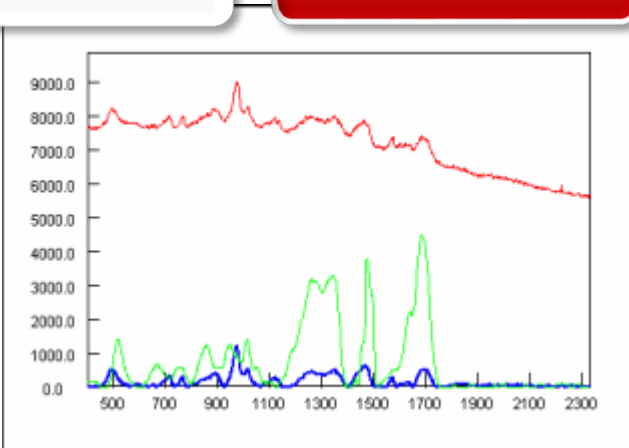
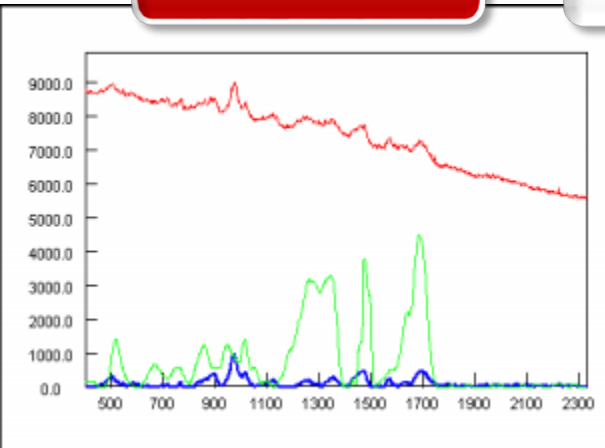


Protein

Silicone

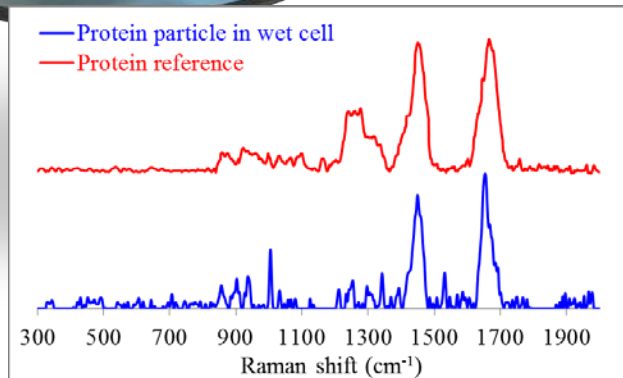
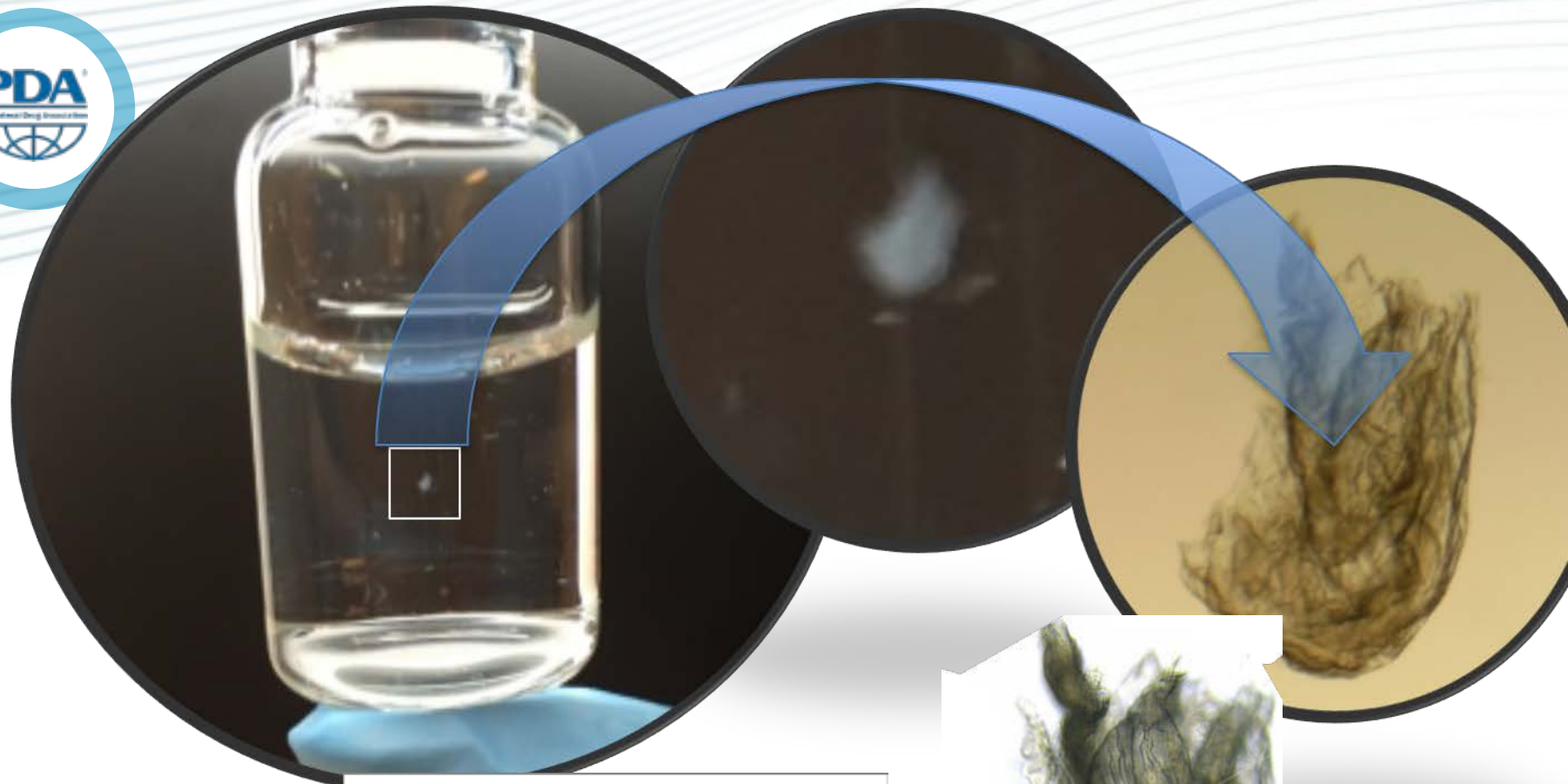
Protein

Silicone

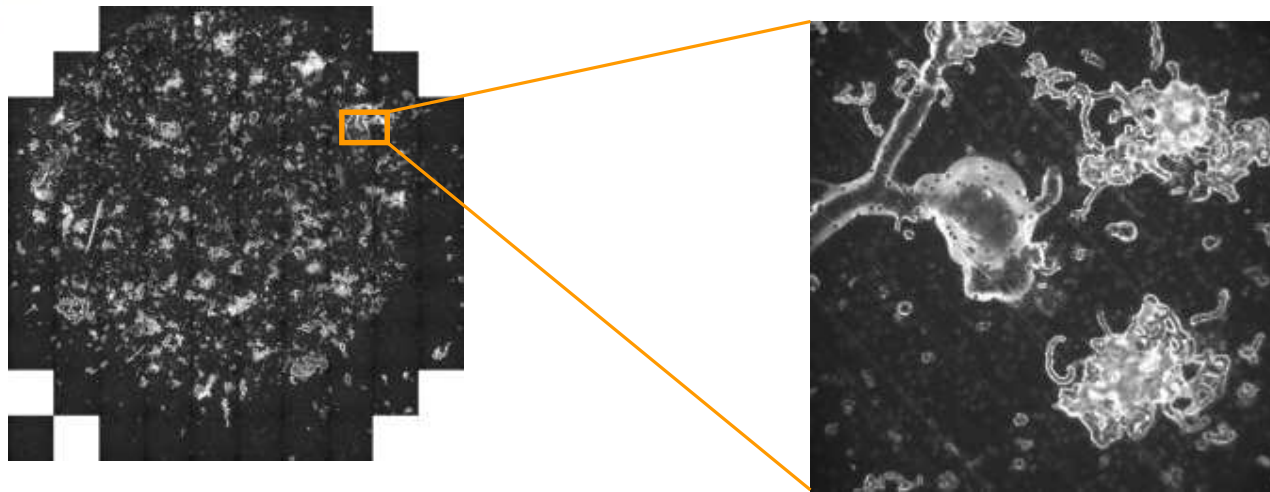




VISIBLE INHERENT PARTICLE



Increasing number of rejects in visual inspection with time



Size and Substance Distribution of Measured Particles					
Substance	Number	Size Distribution [μm]			
-	-	≥ 10	≥ 25	≥ 50	≥ 100
Proteine	6	0	0	1	5
Fluorescence	18	0	0	1	17
Coating	185	23	44	32	86
<i>Skipped particles</i>	3058	2142	657	232	27
All particles	3267	2165	701	266	135



thank you for your attention !

More information:

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contact: