Testing of Pre-filled Syringes

Siliconization, Visual Inspection

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Outline

- Introduction of rap.ID
- Motivation for Siliconization and Silicone layer control
- Visual Inspection (USP<790>, USP<1790>)
- Technology, advantages and comparison of lubrication control and investigation strategy
- Examples of silicone thickness and distribution and stability measurement in pre-filled syringes and baked-on cartridges
- Relationship between inhomogeneous silicone oil distribution and protein aggregation

rap.ID group

rap.ID GmbH → Headquarter Berlin, Germany:

R&D and Manufacturing

Contract Testing, Service Global

rap.ID Inc. → Monmouth Junction, NJ, USA:

Contract Testing, Service US

rap.ID Quality Support

Instrument Manufacturing:

- Particle Explorer → ID of particles, main application: Foreign Particulate Matter
- Layer Explorer → Lubrication control in pre-fillable syringes

FDA inspected, GMP compliant Contract Testing Services

- Industrial Forensics + particulate matter control concepts/training, Particle Counting, Visual Inspection…
- Combination Product testing: e.g. ISO 11404-4 Annex E, D and correlation with Layer Explorer, Stability Syringe Testing after ISO 11608 and More

Standard in 10 years

GERRESHEIMER BD MedImmune
SCHOTT glass made of ideas
Nuova Ompi glass division Stevanato Group
NIPRO AMGEN REGENERON
TEVA TEVA PHARMACEUTICAL INDUSTRIES LTD.
SANOFI abbvie GILEAD
Genentech NOVARTIS
Alcon gsk GlaxoSmithKline Cilag Pfizer
Roche

Regulatory, safety and quality

Example CFR Guidelines and ISO

PMOA (primary mode of action) triggers → 21 CFR 3.2 (e) CBER / CDER

- Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches

Tests and Procedures related to the functionality of the delivery system

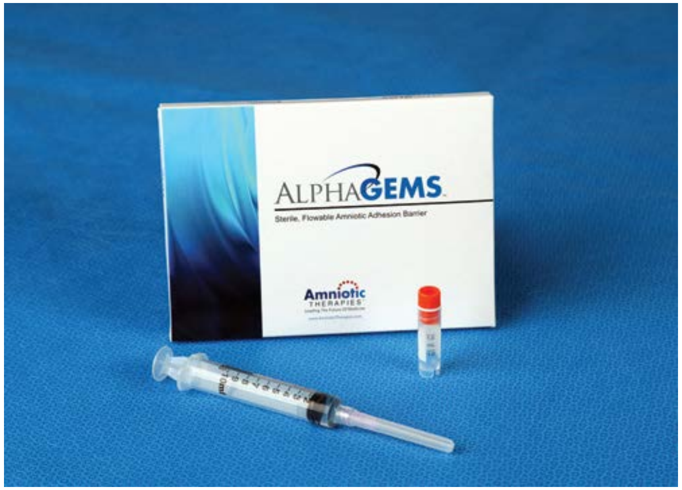
- 21 CFR 211.84 /.103 /.102/.137 /.165/.166/.167/.170

ISO 11608

- e.g. temp. challenge, shock resistance, container integrity testing, shelf life study, human factor study

ISO 11040

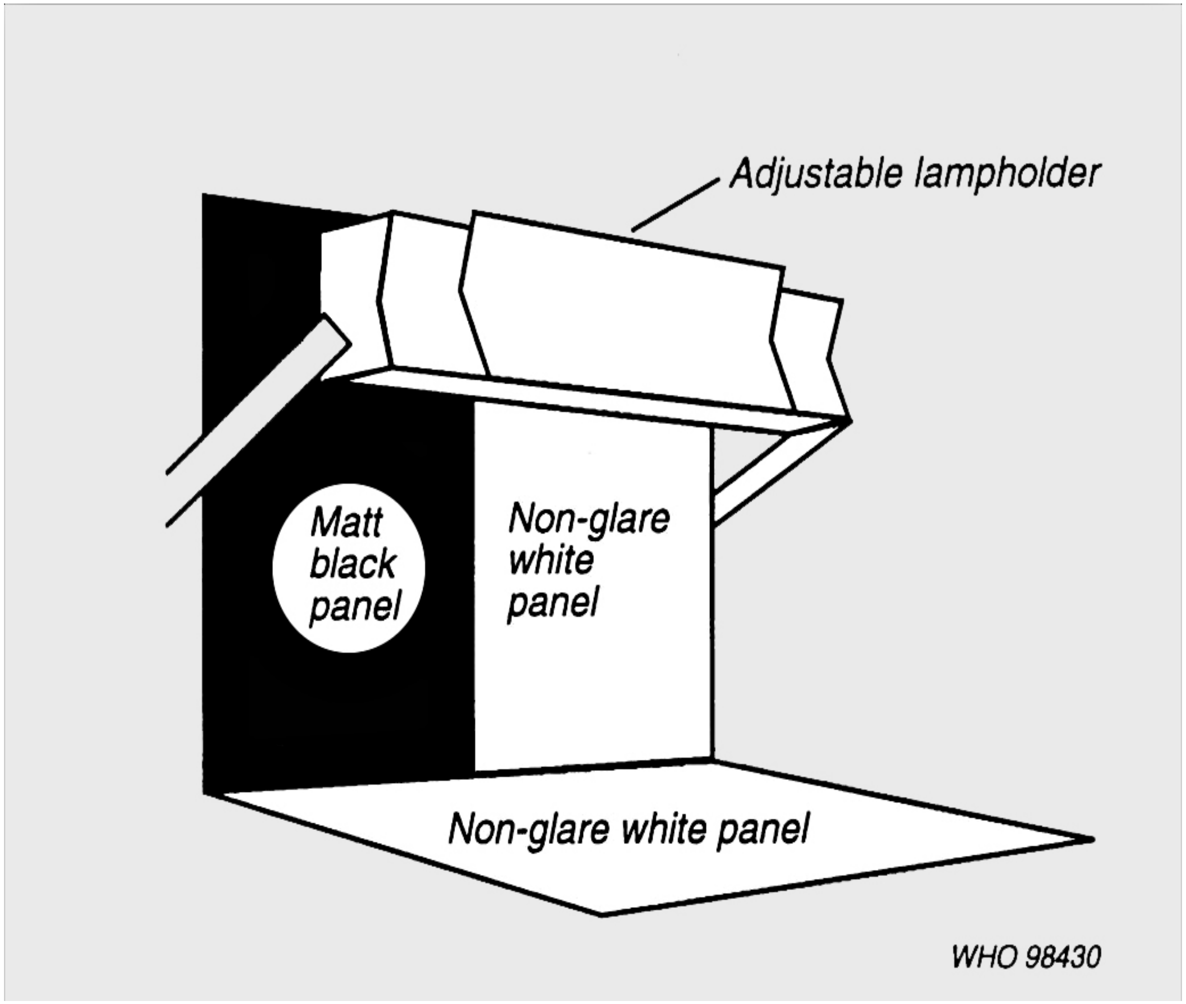
- Siliconization and other attributes of a glass syringe
  - e.g: Particles (USP<788>, ISO 16232); Gliding Force,



Control Aspect	Control measure	Impact
Glass	Select syringe supplier	Compatibility
		Particles
		Cracks / Inclusion
		Dimensions
Plunger	Siliconization	Control teh amount of silicone
	Particle monitoring	Control of particle load
Processing	Handling + rinsing	Avoid glass2glass contact reduce cracks etc.
	Certificate of analysis	incoming controls
	Autoclavation	Sterility test impact on silicone distribution / amount
	Particulate monitoring	Control of particle load of container and closure
Silicone	Amount of silicone	Control of break loose, travel force, silicone mapping
	Homogeneity of the layer	Device funcionality, formulation stability, particles
	Leaching into formulation	Determination of silicone oil leaching into formulation
		Control changes in homogeneity during stability
	Silicone spiking study	Evaluate the vulnerability of the formulation to silicone
Tungsten	Limit 500 nm/barrel	Control the amount of tungsten
	Tungsten spiking study	Evaluate the vulnerability of the formulation to tungsten
Needle shield	Select your vendor +formulation	Establish leachable profile
	Siliconization	Minimize and control pull out force
Needle	Dimensions / Shape	Injection force test, injection time, dimensions
	Siliconization	Minimize and control pull out force + pain

Control Aspect	Control measure	Benefits and Trends
Glass	Select syringe supplier	Reduce particles and loss of efficiacy Reduce particles Reduce cosmetic and functional defects Better functionality in the device
Plunger	Siliconization Particle monitoring	Reproducable machinability Reduce particles
Processing	Handling + rinsing Certificate of analysis Autoclavation Particulate monitoring	Reduce particles + other defects Reduce particles, less rejects
Silicone	Amount of silicone Homogeneity of the layer Leaching into formulation Silicone spiking study	Better functionality in the device / less particles
Tungsten	Limit 500 nm/barrel Tungsten spiking study	Reduce particles
Needle shield	Select your vendor +formulation Siliconization	 Improved funcionality
Needle	Dimensions / Shape Siliconization	Improved funcionality less pain

European Pharmacopeia



USP <790> Visible Particulates in Injections

Inspection conditions defined

– Harmonized with Ph.Eur.

– 2,000-3,750 lux

– Black and white backgrounds

– No magnification

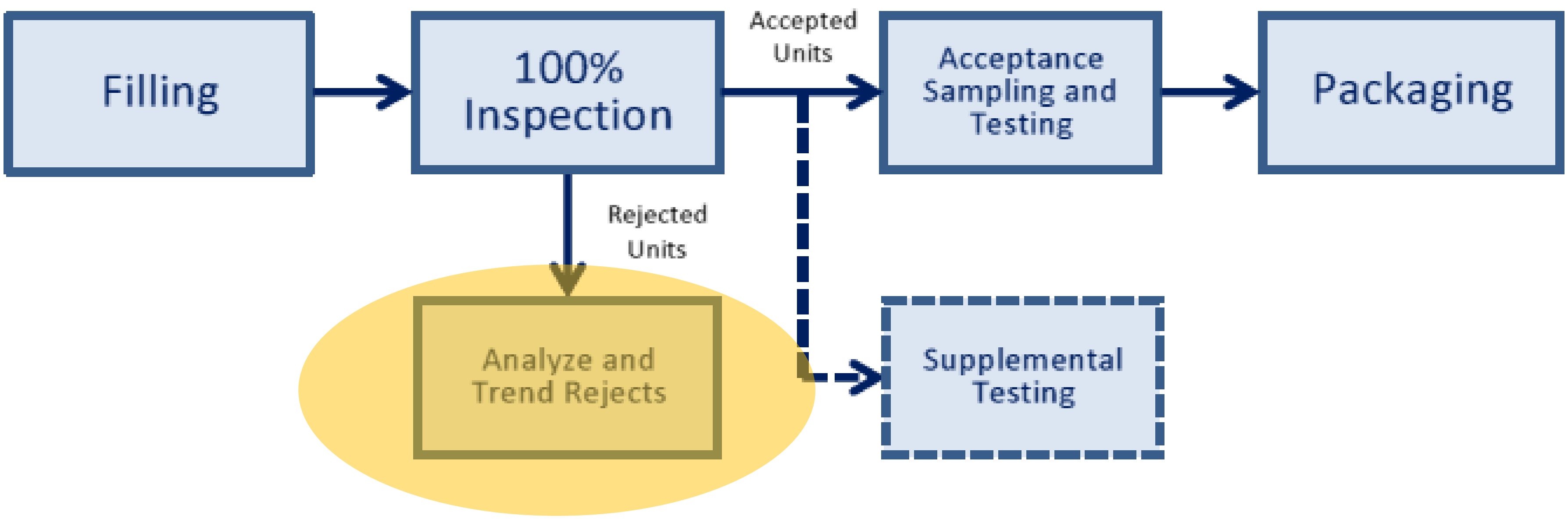
– 5 sec viewing against each background

– Swirl and/or invert sample

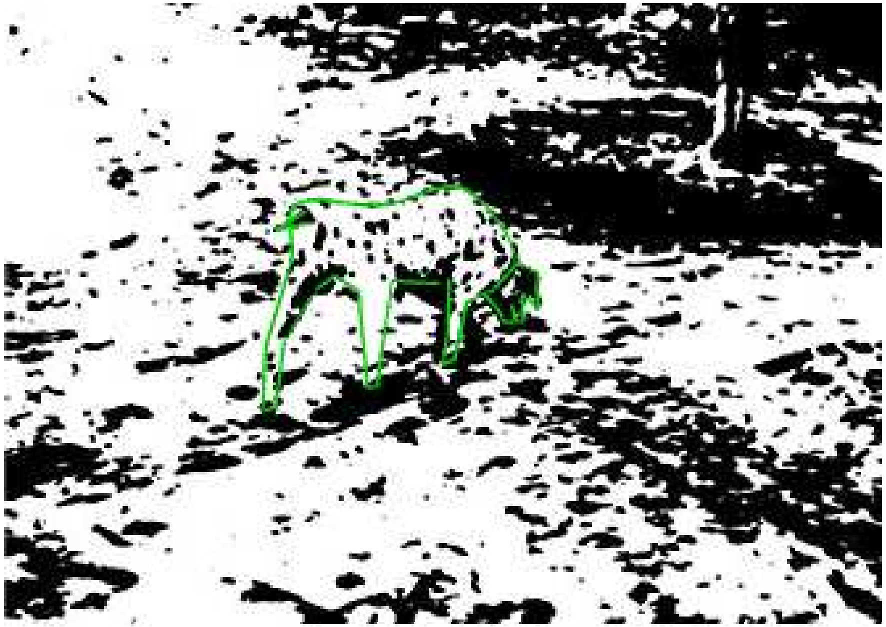
Biopharmaceuticals exempted.

– Addressed in individual monographs or approved regulatory filings

USP 1790 Typical Process Flow



Training



You have to know what your are looking for: Training is essential

Level 1 - Visible Characterization

Position	*Select*
In Solution	[ ]
Adjacent to Vial Wall	[ ]
Adjacent to Stopper	[ ]

Buoyancy	*Select*
Floats ↑	[ ]
Neutral ↔	[ ]
Sinks ↓	[ ]

Shape	*Select*
Compact	[ ]
Fibrous	[ ]
Amorphos	[ ]
Notes:	

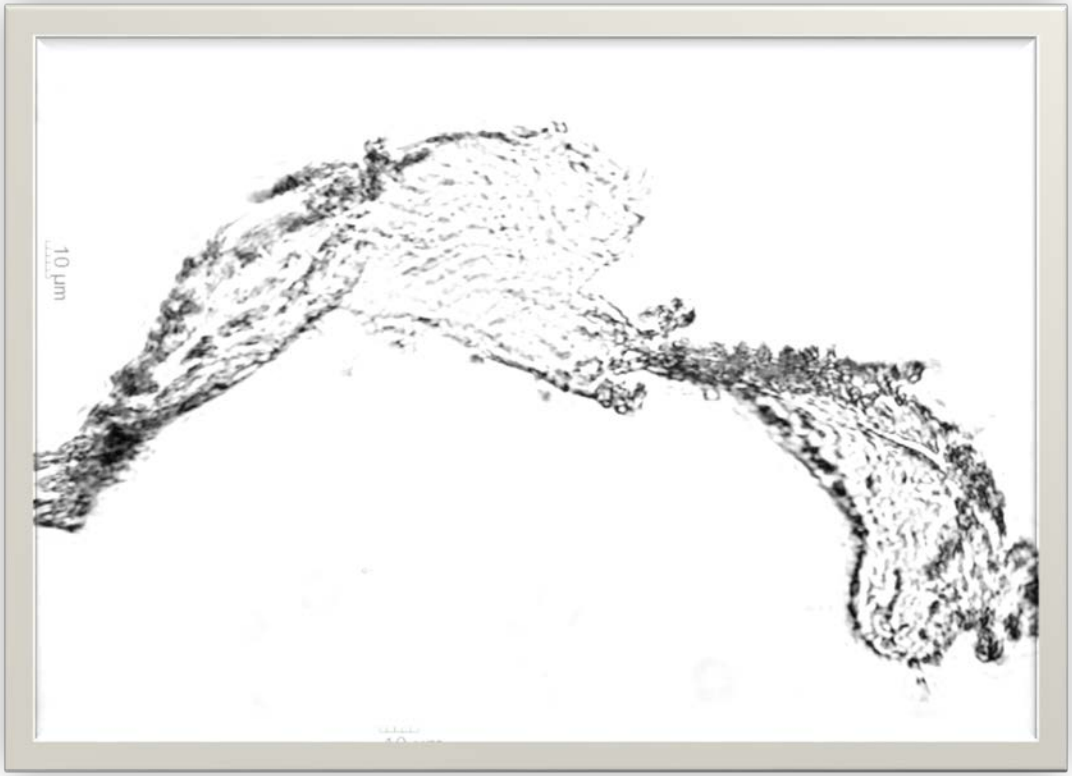
Color	*Select*
Observed Color	________
Light	[ ]
Dark	[ ]
Transparent	[ ]
Opaque	[ ]
Reflective - Shiny	[ ]

Level 1 - In situ microscopy

Level 1

Position:	at bottom
Buoyancy:	fast sinking
Shape:	particle
Color:	transparent
Appearance:	trigonal, 300 µm

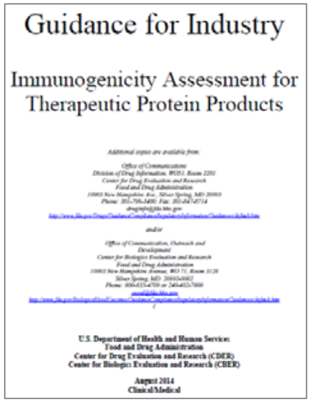
Level 1



Position:	at bottom
Buoyancy:	sinking
Shape:	particle
Color:	bright
Appearance:	oblong, 400 µm


Compatibility?

Silicone Formulation Interface

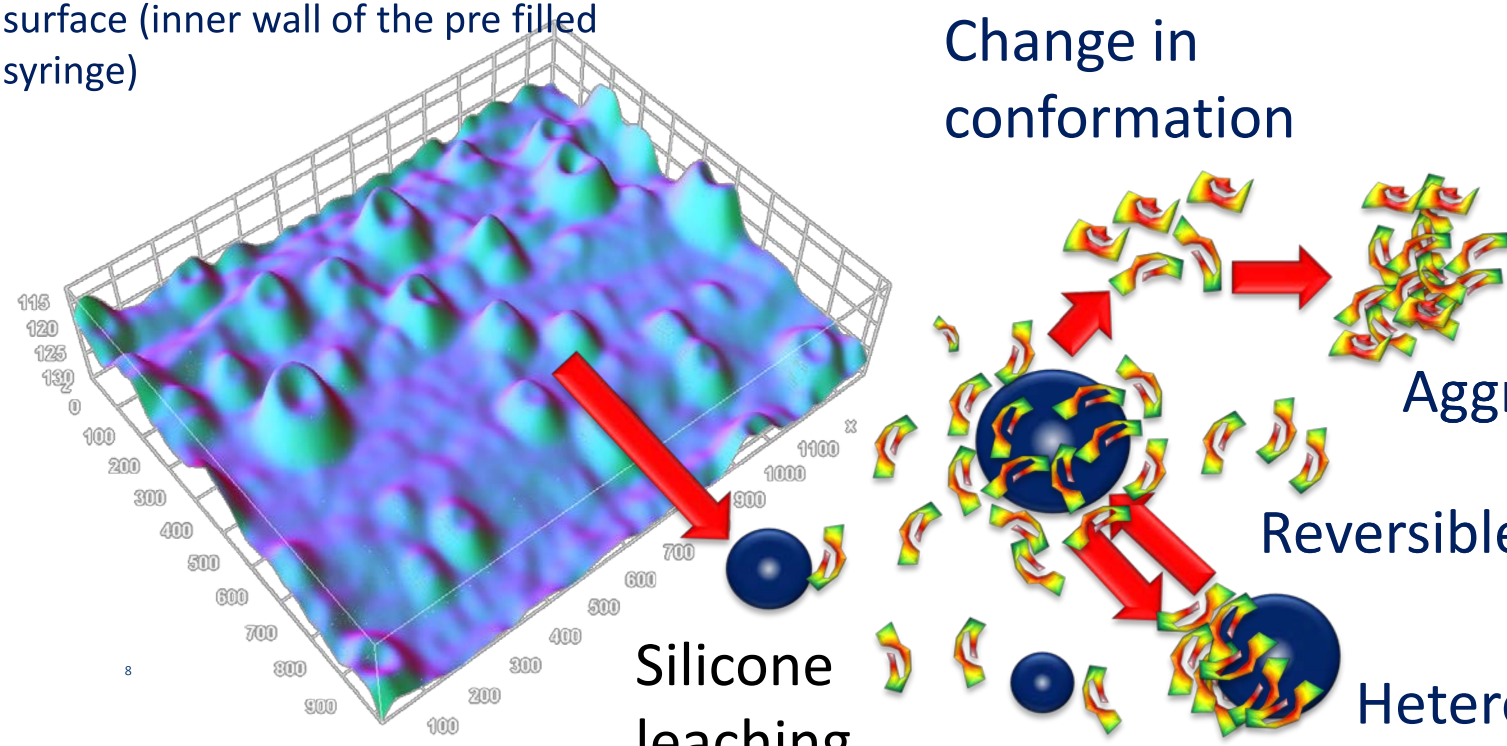

Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

Layer Explorer result showing droplet formation on siliconized surface (inner wall of the pre filled syringe)



Compatibility Study

- Tungsten Spiking
- Silicone Spiking
- Stability (orienting) at different temperature/ time points:
  - Thickness and homogeneity of the Silicone Layer
  - Break loose and gliding force
  - Number and size of visible/subvisible protein/protein, protein/silicone and silicone droplets
- Amount of silicone leaching into formulation


Layer Explorer Technology

Layer Explorer

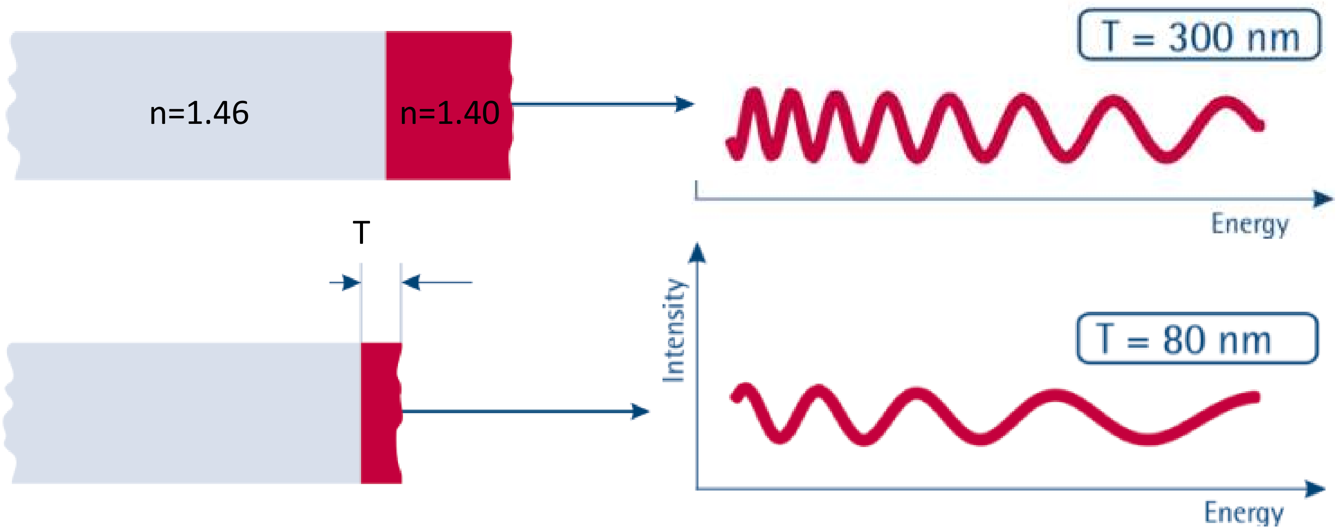
- Homogeneity
- Layer Thickness

@ 20 nm LOD

Measurement Principle

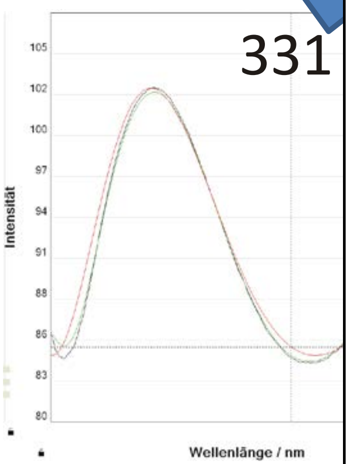
23

Reflectometry → Thickness



How does the LE work?

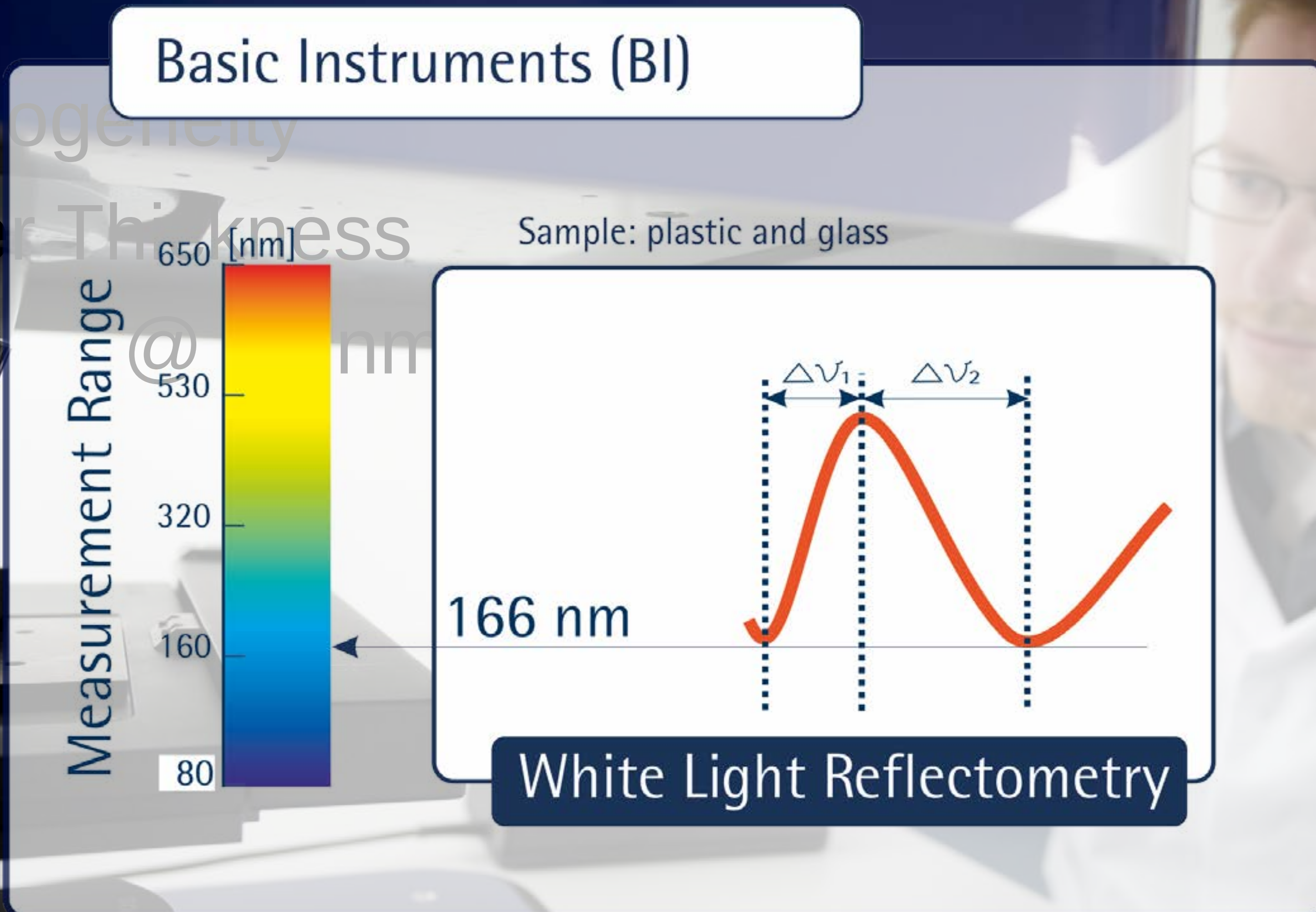
rement Area



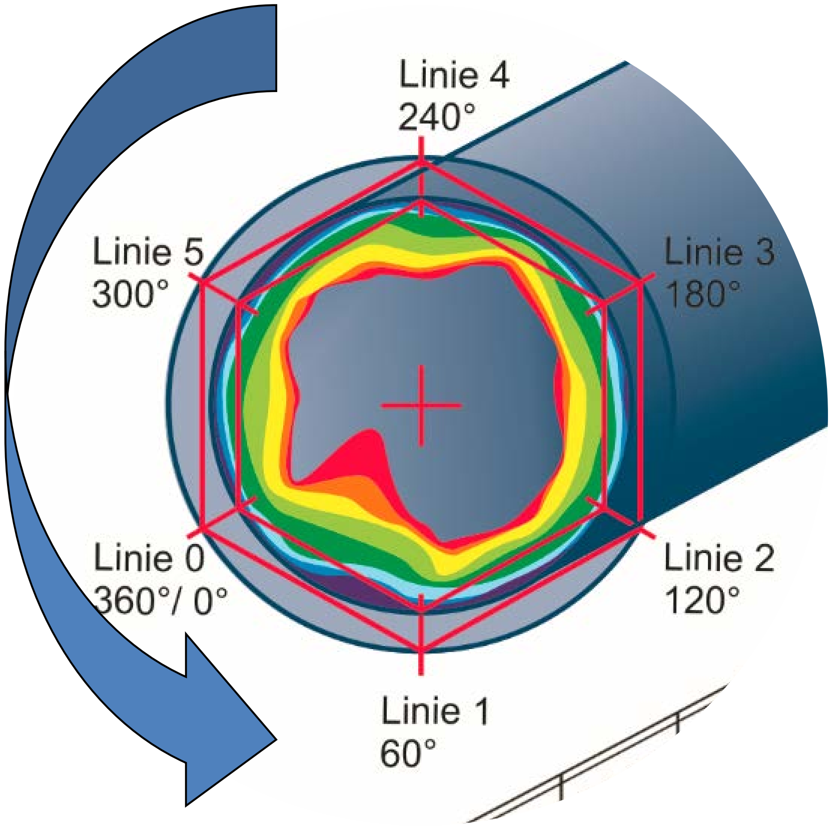
Homogeneity

Layer Thickness

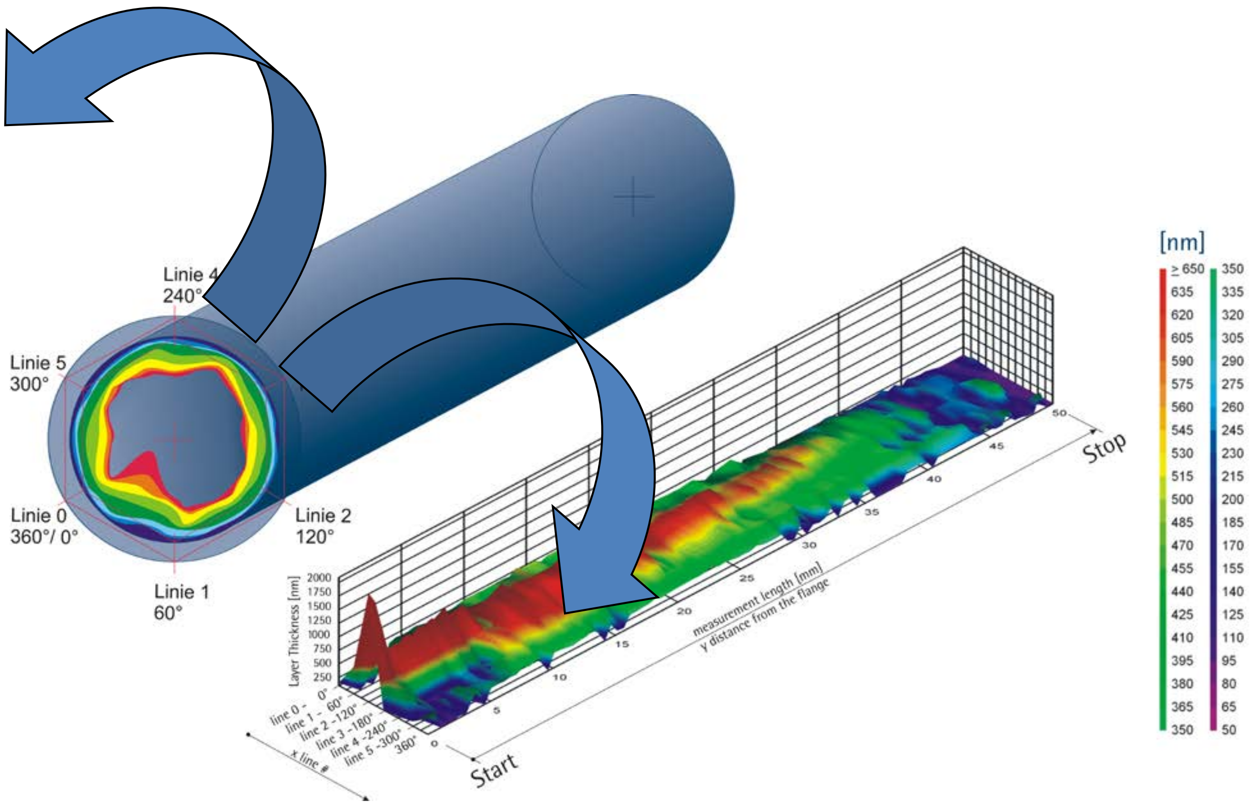
@ nm



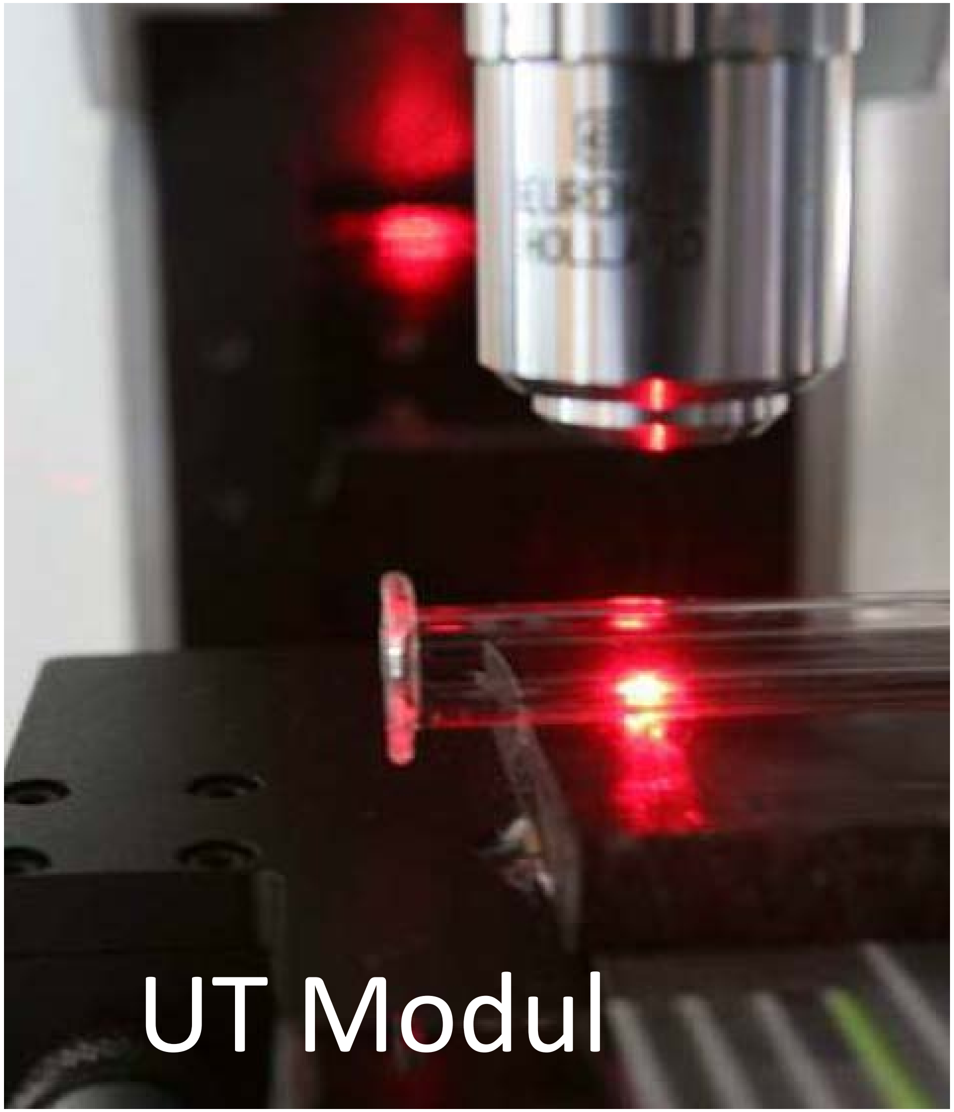
Rotation → 3D-Map



Silicone oil distribution

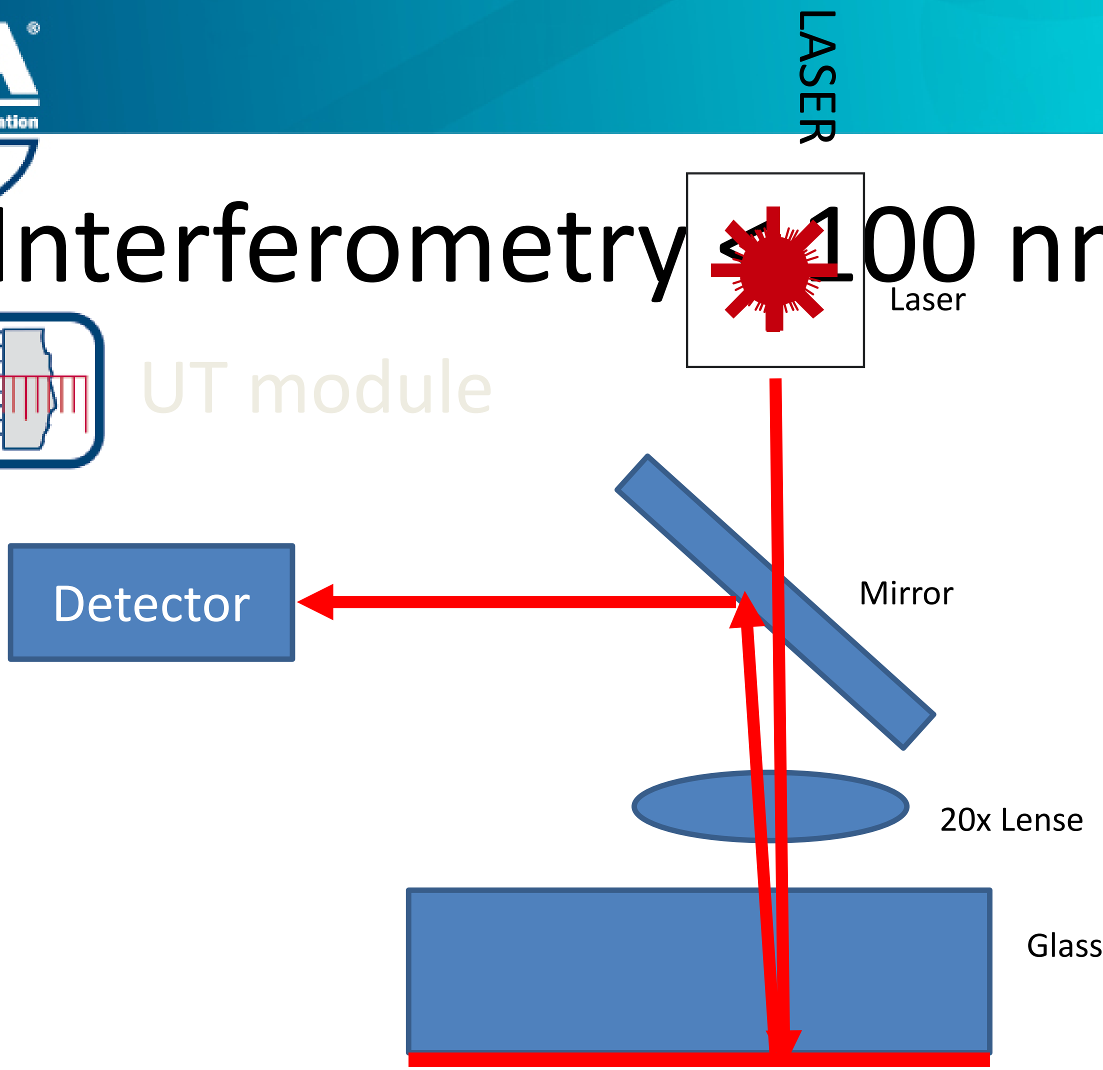


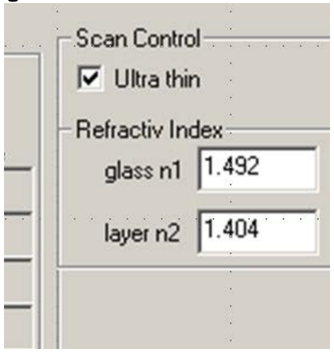
Measurement from 20-100 nm

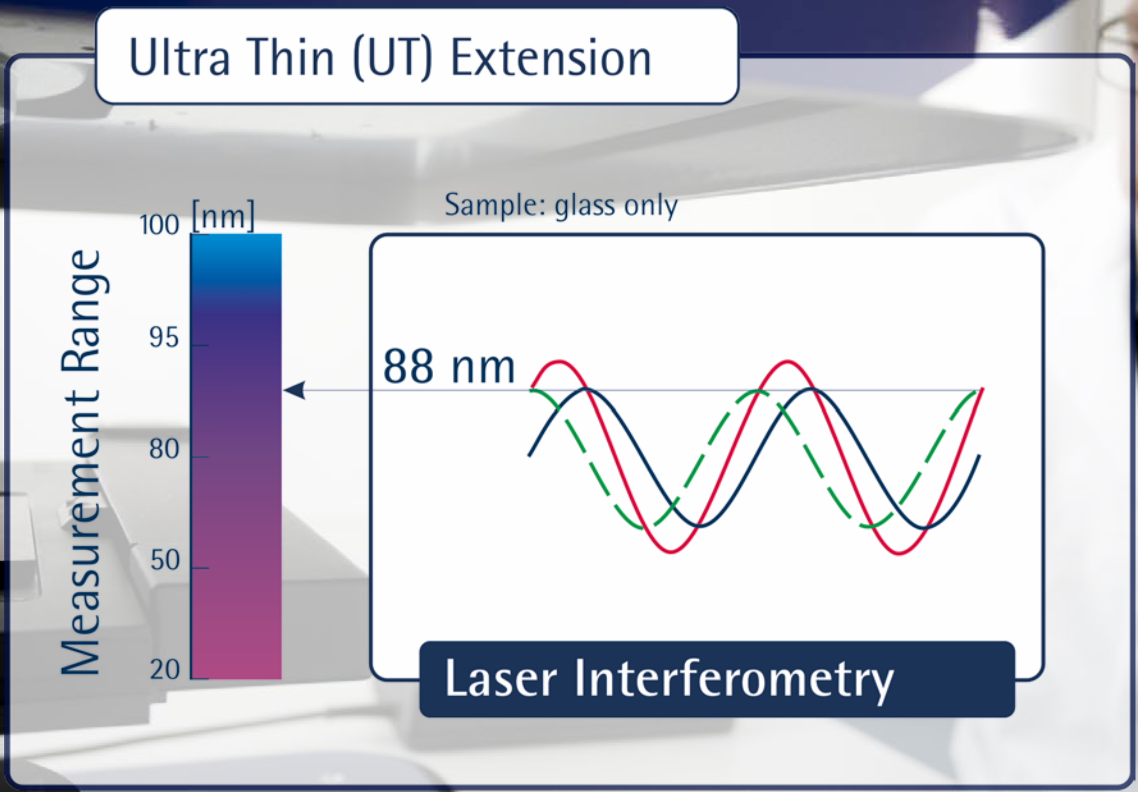


Interferometry < 100 nm

UT module

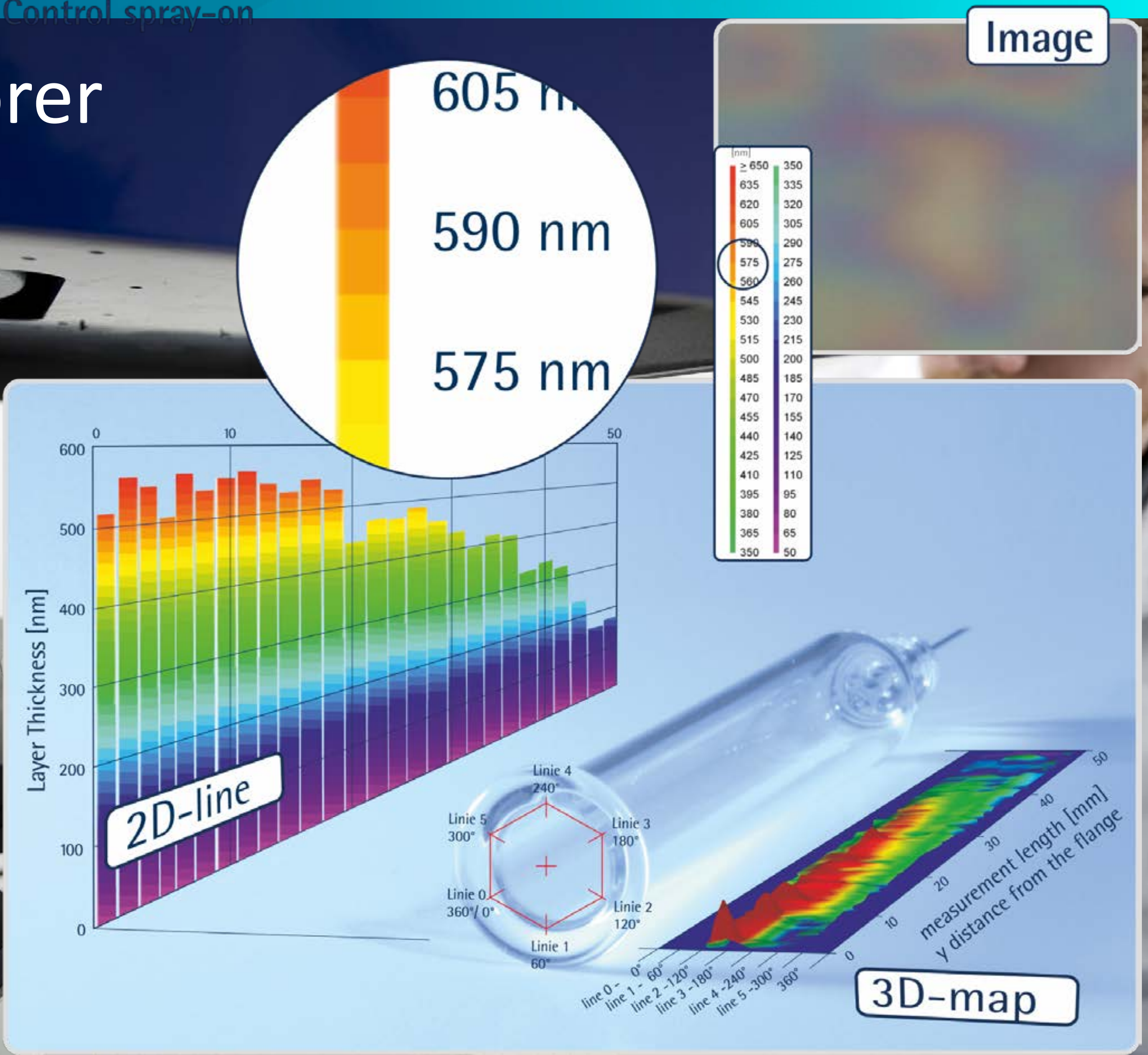





Ultra Thin (UT) Extension
Measurement Range
100 [nm]
95
80
50
20
Sample: glass only
88 nm
Laser Interferometry

Control spray-on

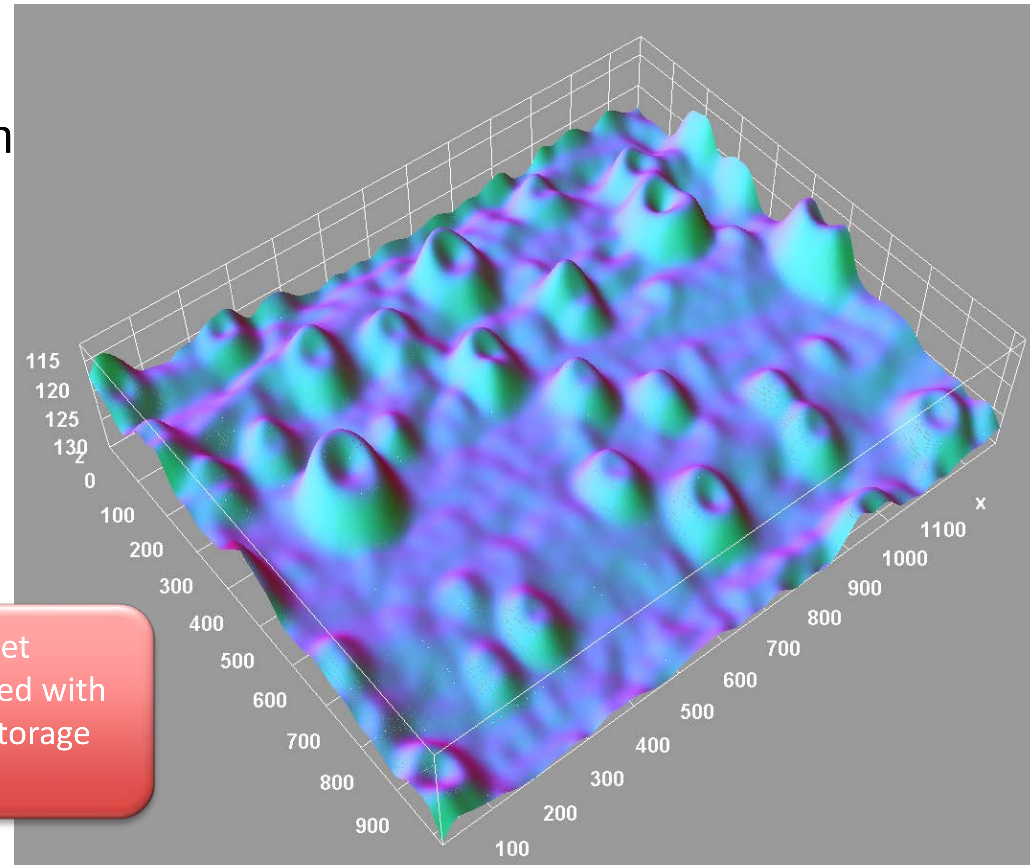
Layer Explorer Results



Technology outlook

Measurement of filled syringes Nov.

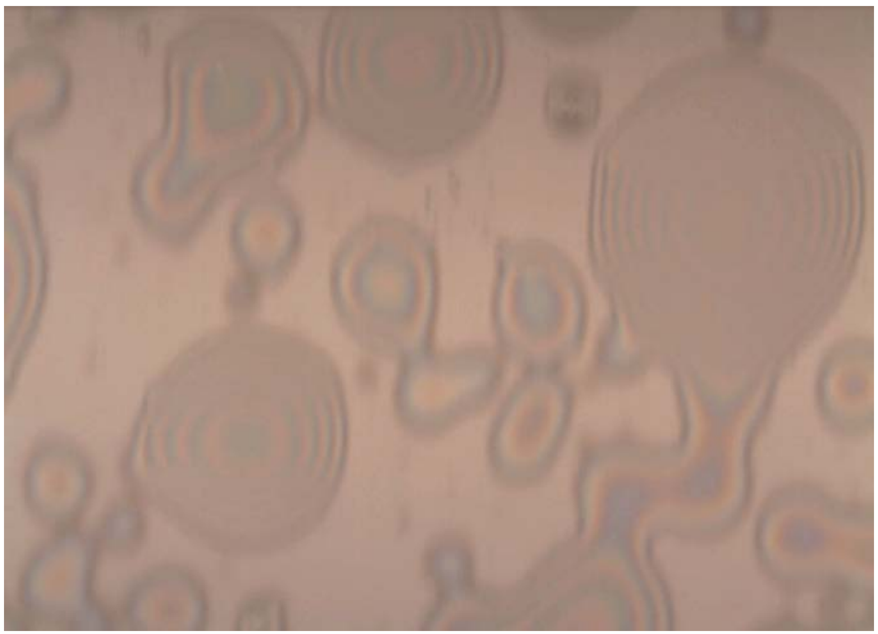
Visualization of the re-distribution an



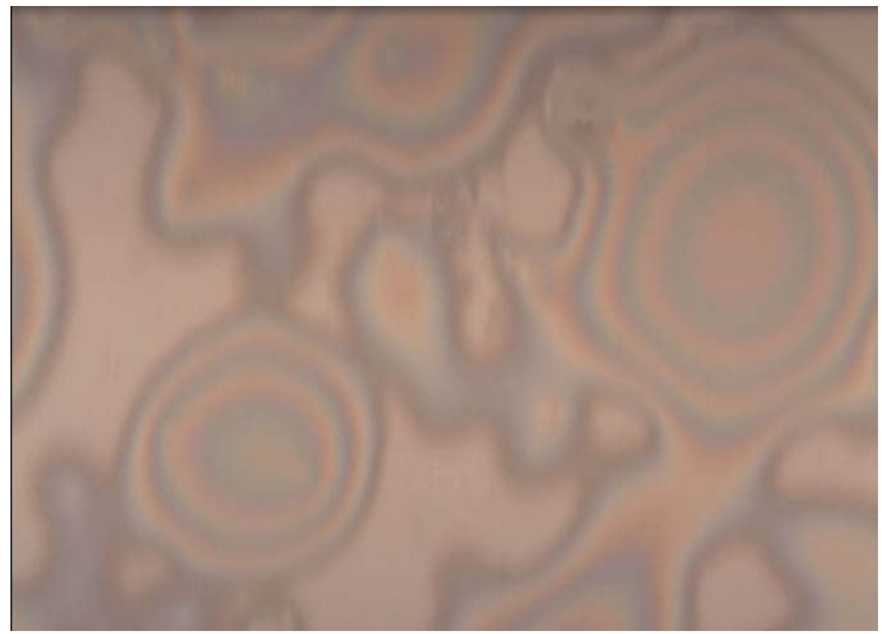
Representation of silicone oil droplet formation in a pre-filled syringe filled with water and 1% PS20 after one day storage at 20°C

LE-video –after draining

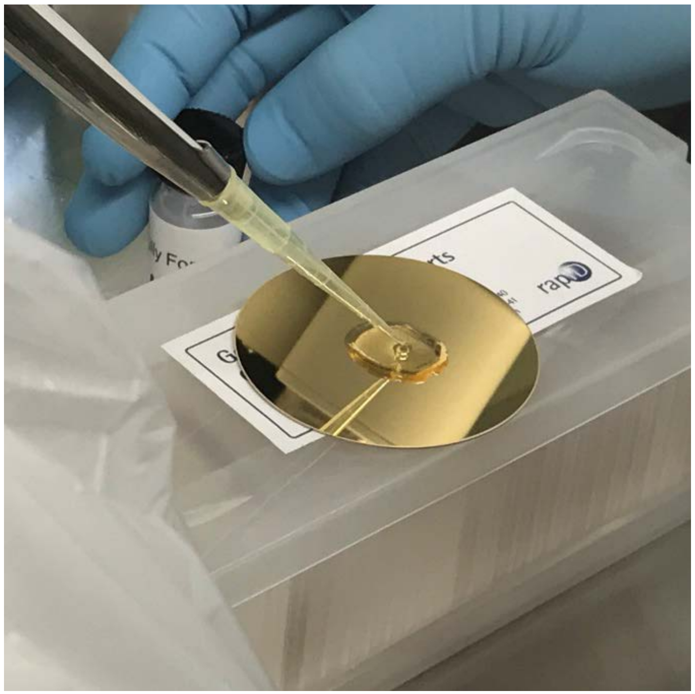
Start

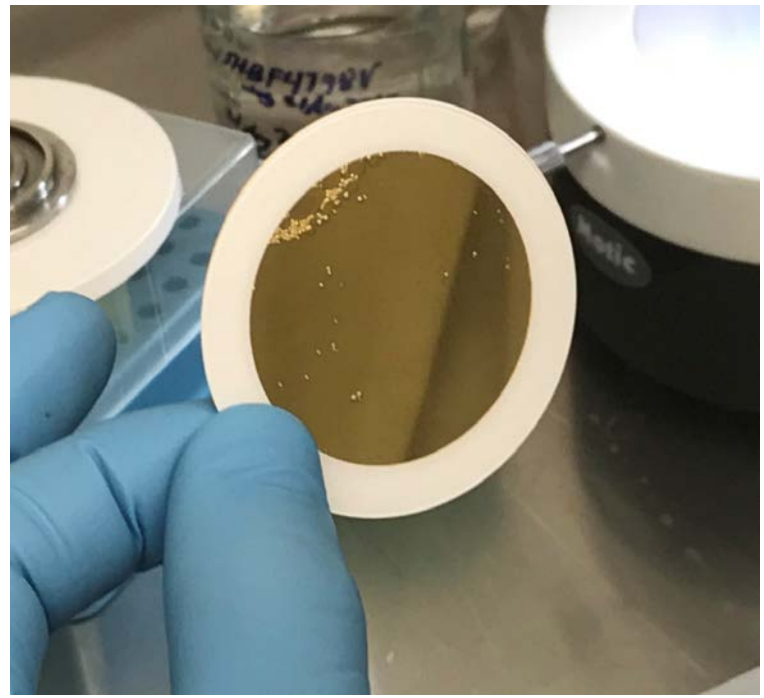


→ after 1.3 hours



Wet-dispersion.AID sample prep





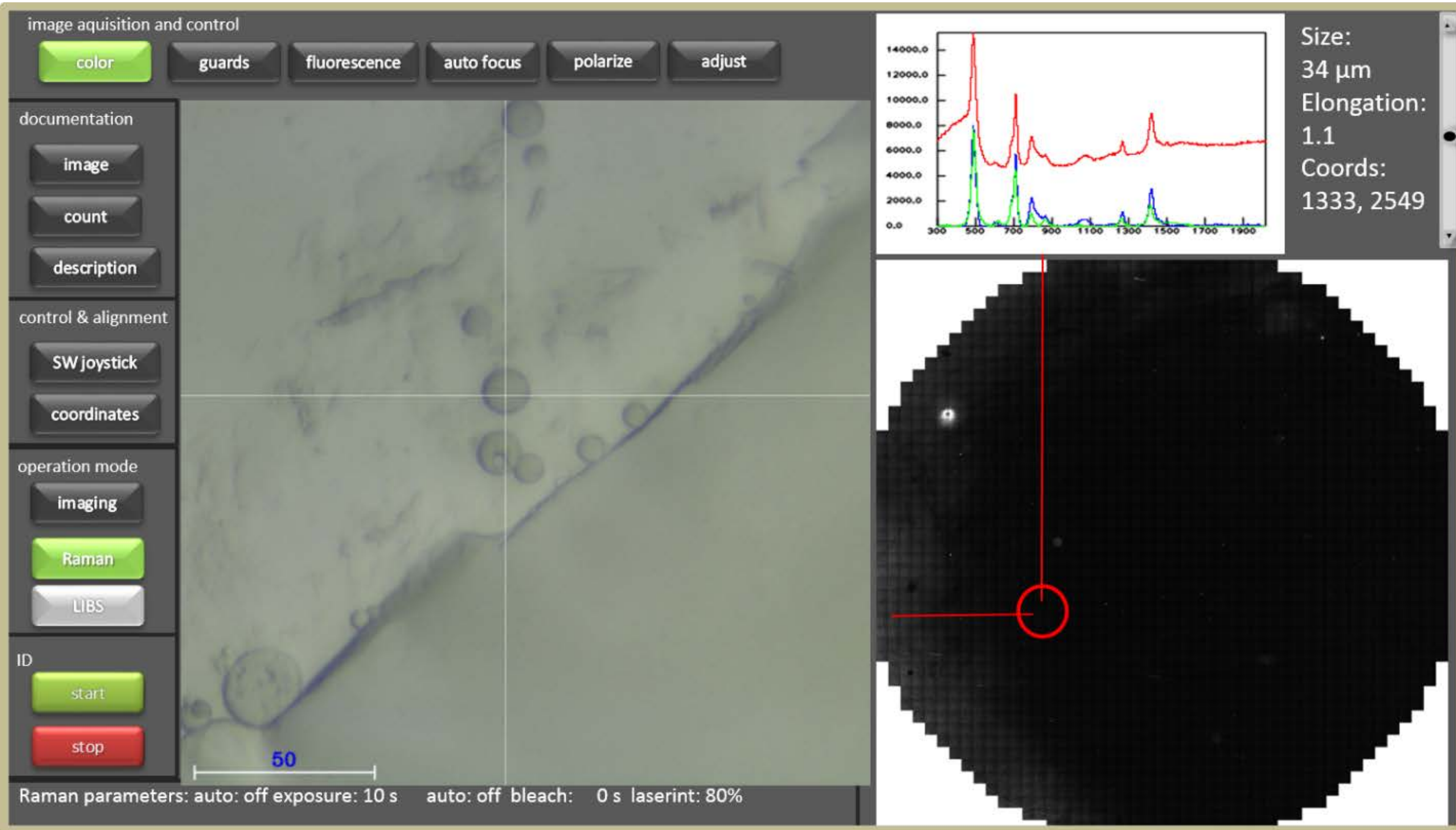
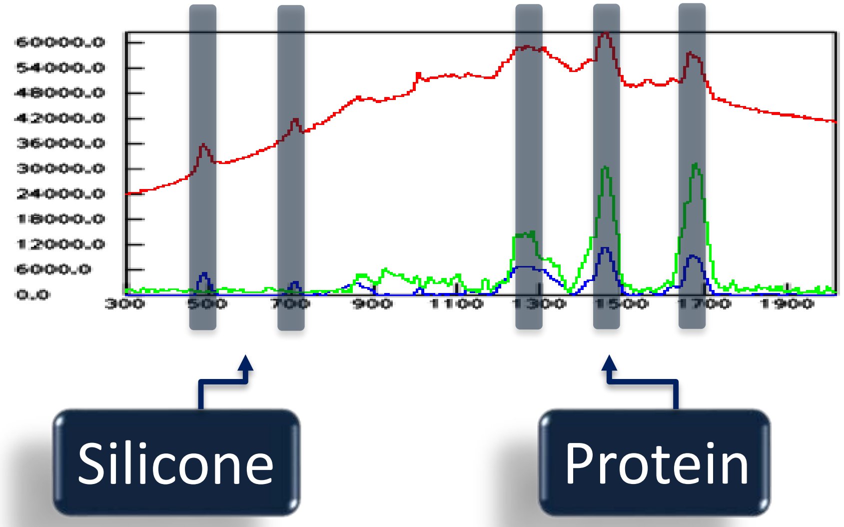
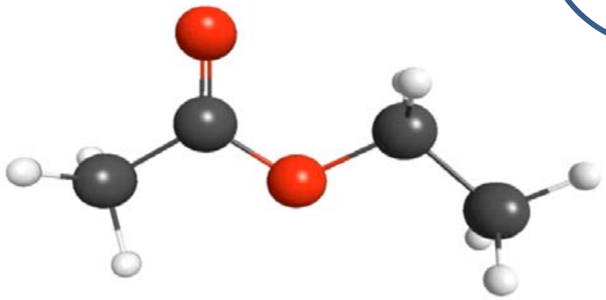


image aquisition and control
color
guards
fluorescence
auto focus
polarize
adjust
documentation
image
count
description
control & alignment
SW joystick
coordinates
operation mode
imaging
Raman
LIBS
ID
start
stop
50
Raman parameters: auto: off exposure: 10 s auto: off bleach: 0 s laserint: 80%
14000.0
12000.0
10000.0
8000.0
6000.0
4000.0
2000.0
0.0
300
500
700
900
1100
1300
1500
1700
1900
Size:
34 µm
Elongation:
1.1
Coords:
1333, 2549

Raman on Silicone and Protein



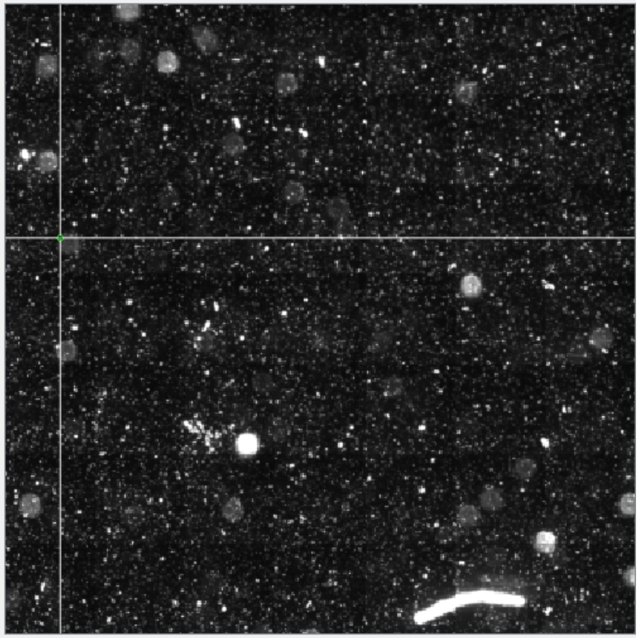
3159 cm-1



Wet-dispersion.AID data

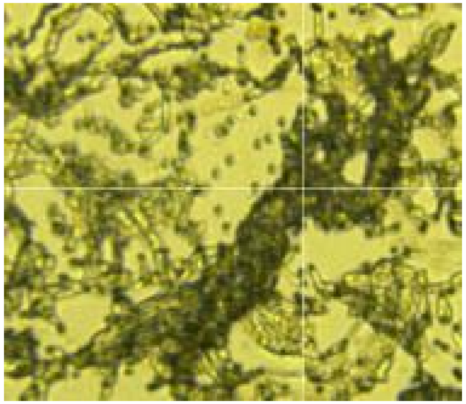
	Number	1 to <2	2 to <5	5 to <10	10 to <20	20 to <30	30 to <5
protein_silicone	222	0	0	0	103	73	38
background_formulation	218	0	0	0	93	91	17
silicone_protein	16	0	0	0	6	4	5
protein_peak500	15	0	0	0	6	8	1
protein_silicone_A	13	0	0	0	2	7	4
silicone_protein_FFA	8	0	0	0	3	2	2
Fluorescence	3	0	0	0	0	2	0
PS20_special_no_900	2	0	0	0	1	0	1
quartz	2	0	0	0	1	1	0
titanium-dioxide	1	0	0	0	0	0	1
All analyzed particles	**500**	**0**	**0**	**0**	**215**	**188**	**69**
Skipped particles	29626	11560	12130	4715	1220	0	0
All particles	**30126**	**11560**	**12130**	**4715**	**1435**	**188**	**69**

Total scan image

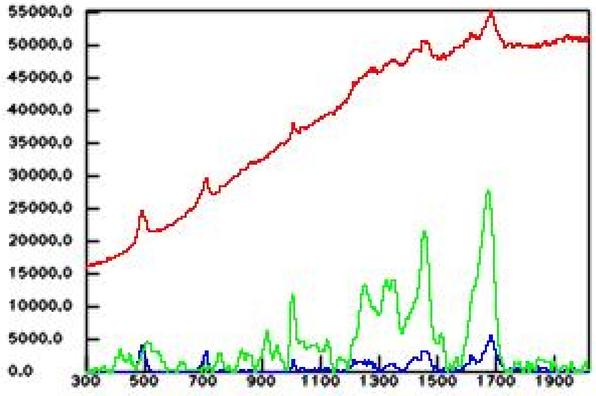


P05.01, ('protein', 701), form: (29.1, 1.756), glb.coords: (1123.8, 263.1), SN: 58.4, Field = (0, 4)

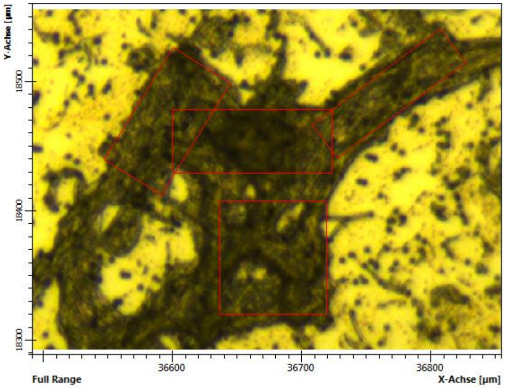
Protein + Silicone → visible Particle + Level III ID

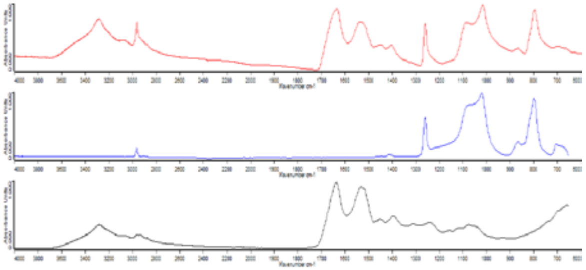


Raman

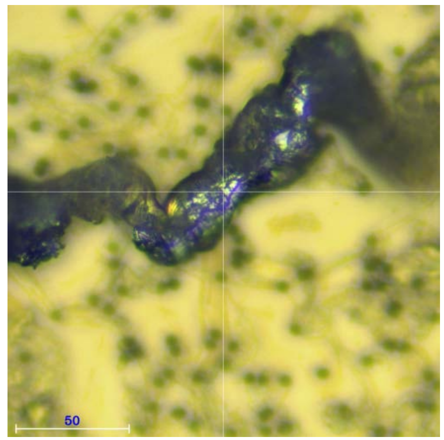


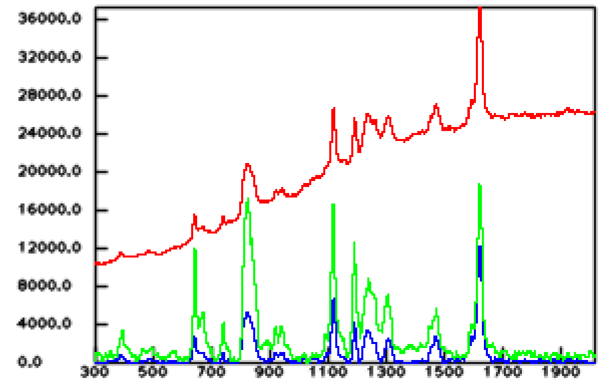
IR





Raman


50


36000.0
32000.0
28000.0
24000.0
20000.0
16000.0
12000.0
8000.0
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300
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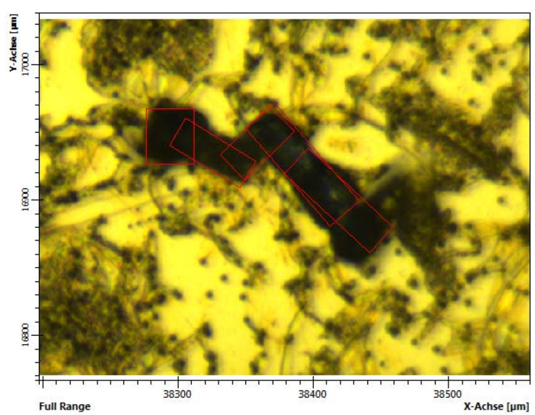
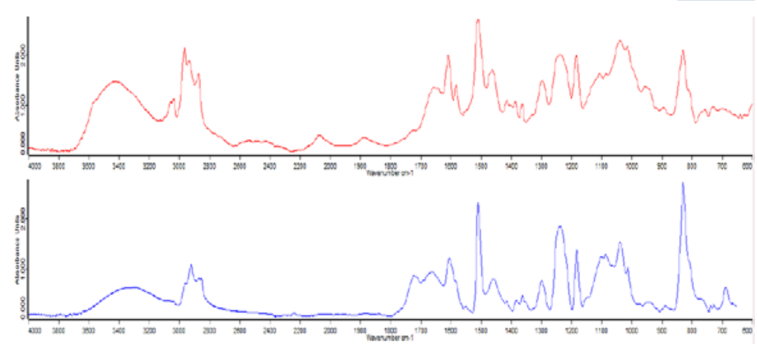
700
900
1100
1300
1500
1700
1900

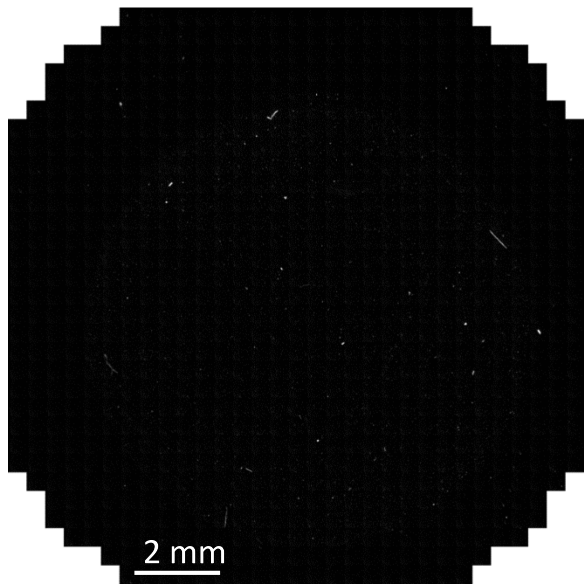
IR


Y-Achse [µm]
17000
16900
16800
38300
38400
38500
Full Range
X-Achse [µm]



ISO 8871-3 Elastomeric Particle Release

Gold filter, dark field mode



Magnification: 200x
Diameter: 13.5 mm
Number of fields: 961
Scanning and counting time: 11 minutes

Size Distribution of Measured Particles

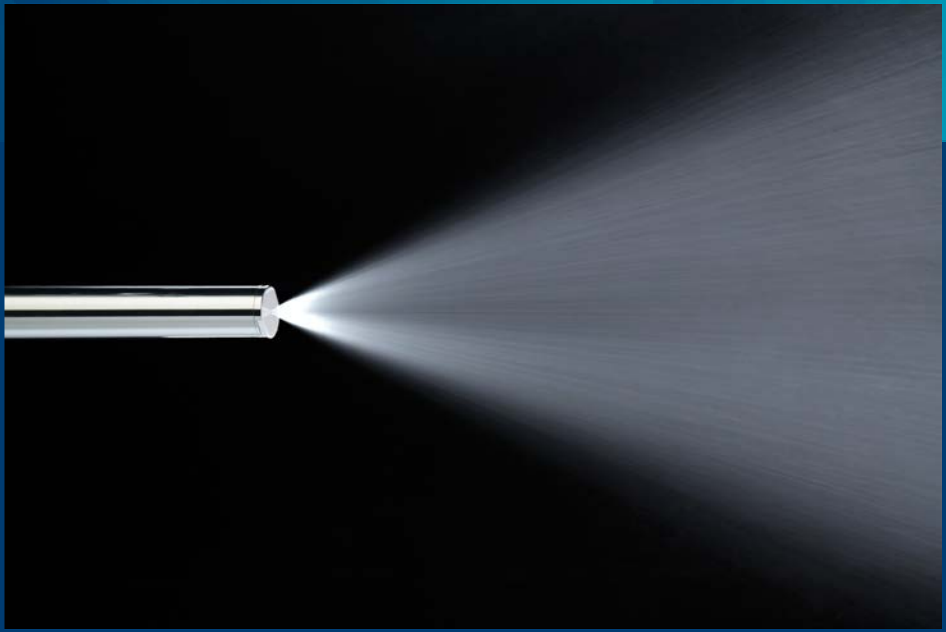
From 25 piston

Total	>=5 to <10 µm	>=10 to <25 µm	>=25 to <50 µm	>=50 µm
22646	16020	6290	295	41

ISO 16232 – Particles from Syringes

Size and Substance Distribution of Measured Particles from 40 Syringes (Extraction: 2 min sonication, rinsing with 10 ml each)						
Substance	Number	Size Distribution [µm]				
		2 to <5	5 to <10	10 to <25	25 to <50	>=50
Unknown Substance	194	47	128	19	0	0
Calcium Carbonate	144	20	83	39	2	0
Quartz	3	0	3	0	0	0
Fluorescence	2	0	0	2	0	0
Cellulose	2	0	0	0	0	2
Glass (clear)	1	0	0	0	0	1
Hydrogenphosphate, Potassium	1	0	0	1	0	0
Talc (SiO2)	1	0	1	0	0	0
Polystyrene and TiO_2	1	0	0	0	0	1
Polystyrene	1	0	0	1	0	0
Skin flake	1	0	0	0	1	0
All analyzed particles	351	67	215	62	3	4
Skipped particles	378	378	0	0	0	0
All particles	729	445	216	62	3	3

Spray on silicone control



Paramters for spray siliconization

Silicone oil Viscosity e.g. 360 cSt

Nozzle diameter e.g. 0.3 mm

Tube diameter

e.g. 0.8 mm

Temperature e.g. 140°C

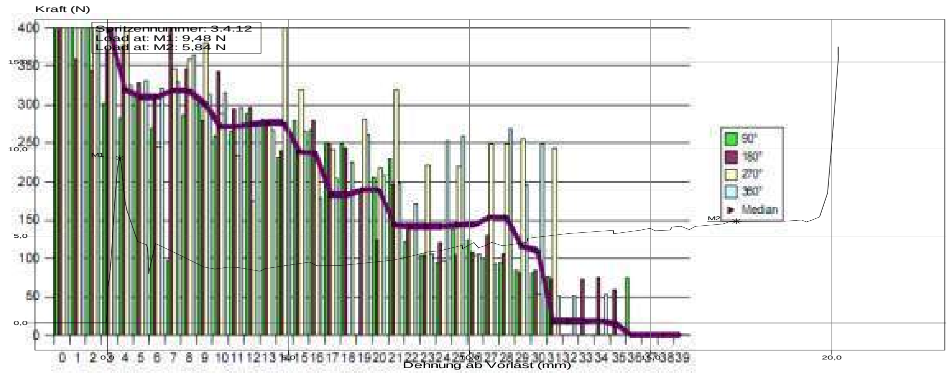
Air pressure

e.g. 2 bar

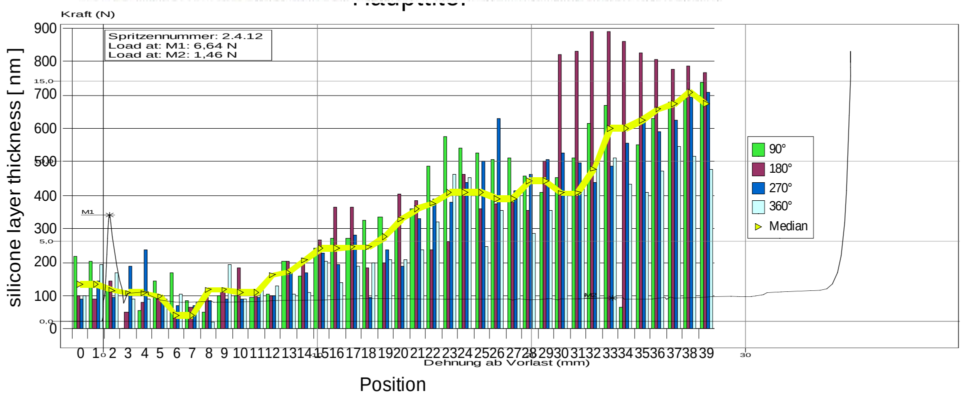
Dosage

e.g. 0.00045g

Spray Pattern Optimization



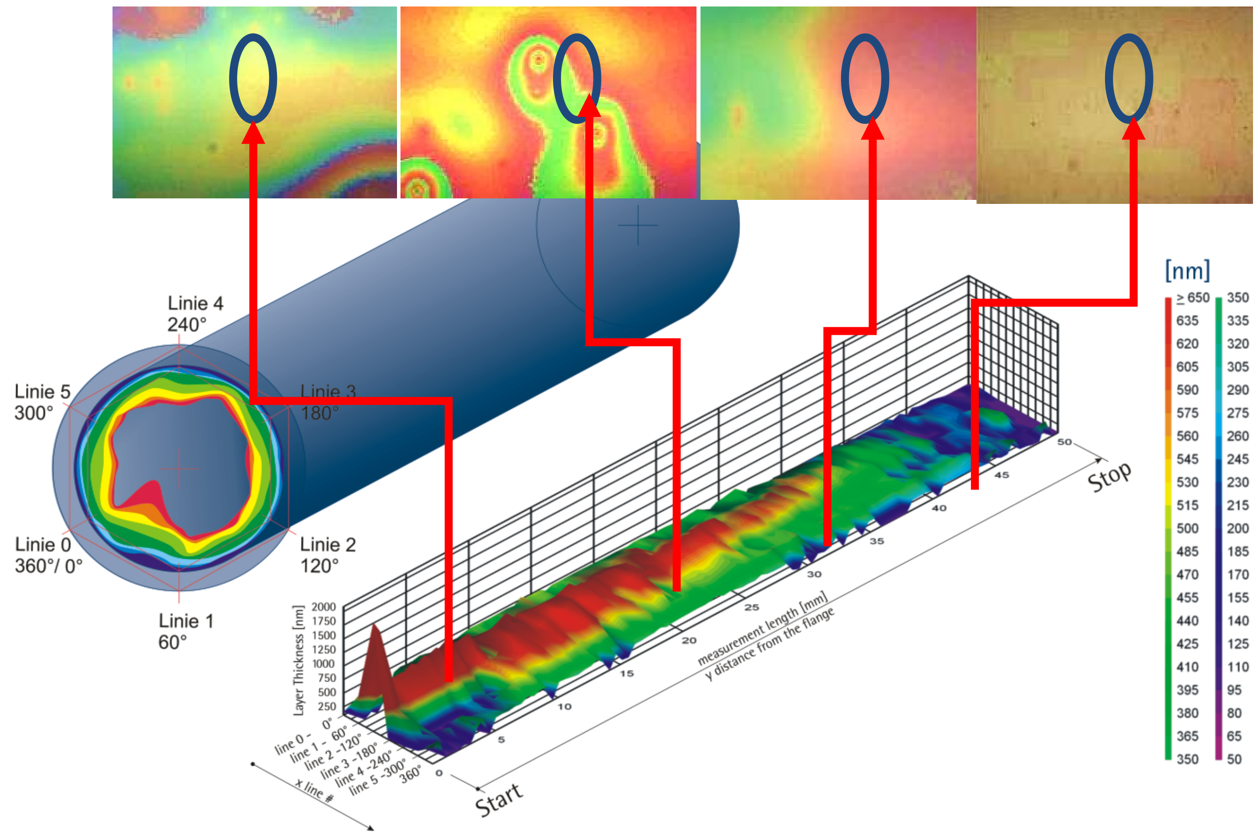
Static



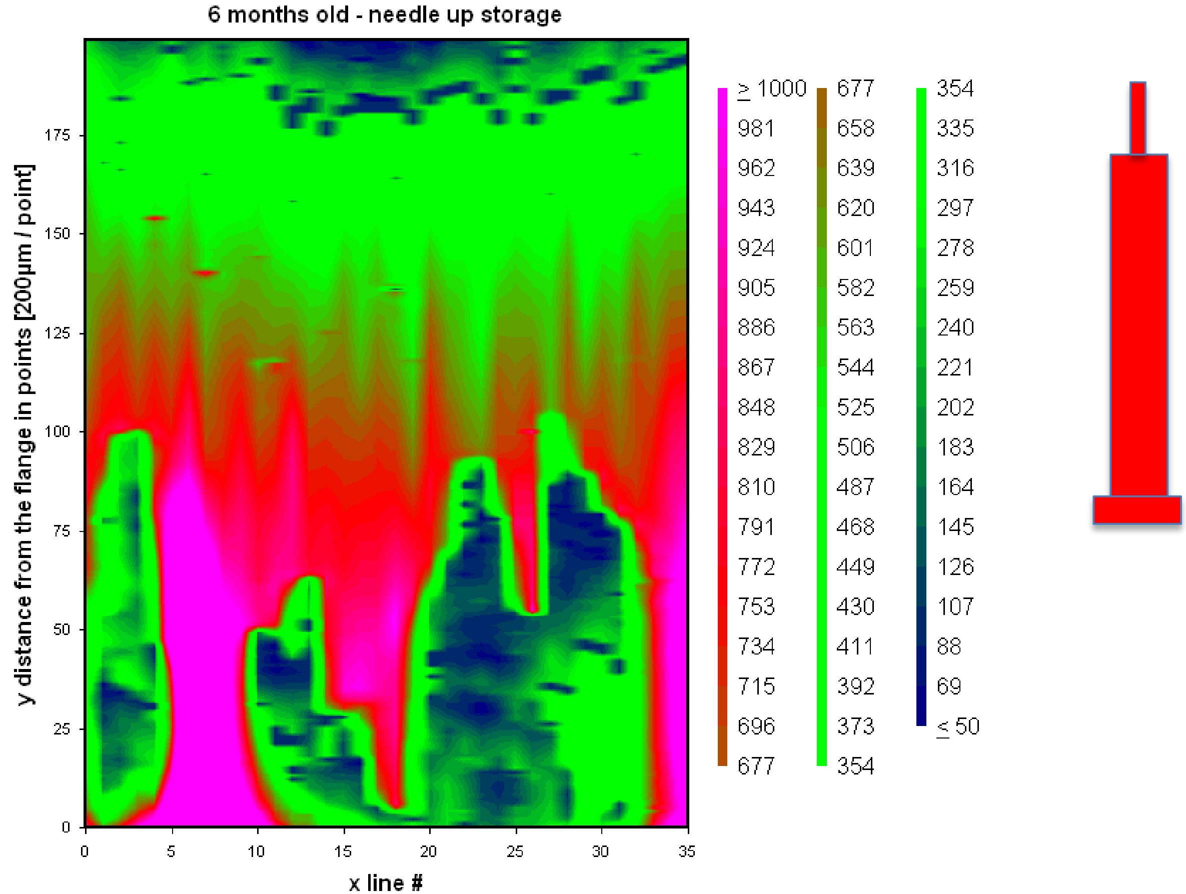
Dynamic

Redistribution and stability

Horizo[redacted]age



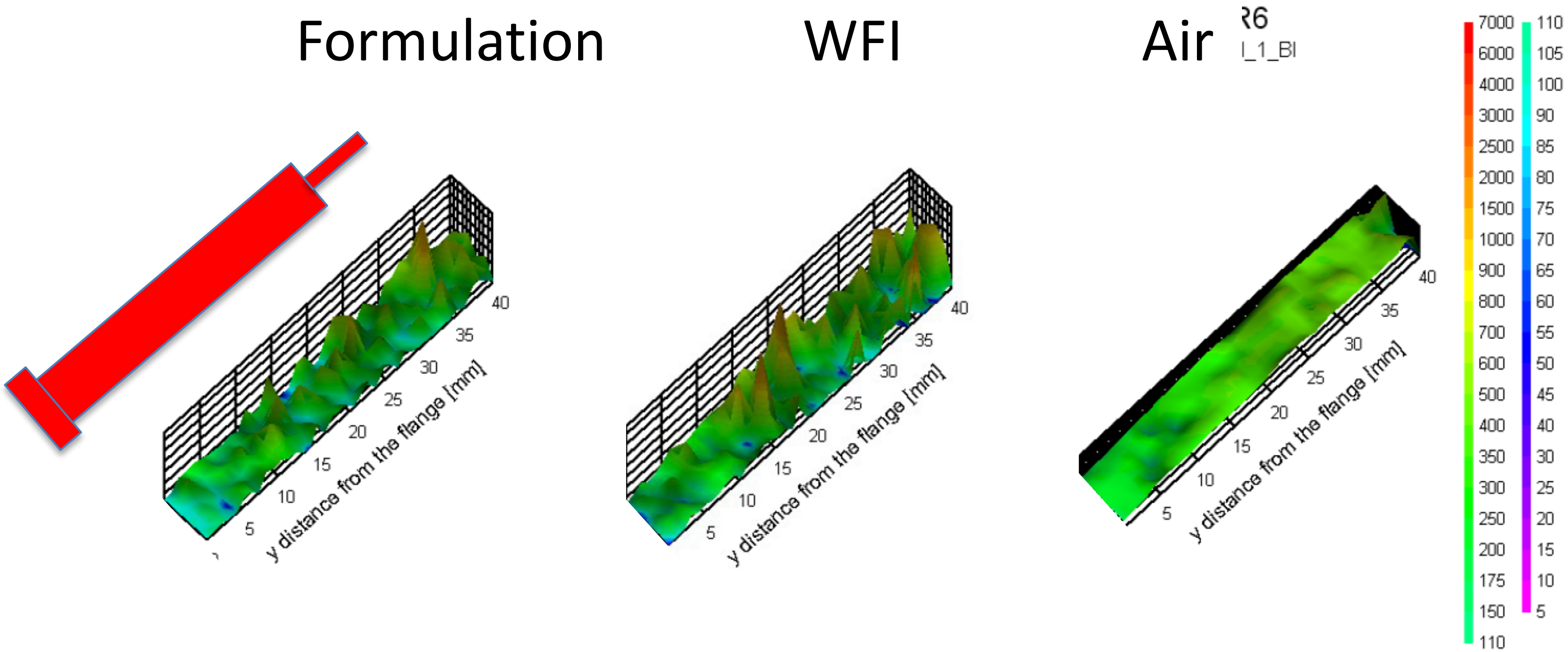
Upright storage



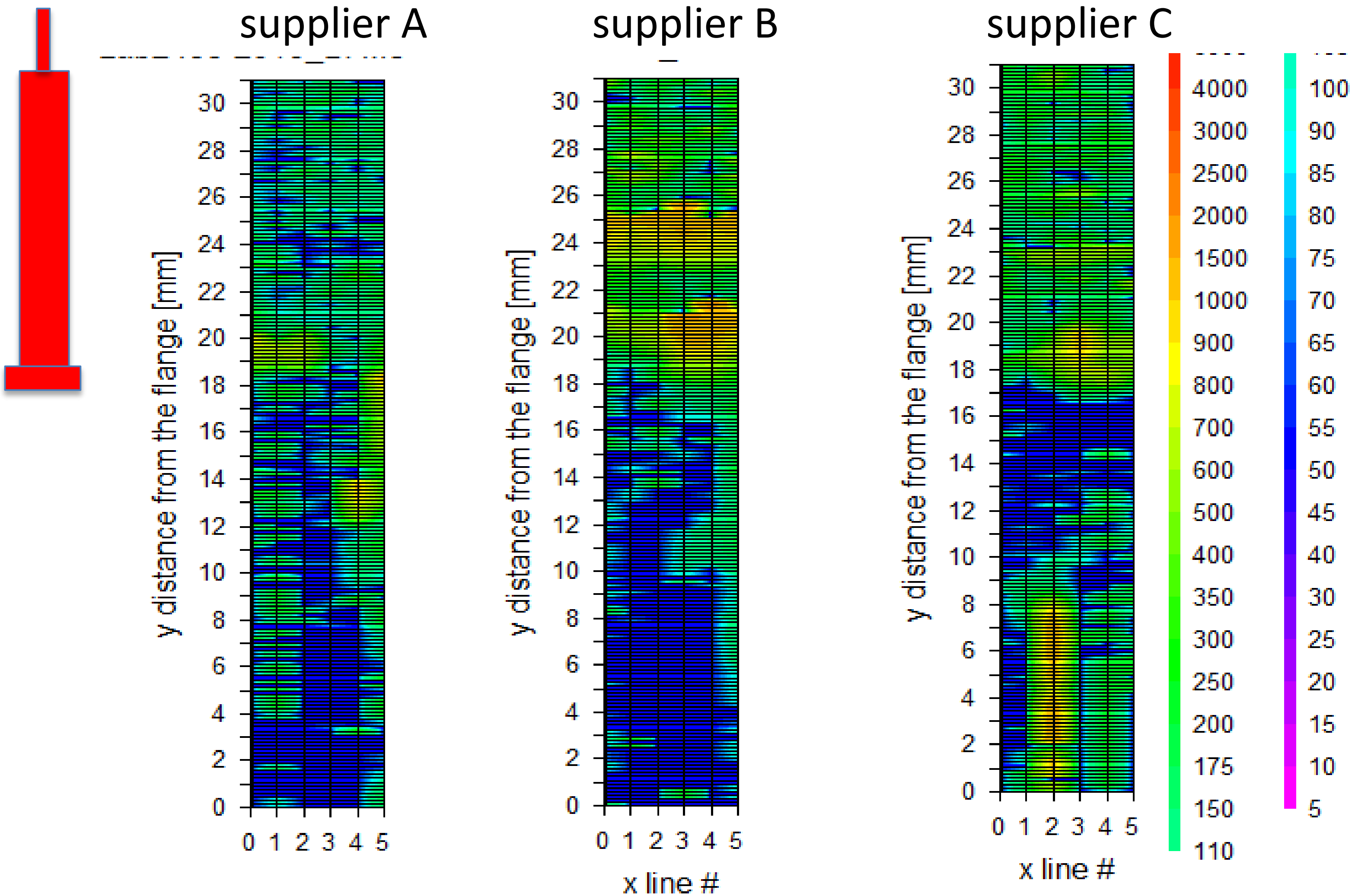
Stability Study

Spray Siliconized

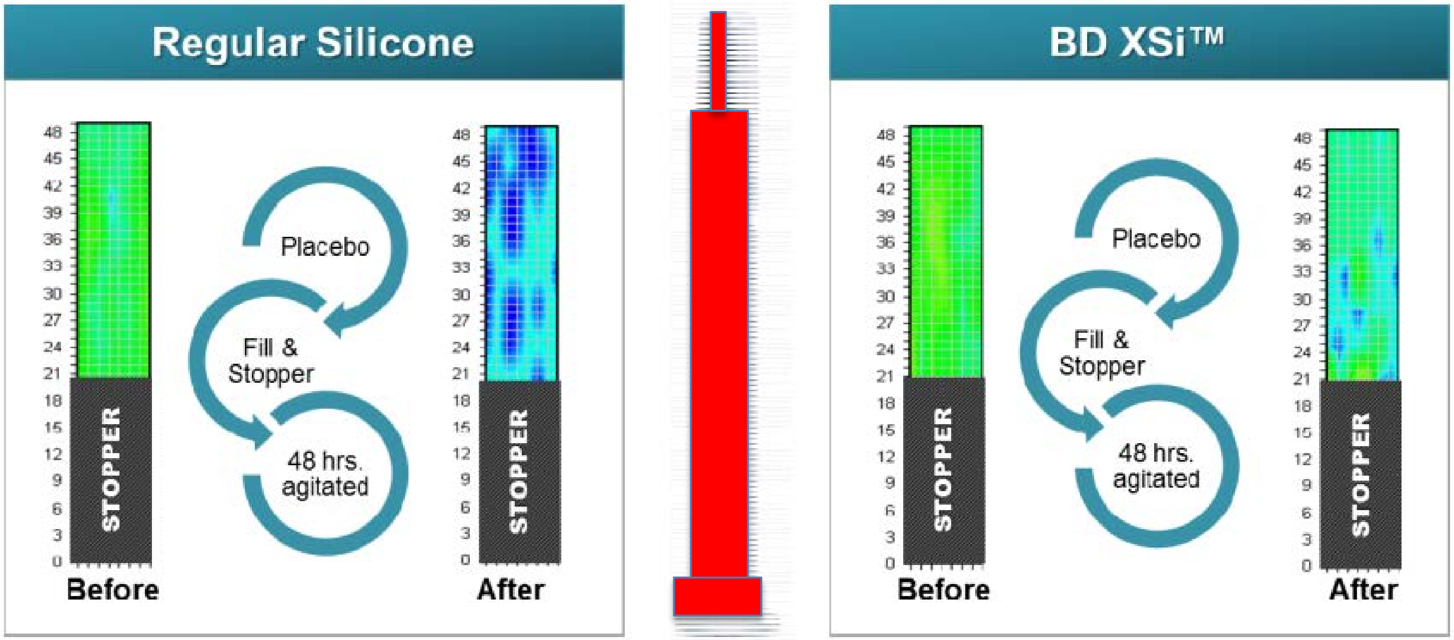
Formulation WFI Air



PFS - Comparision Study



BD Xsi ™ Coating development



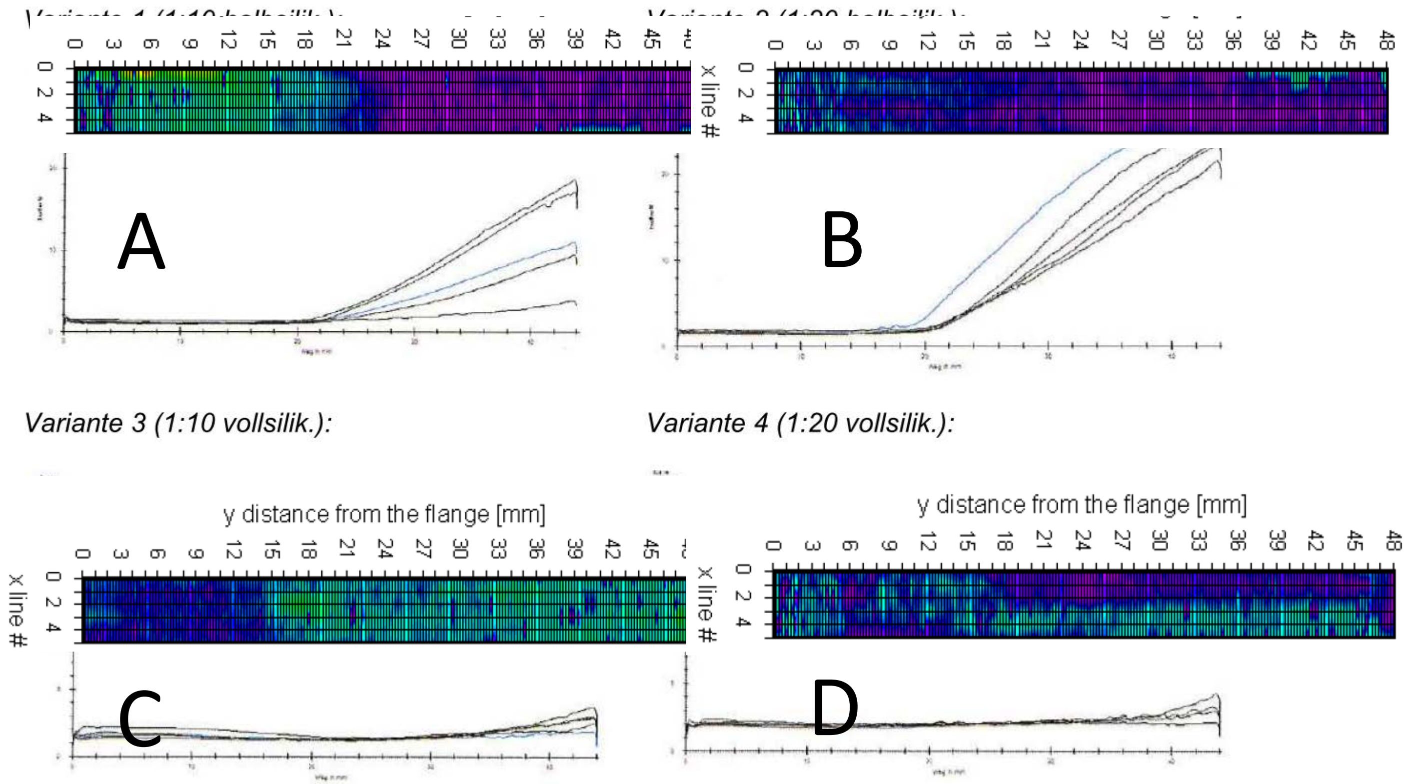
After exposure to protein therapeutics/excipients and 48 hrs agitation, the syringe coating layer demonstrates exceptional stability (reflectometry)

Source: Becton Dickinson

Comparison LE vs.

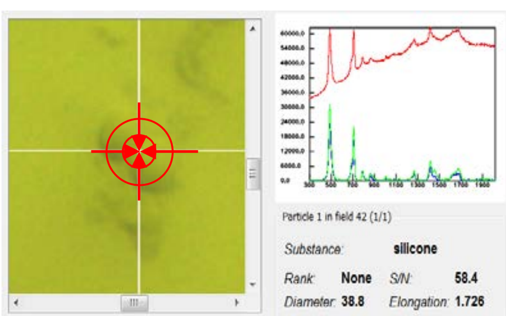
Sample	Layer Explorer	Extraction + FT-IR
A (1:10) ½	80 µg	81 µg
B (1:20) ½	40 µg	39 µg
C (1:10) 1	90 µg	110 µg
D (1:20) 1	60 µg	70 µg
E (1:40) 1	40 µg	30 µg

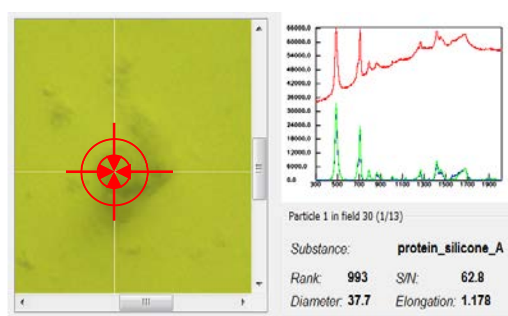
Silicone Patterns vs. Gliding Force

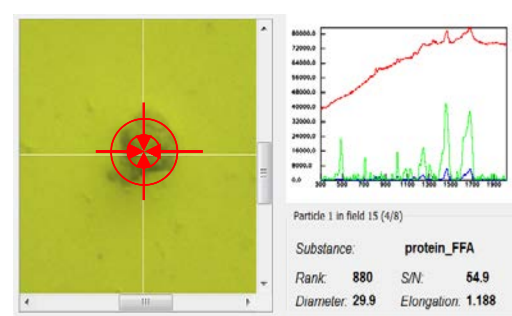


Silicone in Solution and Particles

Sample (>2 µm) in 300µL	Si (>2 µm) in 300µL	Si+Aggregate (>2 µm) in 300µL	Aggregate (>2 µm) in 300µL	Extraction of 5 mL Formulation
A (1:10) ½	1784	674	943	5 µg
B (1:20) ½	987	563	756	3 µg
C (1:10) 1	2145	786	1897	7 µg
D (1:20) 1	1324	896	1128	4 µg
E (1:40) 1	634	234	432	1 µg



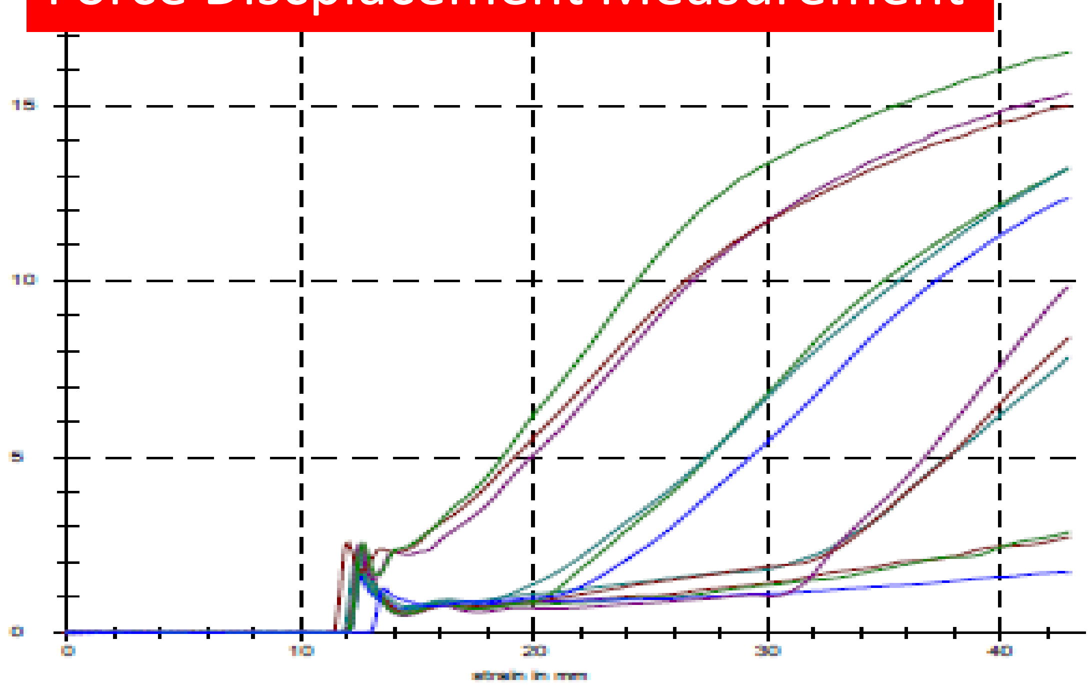




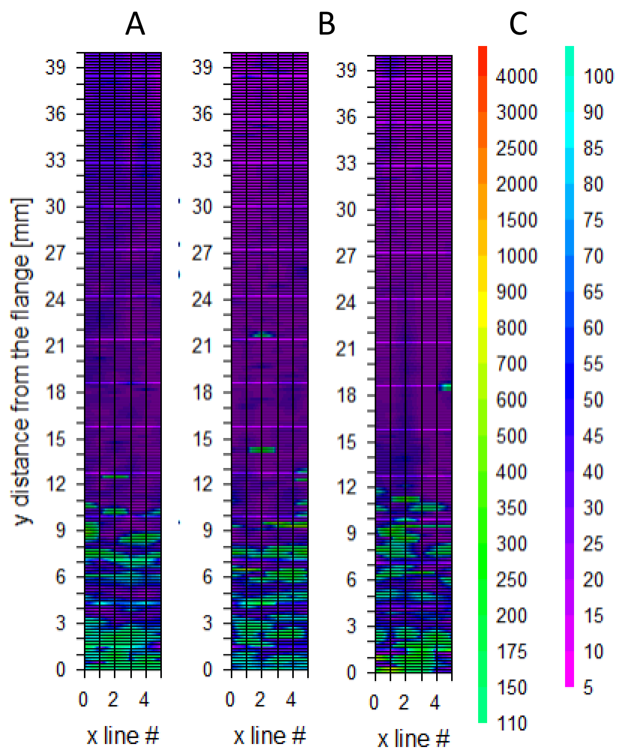
Telling good from bad containers

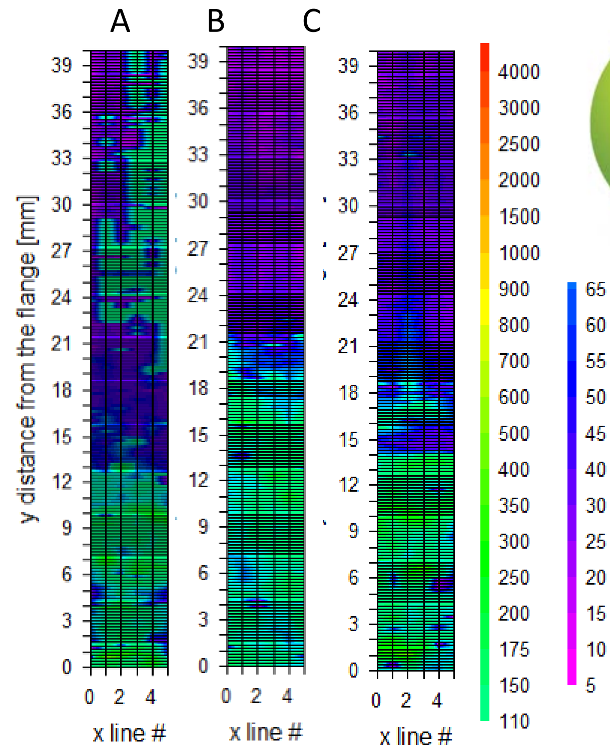
Good vs. Bad

Force Discplacement Measurement



2 D Maps (3 Samples)





- Cartridges show scattered silicone oil layer > 200 nm in the first 15 mm of the cartridge
- From mm 19-40 layer does drop below 20 nm
- Total amount: 15-25 µg

- Cartridges show silicone oil layer > 300 nm in the first 15 mm of the cartridge
- From mm 18-40 layer doesn´t drop below 50 nm
- Total amount: 70-85 µg

Silicone & Particles CQA

- Quality of the silicone layer is an important factor in product functionability and stability
- Distribution is affected of time, temperature and orientation
- The formulation has a great impact on the stability of the silicone layer since surfactants enhance the mobility and some proteins show a great attraction to silicone
- Measurement methods and therefore control is available
- Thorough investigations and clear benchmarks for the quality of siliconization should be determined and controlled before filling precious product

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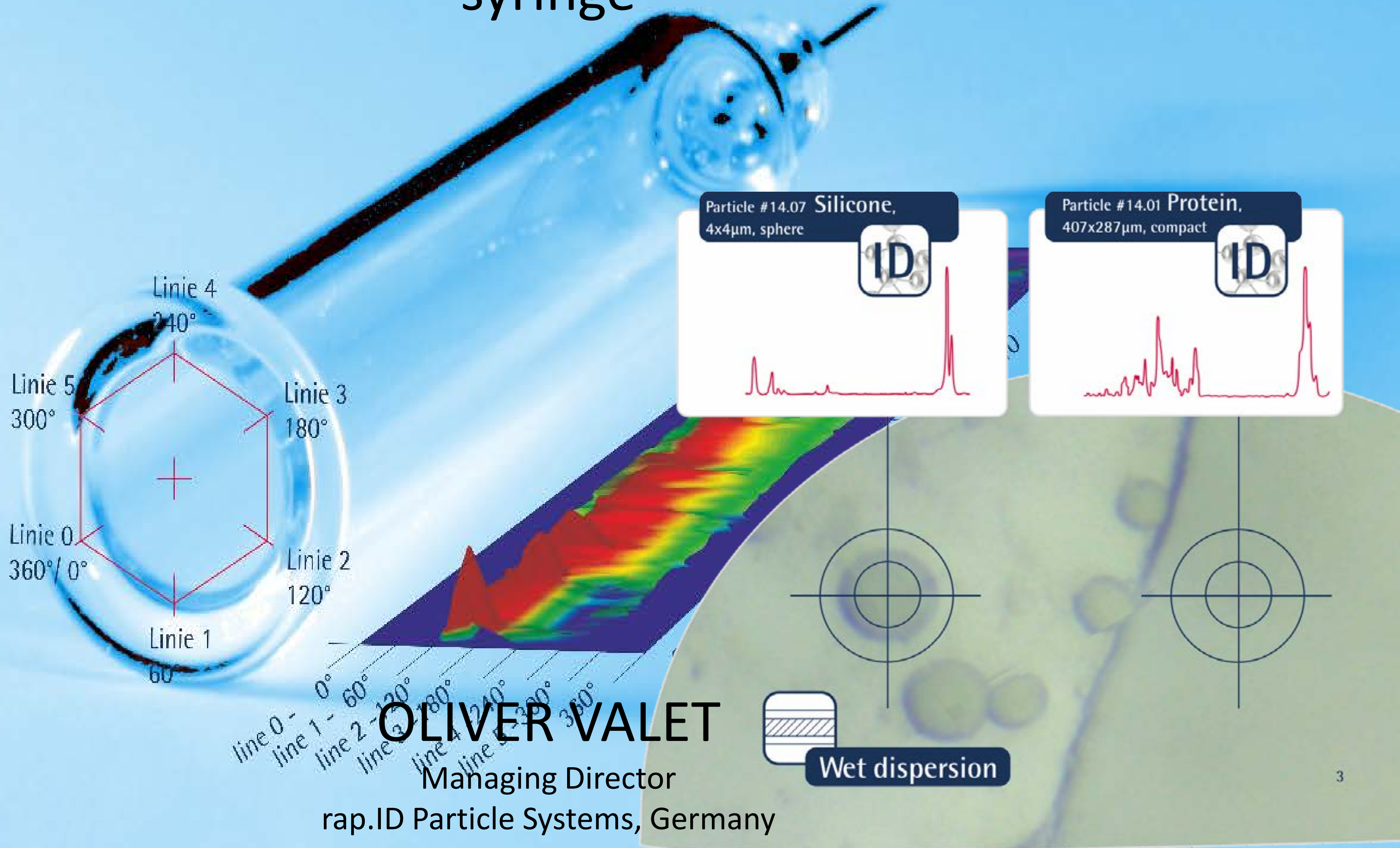
Characterization of silicone oil distribution in syringes and correlation with critical functional parameters of a pre filled syringe

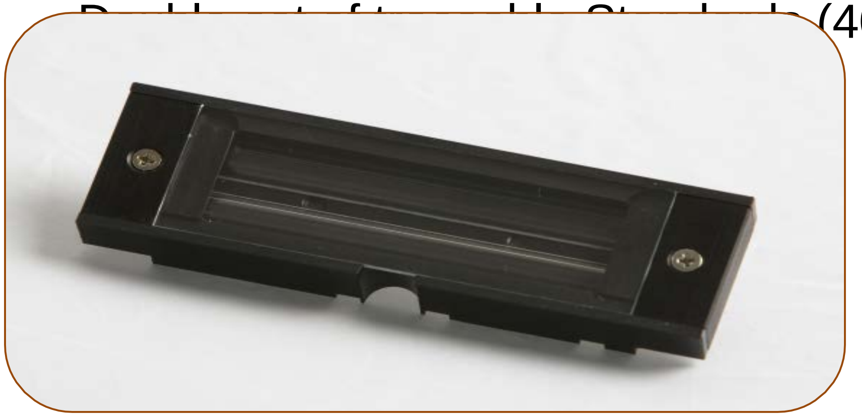


OLIVER VALET
Managing Director
rap.ID Particle Systems, Germany

Traceability

Traceable Standards:

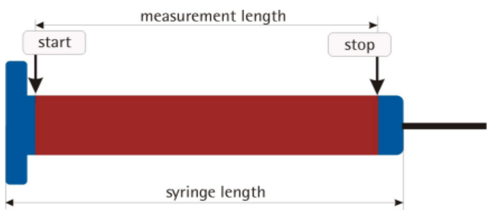
Dual layer set of traceable Standards (40, 80, 120, 500 nm)



- LE BI: 80 nm

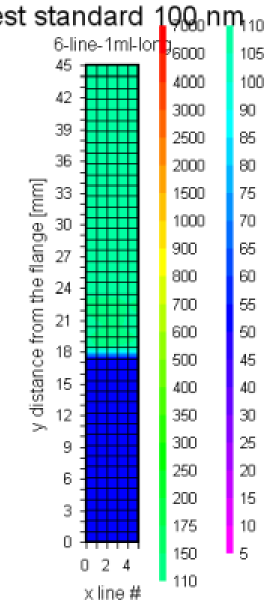
Calculations of silicone mass

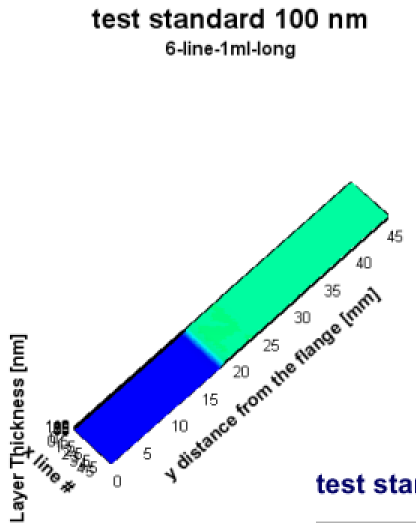
m= mass
d = inner diameter
L =syringe length
T = average thickness of the silicone layer
δSpecific gravity [Baked-on] = 0.971 g/mL a … cosity 350 cSt (25 °C) RI =1.4042)
δSpecific gravity [Spray-on] = 0.973 g/mL at … scosity 1000 cSt (25 °C) RI =1.4046)

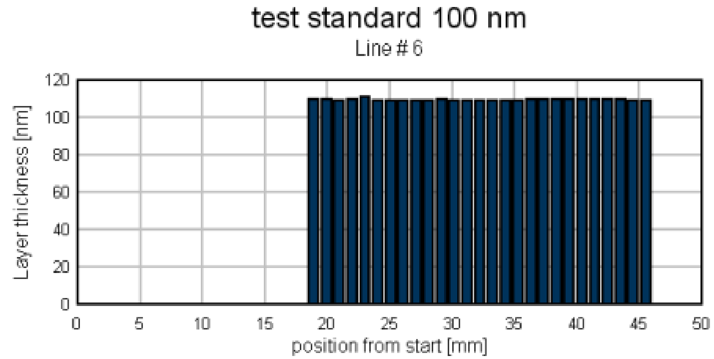


$$m = \pi d\ [mm] * L\ [mm] * \delta\ [g/cm^3] * T\ [nm] = [mg]$$

Results from measuring the standard (100 nm)







All Lines Data

anReflection

test standard 100 nm

Line #	Layer Thickness [nm]	RSD%
0°	109	0
60°	110	1
120°	110	1
180°	110	1
240°	109	0
300°	109	0

- mean silicone: 109nm
- RSD%: 0
- silicone weight: 116 µg

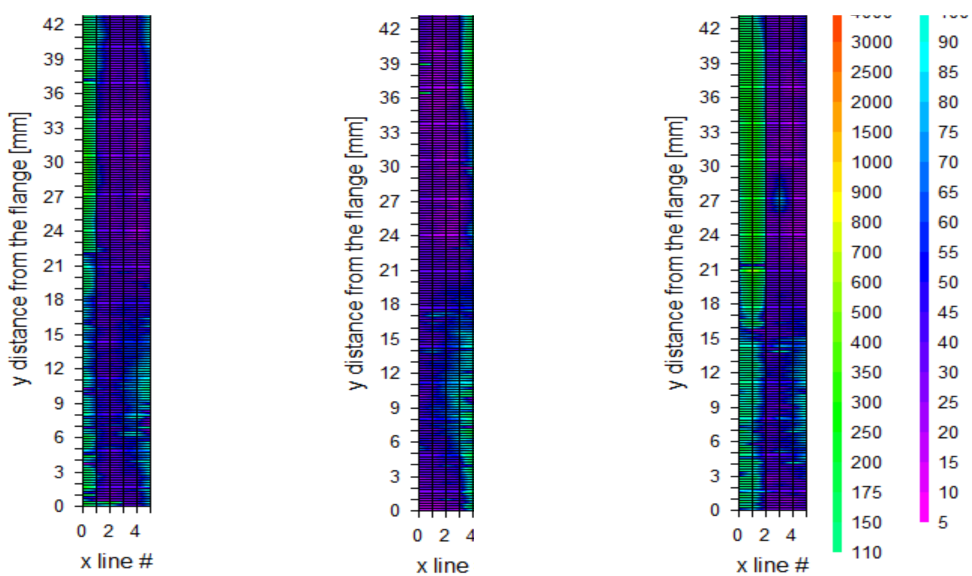
Inter-machine comparison (traceable st

Layer Explorer	488 nm cert.	146 nm cert.	78 nm cert.	37 nm cert.	Operator	Date
Instrument A	474	139	74	32	A	13.06.17 (PM)
Instrument B	474	142	78	33	B	14.06.17 (PM)
Instrument C	472	142	81	30	A	22.06.17 (PM)
Instrument D	473	139	78	31	A	22.06.17 (PM)
Instrument E	474	141			B	20.07.17 (PM)
Instrument F	473	142			A	02.08.17 (PM
Average	473	141	77.75	31.5		
%RSD	0.2%	1.0%	3.7%	4.1%		

Performance qualification

What is the right resolution?

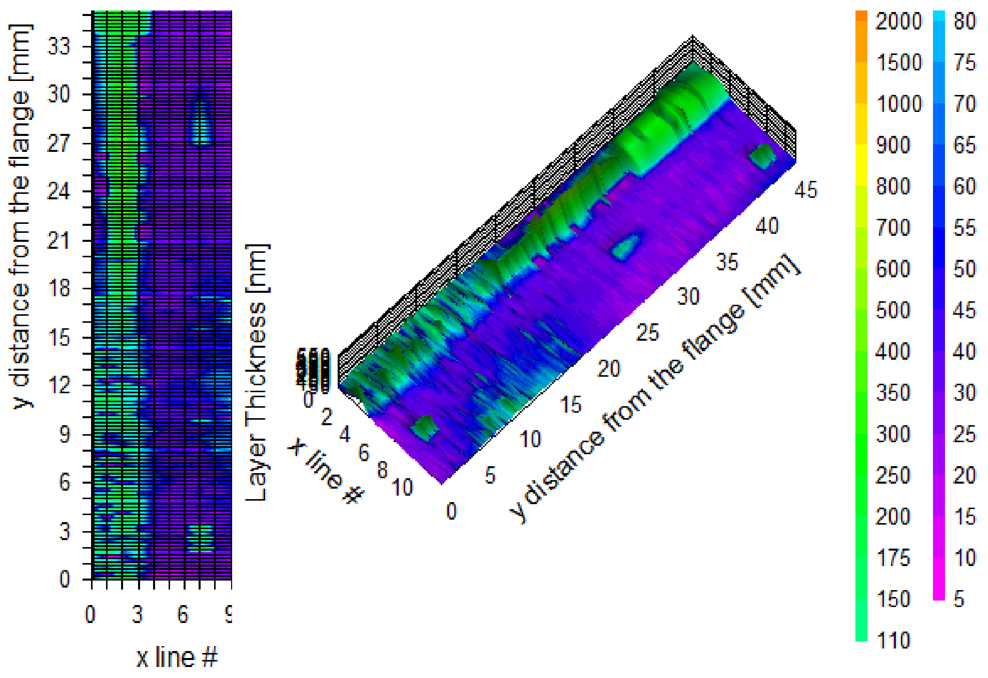
M1: 114 µg M2: 104 µg M3: 116 µg



Reproducability @ 6 lines

Same sample → 12 lines

M4: 107 µg



Resolution vs. Repeatability

Same Syringe 2 Operators
Different Days

Measurement	µg	Dev
M1 (6 Lines)	114	-4%
M2 (6 Lines)	104	5%
M3 (6 Lines)	116	-5%
M4 (12 Lines)	107	3%
Mean	110	

Strategy to apply ICH

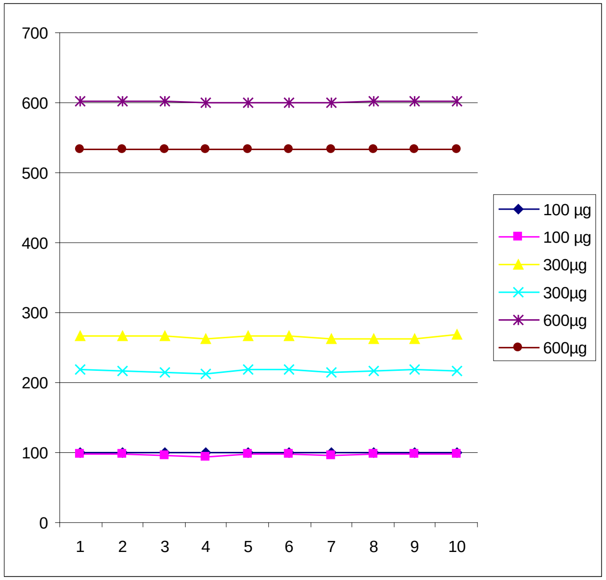
Validation approaches

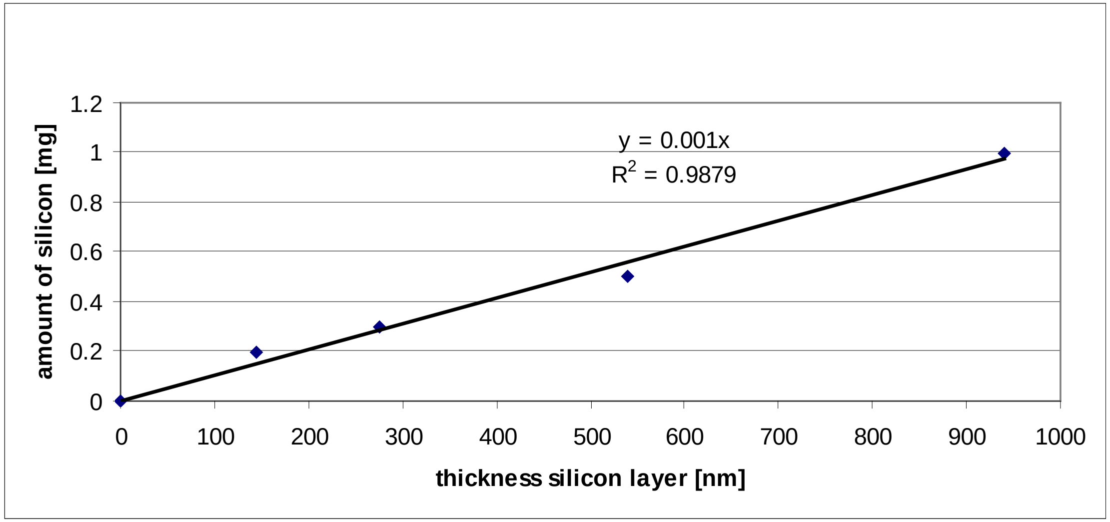
Amount of silicone vs. layer thickness

Determination of silicone content with LE:

- Measuring parameters: 25 points in 2 mm distance, spotsize of each point: 50 µm
- Mean Layer thickness calculation of the mean of 25 measured points along the barrel
- Manufacturing of 5 different siliconized syringes, 1 ml, not filled
- Silicone oil viscosity 1000 cSt, type: DC360)
- Silicone content per Syringe: 0 mg, 0.2 mg, 0.3-0.4 mg, 0.5 mg, 1 mg

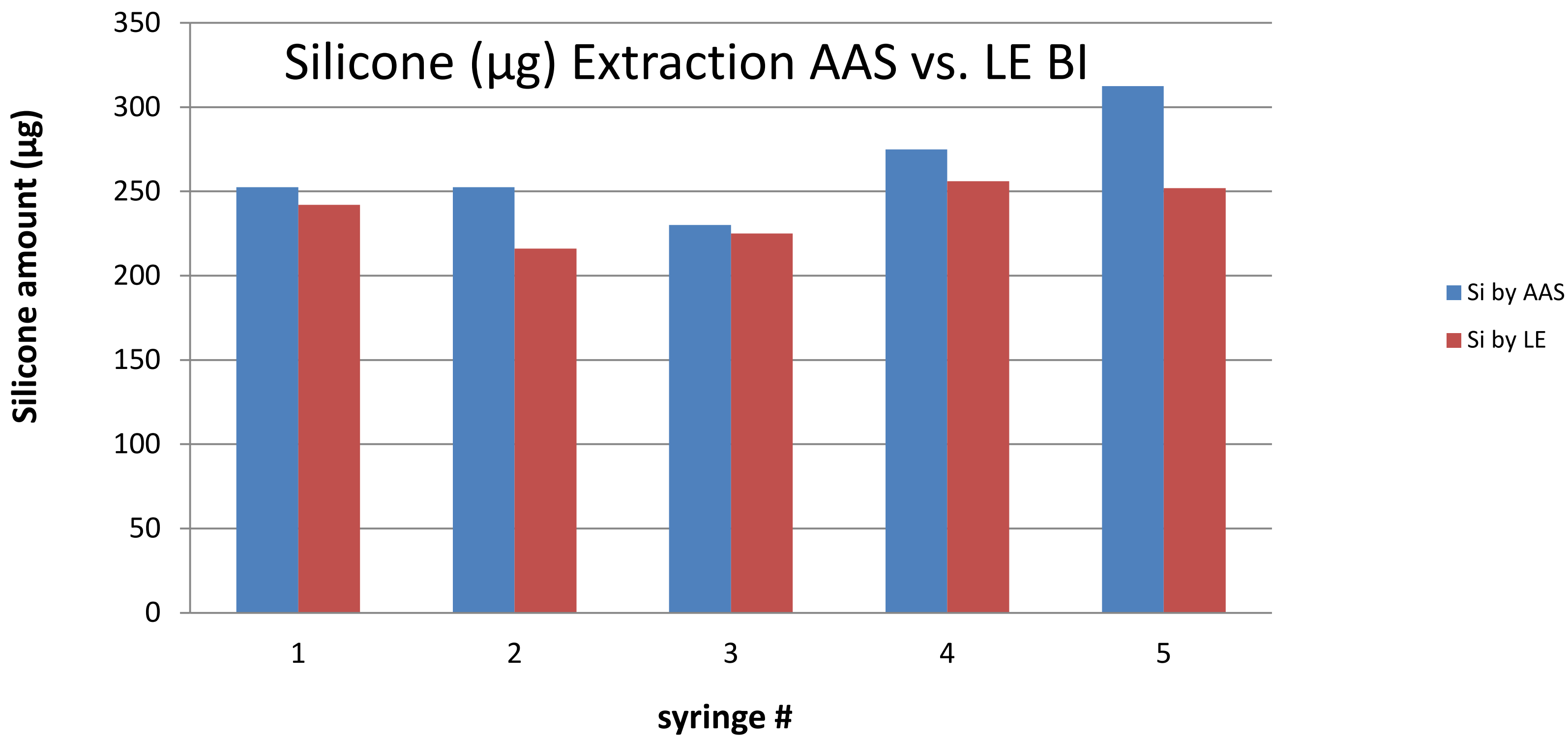
Linearity of the Measurement





Good correlation between layer thickness and amount of silicone oil

Accuracy (I) – comparison with other techniques

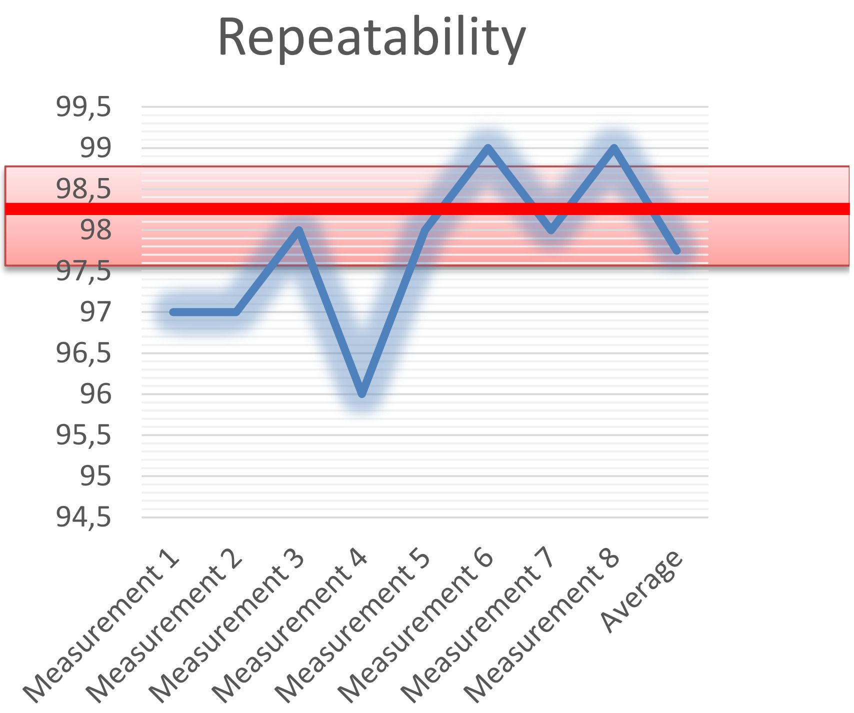


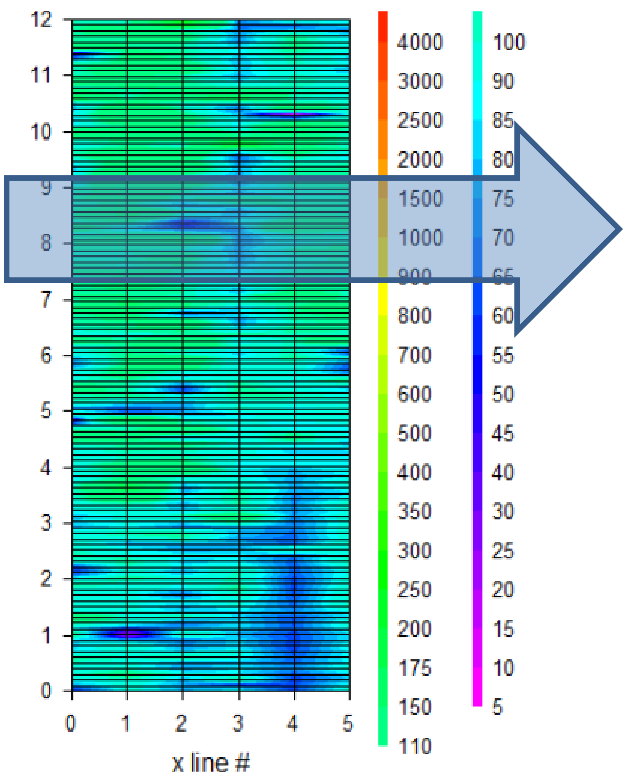
Source: BD – **Jianxiu Zhao, PhD**Franklin Lal

Repeatability -Baked-in cartridge over 8 days

Measurement	nm	µg	Date	Time	Operator
Measurement 1	97	186	20.5.	09:06	User A
Measurement 2	97	186	20.5.	17:18	User B
Measurement 3	98	187	21.5.	08:46	User A
Measurement 4	96	184	26.5.	08:13	User B
Measurement 5	98	187	22.5.	10:11	User A
Measurement 6	99	189	22.5.	15:37	User B
Measurement 7	98	187	27.5.	09:17	User A
Measurement 8	99	189	28.5.	08:11	User A
Average	98	187			
%RSD	1.1%	0.88%			

Repeatability - Intermediate Precision





%RSD= 1.1%