



Particles in Packaging Components: Numbers and Chemical Compositions

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Overview

- Motivation
- Technology
- Top Ten visible / sub-visible
- Packaging / syringes
- Time dependent particle phenomena
- Particles applied to the patient
- Summary



What are the most common types of particles found during visual inspection?

	2014	2008	2003	1996
Lint/Fiber	1	1	1	1
Glass	2	2	2	2
Product Related	3	3	4	3
Rubber/Elastomer	4	4	5	5
Metal	5	5	3	4

PDA Survey 2014



Motivation

- Particles are treated differently in regulation depending on size (USP 788, 790)
- Separate treatment of particles might hide the link between visible and sub-visible particles
- What are main components of visible and sub-visible contamination
- Are visible particles found in parenteral drugs similar to sub-visible particles in terms of material ?
- Do they have the same source ?



Technology

ID of visible particles is a standard procedure accessible in many laboratories by microscopy, SEM/EDX, IR spectroscopy, Raman spectroscopy

ID of sub-visible particles: same technologies usable but consider differences:

- More particles !
- Size is small: weaker signal, IR of limited use

Use of highly automated high throughput systems commercially available for SEM/EDX and Raman microscopy. Throughput ~ 100-1000 particles / hour

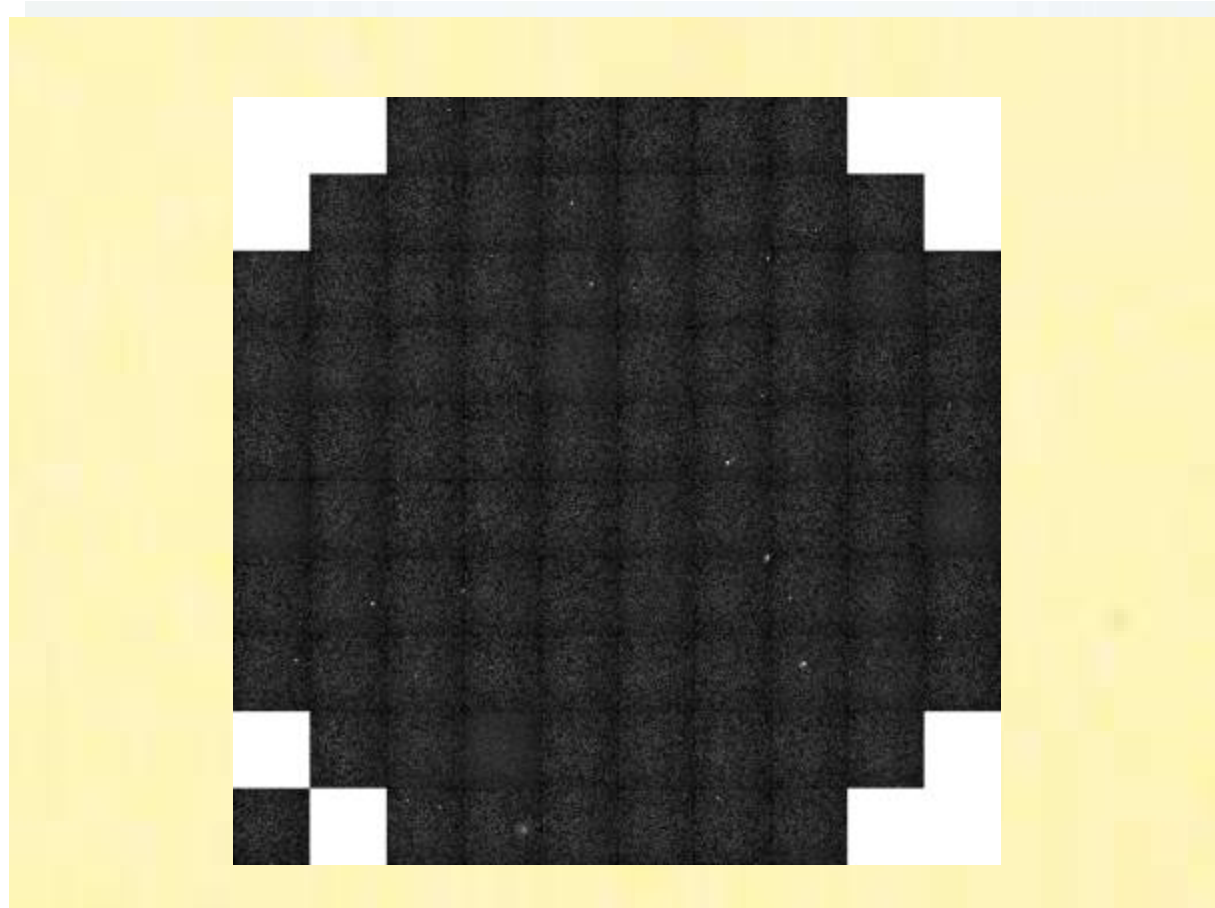
Routine ID of sub-visible particles since 2004

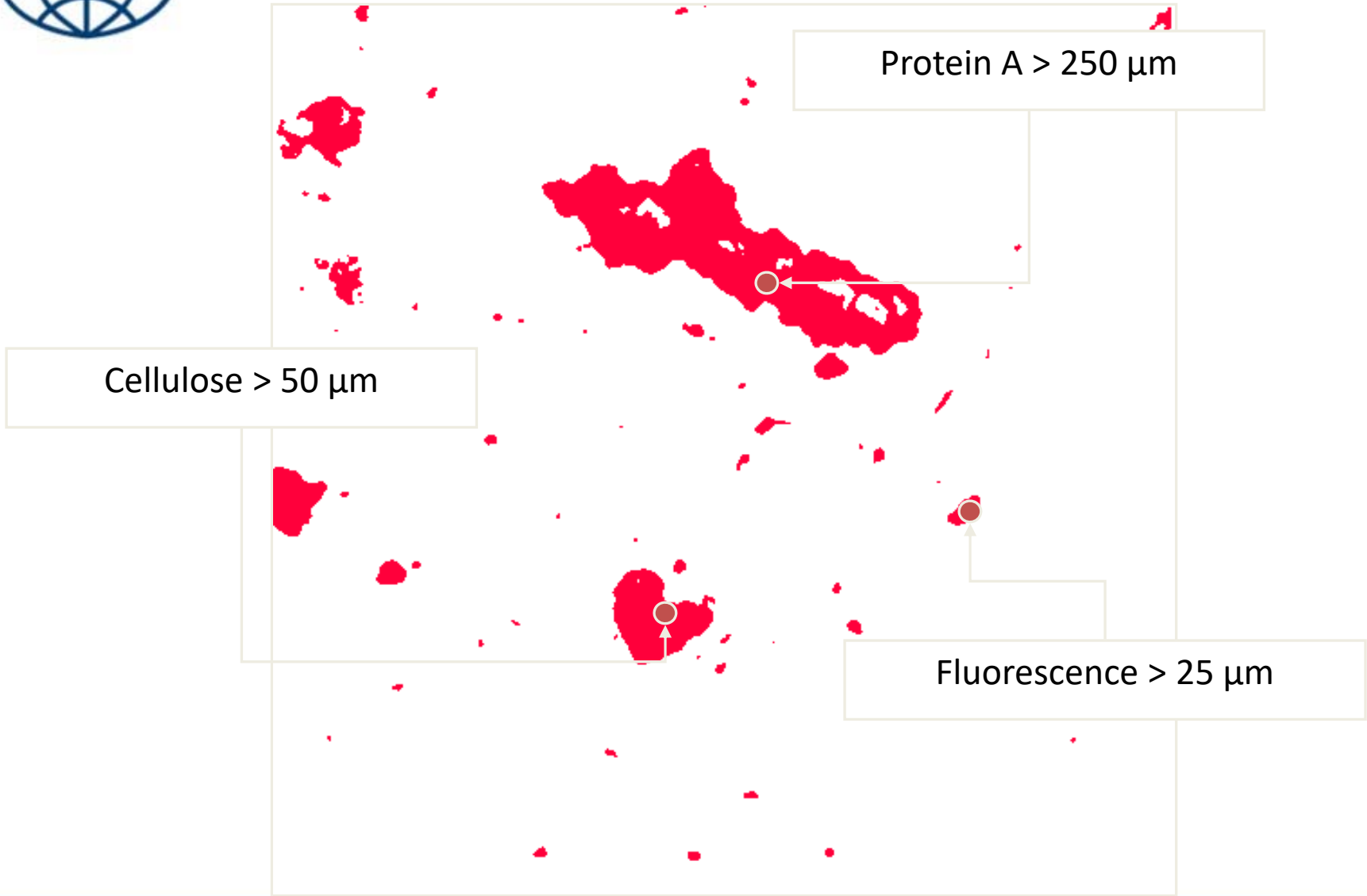
Database of ~ 2.150000 identified particles > 10 μm



Filter → Scan Fields

- Membrane (0.8 μm , 3 μm) RAMAN inactive





Substance	Number	Size Distribution [μm]		
		>10	>25	>100
Graphite	45	1	44	0
Titaniumoxide Anatase	12	12	0	0
Fluorescence	32	23	9	0
Unidentified substance	5	5	0	0
Protein	99	81	16	2
Silicone / Protein mix	127	92	32	3
Silicone Oil	129	95	34	0
Analyzed Particles	449	309	135	5

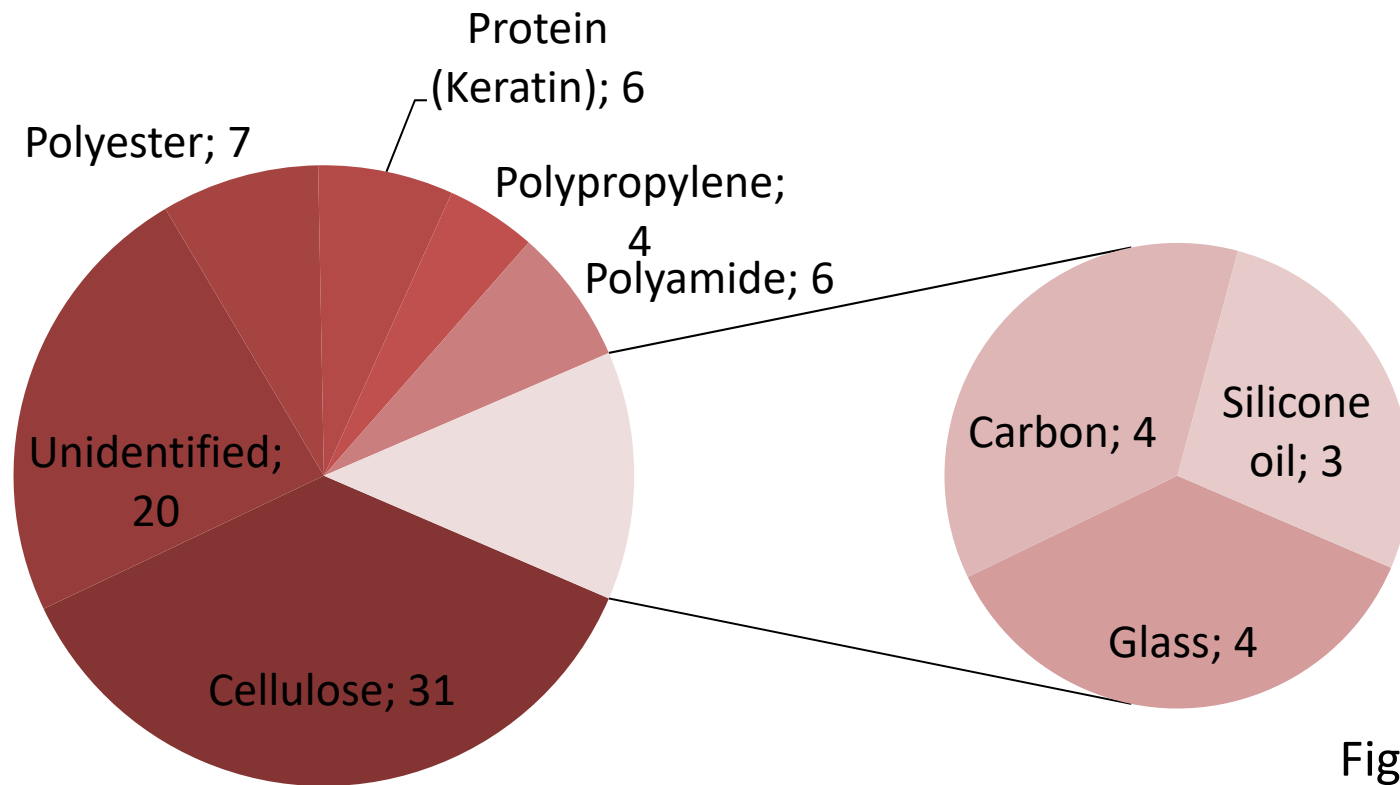
- Results are displayed as a table.
- 300 particles >10 are usually identified
- Channel > 10 and > 25 μm are treated as sub-visible channel



Top Ten

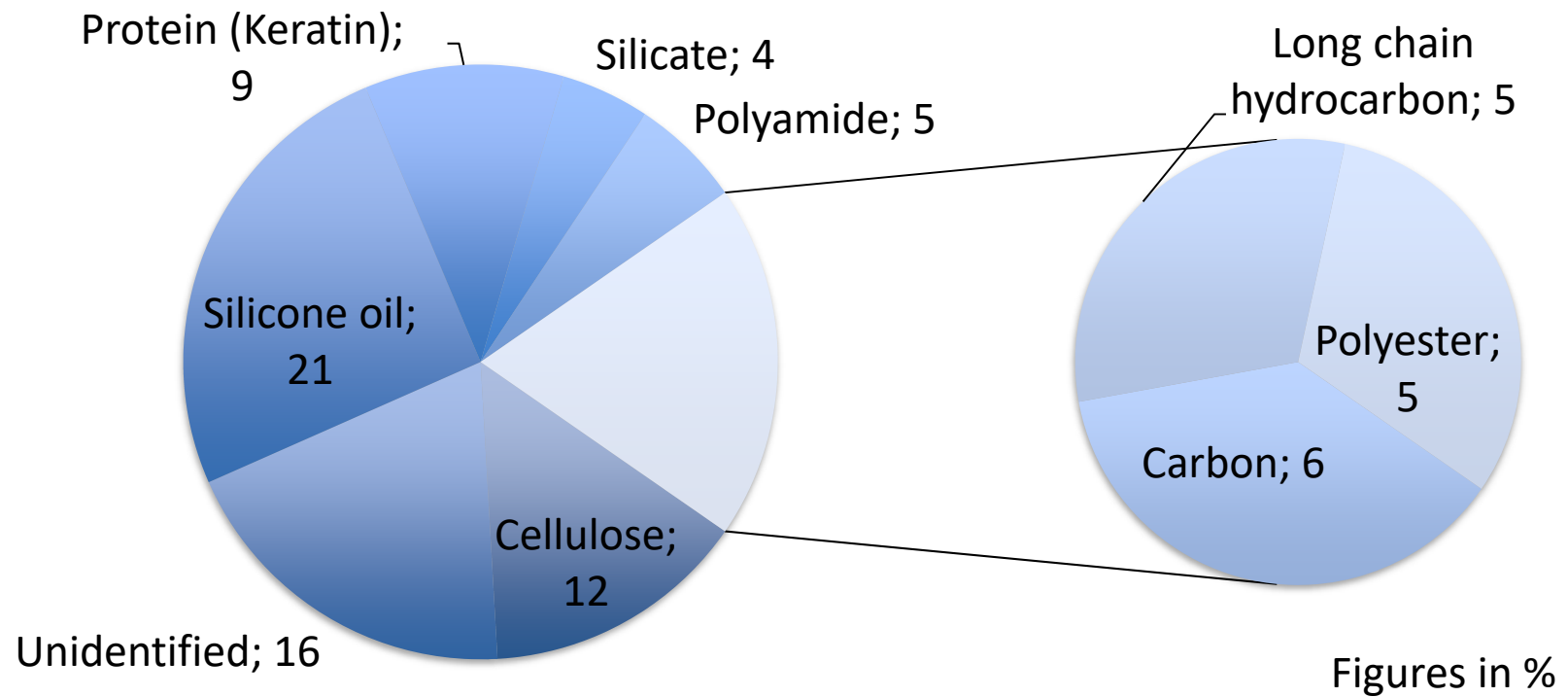
- Data was extracted out of ~11000 measurements
- Top ten data was filtered for special contamination like precipitation, protein agglomeration, delamination
- 200-500 particles per analysis are identified in the range of $> 10 \mu\text{m} - 2000 \mu\text{m}$

Visible Particles



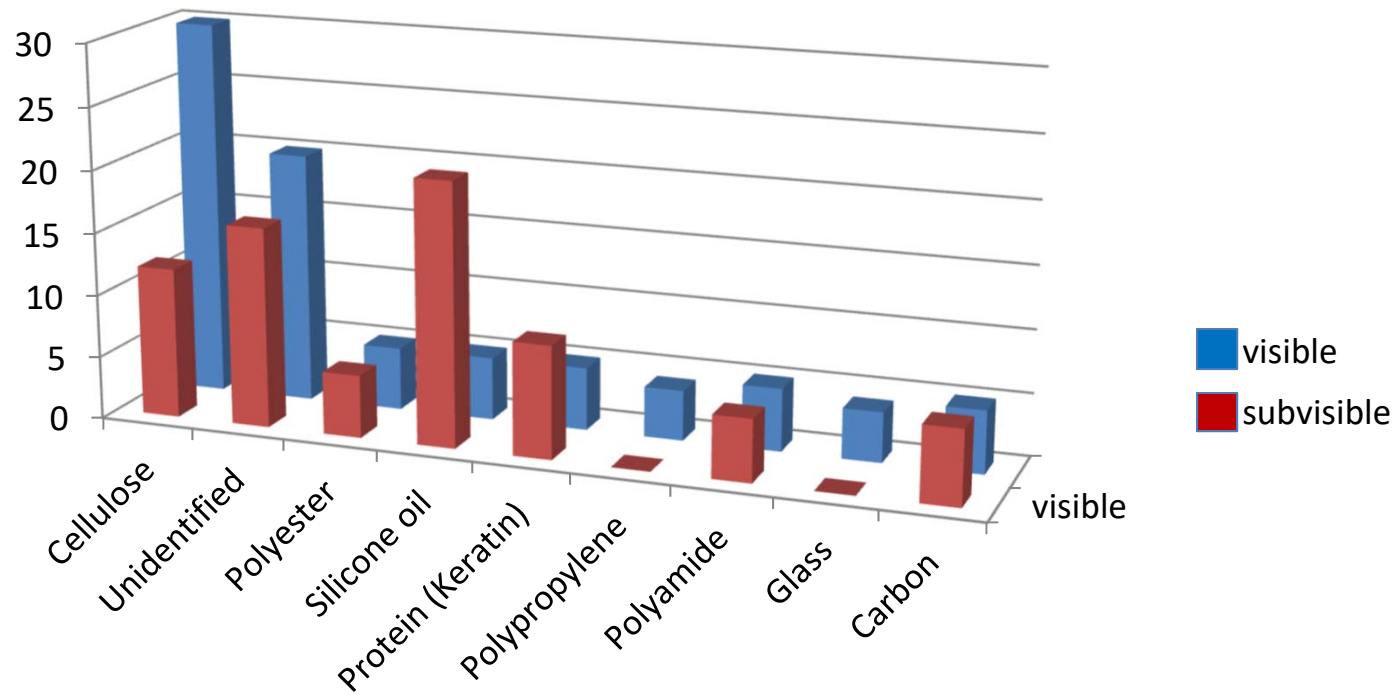
Figures in %

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

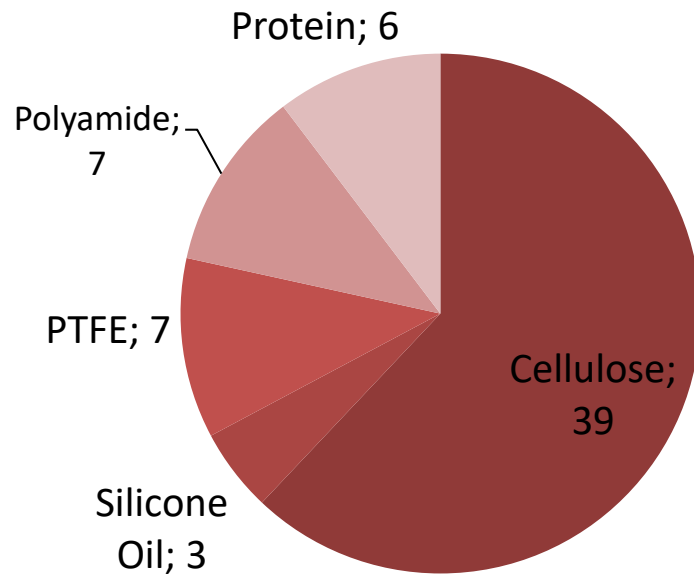


Silicone oil, Protein, Cellulose particles are the most often found contaminants

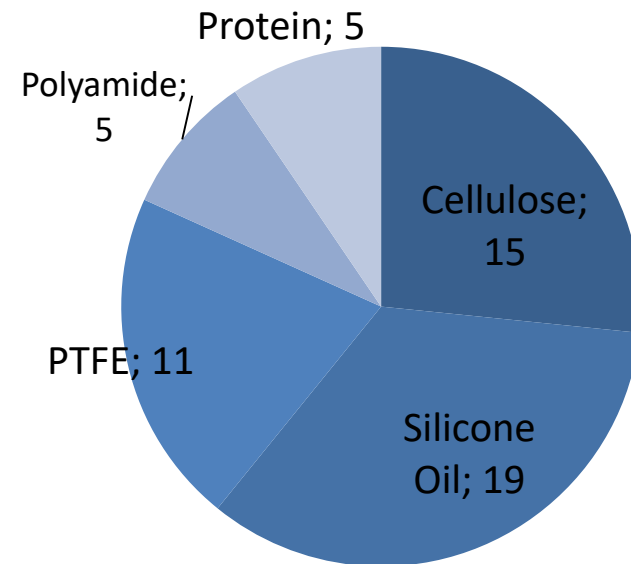
Comparison



Visible Particles



Sub-visible Particles



Top Ten in more detail

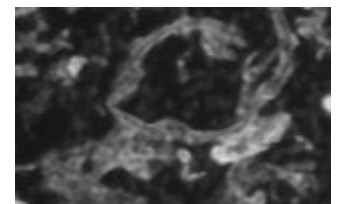
- **Cellulose:** mostly fibres
 - source: clothes, **towels**, wipers, autoclave paper



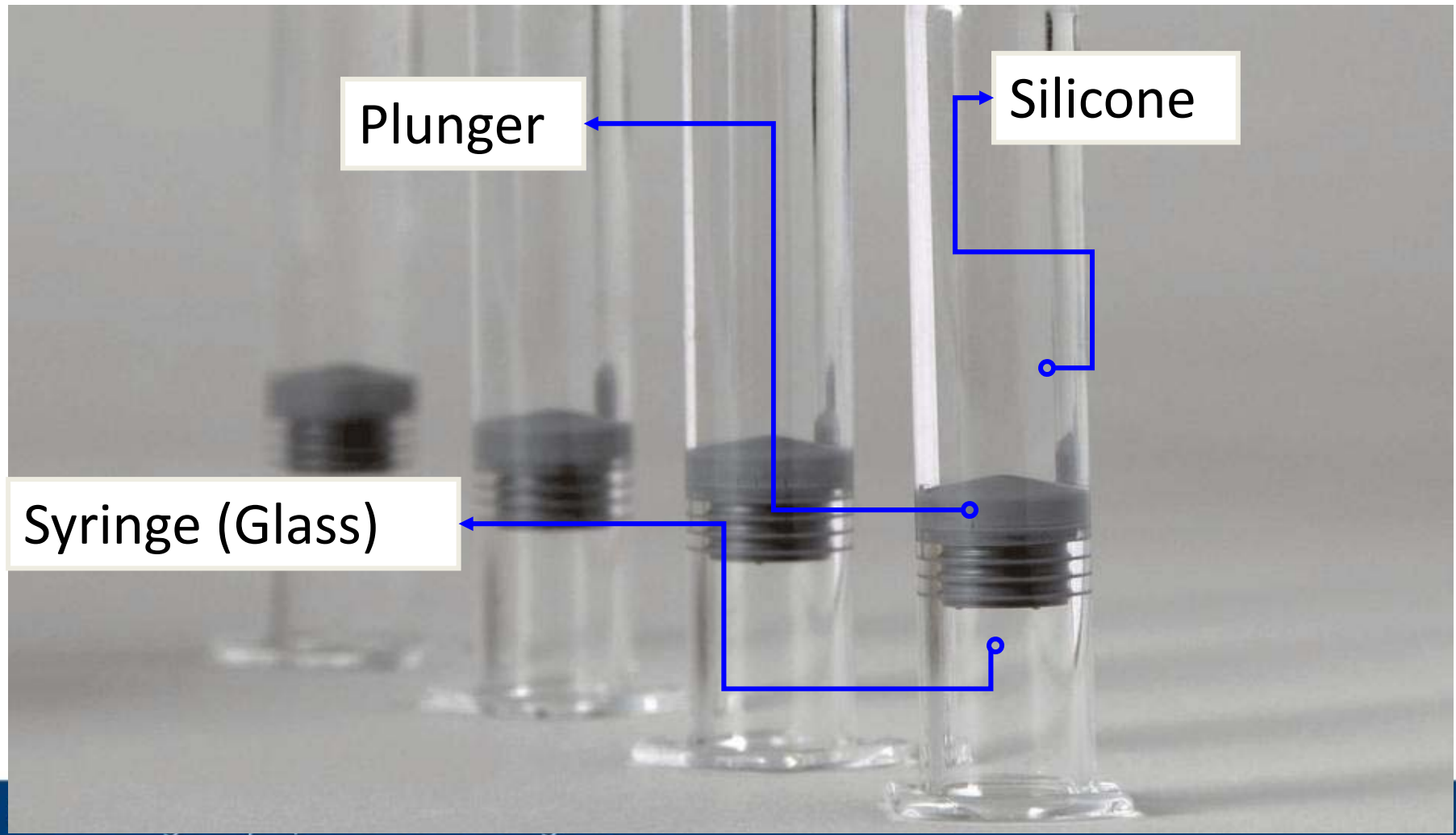
- **Longchain hydrocarbon**
 - source: rubber (stopper), PE (bottles)

Top Ten in more detail

- **Polyester:** fibres and particles
Source: Cleanroom clothes and defect filter
- **Protein:** mostly flakes
Source human dust, protein particles from protein solution were not counted
- **Silicone oil:** compact particles
Source: sealings, siliconisation



Control Your Packaging Material

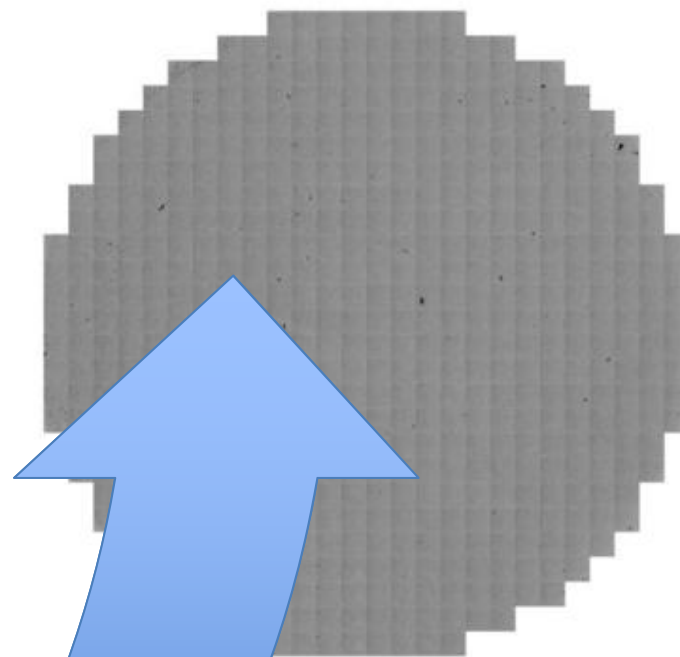
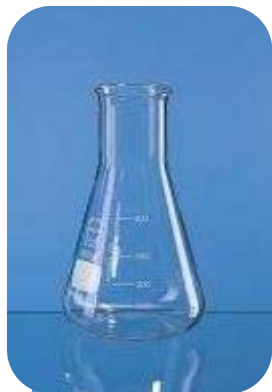


DEUTSCHE NORM

September 2004

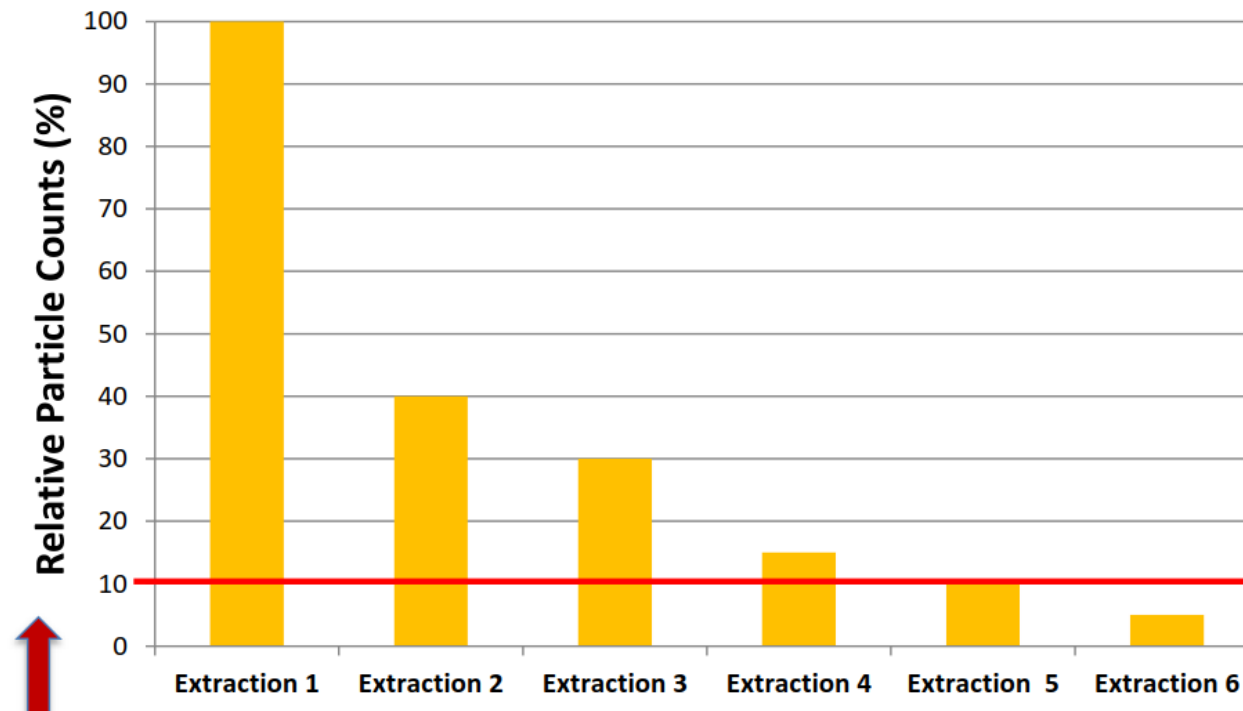
	DIN EN ISO 8871-3	<u>DIN</u>
ICS 11.040.20	<p style="text-align: right;">Ersatz für DIN ISO 8871/A1:1996-06</p> <p>Elastomere Teile für Parenteralia und für Geräte zur pharmazeutischen Verwendung – Teil 3: Bestimmung von herausgelösten Partikeln (ISO 8871-3:2003); Deutsche Fassung EN ISO 8871-3:2004, Text Deutsch und Englisch</p> <p>Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 3: Determination of released-particle count (ISO 8871-3:2003); German version EN ISO 8871-3:2004, text german and english</p>	

ISO 8871-3



- 2 methods for visible and subvisible particles similar to 788
- Sample size proportional to surface visible particles ~100 cm² Strong scatter in results => larger sample size
- No qualification required but would be beneficial

Extraction curve



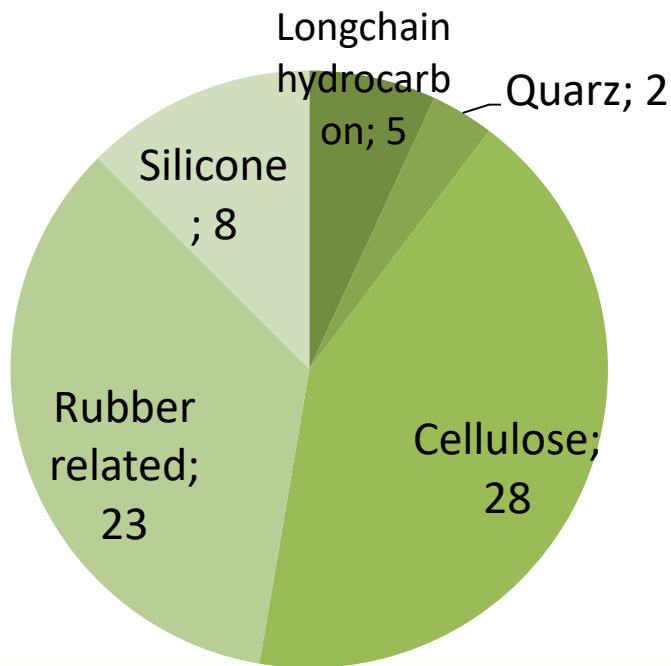
ISO 16232
Extraction is efficient when achieve 10% of starting value

K Wormuth Part in Inject 2017

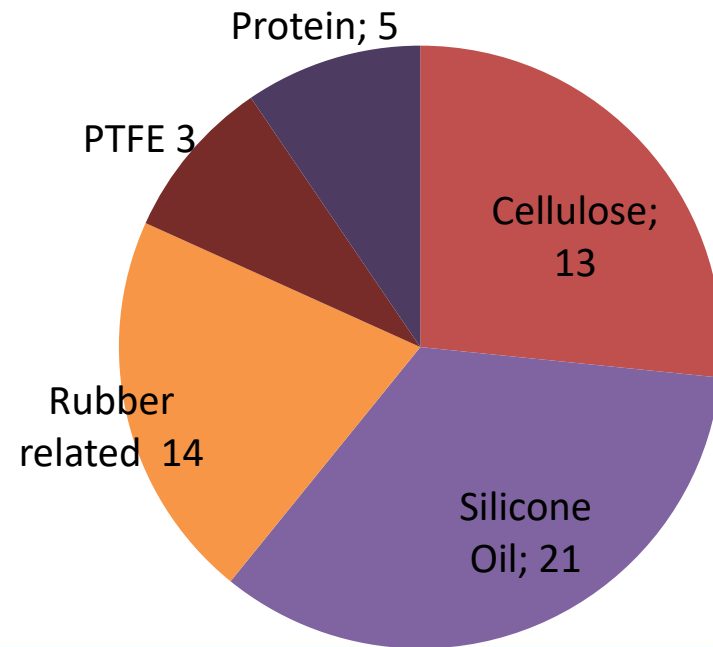
Stopper



Visible particles found in stoppers, extracted by rinsing and filtration



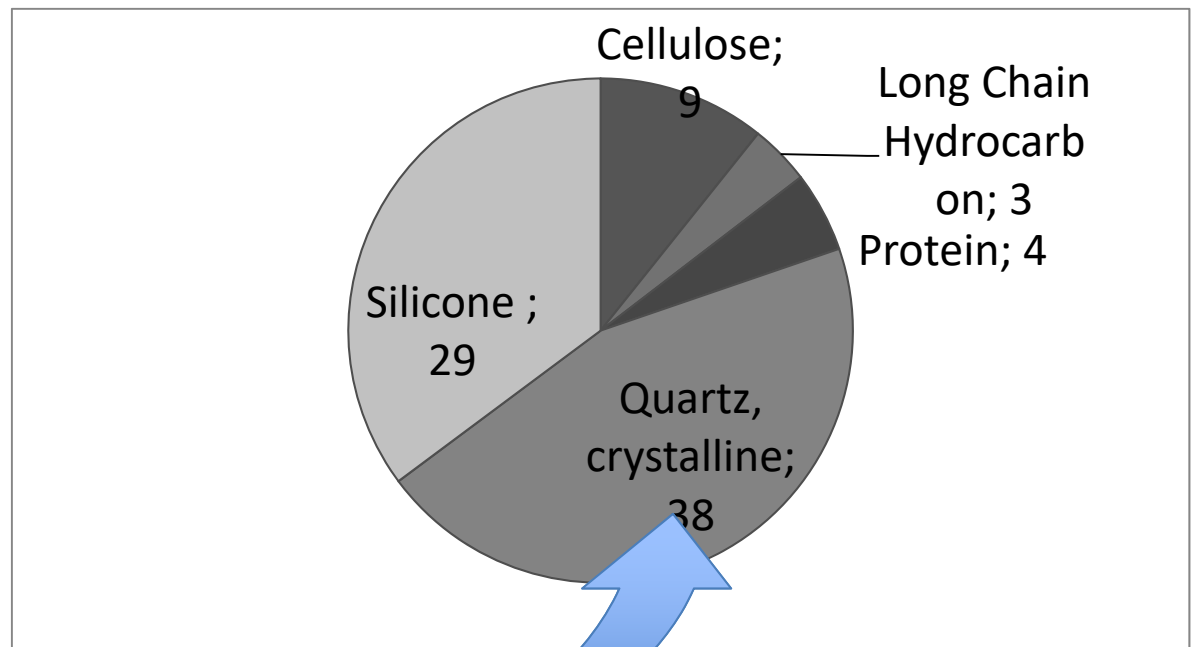
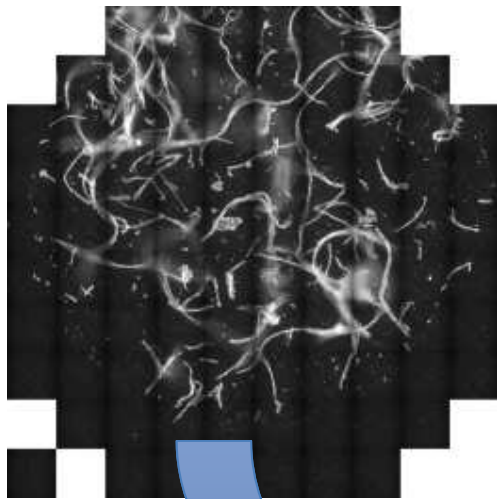
Sub-visible particles found in stoppers, extracted by rinsing and filtration



Bags might reflect stopper quality in terms of particles



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



Time dependent phenomena /Protein aggregation



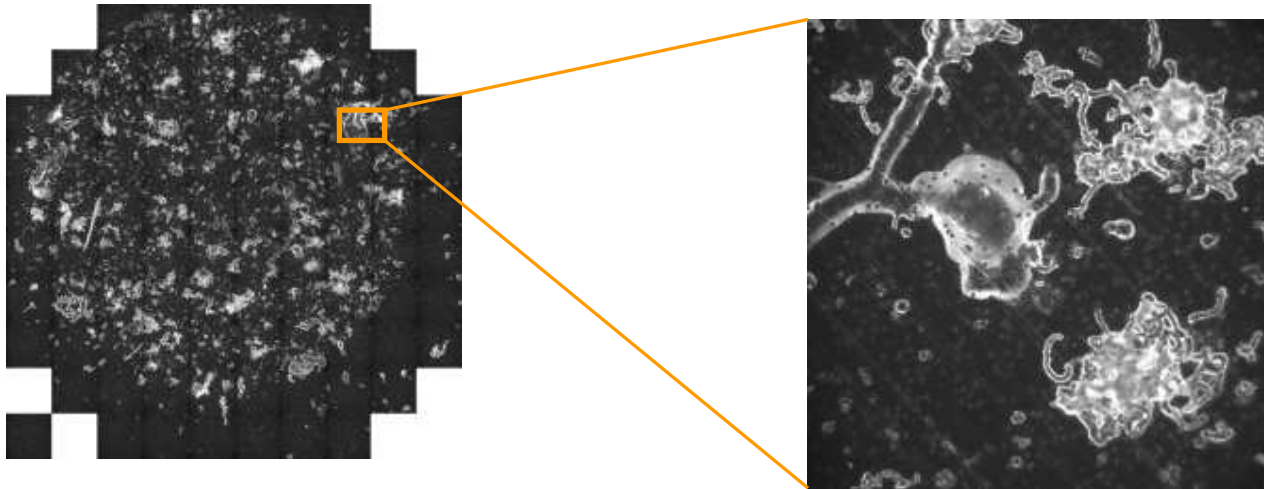
Substance	Number	Size Distribution [μm]			
		>2	>10	>25	>100
Graphite	46	1	1	44	0
Titaniumoxide Anatase	126	114	12	0	0
Fluorescence	107	75	23	9	0
Unidentified substance	120	115	5	0	0
Protein	622	523	81	16	2
Silicone / Protein mix	743	616	92	32	3
Silicone Oil	870	741	95	34	0
Analyzed Particles	2634	2185	309	135	5

Inherent particles or particles which develop over time might be detected early by monitoring sub-visible particles

Coating



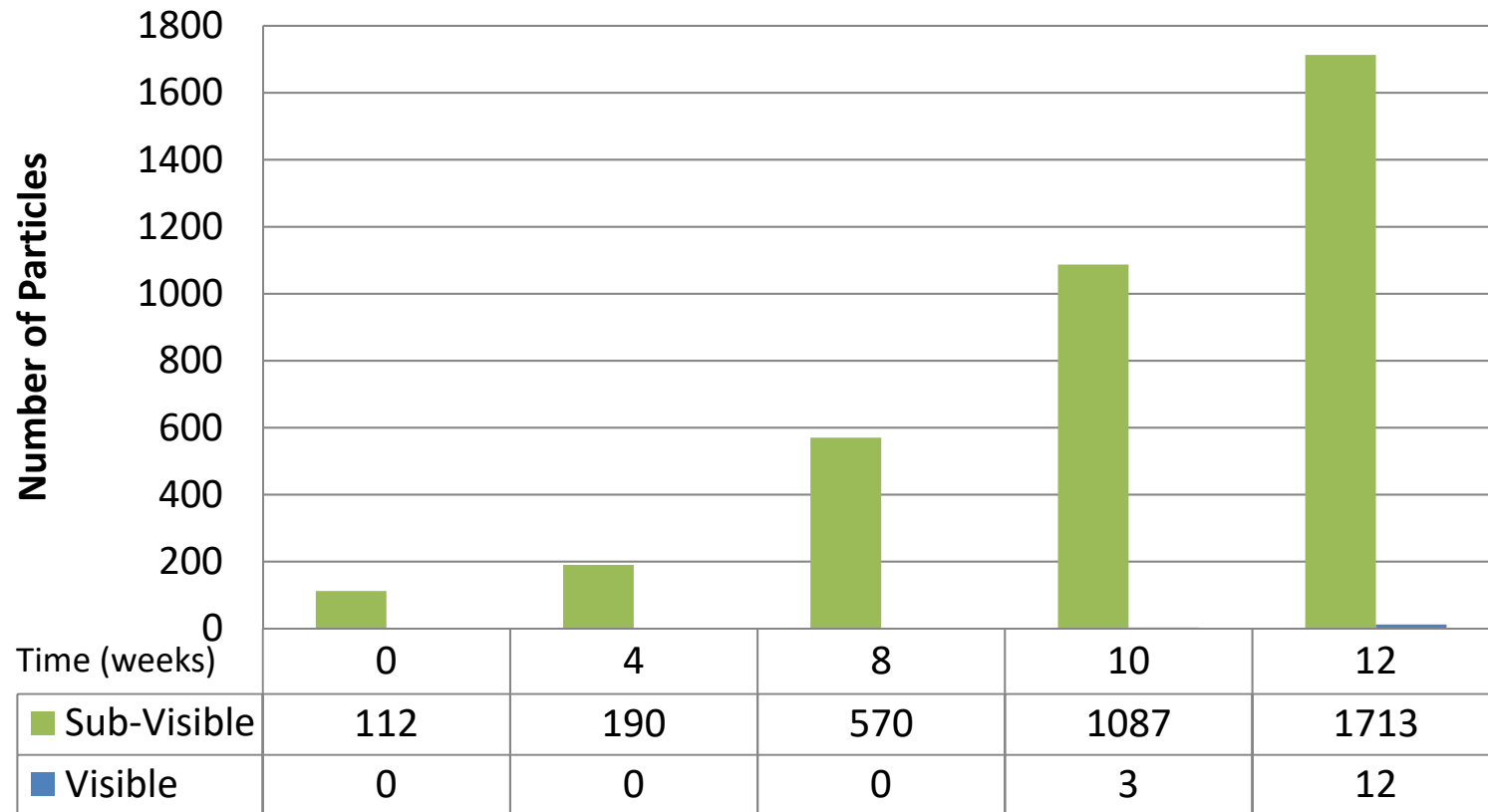
Increasing number of rejects in visual inspection with time



Size and Substance Distribution of Measured Particles					
Substance	Number	Size Distribution [µrn]			
-	-	>=10	>=25	>=50	>=100
Proteine	6	0	0	1	5
Fluorescence	18	0	0	1	17
Coating	1885	1223	444	132	86
All particles	1909	1223	444	134	108

Inherent particles or particles which develop over time might be detected early by monitoring sub-visible particles

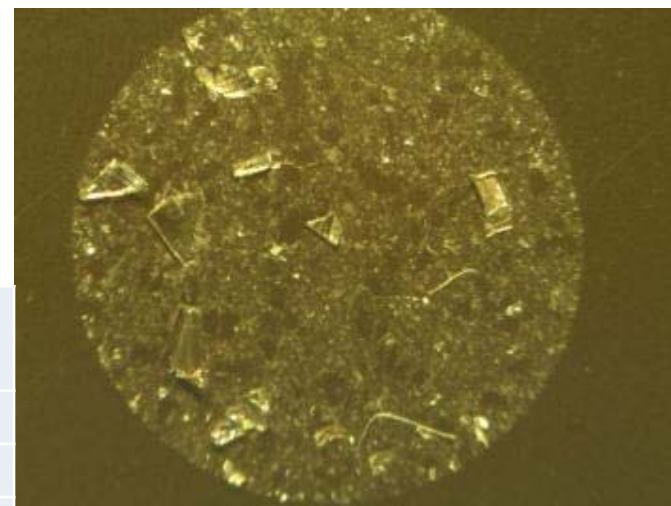
PTFE Coating Particles



Early detection of coating / stopper incompatibility by detection of PTFE particles

Infusion Tubing






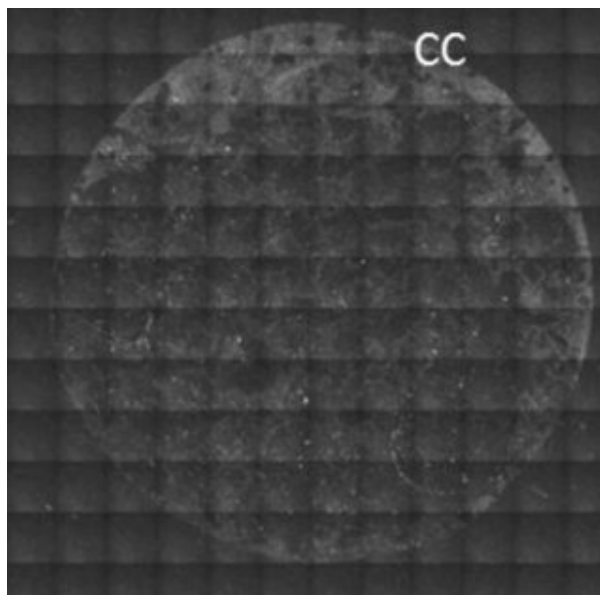
Size and Substance Distribution of Measured Particles				
Substance	Number	Size Distribution μm]		
		5 to <10	Subvisible	Visible
Glass	1766	1163	621	12
Polyester	106	0	105	1
All particles	1872	1163	726	13

- Majority of particles in ampoule samples after breaking the ampoule is glass.
- Other particles are hard to classify.

July 2013

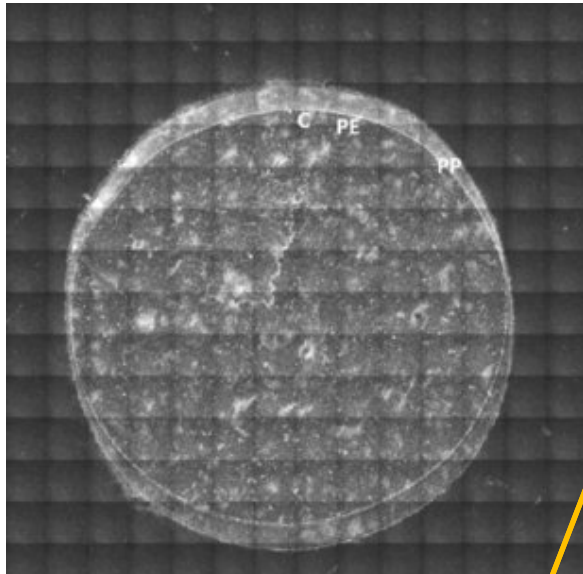
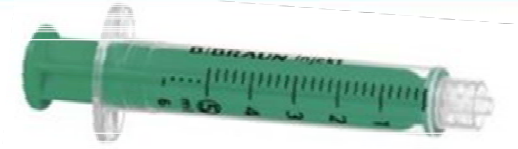
	DIN EN ISO 8536-4	
<p>ICS 11.040.20 Supersedes DIN EN ISO 8536-4:2011-01</p> <p>Infusion equipment for medical use – Part 4: Infusion sets for single use, gravity feed (ISO 8536-4:2010 + Amd 1:2013); English version EN ISO 8536-4:2013 + A1:2013, English translation of DIN EN ISO 8536-4:2013-07</p>		

Infusion Set Tubing



Substance	Number	Size Distribution [µm]		
		10 to <25	25 to <50	>=100
All particles	207	196	11	0
Unidentified	48	44	4	0
Calcium Carbonate	9	9	0	0
Fluorescence / Protein	58	55	3	0
Polystyrene	2	2	0	0
Longchain hydrocarbon	39	36	3	0
Cellulose	3	0	3	0
All analyzed particles	159	146	13	0

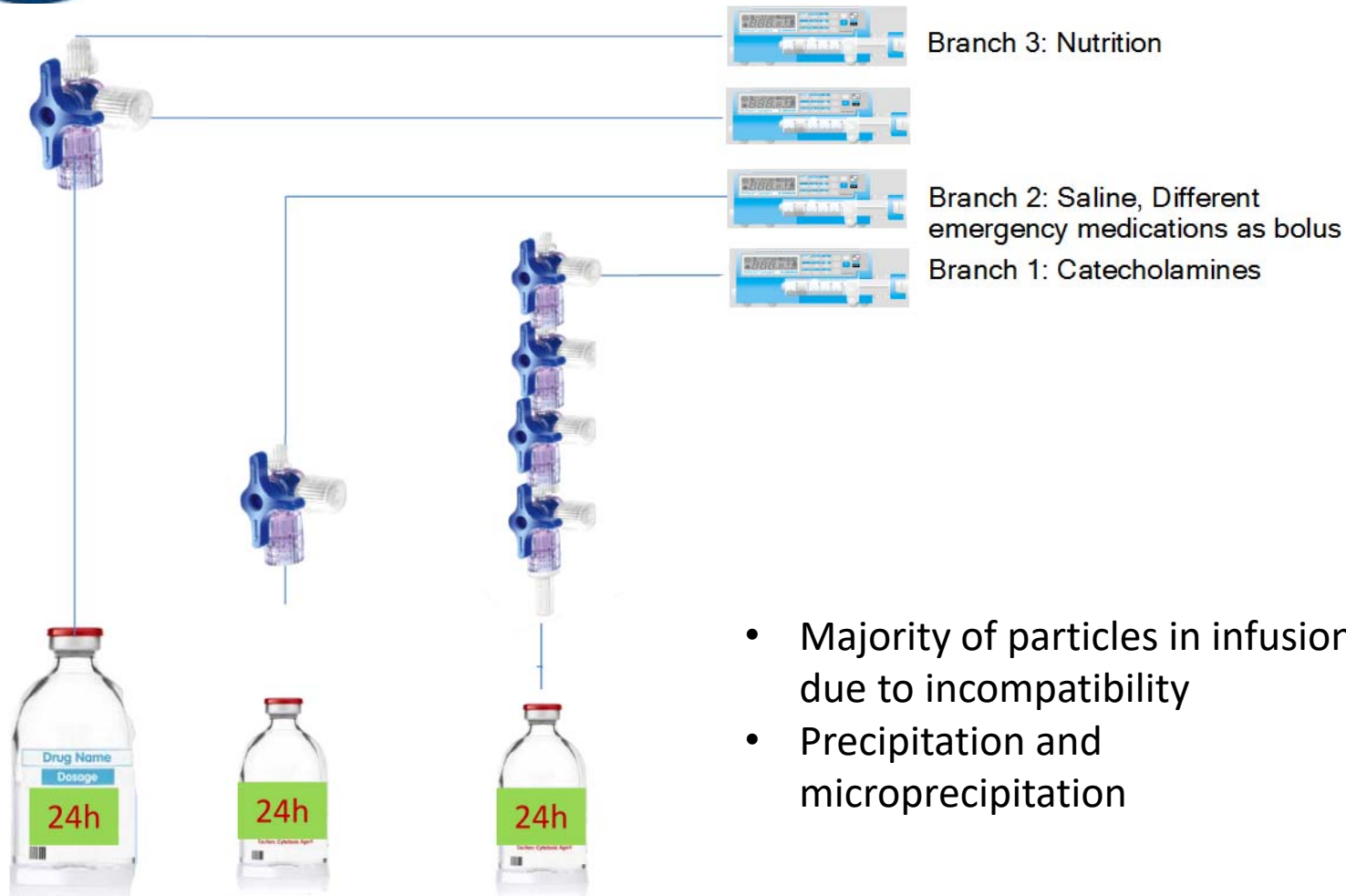
Syringe silicone free



Substance	Number	Size Distribution		
		10 to <25	25 to <50	>=100
All particles	1760	1635	113	12
Erucamide	154	60	86	8
Fluorescence	30	10	18	2
Polyethylene	7	3	4	0
Cellulose	3	1	1	1
Long Chain Hydrocarbon	3	1	2	0
Polypropylene	1	0	0	1
Background	2	0	2	0
All analyzed particles	200	75	113	12

Might be slipping agent

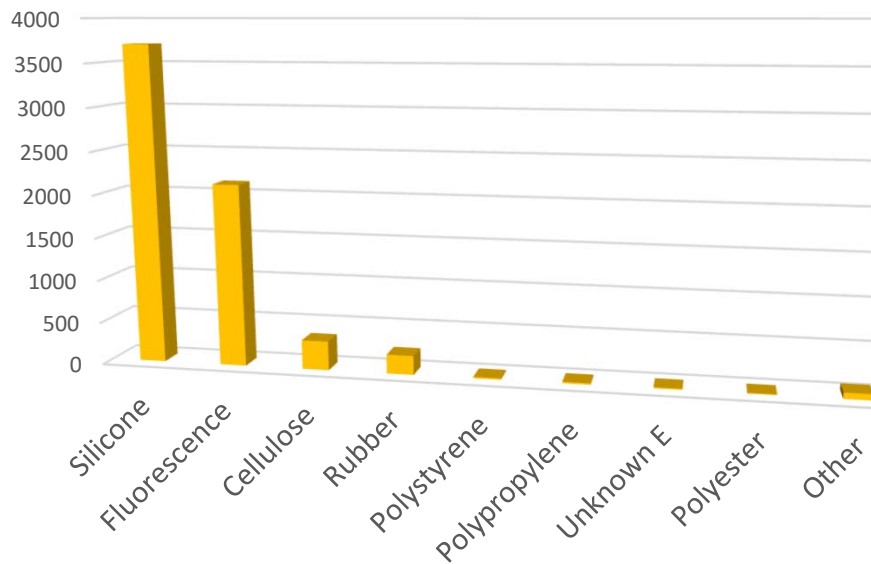
Particles in infusions



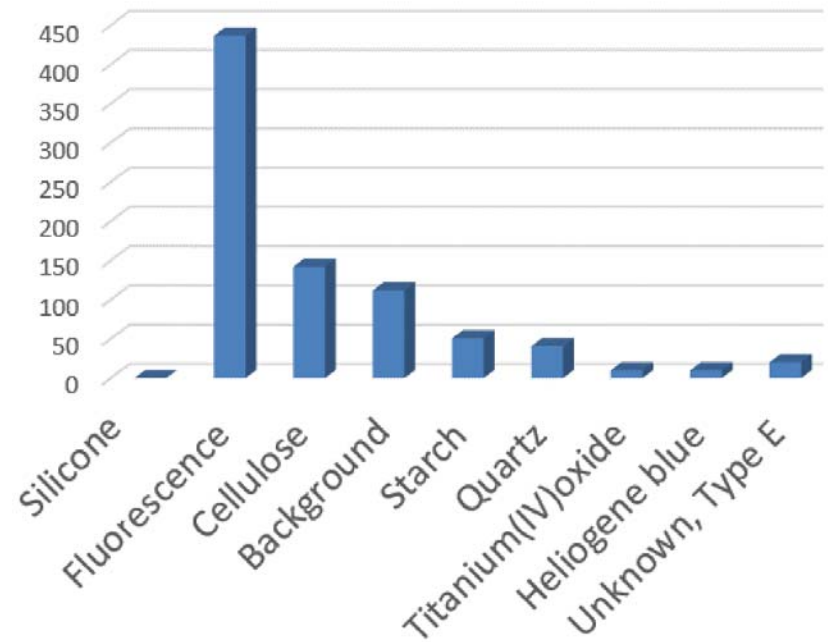


Which particles are reduced ?

Catecholamine infusion

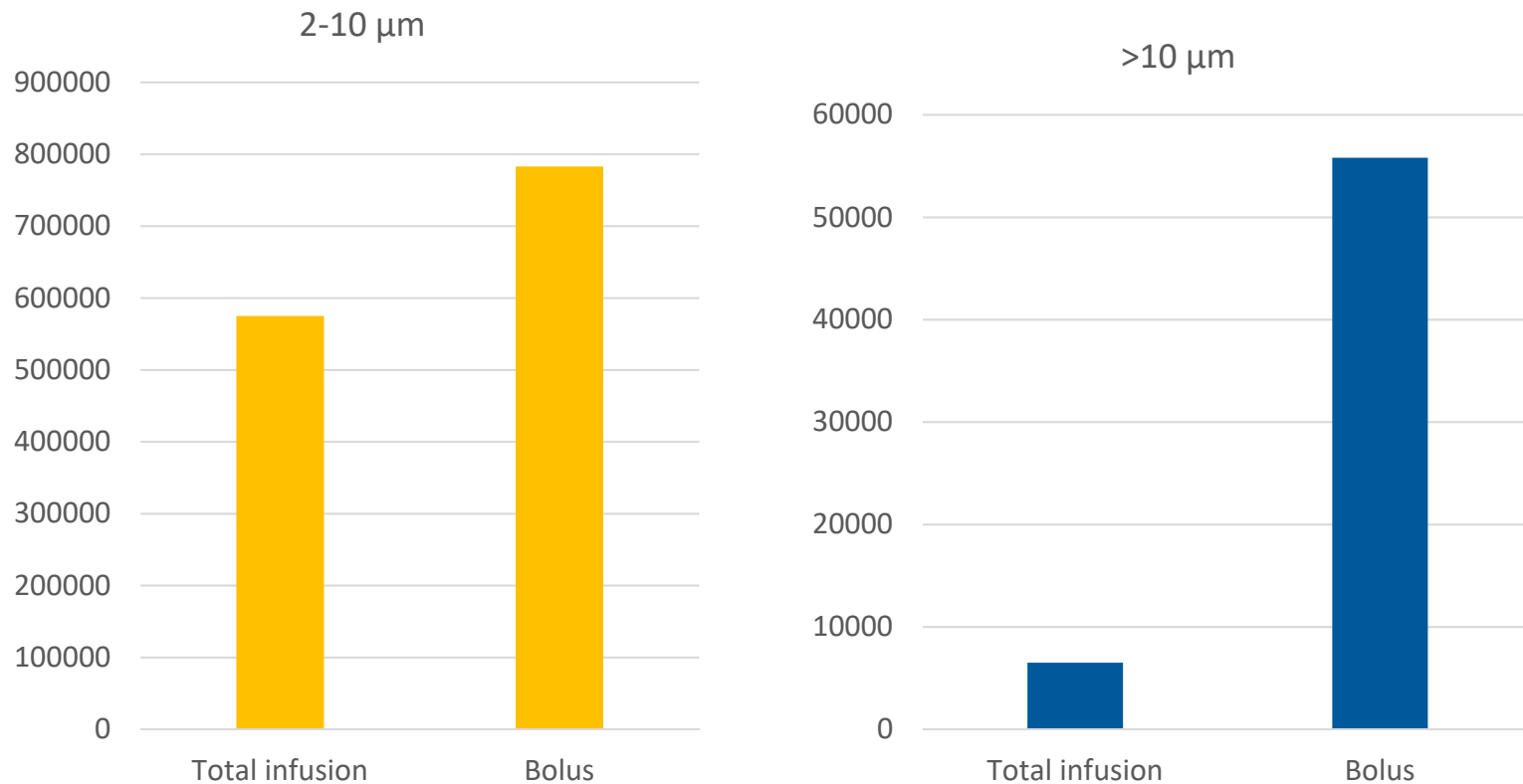


Catecholamine infusion: Use of Filter



88% reduction of particles >2 μm

Bolus injection



Dramatic increase of particles. Particle numbers of the total 3 day infusion compared with one bolus injection

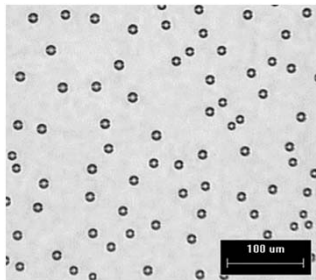
Syringe



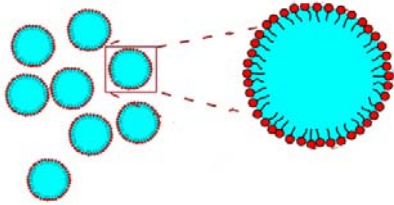
Usual silicone content 50 ml syringe:
1,5 – 3 mg (silicone determined by reflectometry)



Loss of silicone due to plunger movement:
0,1 to 0,9 mg (silicone determined by reflectometry)



Amount is sufficient for the release of
100000 – 900000 silicone droplet (10 μm
size)



Process for stabilization eg. adsorption
into water/oil interface is necessary



Summary

- Differences of the composition between sub-visible and visible particles found in drugs are observable: main components are similar but quantity changes
- 60-70 % of particulate contamination can be attributed to a small number of compounds
- Many contaminations can be related primary packaging. The statistical fingerprint might help to find the source.
- Time dependent particle problems like, protein aggregation and decoating of stoppers, delamination might an be detected early with the help of sub-visible particles
- Different kinds of use of a drug should be considered for the particle load applied to the patient

