Stevanato Group

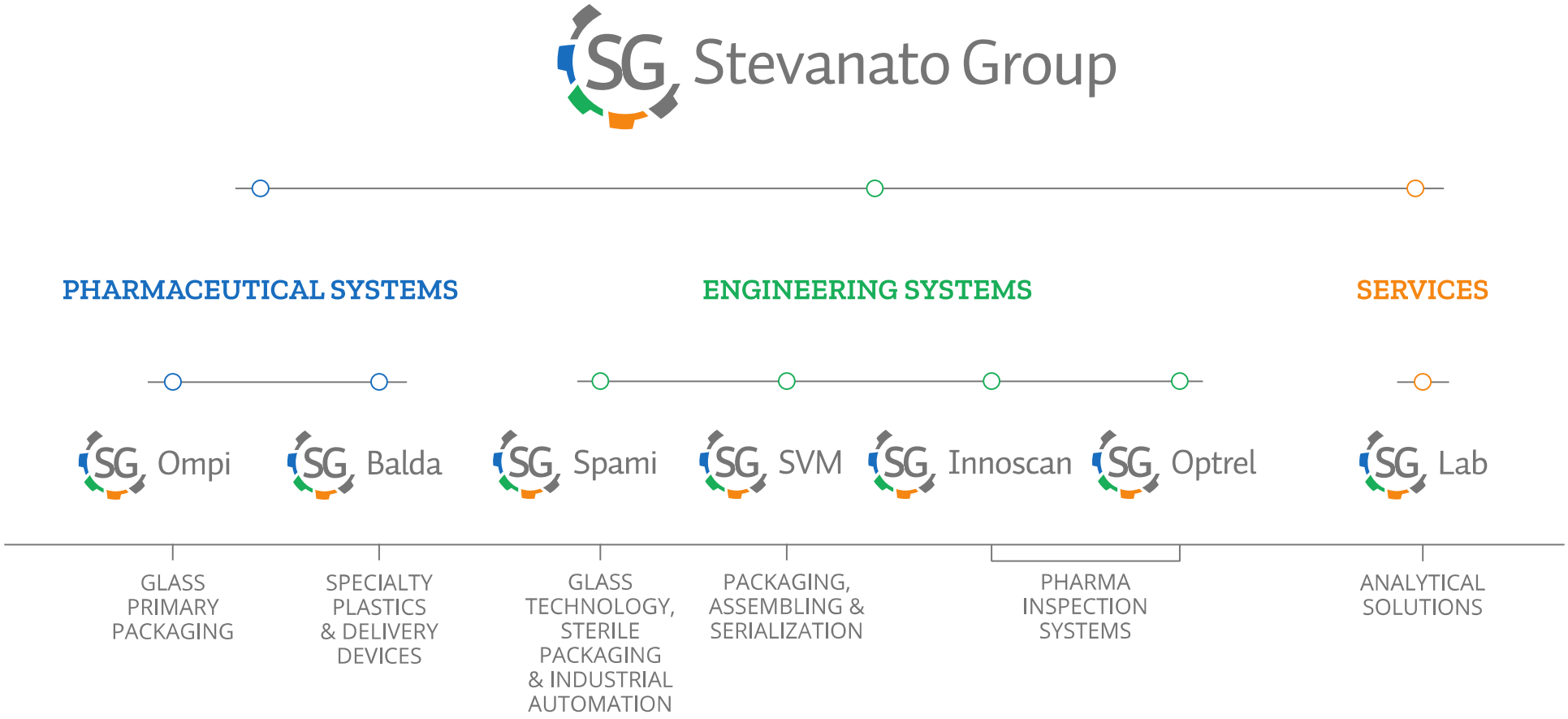
ENGINEERING SYSTEMS

Tools to monitor consistency: visual inspection and inspection technology. Global, regional and national expectations

Gaetano Baccinelli, Sales Manager

Stevanato Group Engineering Systems

Stevanato Group Brand Structure



Different options for inspecting

Technology	Handling	Inspection
Manual	Operator	Operator
Semi-Automatic	Automated	Operator
Fully Automatic	Automated	Automated

Pro's Con's of each Technology

MANUAL

High Variability due to Human Factor

SEMI-AUTOMATIC

Small Batches
Low False Reject
Ideal for Expensive Drugs
Ideal for Lyo/Powder
Variability due to Human Factor

FULLY AUTOMATIC

Large Industrial Batches
100% Cosmetic inspection
False Rejects to keep in consideration (Lyo/Powder)

Inspection Machines Portfolio

VERY HIGH SPEED
Up to 600 pcs/min

CVT Series

- To inspect challenging, high value drugs
- Optical tracking cameras for high accuracy and very high speed

MEDIUM - HIGH SPEED
Up to 400 pcs/min

Plus Series

- To inspect complex products
- High resolution images
- Leak test machine

MEDIUM - HIGH SPEED
Up to 400 pcs/min

Easy Series

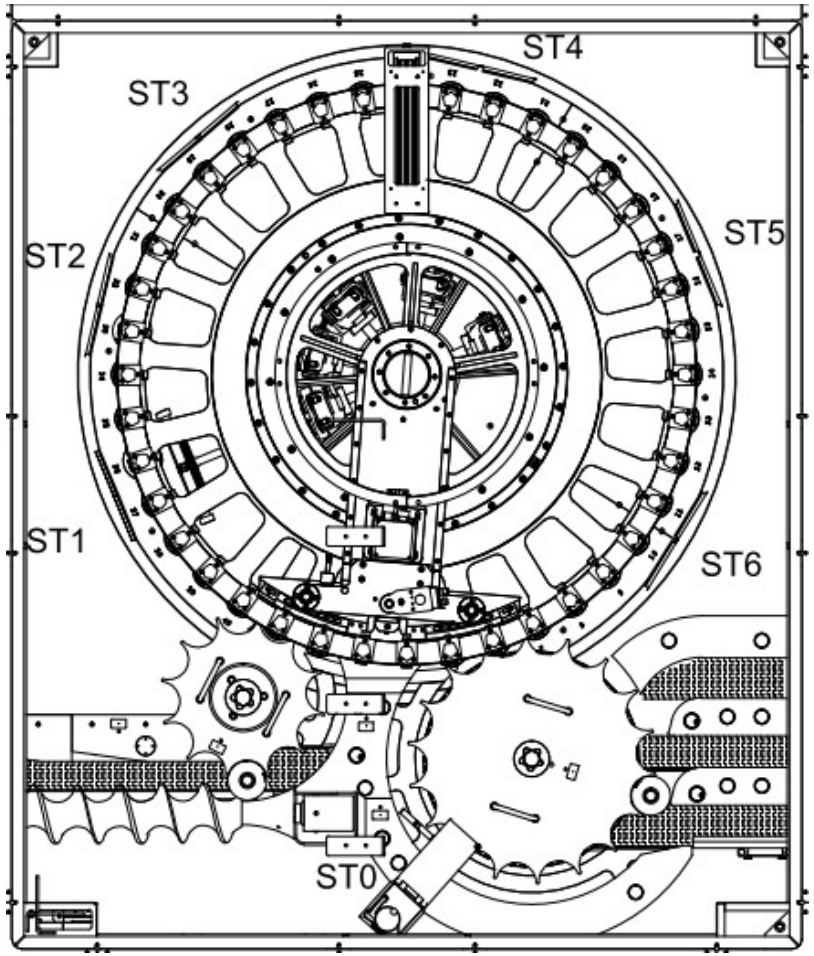
- To inspect water-like products
- Value-for-cost choice
- Easy to maintain

SEMI-AUTOMATIC
Up to 100 pcs/min

PWL Series

- Ideal for small volume inspection or critical products

Controls layout for a typical automatic inspection machine



	Type	Position
ST0	Closure control	Exit
ST1	Crimping control	Turret
ST2	Body control lateral	Turret
ST3	Particle and fill level	Turret
ST4	Particle inspection	Turret
ST5	Particle inspection	Turret
ST6	Floating particles	Turret
ST7	Bottom inspection	Outfeed

Example of defects

Particulate Matter

Closure Integrity

Cosmetic Defects

Standard transparent solutions: particles inspection

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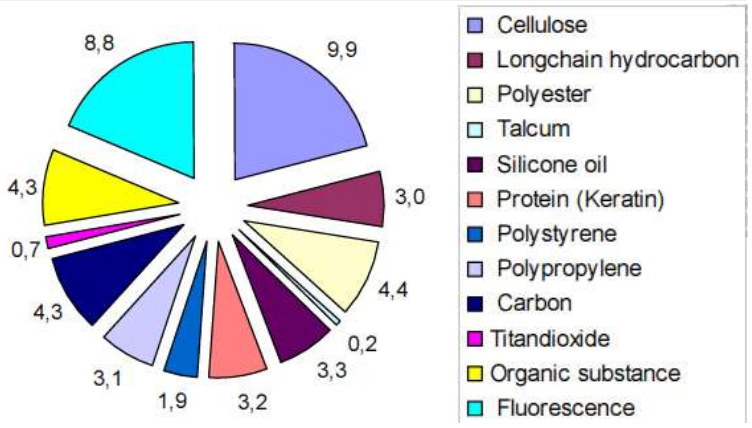
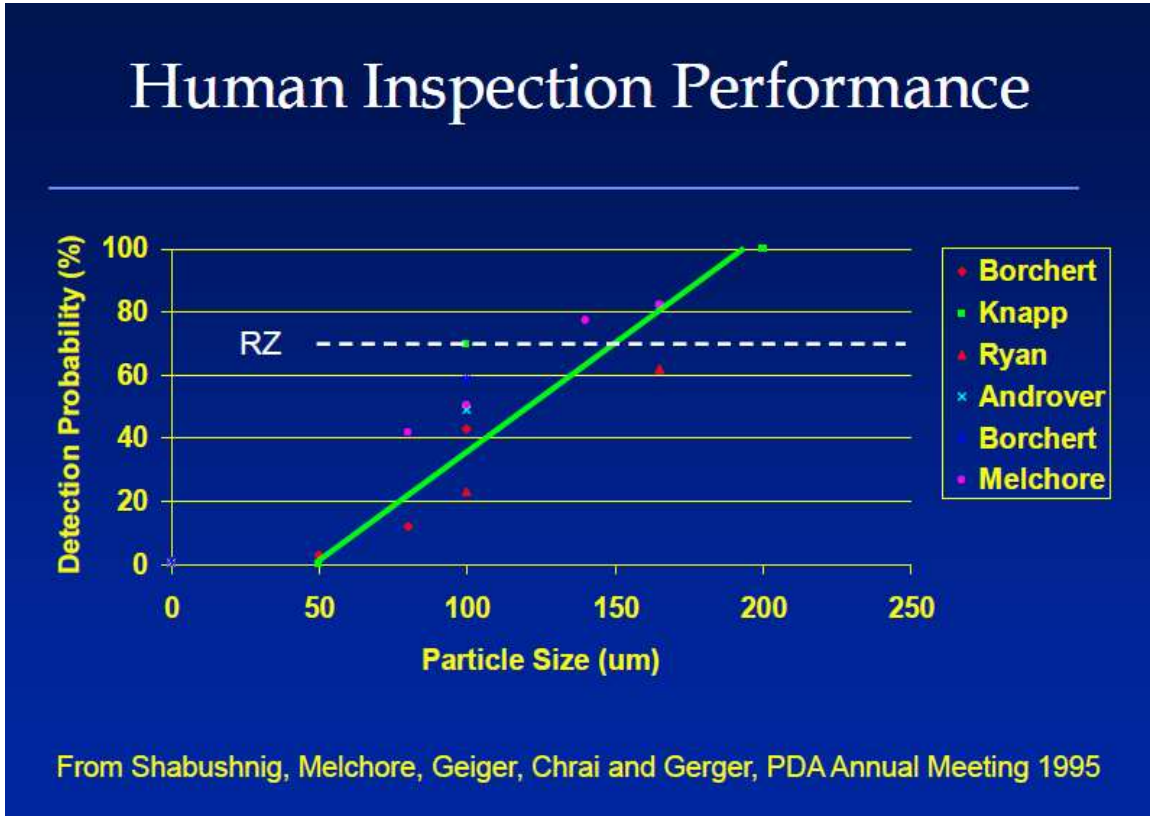
Most common foreign matter found in drug production

Substance	%	Nature	Source
Cellulose	9.9	fibers	clothes, towels, wipers, autoclave paper
Longchain hydrocarbon	3.0	rubber, PE	stopper, bottles
Polyester	4.4	fibers, particles	Cleanroom clothes and filters
Talcum	0.2	product	API
Silicon oil	3.3	particles, drop	Sealing, siliconisation
Protein (Keratin)	3.2	mostly flakes	Human skin dust, hair
Polystirene	1.9		
Polypropylene	3.1		
Carbon	4.3		
Titandioxide	0.7		
Organic	4.3		
Fluorescence	8.8		



Inspection performance limit



100% inspection (human or machine) is needed to detect small quantities of randomly sourced foreign material

- 100% inspection (man or machine) is not 100% effective.
- Zero is not a practical limit.

Different contaminants have different response to light

A reliable detection has to combine the advantages of the various lighting methods in order to detect the largest range of contaminants

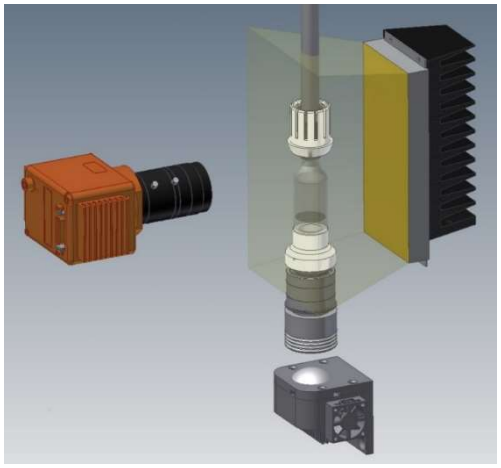
Absorbing
- Carbonization
- Impurities
- Rubber fragments

Reflecting
- Glass fragments
- Crystallization
- Silicone oil
- Delamination

Polarizing
- Fibers
- Impurities
- Product aggregation

Multi-scatter
- Fibers
- Impurities
- Glass fragments

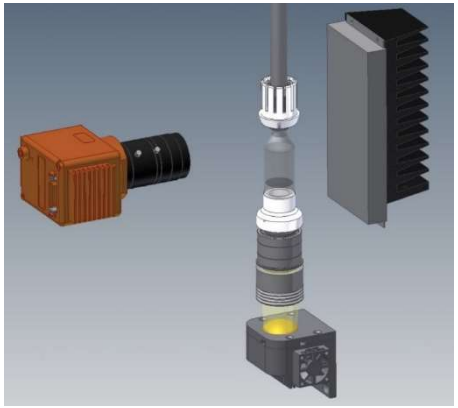
Particles inspection: particle in white background

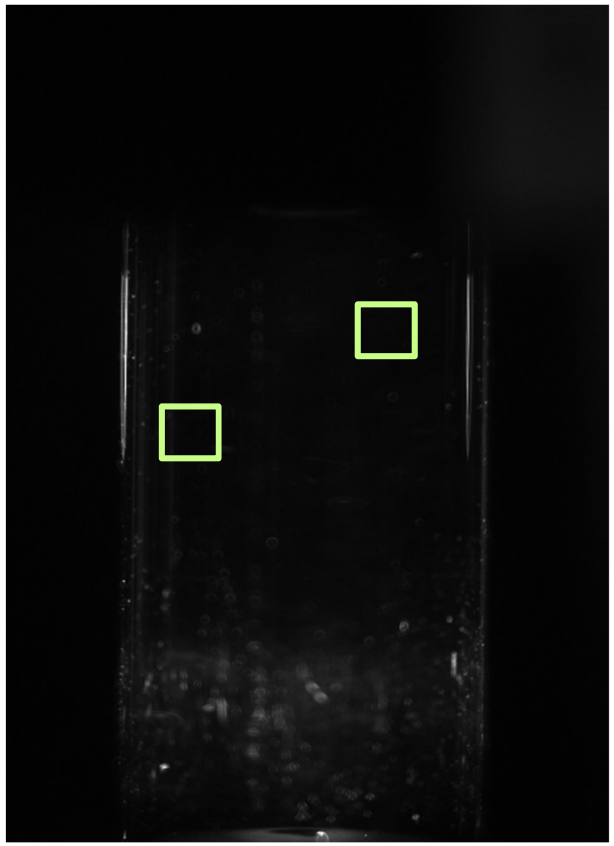


Possible Source

- Product carbonization for improper flame sealing of ampoules tip
- Impurities from API/WFI
- Rubber particles

Particles inspection: particle in black background

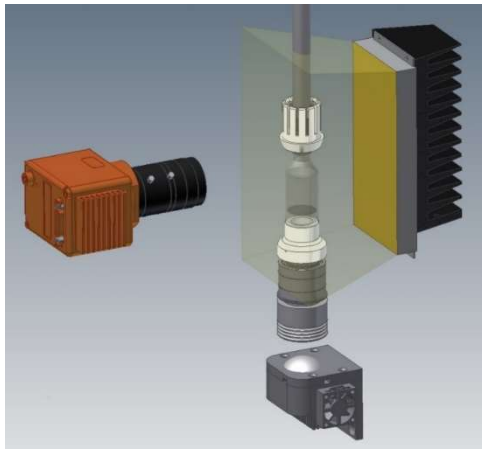




Reflecting Particles

- Glass fragments, filling needle not centered
- Product crystallization
- Silicone oil from stopper/plunger
- Glass Delamination

Particle inspection: fibers in polarized light



Inspection method

- Polarized light illumination

Possible Source

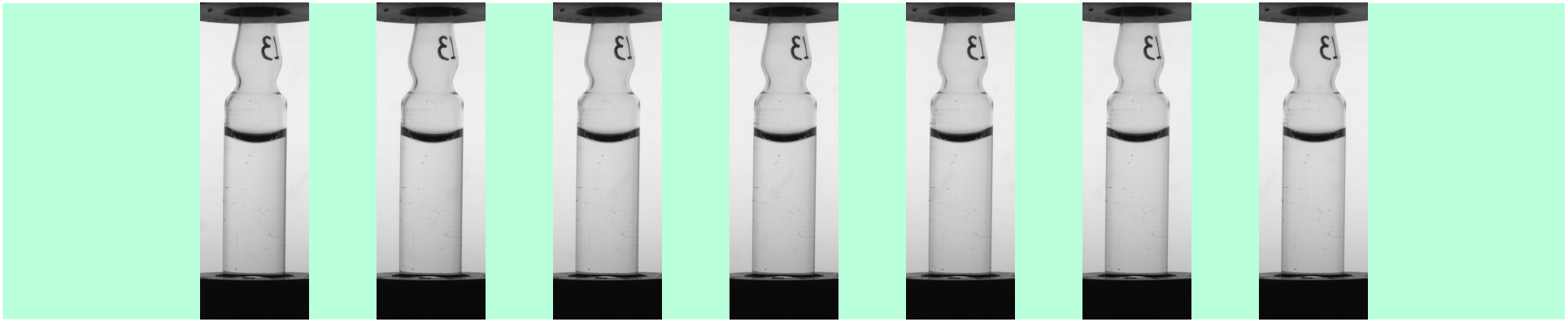
- Fibers from filter/wipper
- Impurities from API/WFI
- Fibers from clothing

How to combine all these setup in a single camera station?

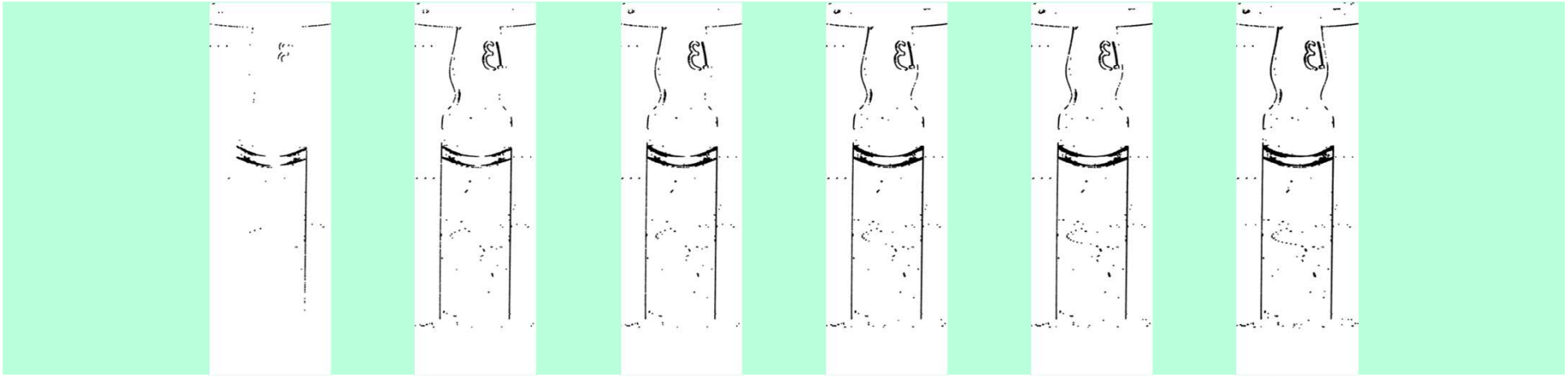
High resolution high speed cameras acquire from **40 to 120 images**, half with one illumination setup half with another to detect all kind of contaminants

Standard interframe analysis

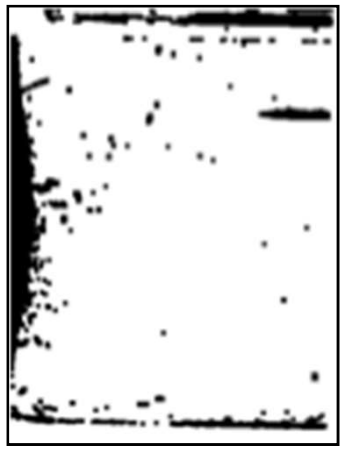
Acquisition of a sequence of 12 up to 120 images from the container under inspection



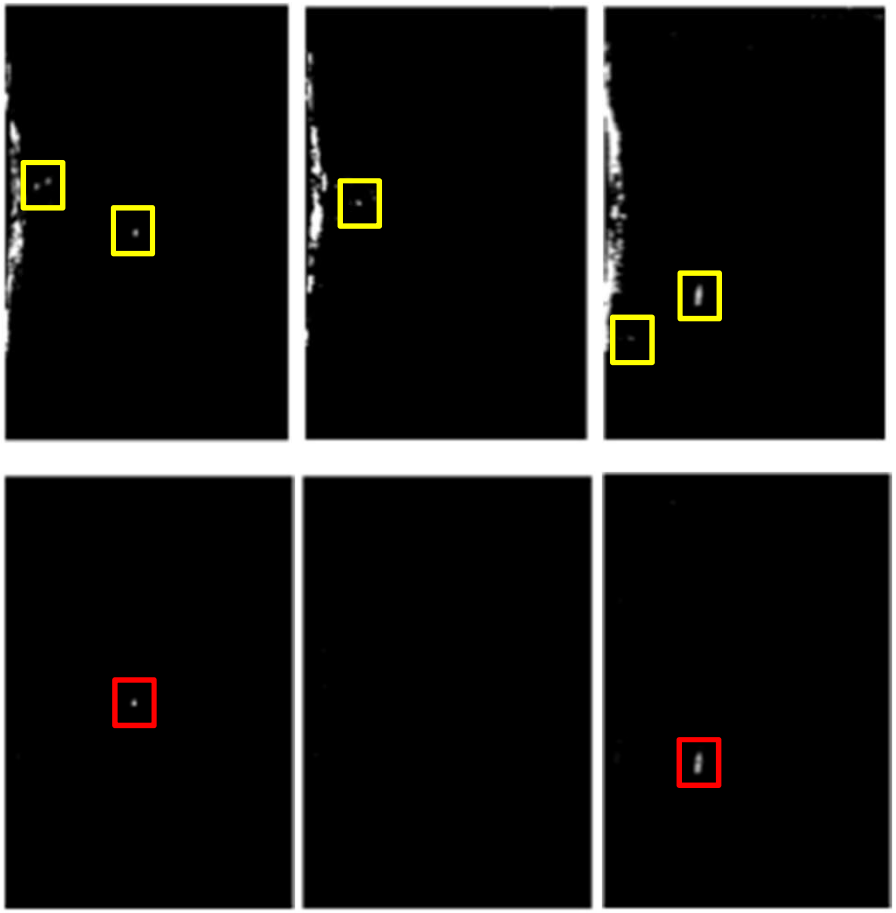
Compute the sequence of differential images one by one



Background subtraction



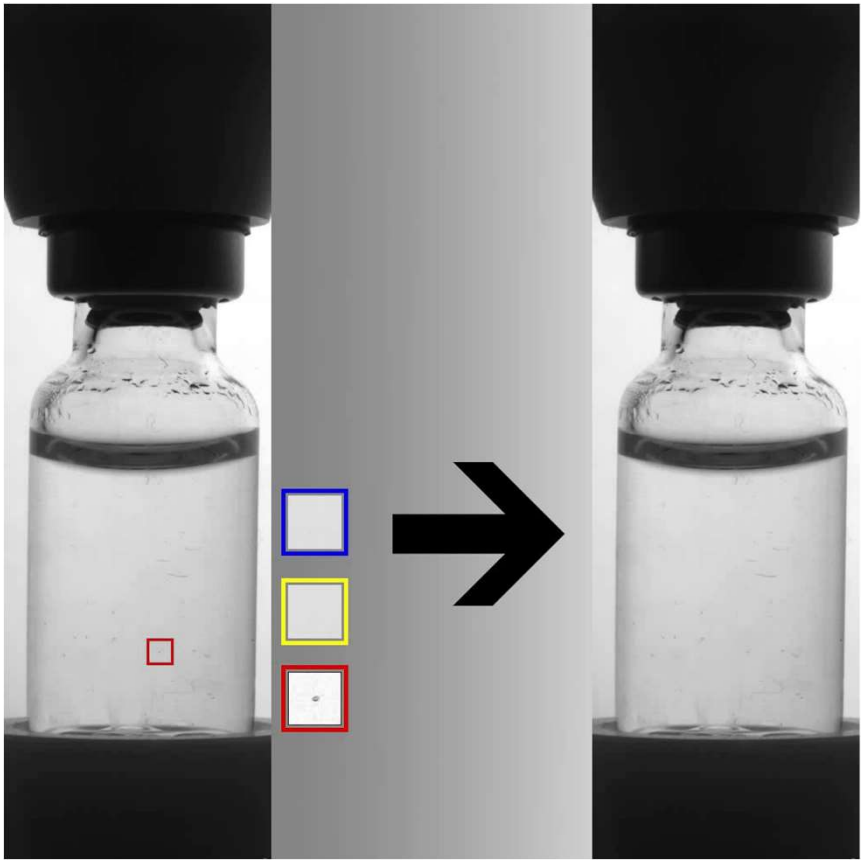
&



Compute the “don’t care” Mask of the images using a Background Estimator on the sequence

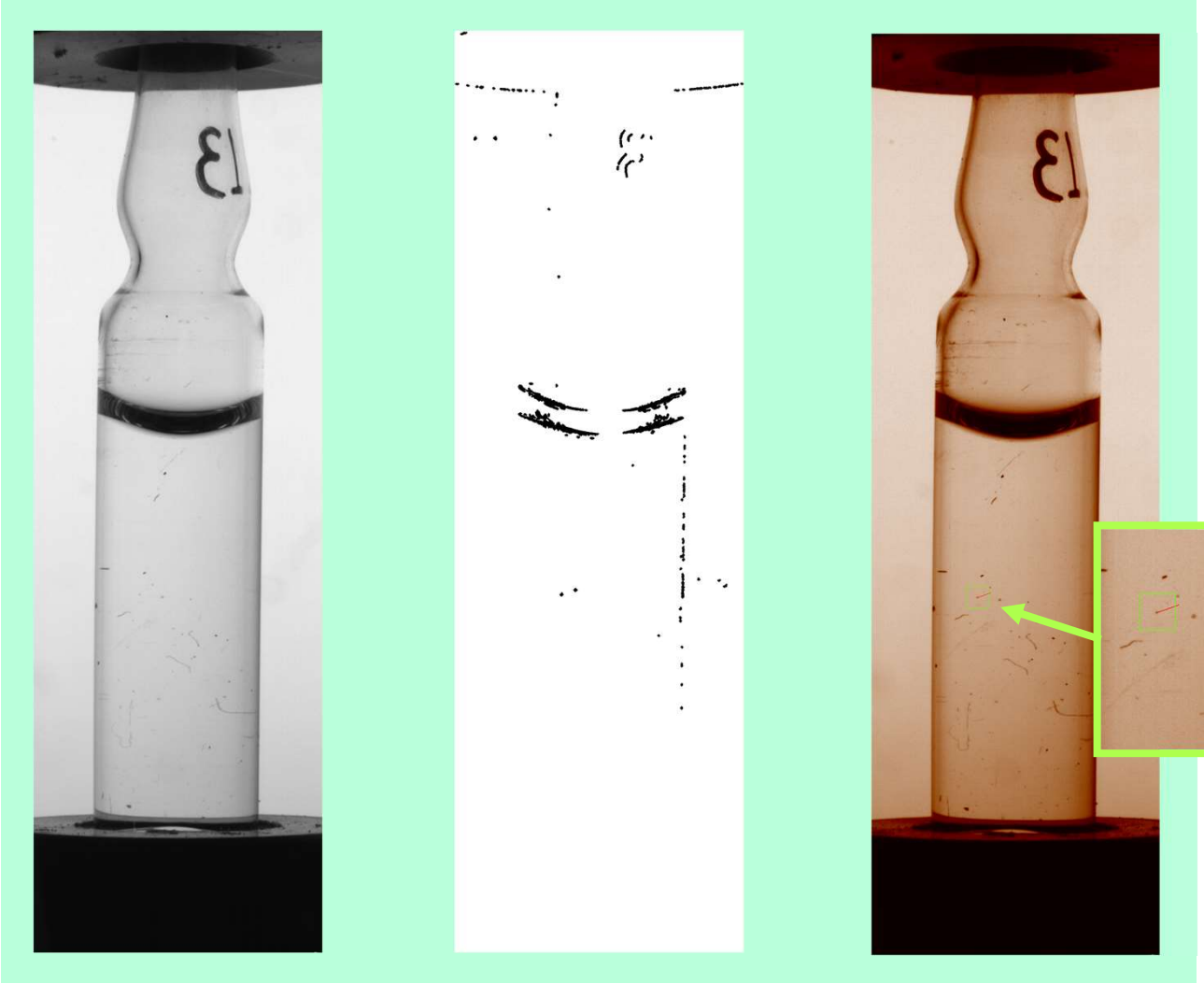
The reflexes are removed but sometimes canceling particles

Optrel: new concept, dynamic analysis

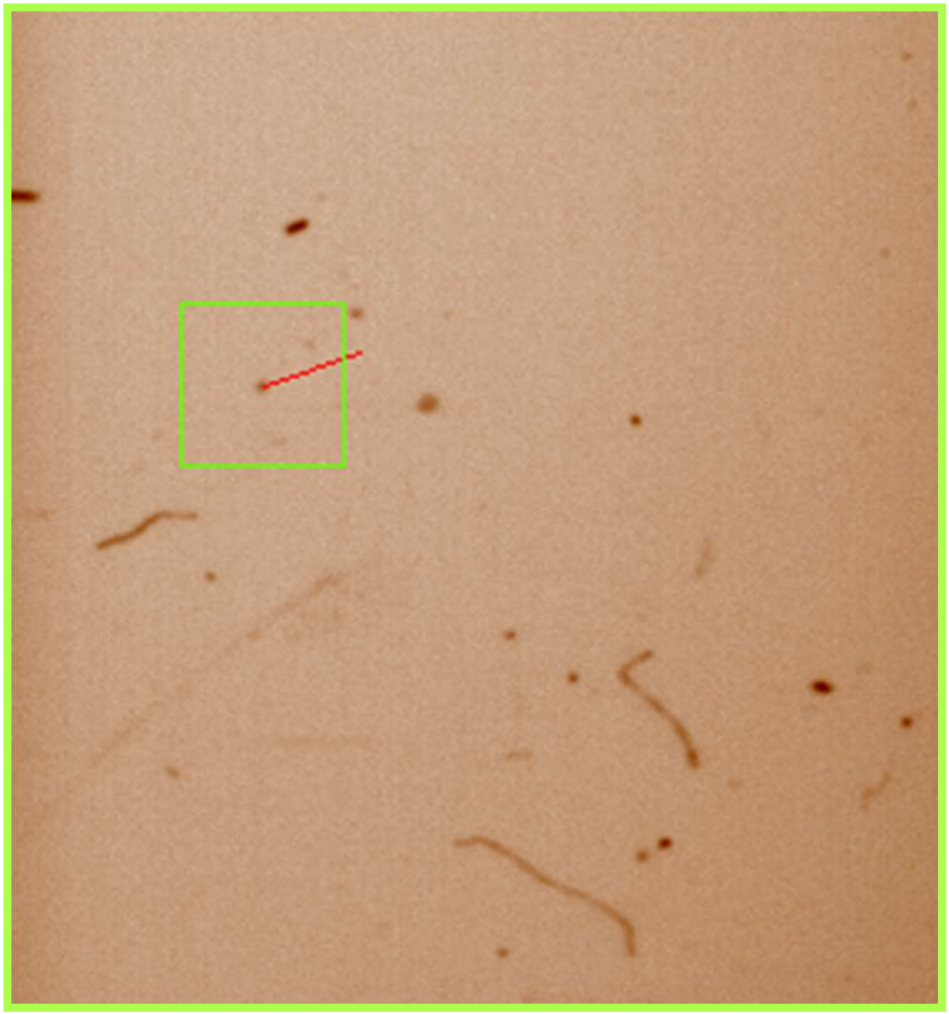


- Particle trajectory reconstruction using the Kalman filter
- Trajectory post analysis filtering
- Analysis of the meniscus
- Analysis of the container bottom

Particles inspection: dynamic vs interframe analysis



Particles inspection: trajectory details



- Diff Threshold =12
- Area Threshold = 5
- Particle size < 50µm
- Trajectory life= 60 frames
- Field of View = 10 ml

Optrel dynamic analysis, trajectory alghoritm

A smart way to reach high efficiency and reduce false rejection in automatic inspection

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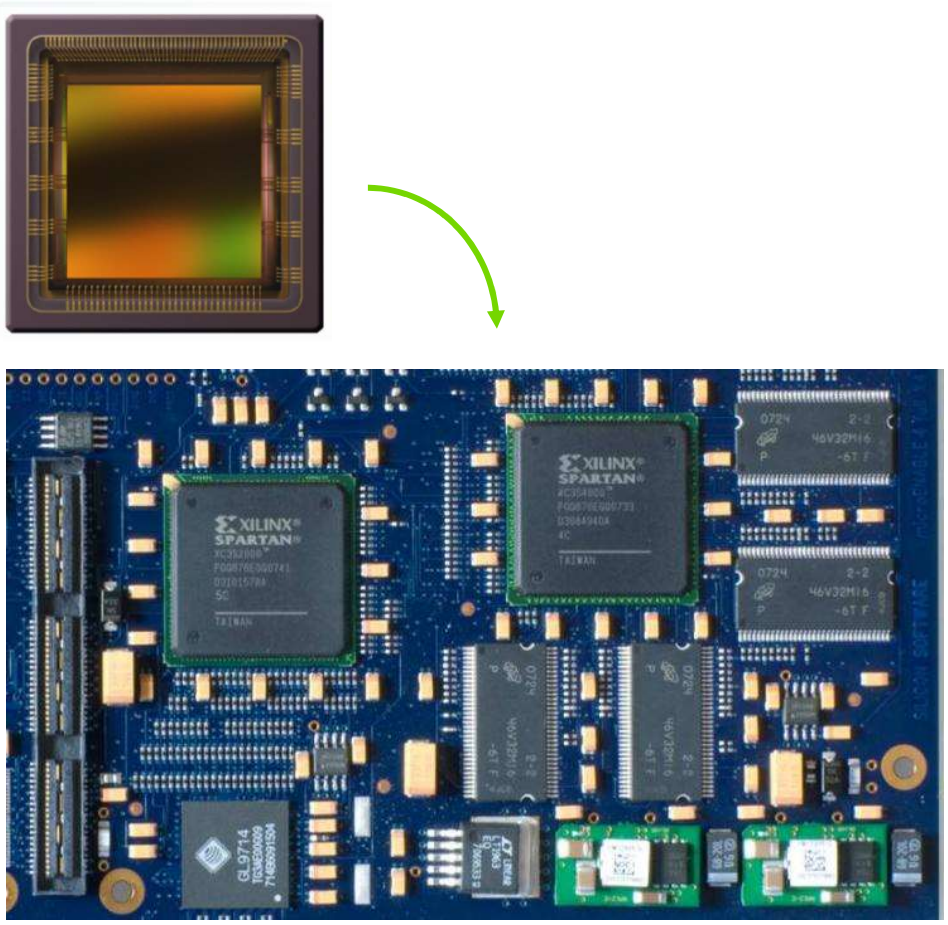
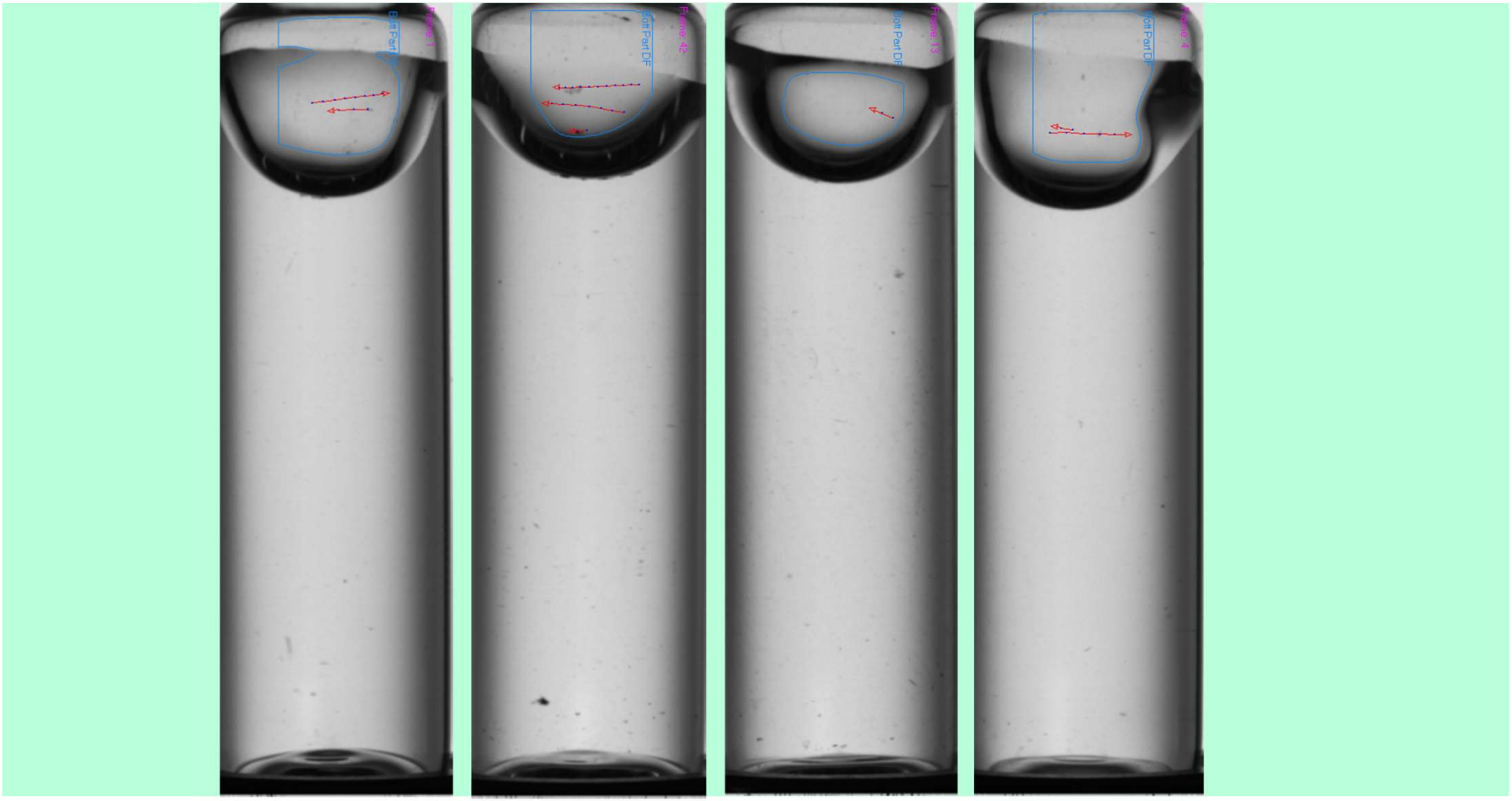
How to achieve those performances?



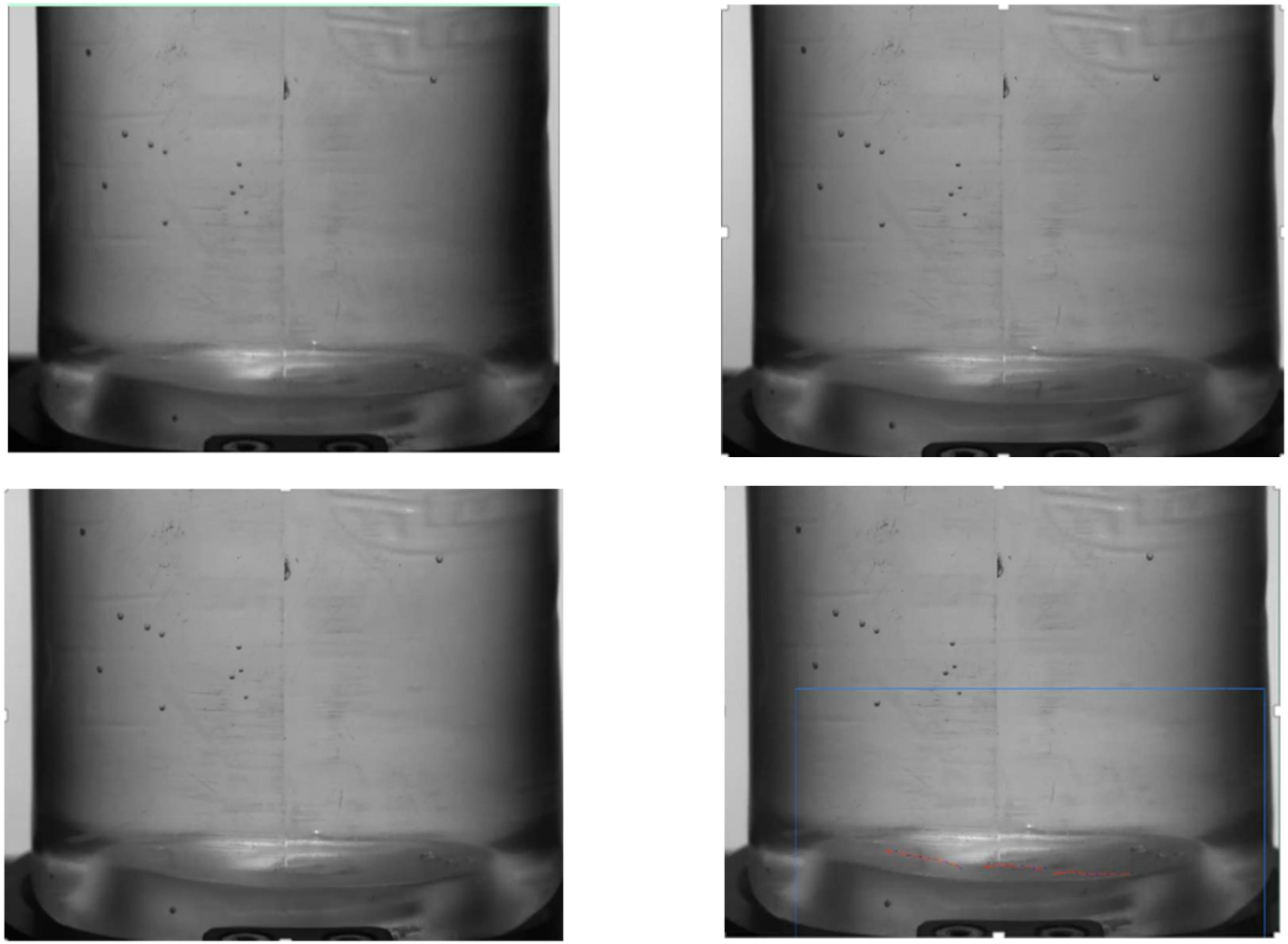
New Generation Advanced Vision System Facts

- 64 high resolution images per container per particle station (2000x2000pxls)
- 256 images per container for particle inspection
- 1GB of particle inspection data per container to process in real-time

Trajectory, best solution for floating particles inspection



Trajectory best performing for bottom particles inspection



View of particles inspection on syringes

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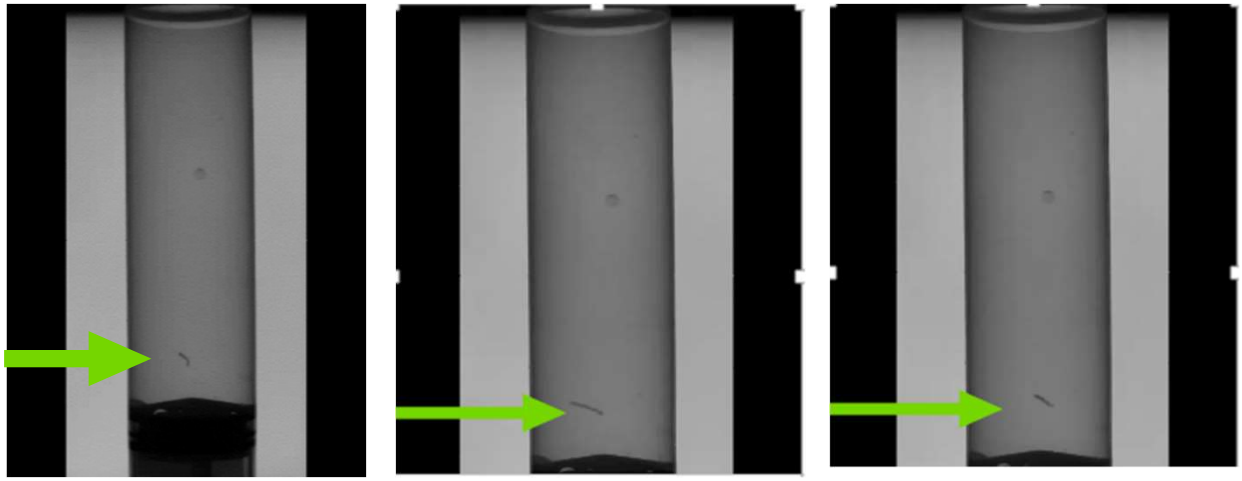
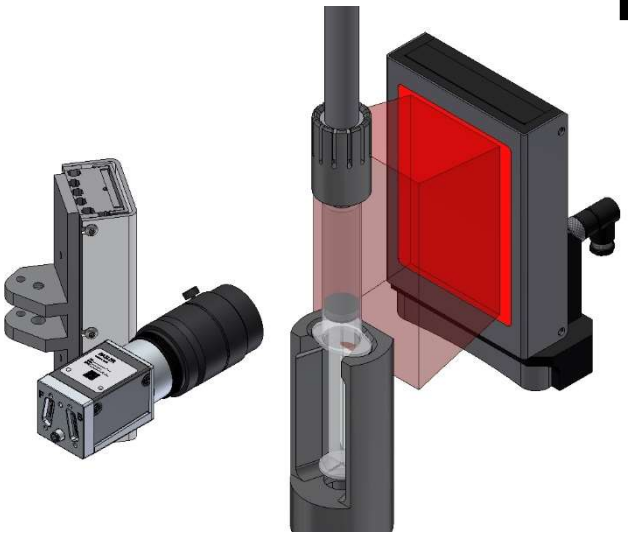
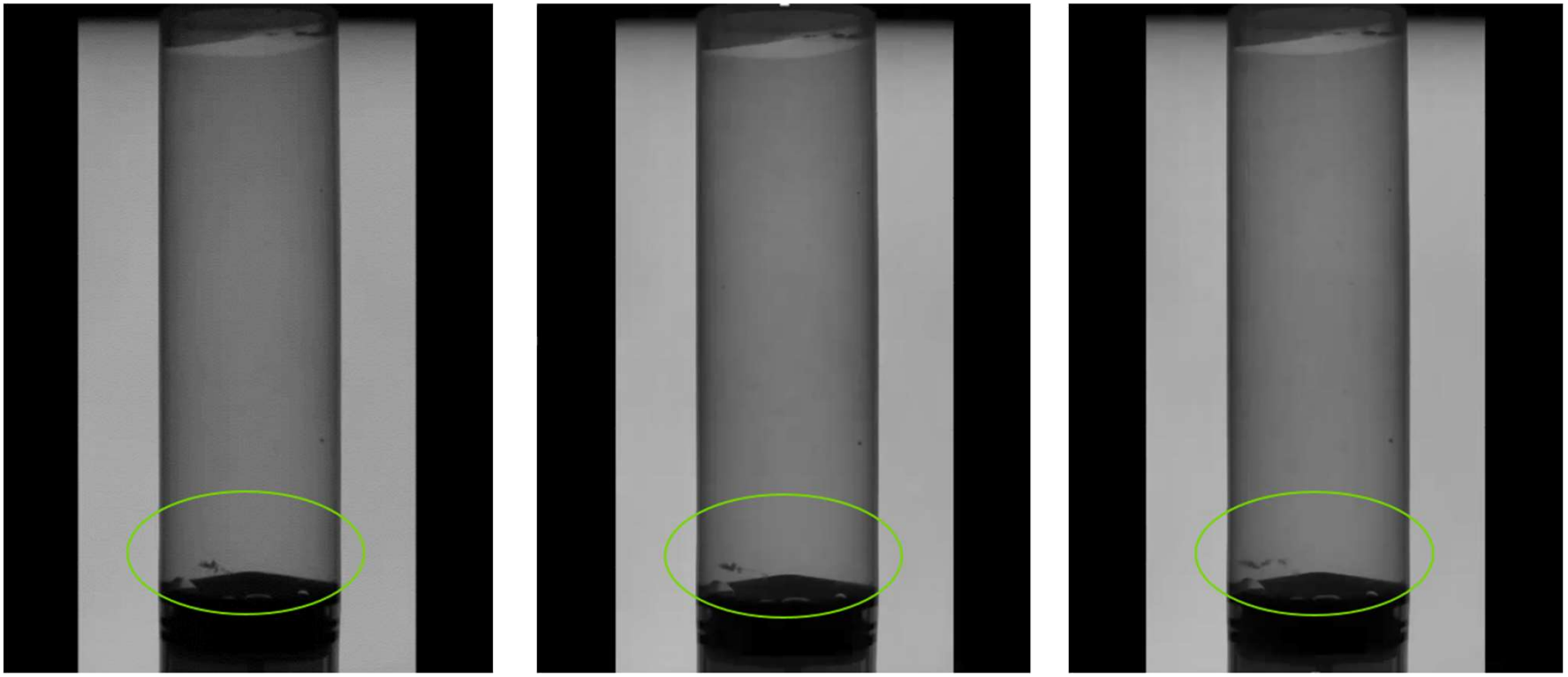
Particles inspection: particle white background



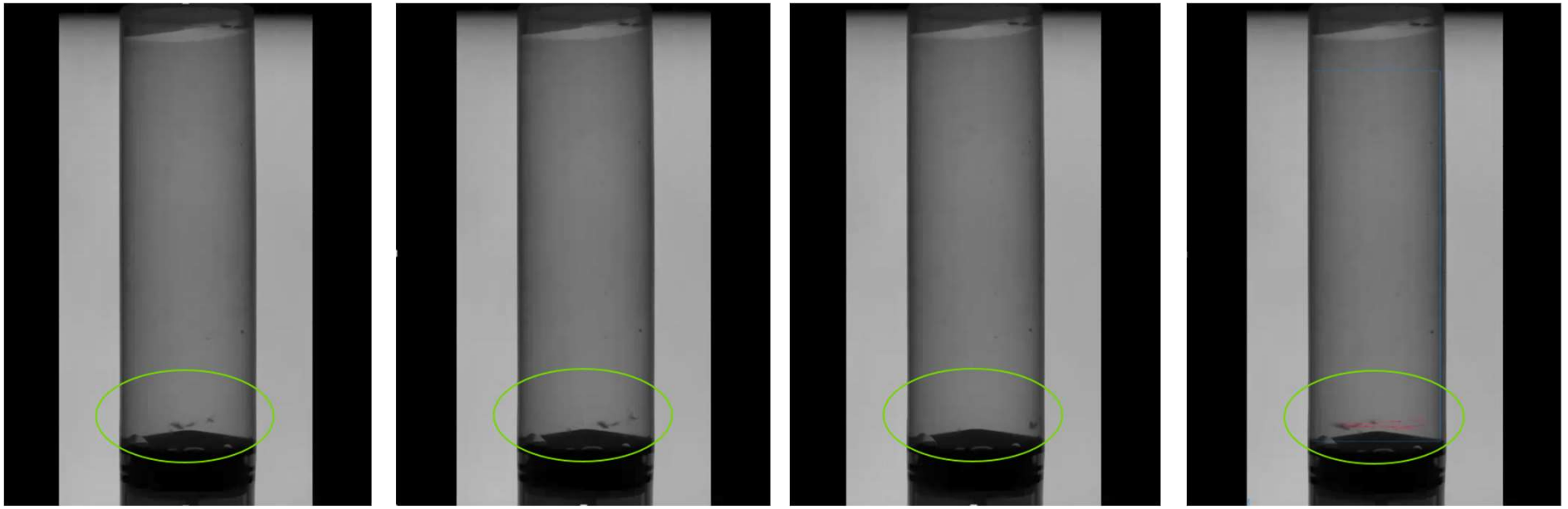


To detect absorbing particles

Particles inspection: particle white background

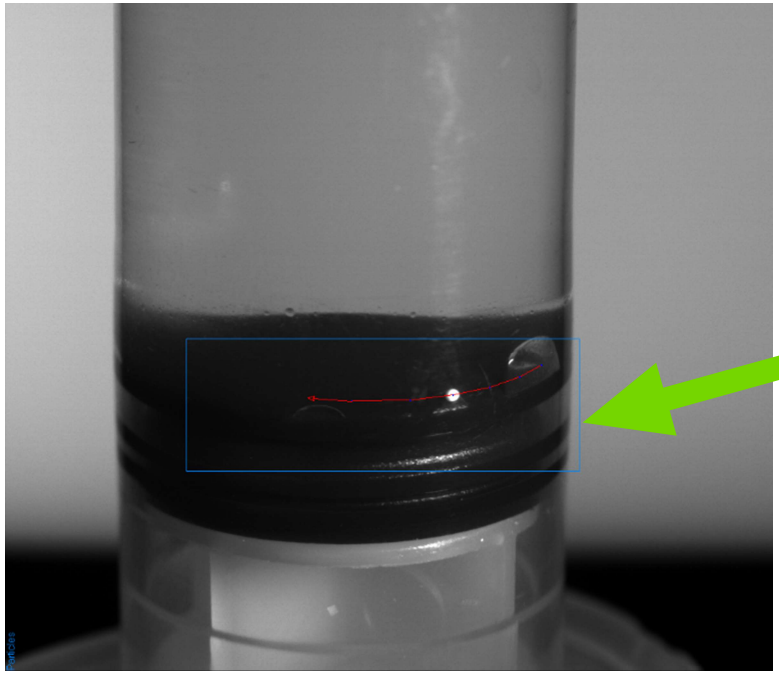


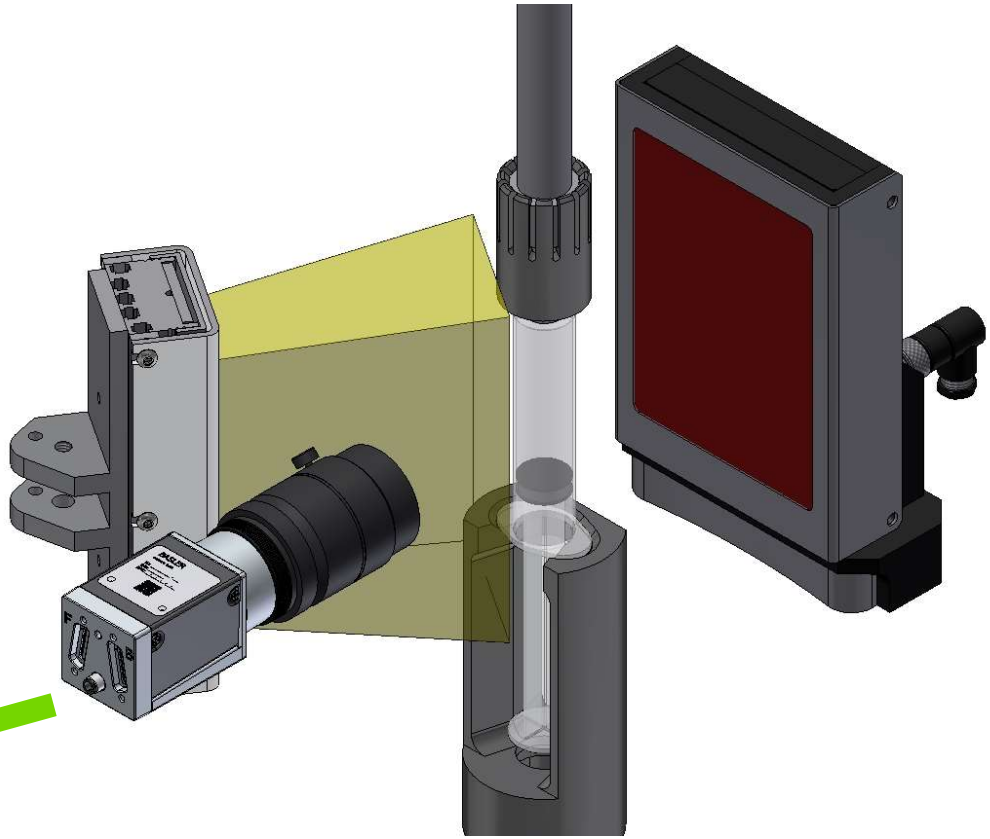
Particles inspection: particle white background



Particles inspection: particle with frontal light

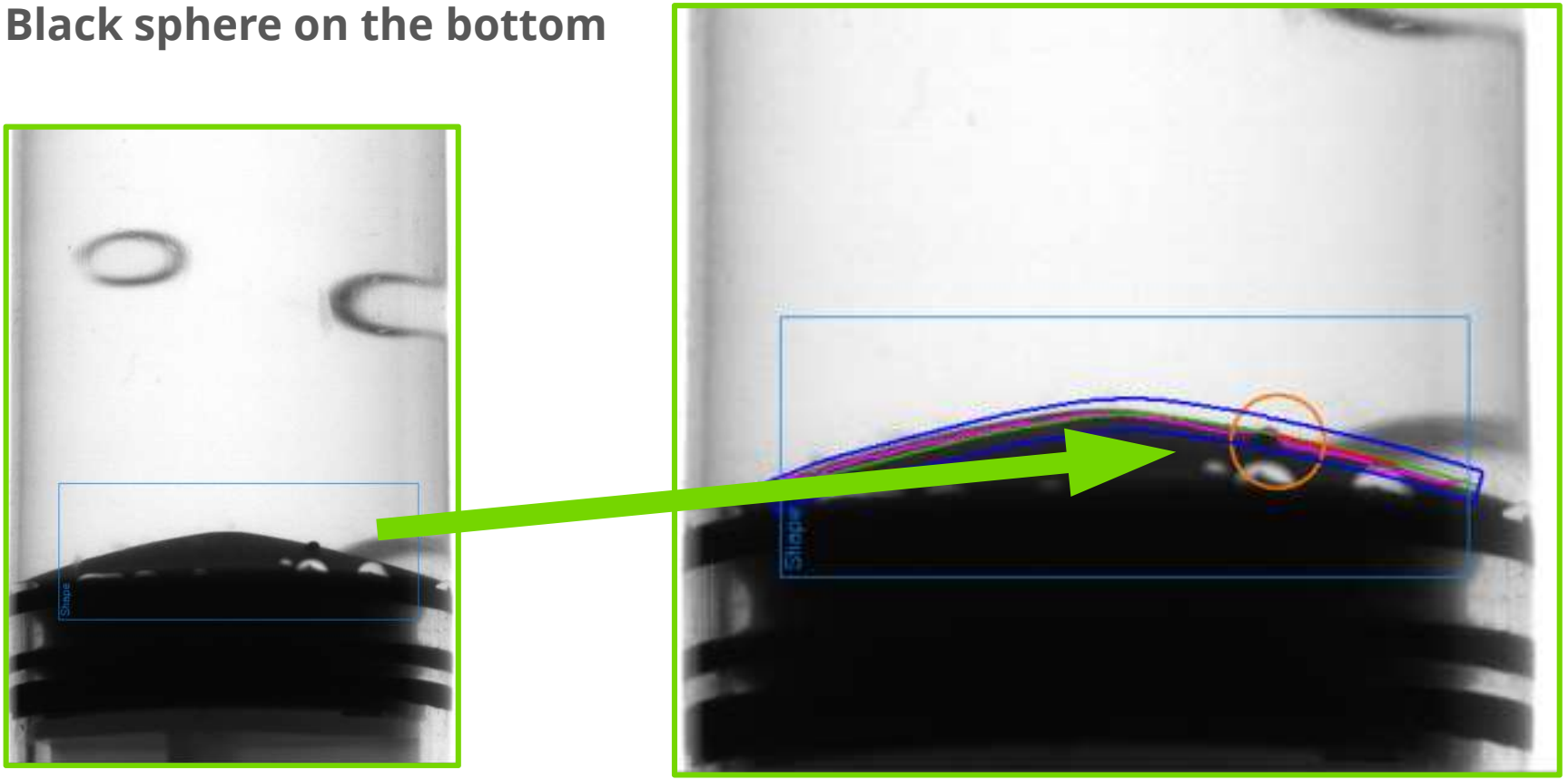
To detect reflecting particles or fibers





Cosmetic inspection: heavy particles

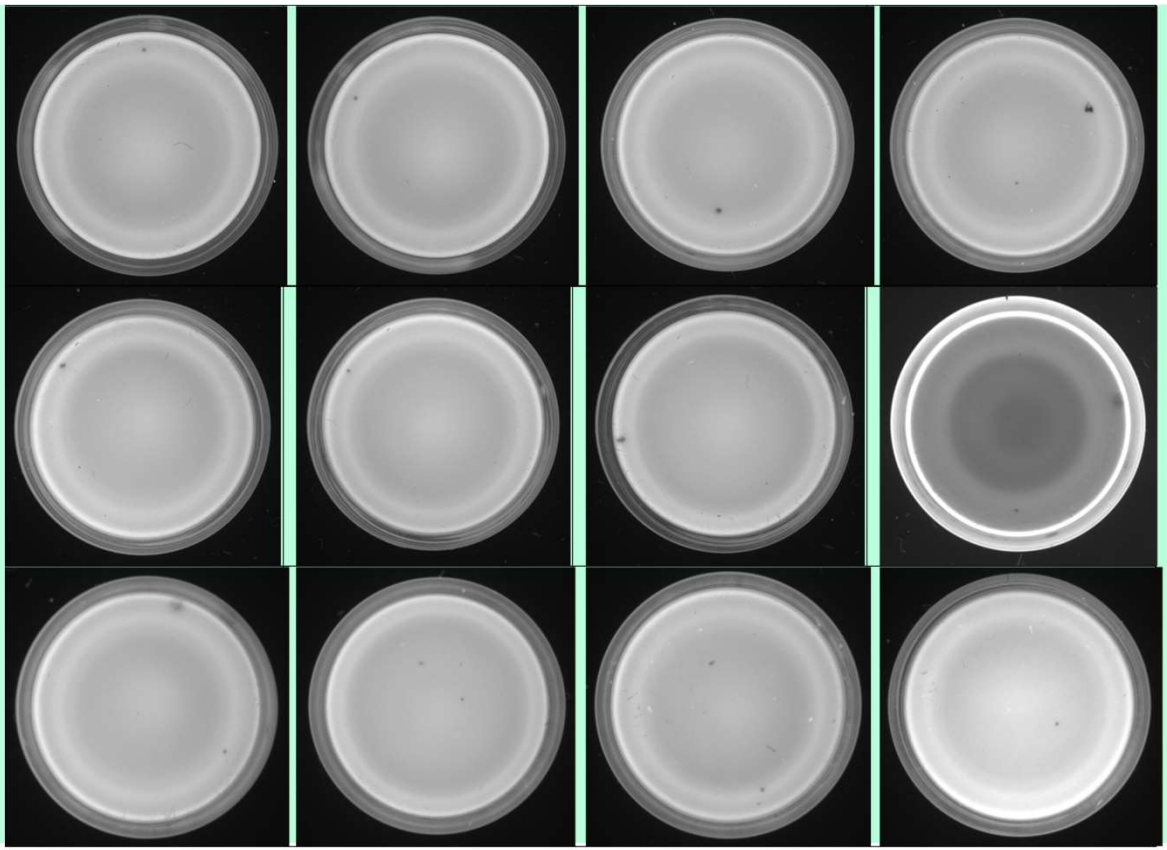
Black sphere on the bottom



The particle detected by the inspection of the bottom profile

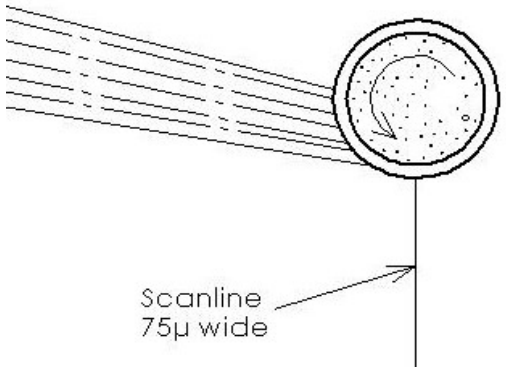
Suspensions solutions: different approach

Bottom inspection

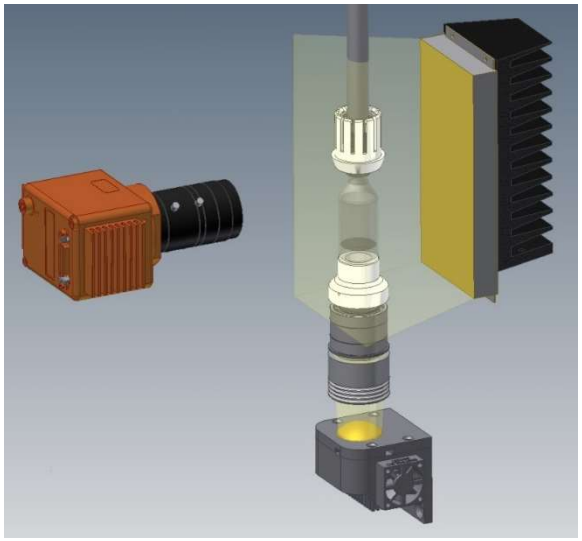


Bottom inspection at infeed complement particle inspection

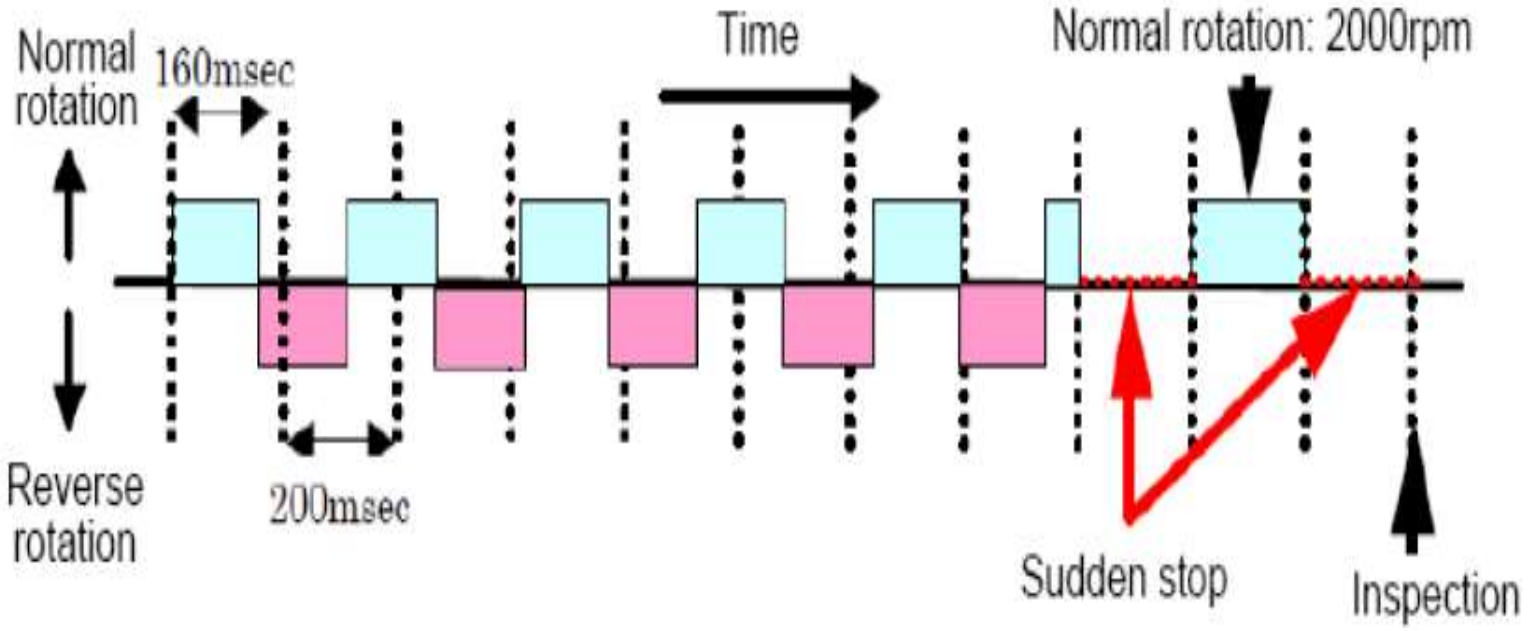
Particles inspection: suspensions products



Patented light



Suspension Products: automatic inspection

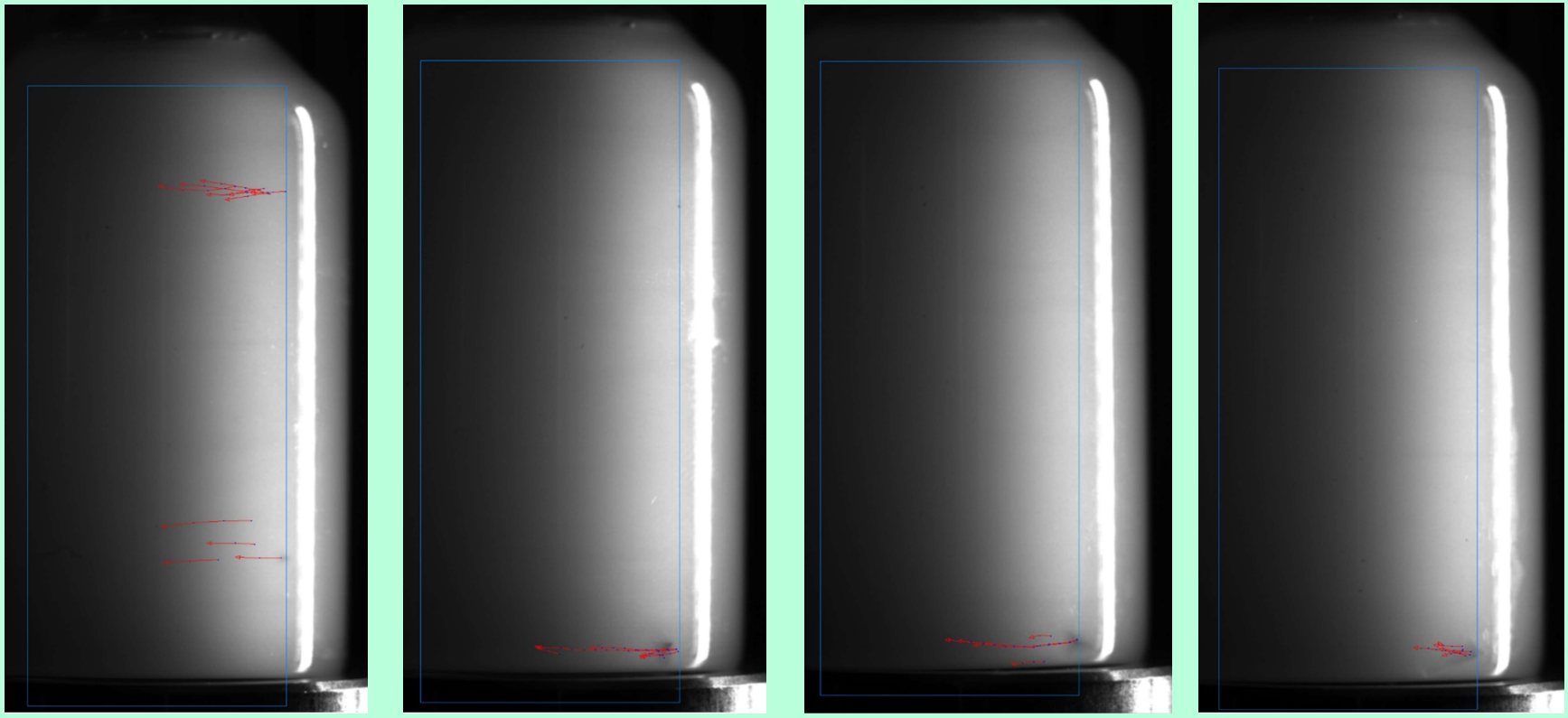


Product preparation is fundamental for suspension

High speed spinning system

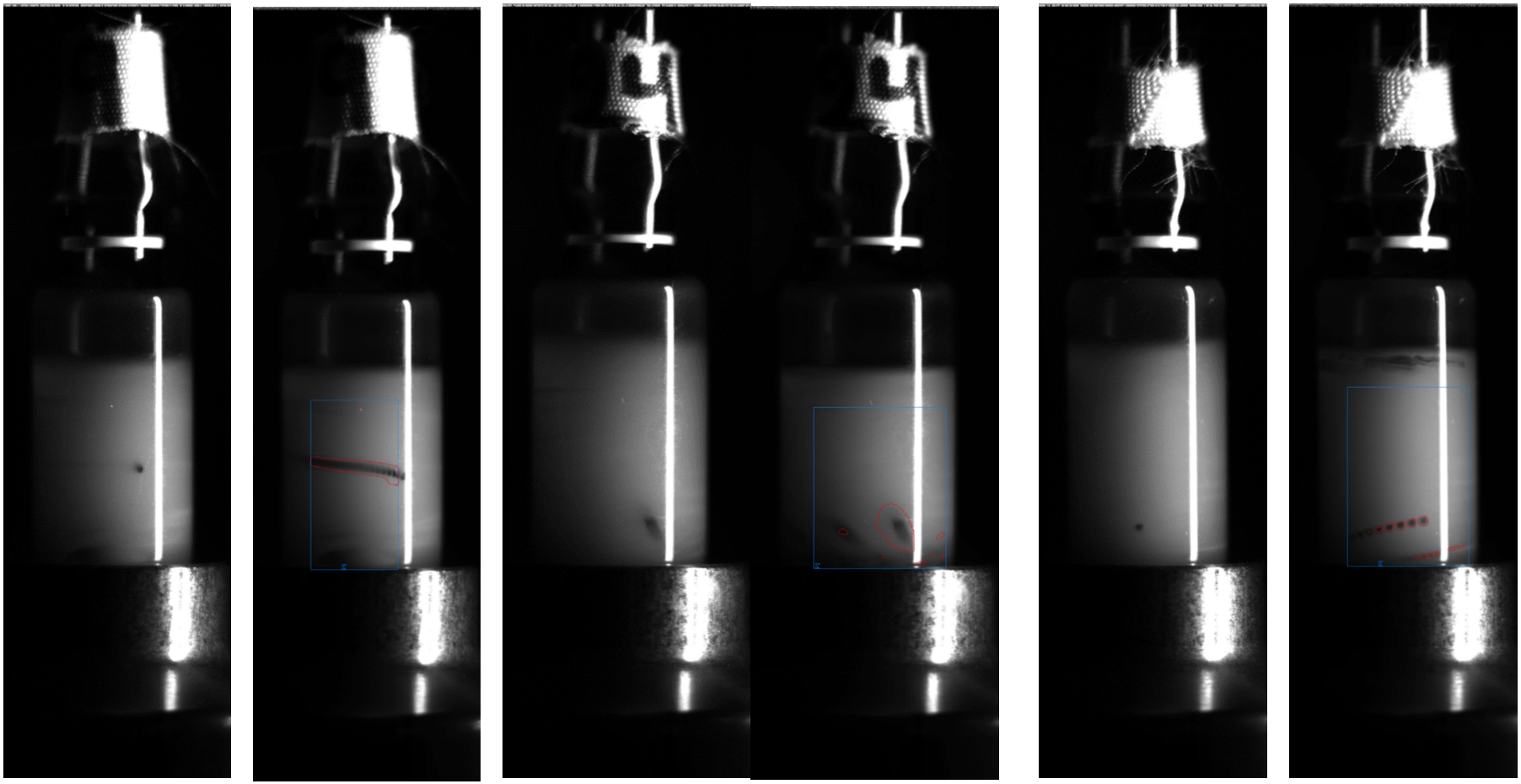
High Speed Spinning System up to 6000rpm

Particles inspection: suspensions



Special light combined with high speed rotation (pat.)

More examples of particles inspection



Sample #09, small glass chip

Figure 3 Sample #24, big glass chip

Sample #09, medium glass chip

More examples of particles inspection

Figure 4 Sample #09, small black particle

Figure 6 Sample #29, white fibre

Freeze Dried Inspection

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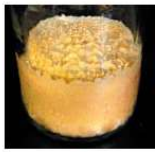
Freeze dried inspection: critical quality attributes

Color Vision

Skin



Bumps

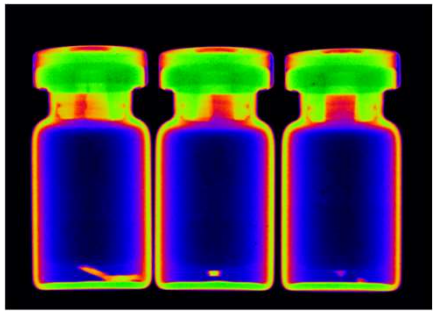
Cracks

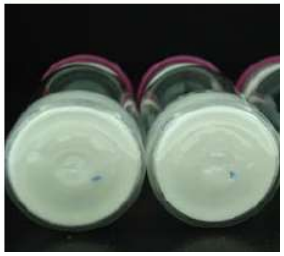
Peak

Dense

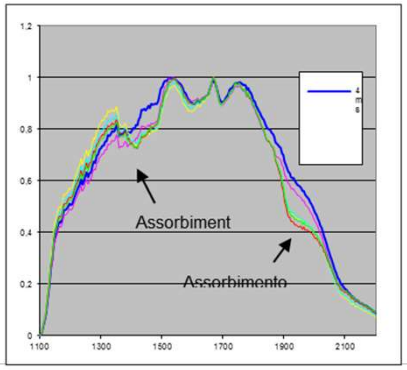
Porous

Vision X-ray Inspection

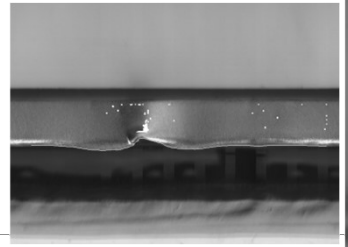


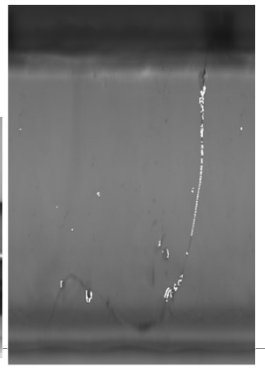


	Physical description	Particles
NIR	Collapse	Container
	Meltback	Integrity



A multivariate approach





View of some defects

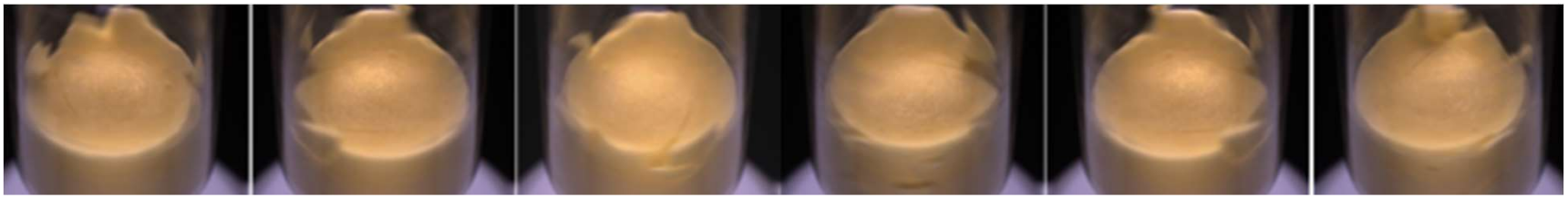
Particulate Matter

Closure Integrity

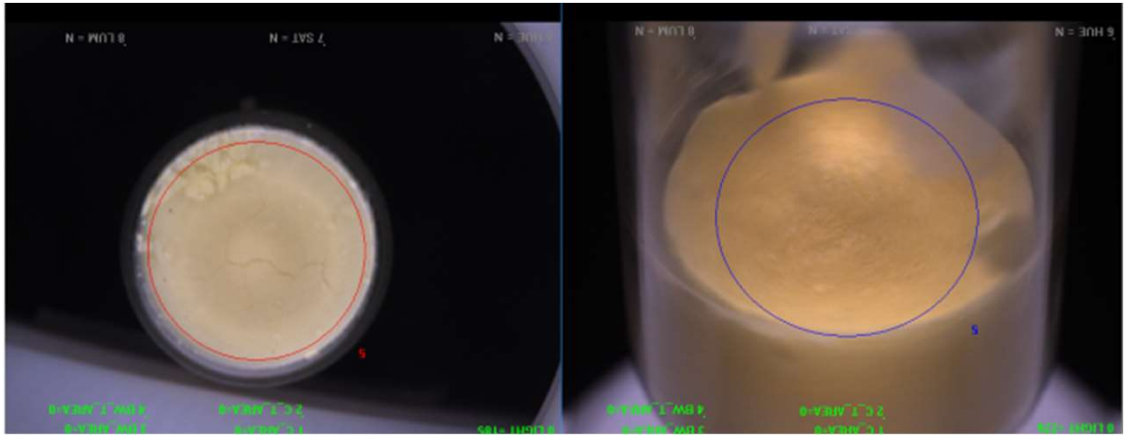
Cosmetic Defects

Freeze dried inspection: color camera

Up to 36 images are taken while the vial is rotating in front of the camera, in order to increase the analysis of the cake.

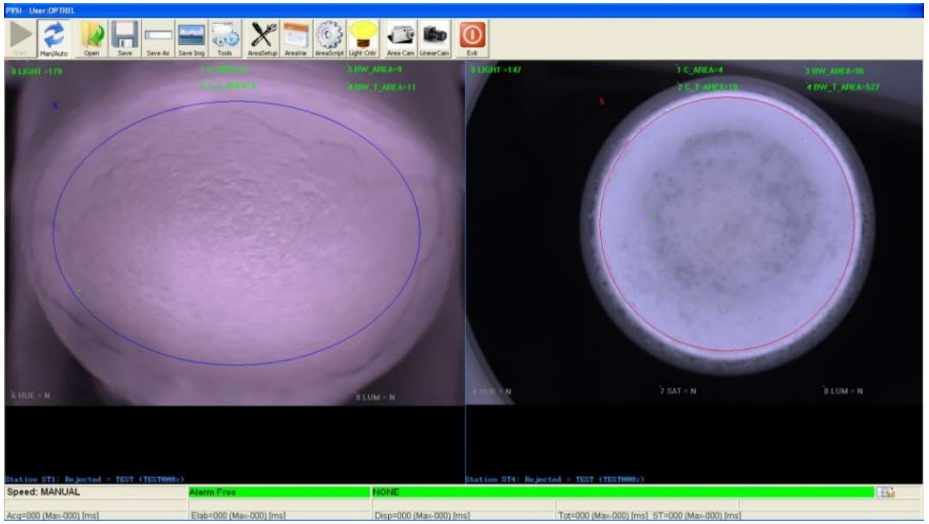


Color high resolution frame camera allows to better detect the defect inside the cake and it allows to recognize alteration on the product's color.

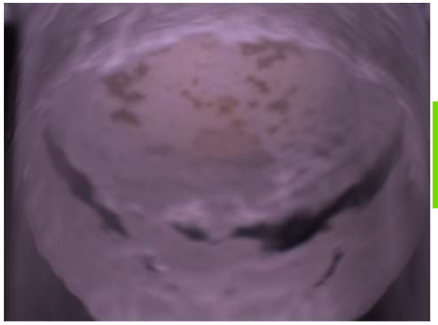


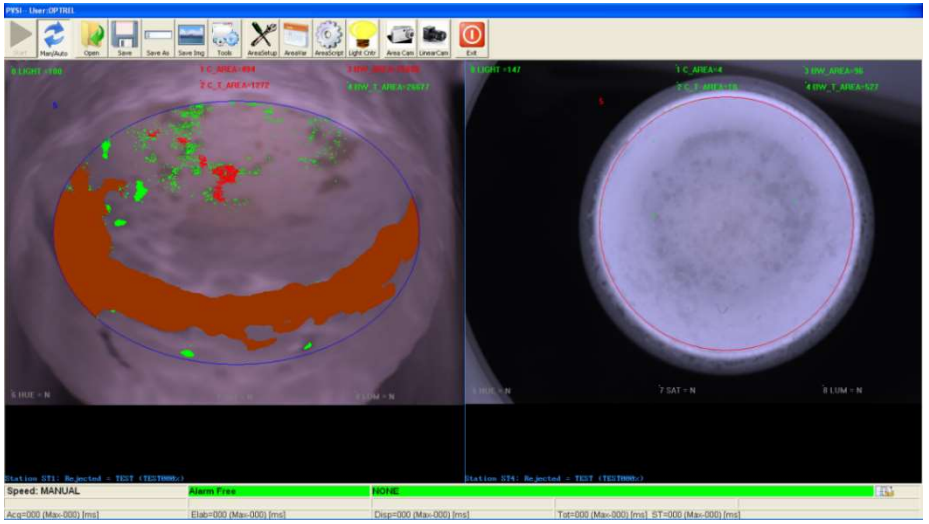
Freeze dried inspection: color camera

Result on the inspection of a good sample

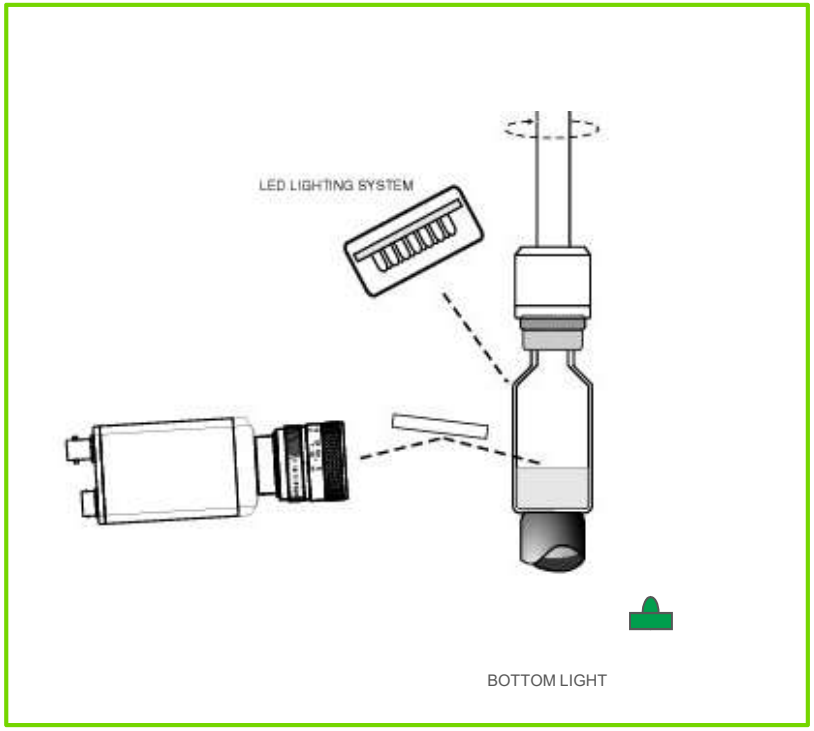


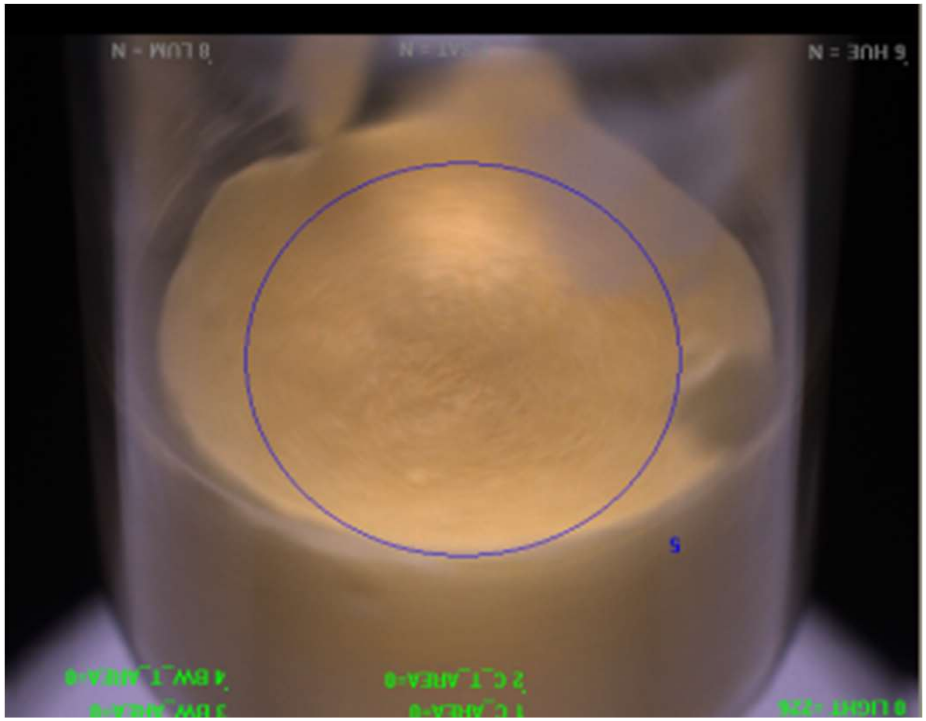
Result of the inspection on a defected sample





Top cake inspection

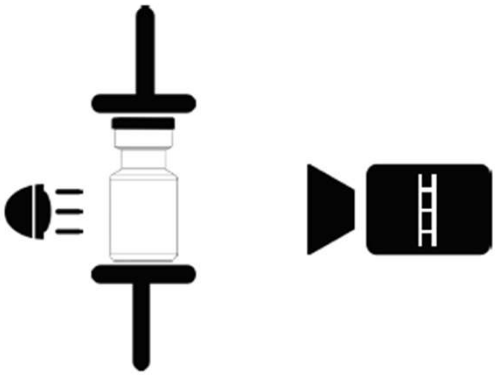


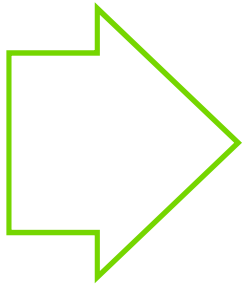


- **Container in rotation for multi-perspective analysis**
- **Color 2000x2000 area camera at high speed (359 frames/sec)**
- **Mixed illumination for lighting cake or powder contamination with programmable intensity control**

Freeze dried lateral side inspection: line scan technology

Linear camera effectively complement standard inspection for more reliable control due to very uniform Illumination





Flip-off presence

Alu-Seal Inspection

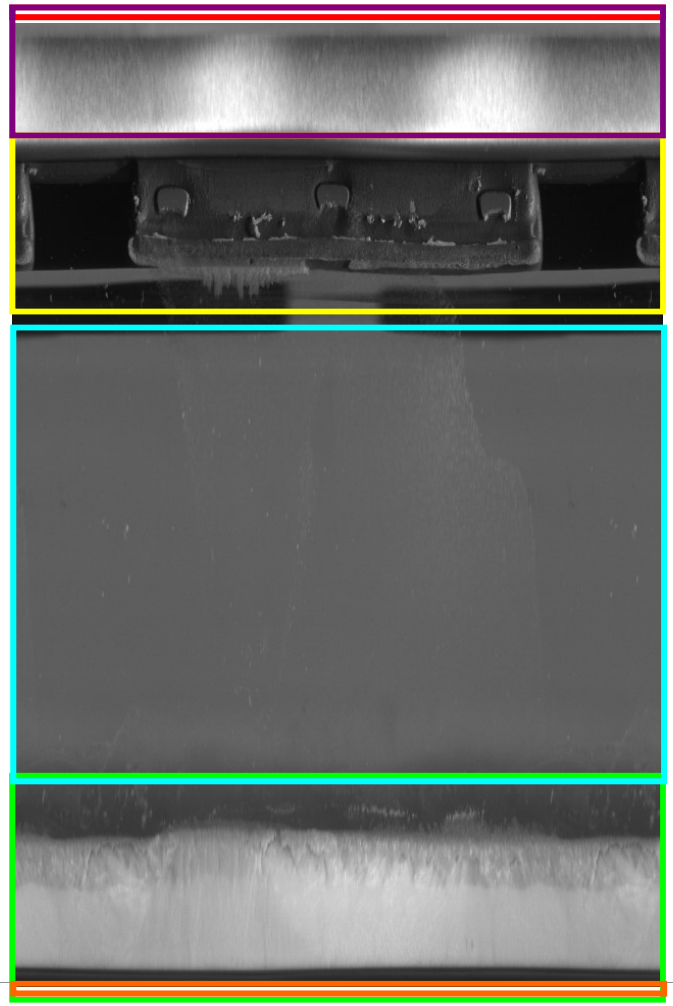
Product in Stopper

Stopper Integrity

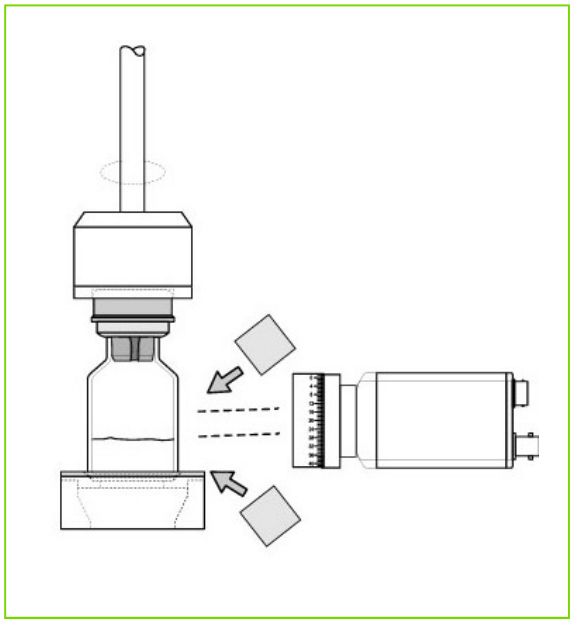
Glass Defects

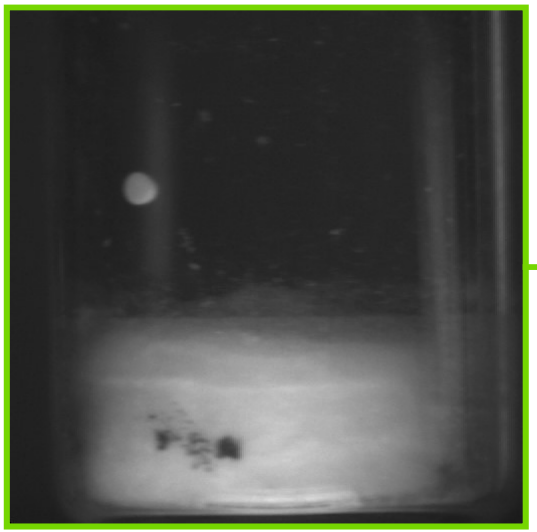
Cake Height

Cake Defects

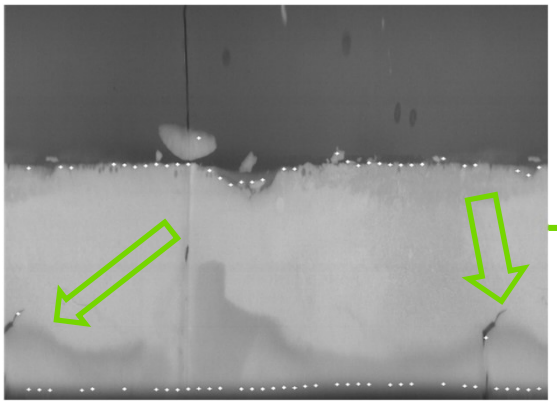


Lateral cake inspection



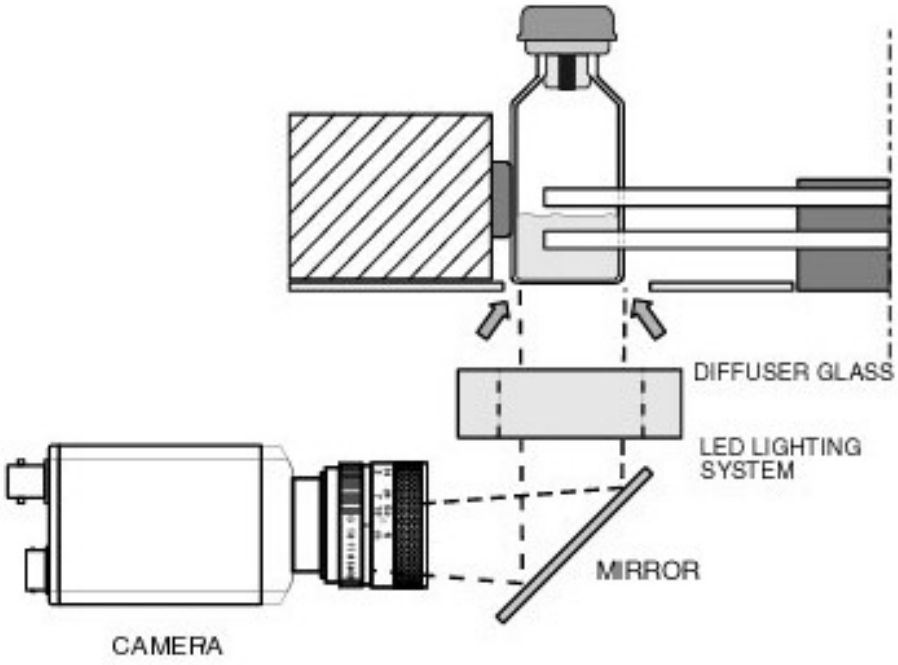


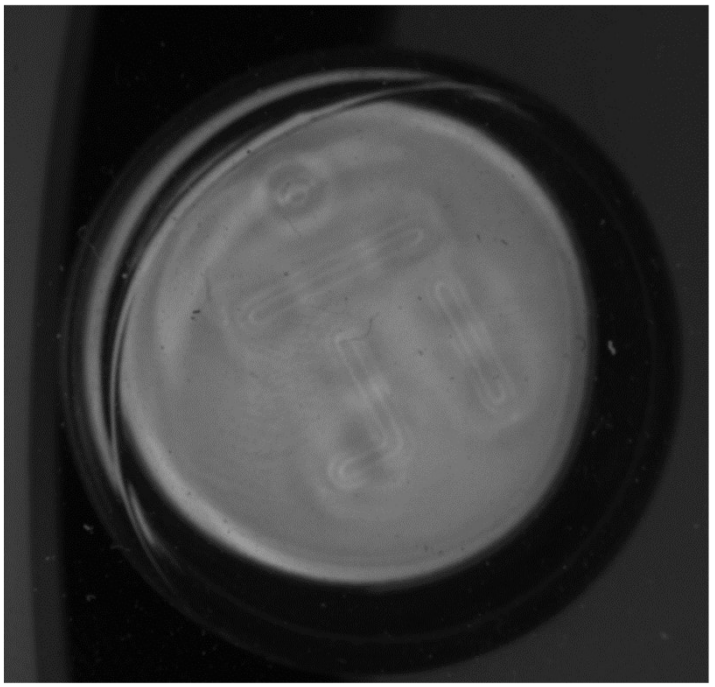
Area Camera
Uneven illumination
Poor contrast
Risk of missing defect
Low resolution 512



Linear Camera
Flat Illumination
High contrast
360° scan
No missing defect
High resolution 2K-4K

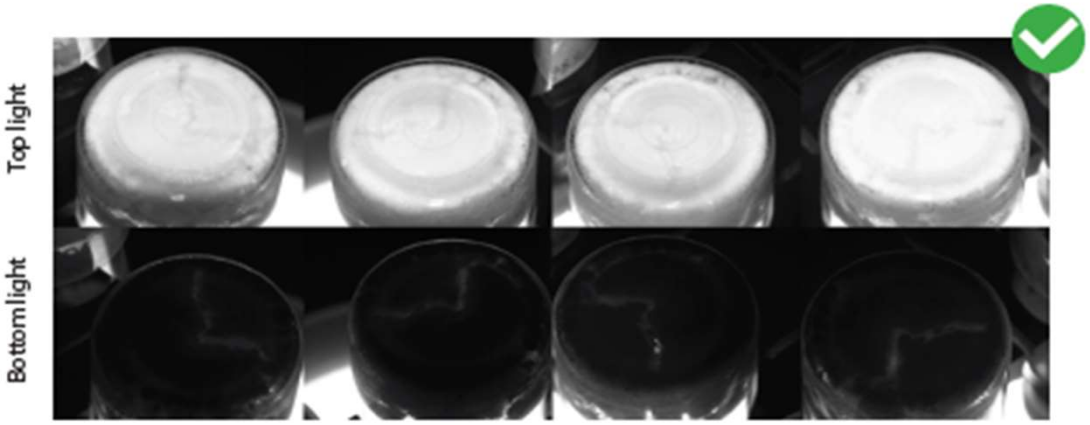
Bottom cake inspection

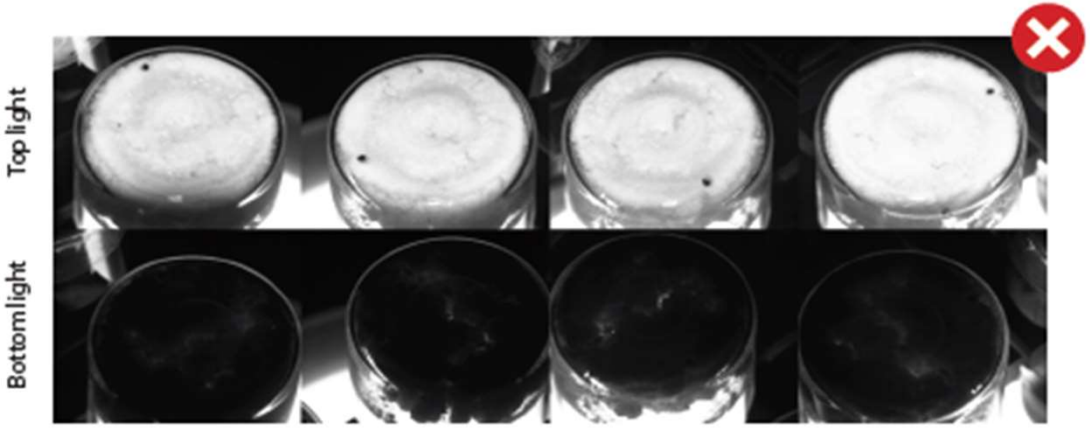




High resolution 1400x1000 pixels area color camera

More from bottom





Contamination inside cake?

Some Idea

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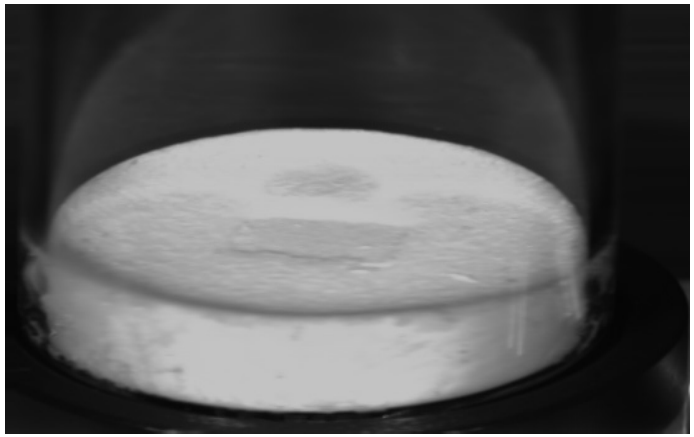
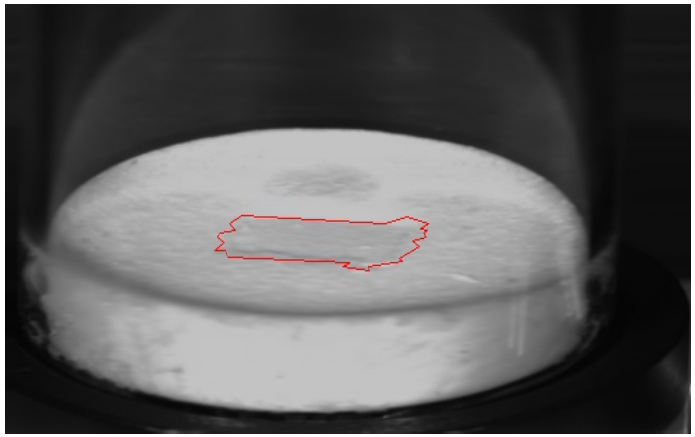
NIR Imaging: identification of contaminants

VIS

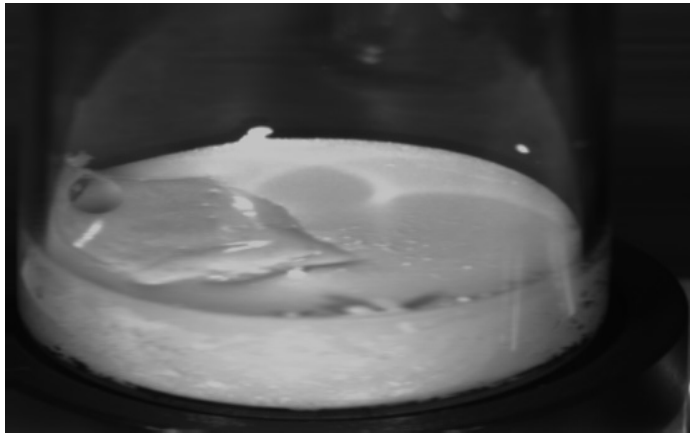
Paper fragment

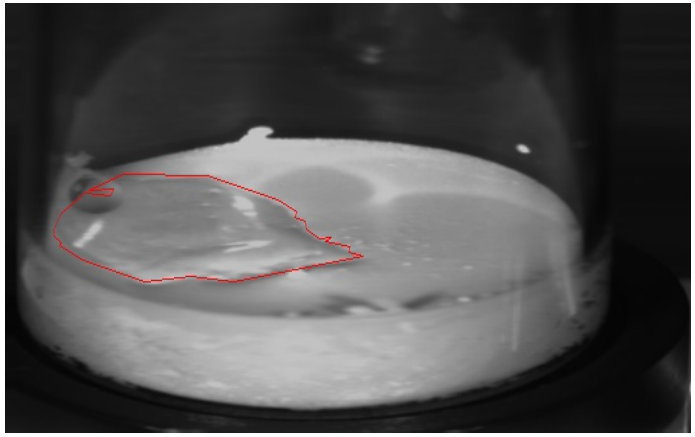
NIR





Plastic trasparent layer



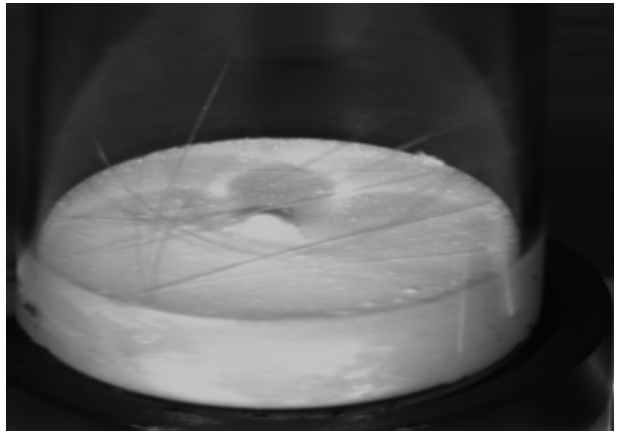


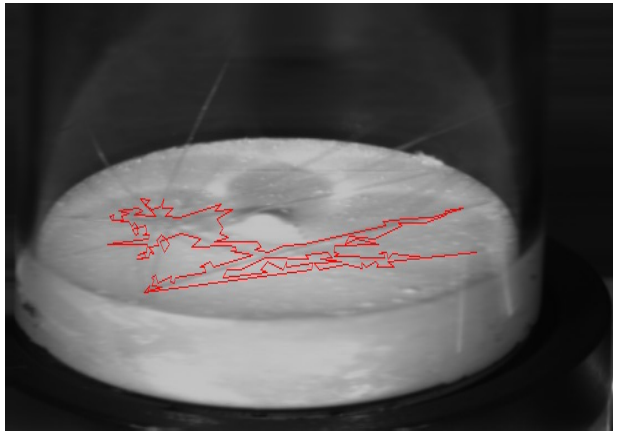
NIR Imaging: identification of contaminants

VIS

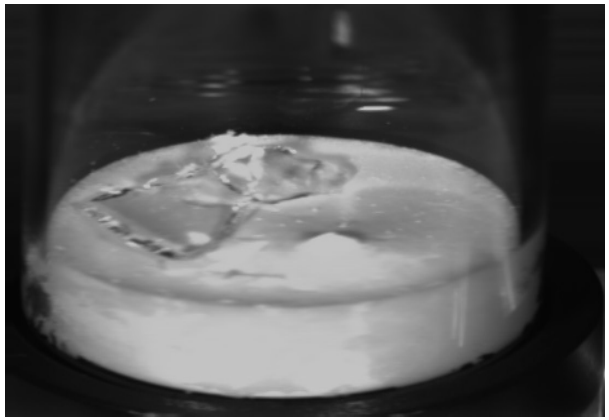
Blonde Hair

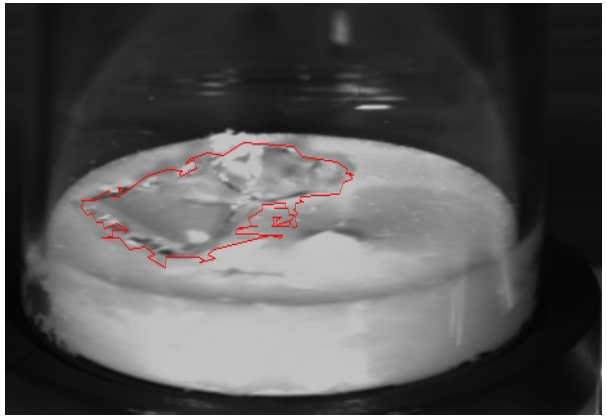
NIR





Glass Fragment

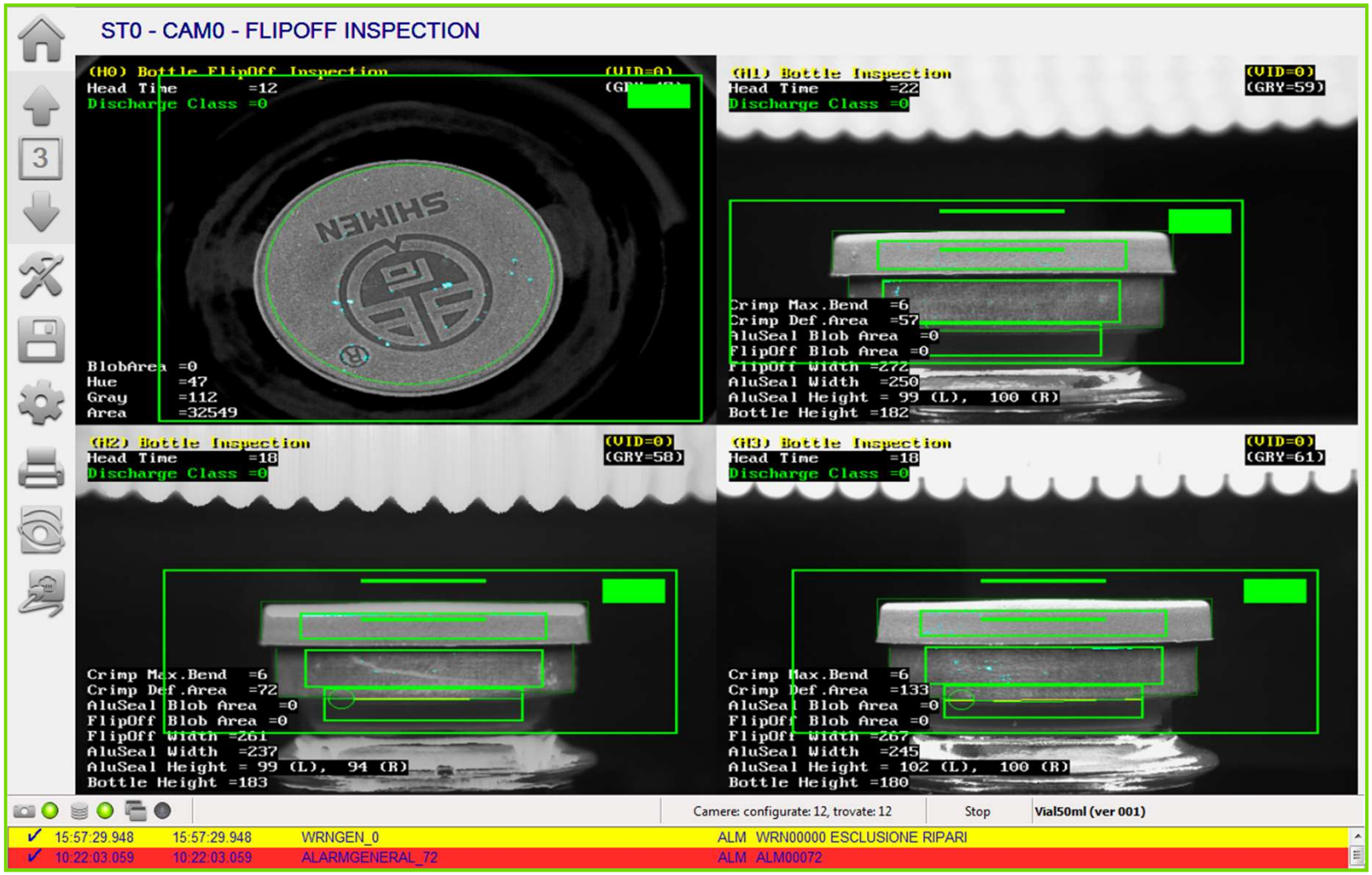




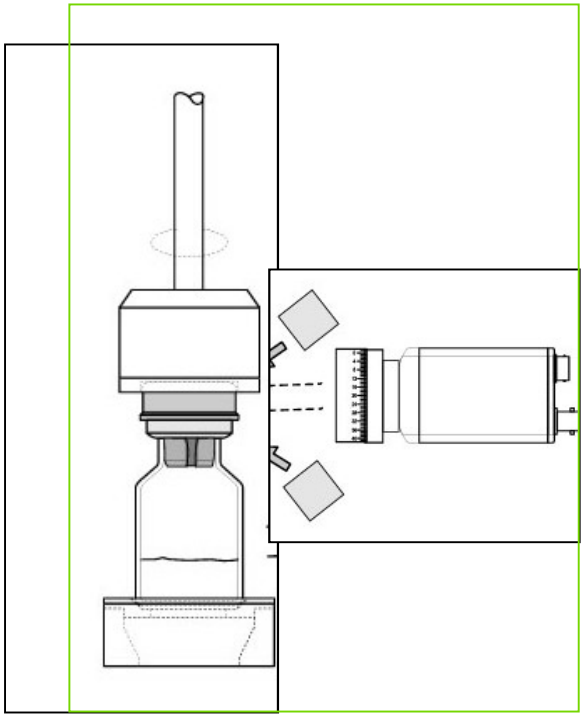
Cosmetic Inspection

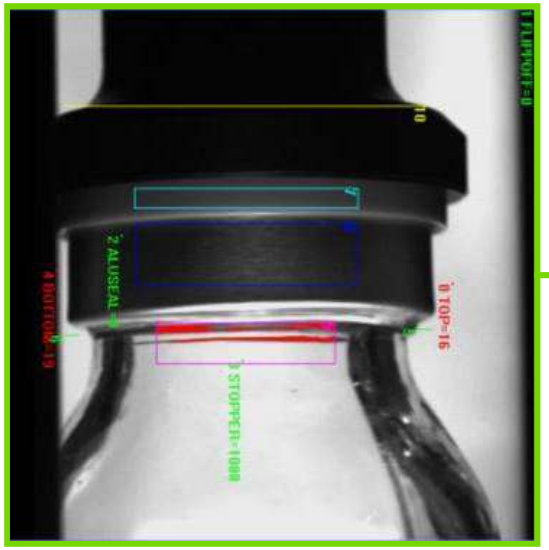
Stevanato Group
ENGINEERING SYSTEMS

Flip Off / Alu Seal inspection: single station

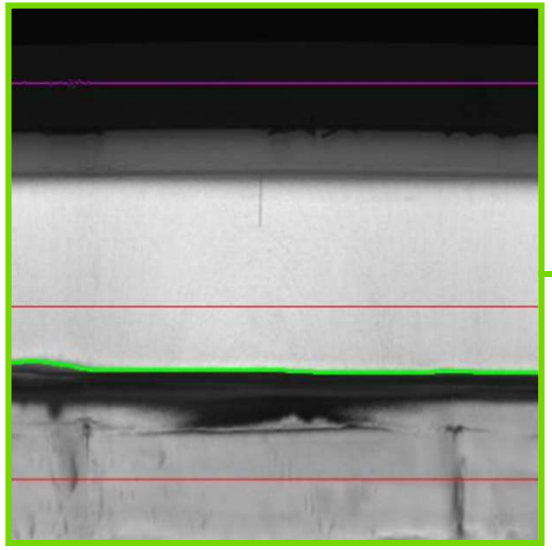


Alu seal inspection



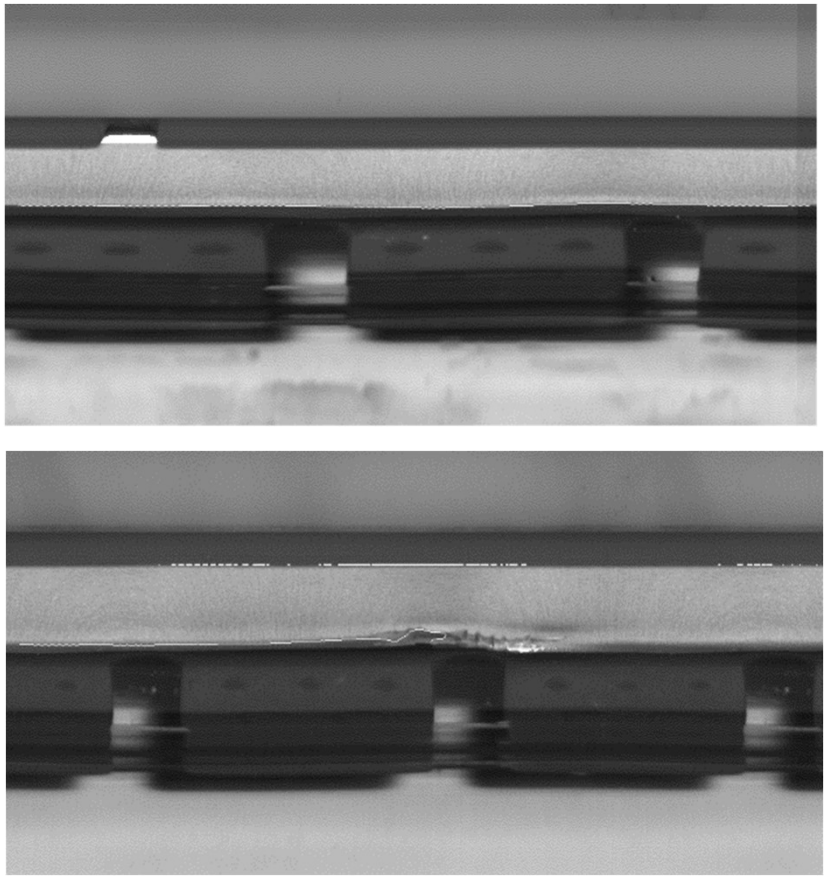


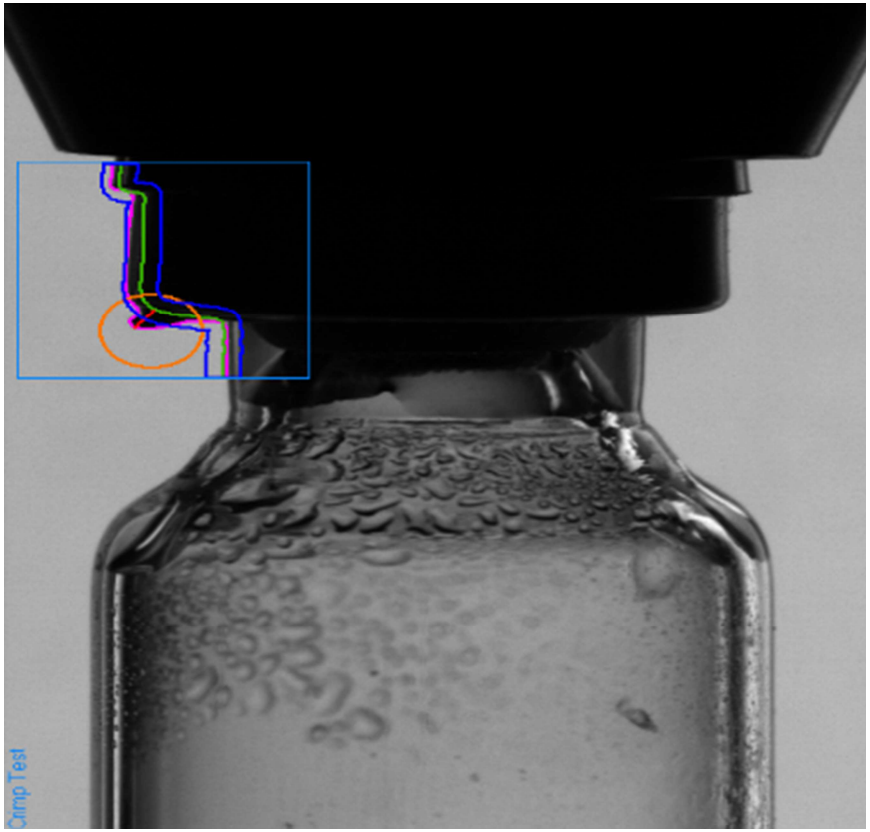
Area Camera
Uneven illumination
Poor contrast
Risk of missing defect
Low resolution 512



Linear Camera
Flat illumination
High contrast
360° scan
No missing defect
High resolution 2K-4K

Inspection technology: linear scan camera and/or matrix camera





Aluseal Inspection

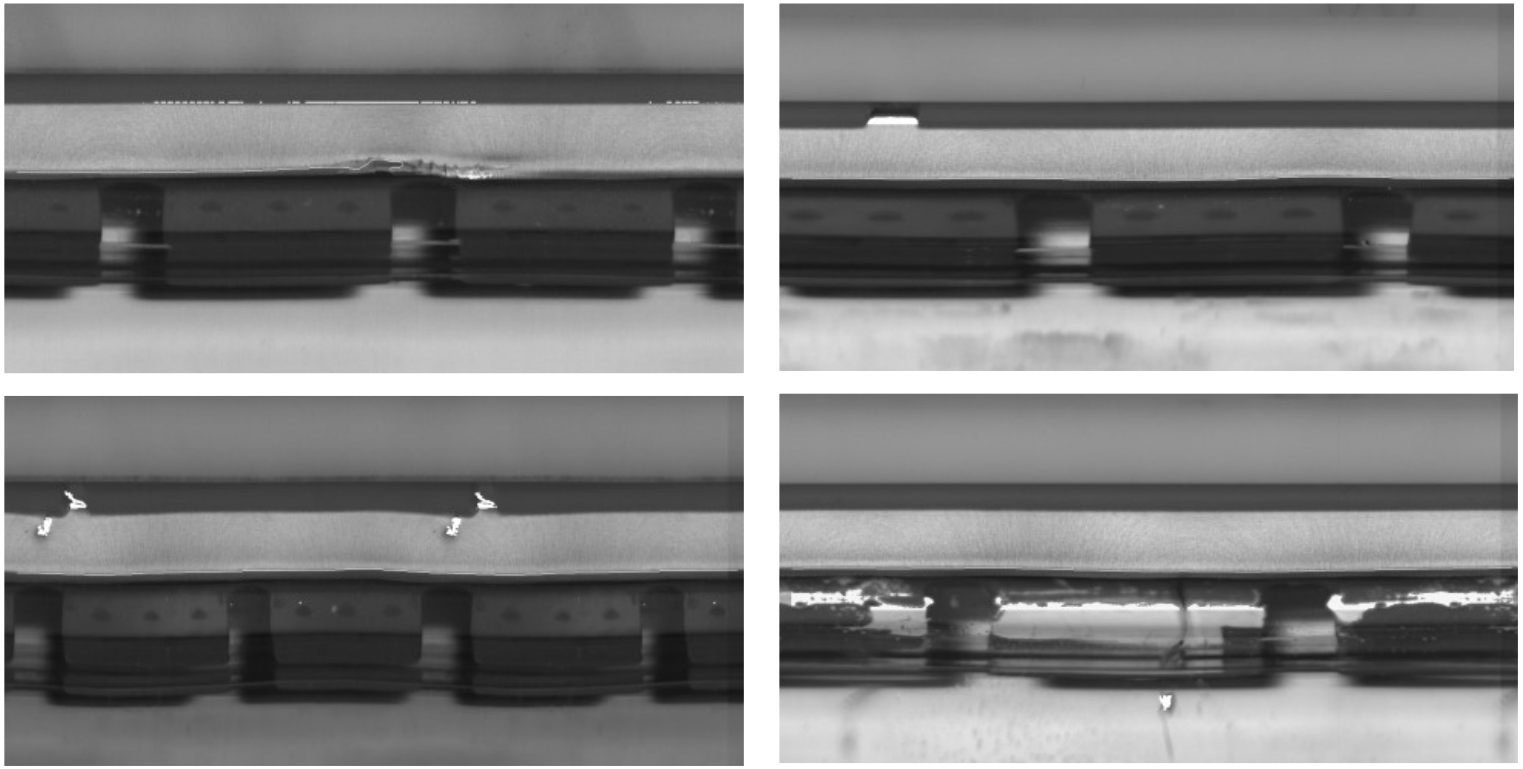
Special technology linear scan cameras

Possible Source:

- Improper crimping station setup
- Variability on closure components

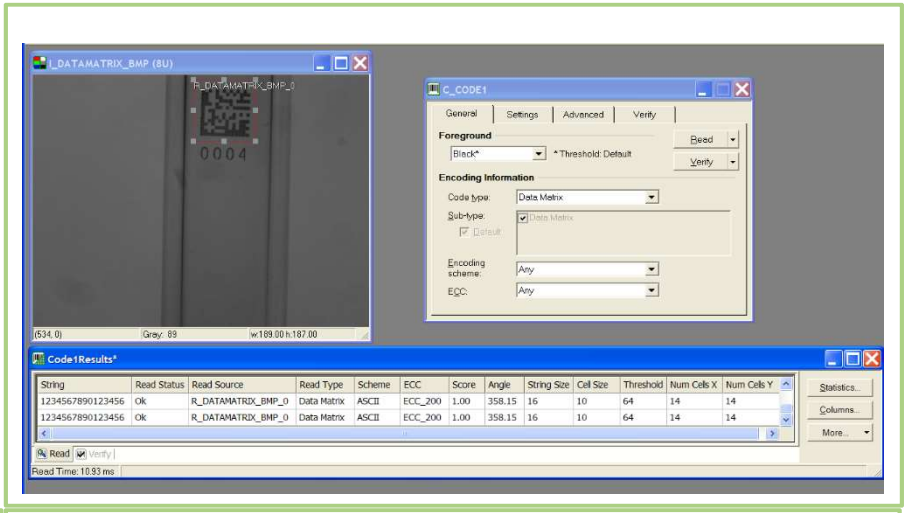
Resolution:

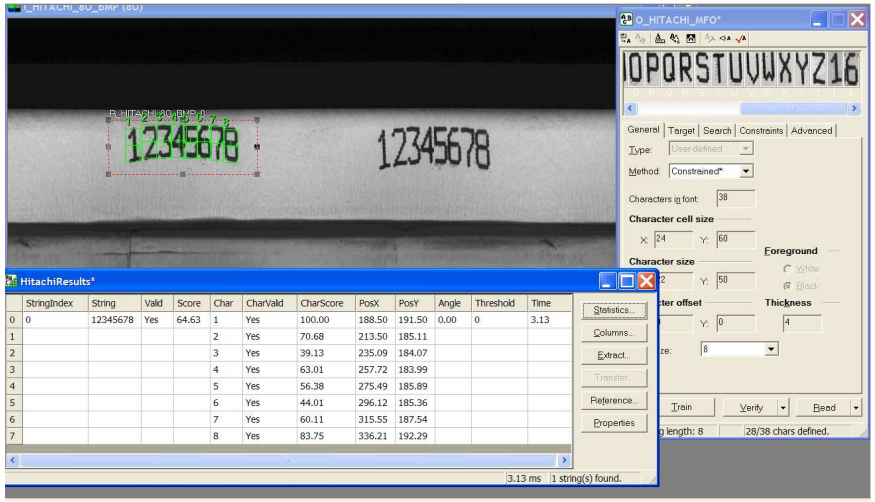
- Detect crimping defect smaller than 50µm

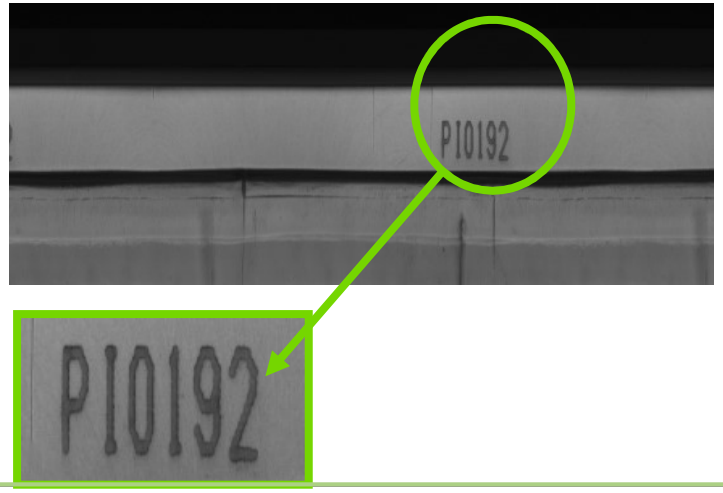


Linear scan camera for OCR control

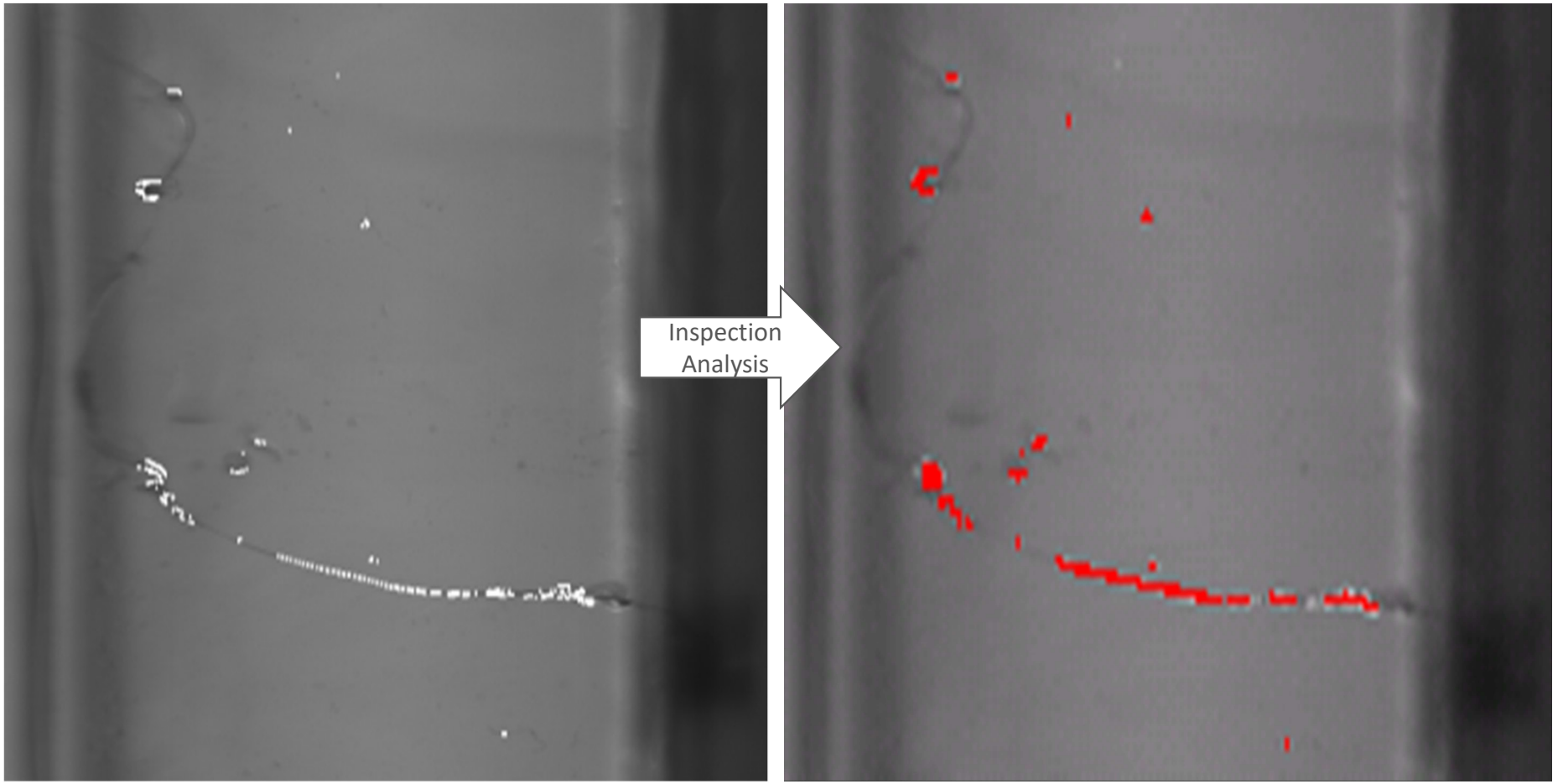
- Interactive definition of **OCR** and **CODE READER**
- High resolution print verification using linear cameras and special illumination techniques on alu-seal and glass surface







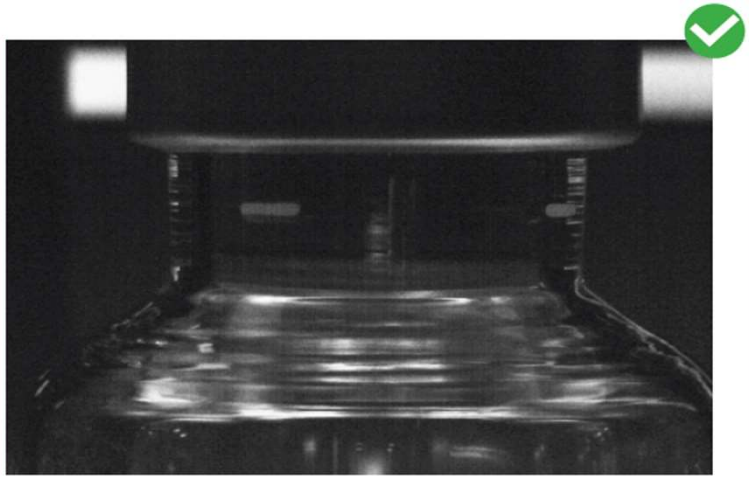
Linear scan camera for glass inspection

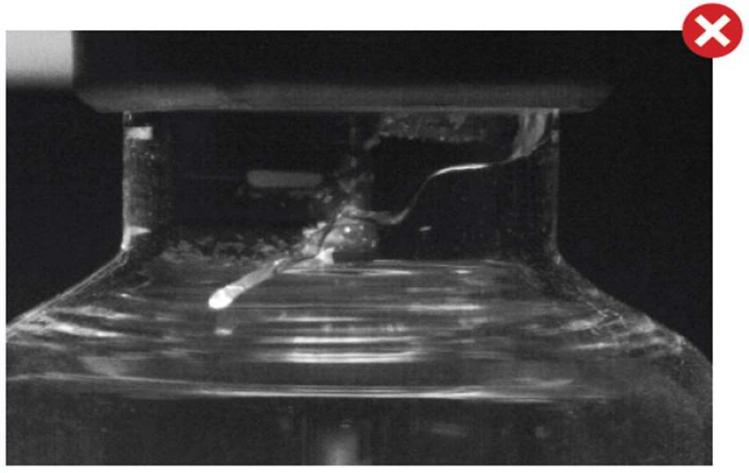


Body inspection (scratch on the surface)

Scratch highlighted in red color

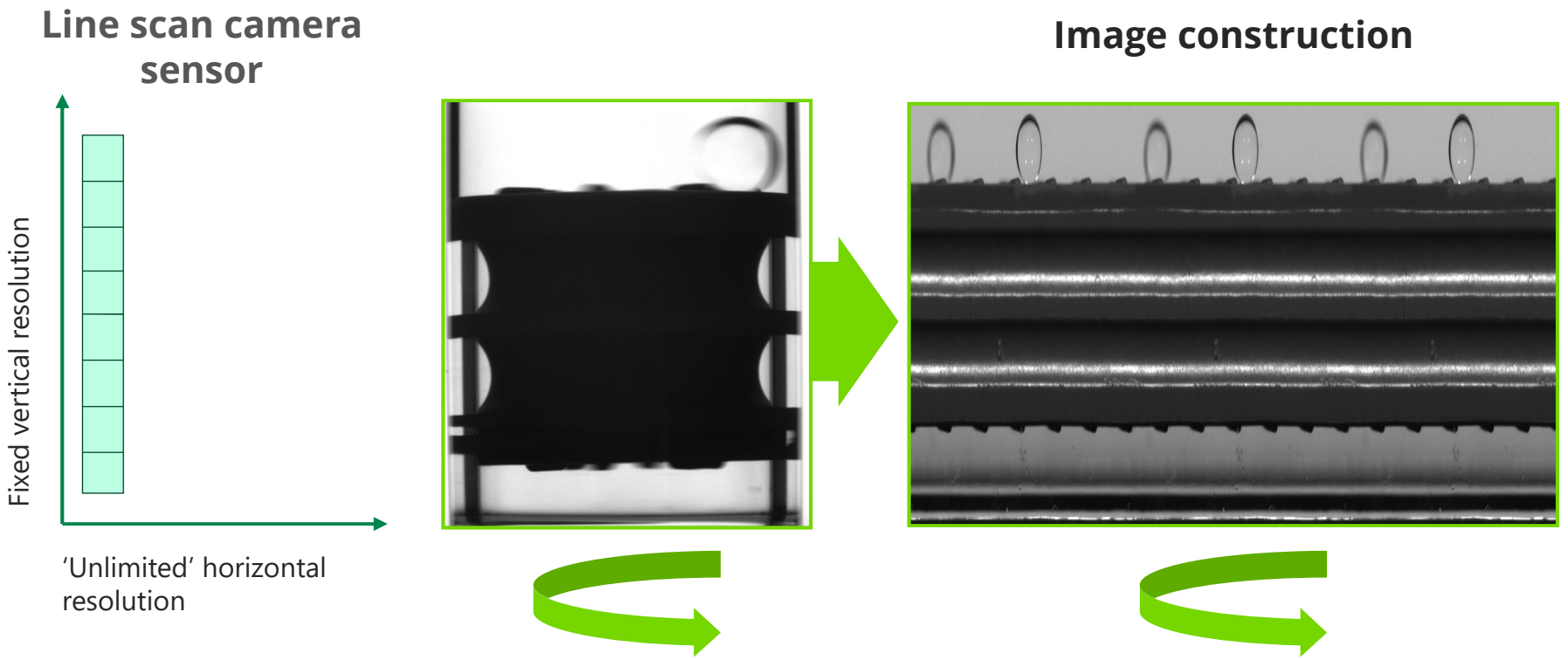
Cracks on neck/ shoulder area





Special Technology Linear Scan Cameras

Linear Scan Cameras for plunger inspection



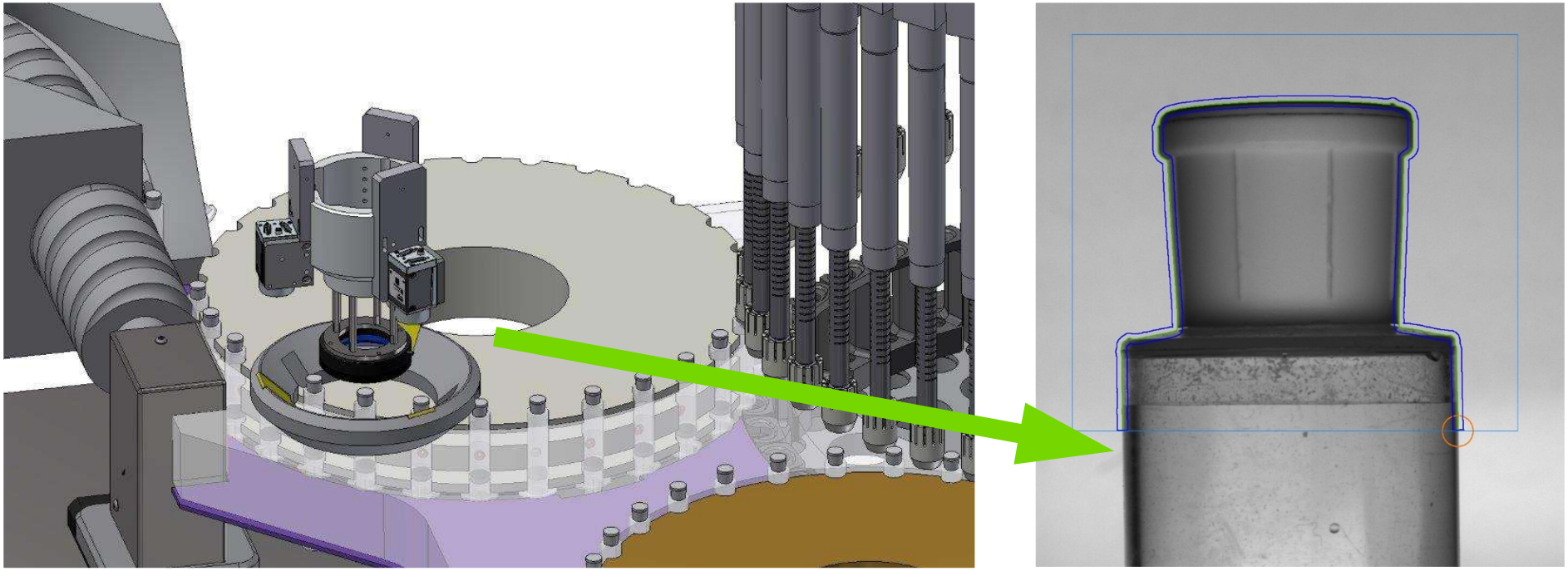
Defects on syringes

Particulate matter

Closure integrity

Cosmetic defects

Cosmetic inspection : tip cap, defect and shape control

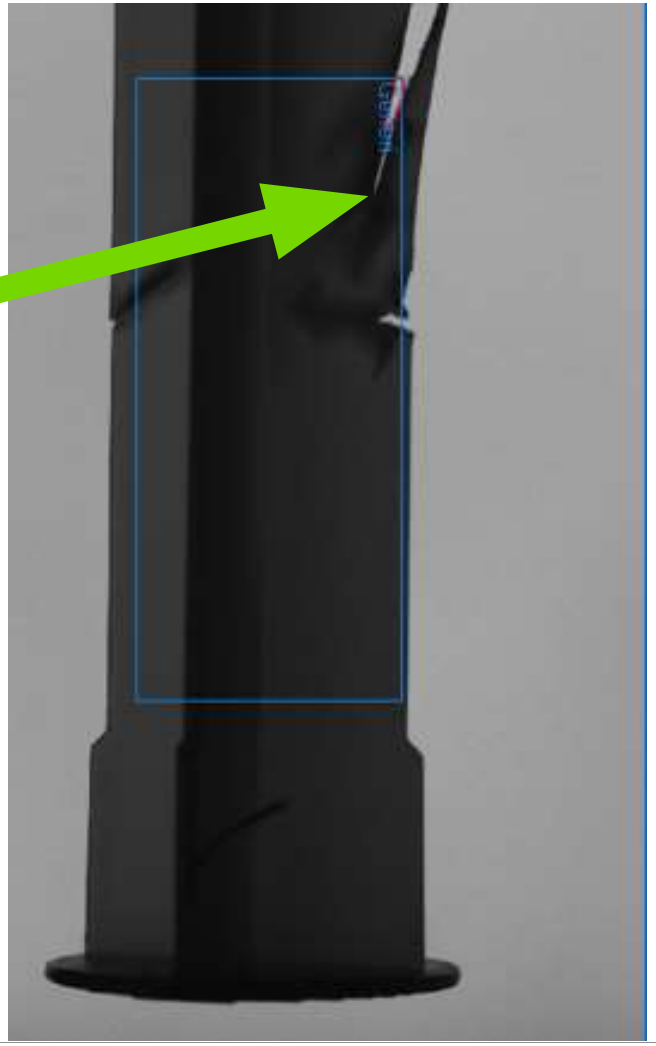


- Performed on the infeed starwheel
- Three high resolution cameras at 120°with back and front illumination
- Rejection before the loading in the turret to avoid the seal breakage when the tip is not correctly positioned.

Cosmetic inspection : needle cover inspection

Cosmetic defect
Good container

Cosmetic defect
Bad container



Finger grip inspection

Inspection Setup

Leak Detection and Containers Integrity

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Container closure integrity: dye ingress leak detection

Dye Method	USP31<381> Ph.Eur. 3.2.9	ISO 8362-5 Annex C
Dye	0.1% aq. Methylene Blue	
Vacuum	-27KPa	-25KPa
Time at Vacuum	10 min	30 min
Time at ambient	30 min	30min
Detection	Visual inspection	

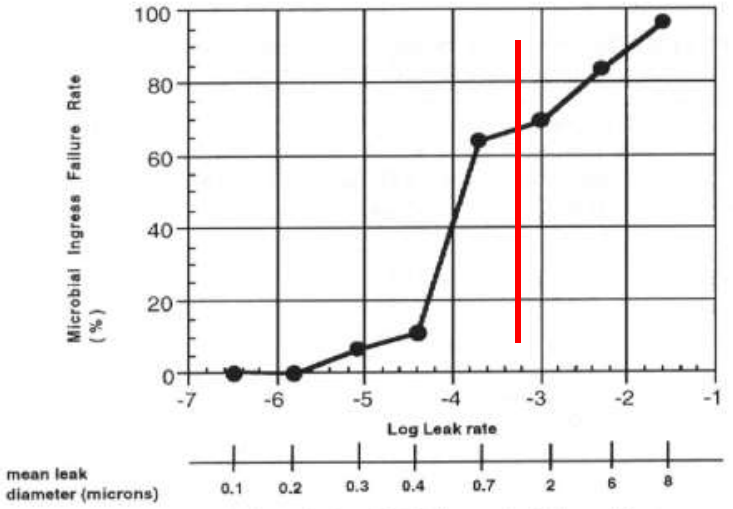
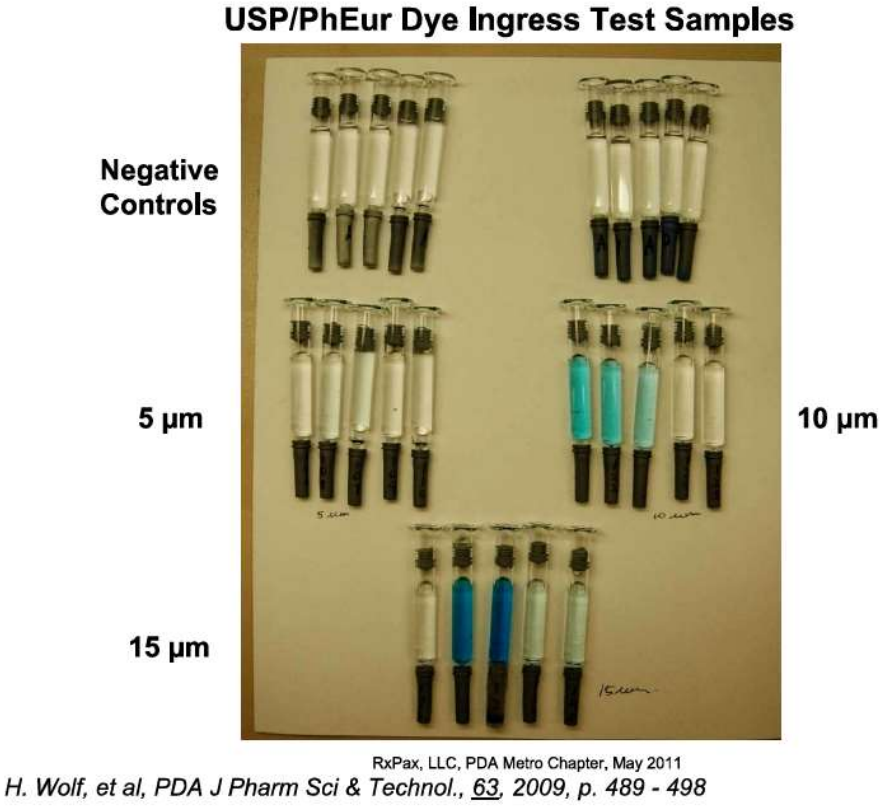


Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was measured by microbial ingress after 24 hour immersion in a bath (37°C) containing 10^8 to 10^{10} *P. diminuta* and *E. coli* organisms/mL and a 13 day, 35°C incubation.

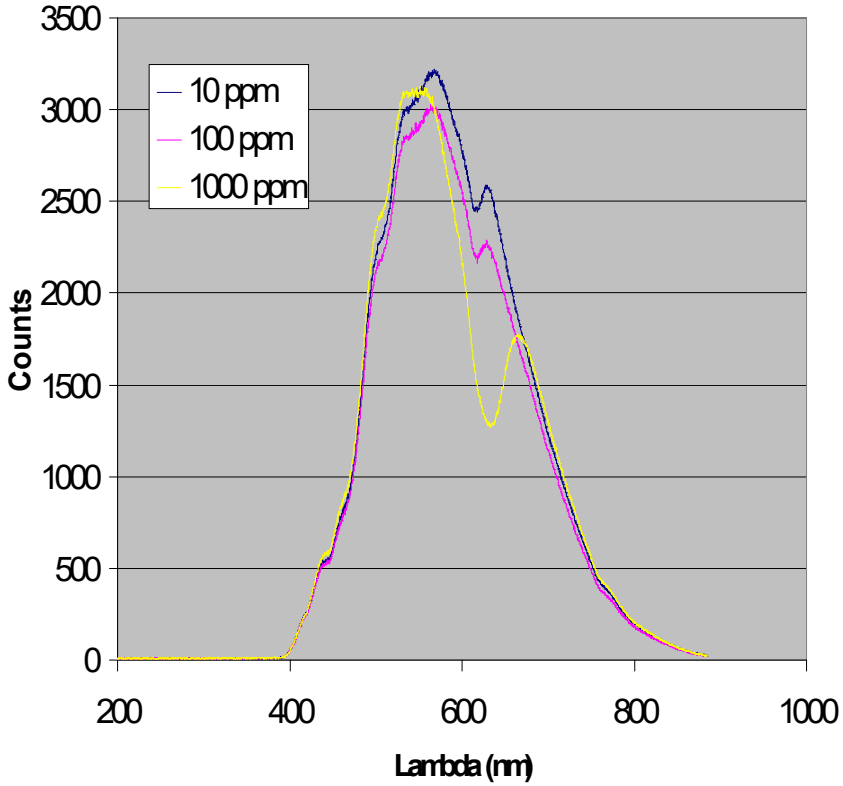
Kirsch, et al, *PDA J Pharm Sci & Technol* 51, 5, 1997 p. 200

Risk Of Microbial Ingress if >1um

Container closure integrity: dye ingress leak detection



Dye Test Not Sensitive Enough for Human Operator

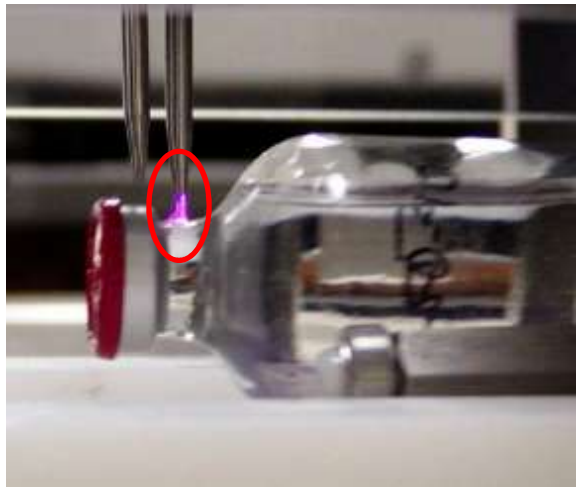


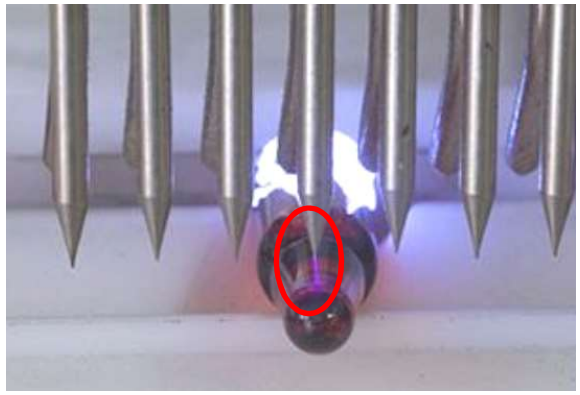
Dye Test Sensitive if in conjunction with automatic spectrometer

Container closure integrity: HV leak detection

- Superior to Dye Test
- Objective
- Fast > 400 pcs/min
- HV better than Vacuum for viscous liquid
- No influence on proteinaceous active products

Vial hole size (µ)	Packages tested (#)	# Packages ID'd as LEAKING DAY 1		# Packages ID'd as LEAKING DAY 29	
		Vacuum decay	HVLD	Vacuum decay	HVLD
PRODUCT-FILLED					
15	10	8	10	2	10
25	10	9	10	2	10
50	10	10	10	3	10
PLACEBO-FILLED					
15	10	10	10	10	10
25	10	10	10	10	10
50	10	10	10	10	10





HV Test Sensitive Enough For Integrity Assurance

HVLD exposure effects on product P-C properties

ImClone Systems Products

HVLD Exposure	Product A				Product B				Product C			
	Monomeric Peak		High MW Species	Low MW Species	Monomeric Peak		High MW Species	Low MW Species	Monomeric Peak		High MW Species	Low MW Species
	Rel. MW	% Purity	% Purity	% Purity	Rel. MW	% Purity	% Purity	% Purity	Rel. MW	% Purity	% Purity	% Purity
None	142	97.6	1.5	1.0	138	98.0	0.5	1.1	170	99.1	0	0.9
1 x 25kV	142	97.5	1.5	1.0	138	98.0	0.5	1.1	170	99.1	0	0.9
10 x 25kV	142	97.5	1.5	1.0	138	98.0	0.5	1.1	170	99.1	0	0.9

Summary: HVLD exposure demonstrated no impact

Source: RxPax, LLC, PDA Metro Chapter, May 2011

Vacuum decay as alternative solution

For dry or liquid products, most package systems

Detects pressure rise from gas or vapor egress limitations

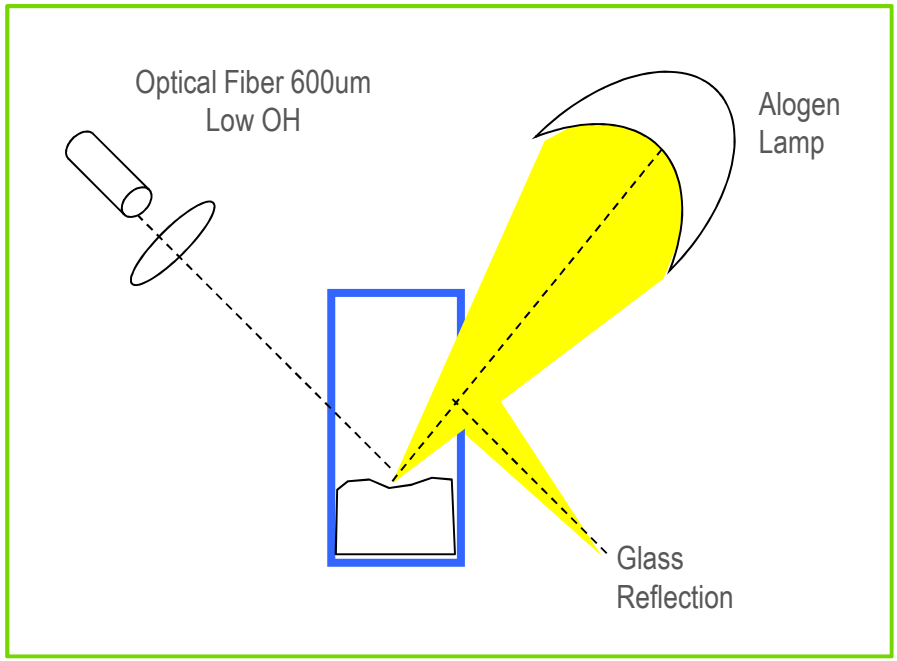
- Protein clogging often prevents leak detection
- Liquid leaks may contaminate test chamber

Considerations

- Faster tests limit sensitivity
- Instrument design/make can influence test results
  - Transducers and internal system design
  - No-leak baseline stability

Source: RxPax, LLC, PDA Metro Chapter, May 2011

NIR Spectroscopy for Lyophilized products

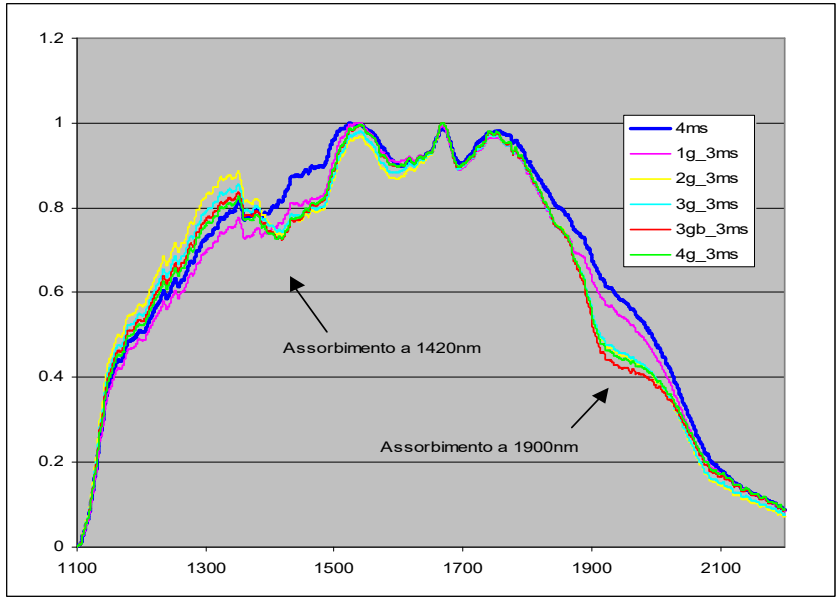


ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
17 (1998) 473–480

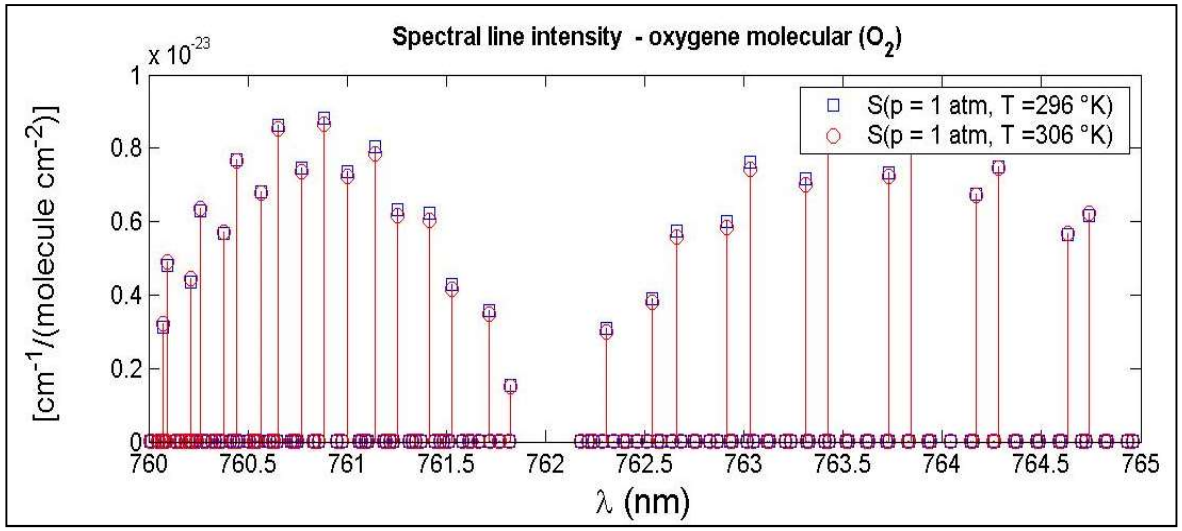
JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

The use of near-infrared spectroscopy in the efficient prediction of a specification for the residual moisture content of a freeze-dried product



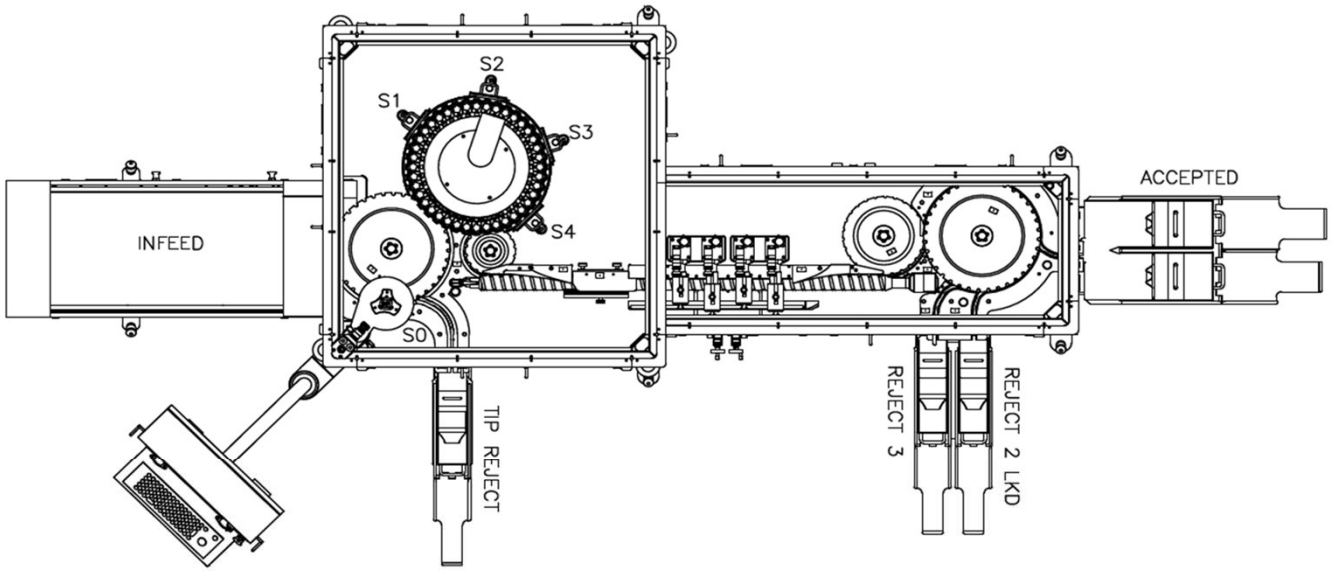
- **Air path layout for easy integration into inspection machine**
- **H_2O Absorption Band 1400 nm and 1900 nm**

Headspace gas analysis measurement layout



Fully integrated solution

Ref. Layout file name



Inspection configuration details

Inspection station	Inspection detail
S0	TIP INSPECTION/ ALU SEAL
S1	GLASS DEFECT ON LATERAL SIDE STILL PARTICLES VISCOUS PRODUCTS
S2	PARTICLES / FILL LEVEL
S3	PARTICLES
S4	PARTICLES

Thank you for your attention!

For further information please visit
www.engineeringstevanatogroup.com

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