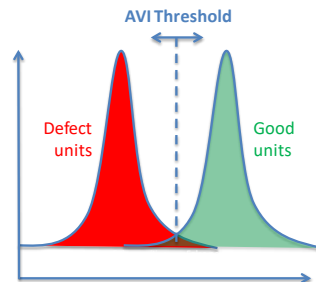


- **Theory 2: Introduction to technical principles of automated inspection machines**



- Camera systems / light / motion
- Image processing and database system
- Interlinkage of parameters:  
Speed, Rotation speed, Inspection parameters,  
Detection probability, False reject rate
- Properties, capabilities and limitations of  
automated inspection systems
- Scope of Automated Visual Inspection
- Leak Testing

- Process / People to master AVI
- Functionality of automated inspection machines
- Camera systems / light / motion
- Image processing and database system
- Interlink age of parameters
  - Speed
  - Rotation speed
  - Inspection parameters
  - Detection probability
  - False reject rate
- Properties, capabilities and limitations of automated inspection systems
- Scope of Automated Visual Inspection



## Best in class organisation for VI (People mgnt)

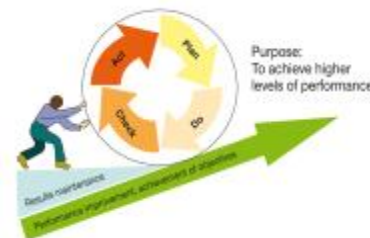
Transformation is not only buy a machine, but build a team/organization for VI

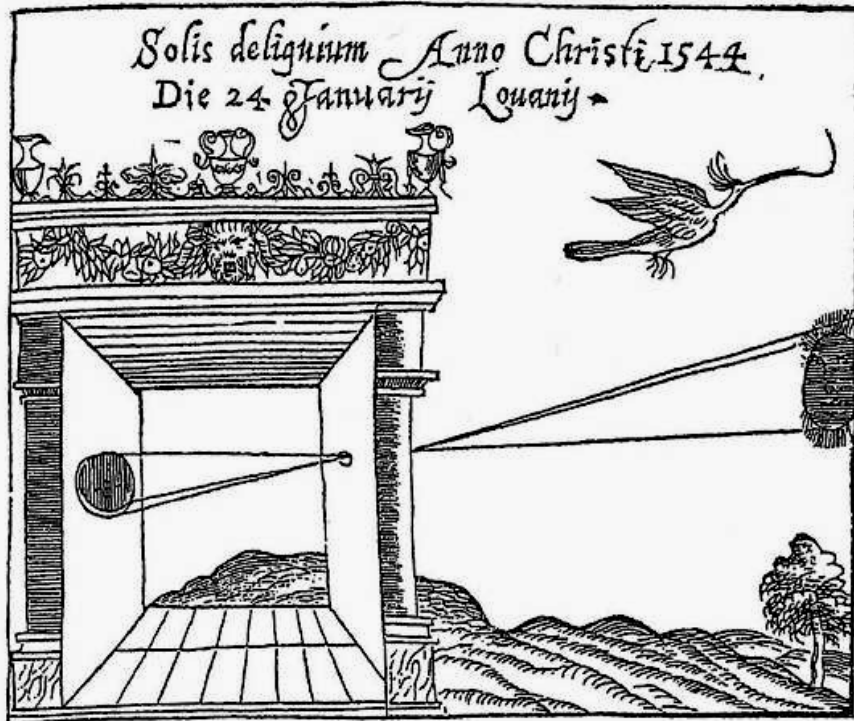
- develop operators / supervisors
- develop maintance (calib./mech./vision)
- develop automation support
- opportunity to develop vision experts / Ext.
- develop a team to supply kits or externalize
- develop AQL quality team
- develop control chart tools & SPC team
- develop defect id. / externalize



## And change mindset by generating a feedback loop and involve the filling & Quality department

Loop with USP<1790> ultimate goal of VI is continuous improvement





Gemma Frisius, 1558

“...and we call invisible, either what is absolutely – as we consider impossible in other cases -,  
Or what is visible by its inherent nature, but in fact it may only be hardly visible or invisible »

Aristotle, De Anima, Book 2, 10

Camera Obscura

- Basic principle Aristotle (384-322 BCE)
- Drawing aid for artists: described by Leonardo da Vinci (1452-1519)
- ....first industrial CCD camera 1975
- 2017 AVI

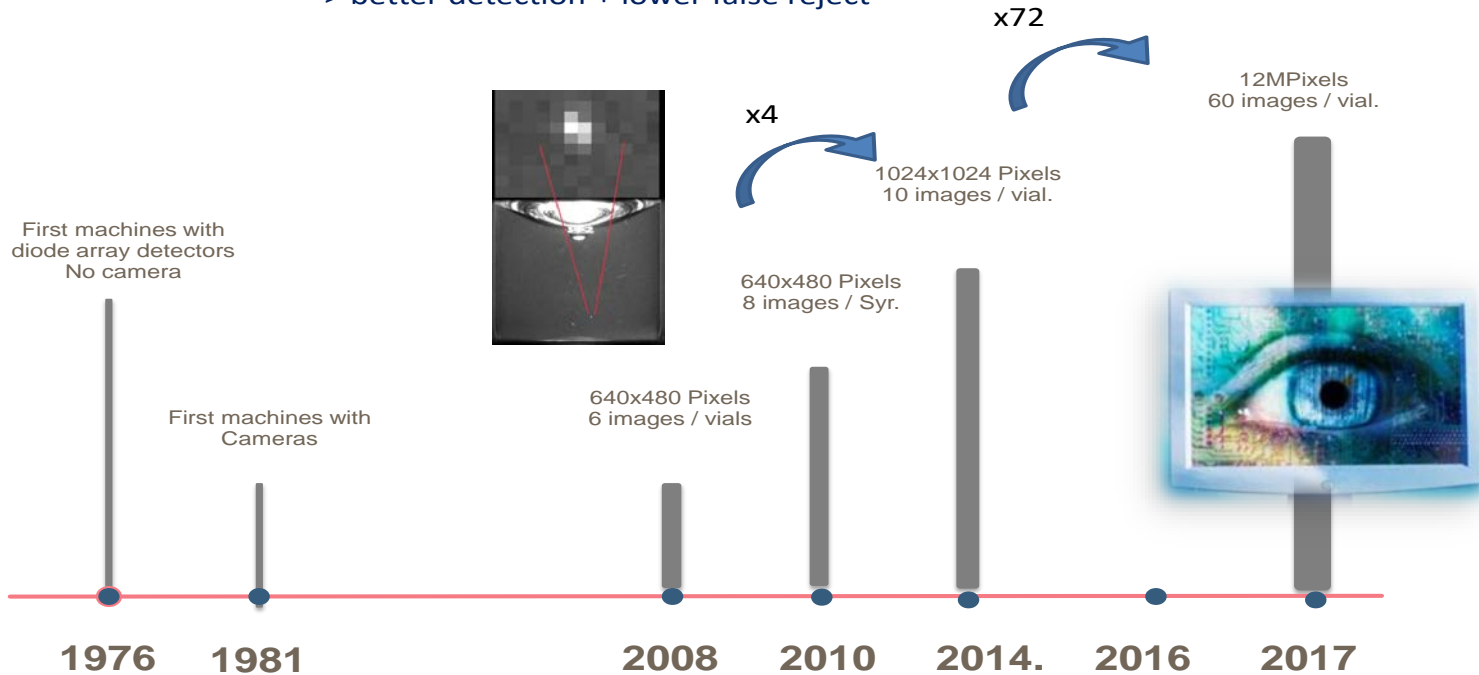
MVI

11µm per cone/6<sup>E6</sup> Cones/ LOD 50-150µm particle

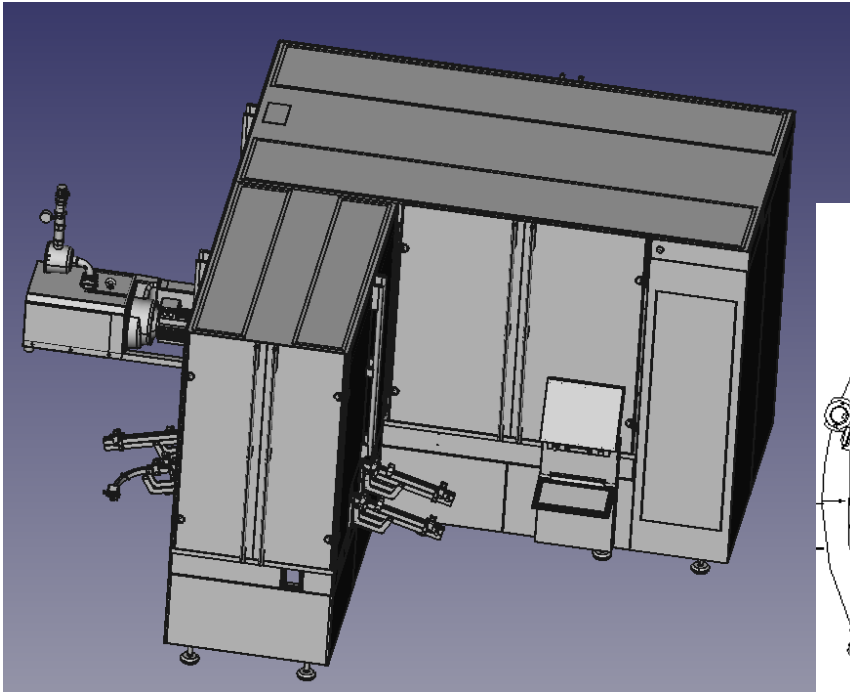
**Image resolution trend**

=> better detection + lower false reject

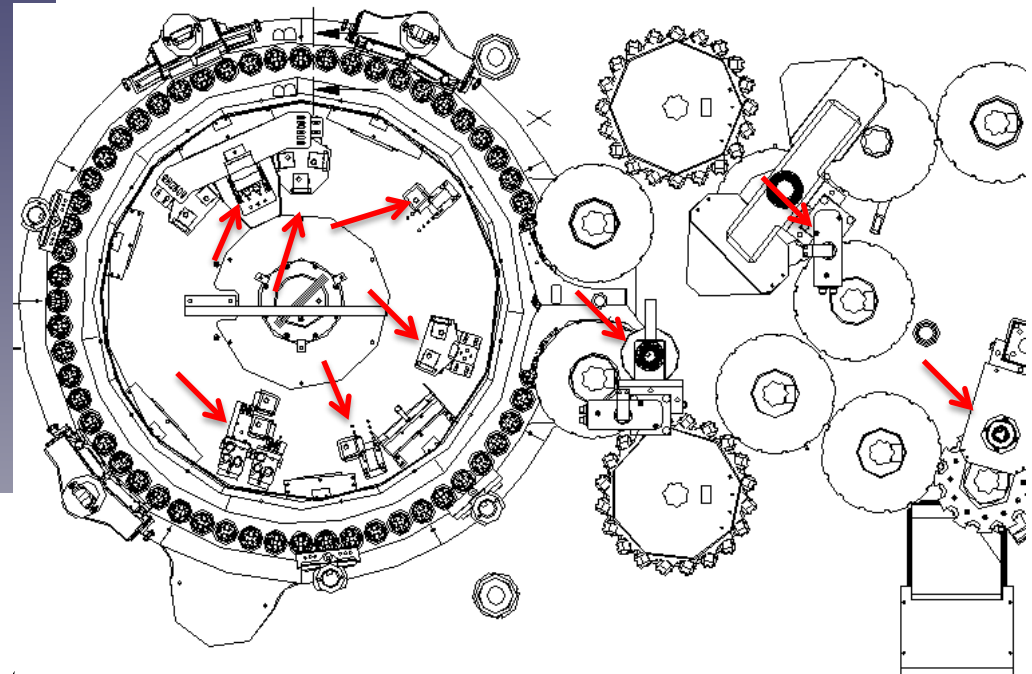
AVI







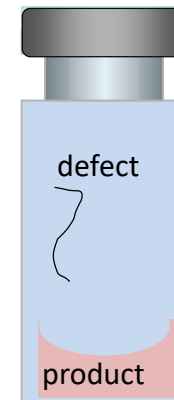
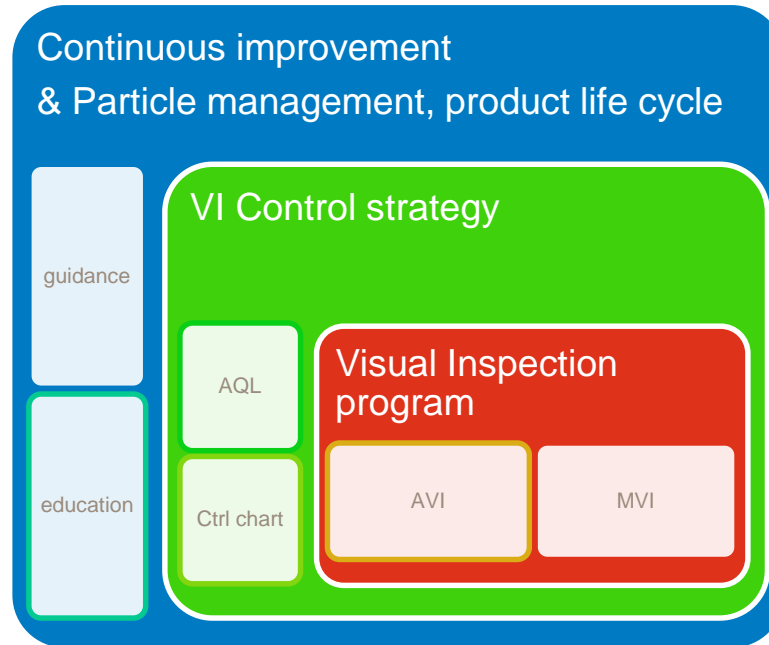
Just a black box



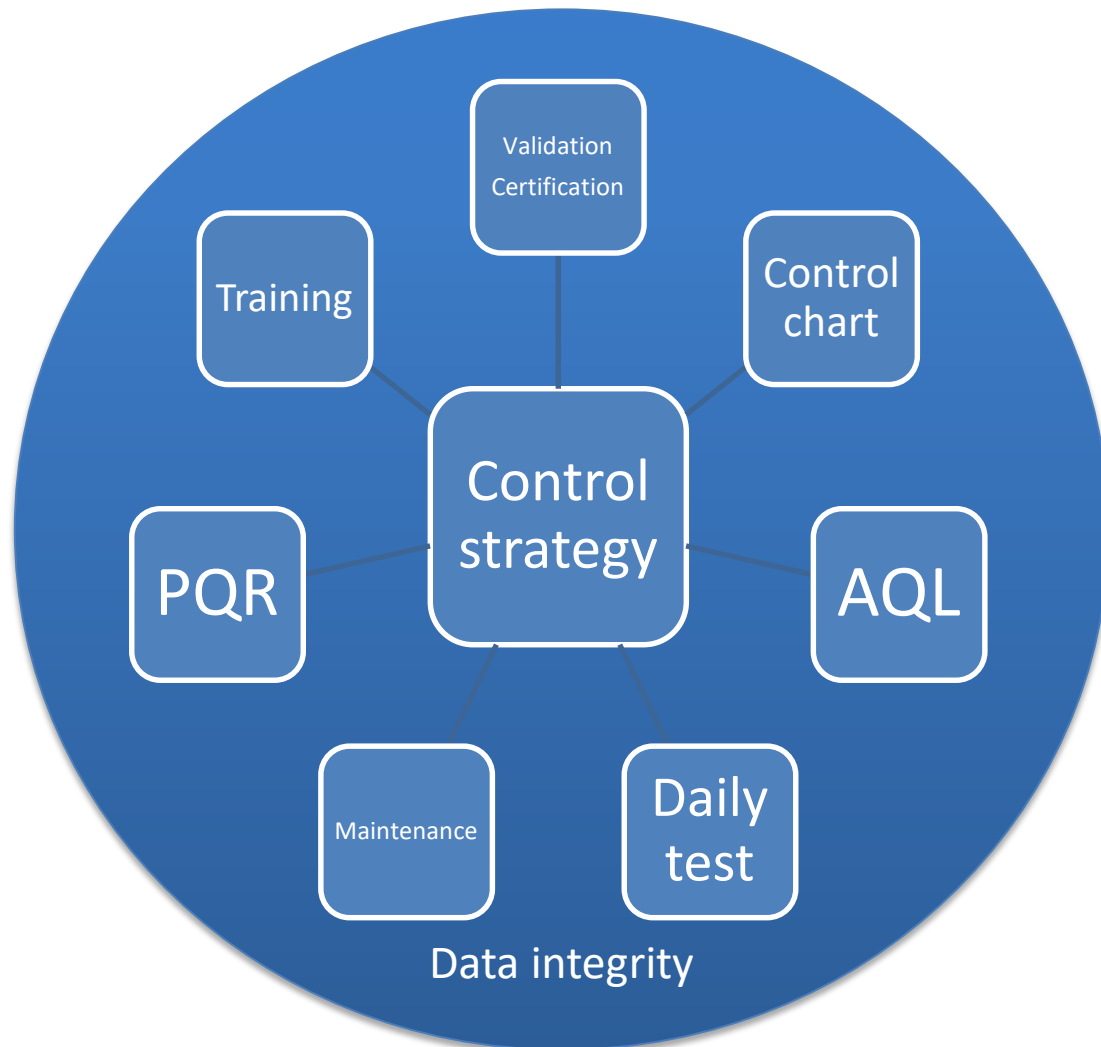
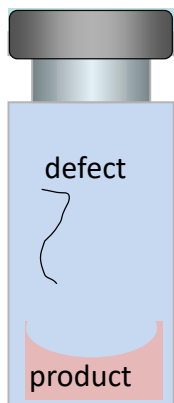
- AVI basic description

Visual inspection program in 3 layers:

- The Core is AVI/MVI program, with strategy for DML / standard work / certification / validation
- The control strategy with ctrl chart and AQL guarantees that VI is kept under control
- Continuous improvement is the goal of all VI activities with CAPA mngt. The Particle management guidance is a key to success with particle control and associated WOW & education, product life cycle approach



- Control Strategy







**Motion of units**

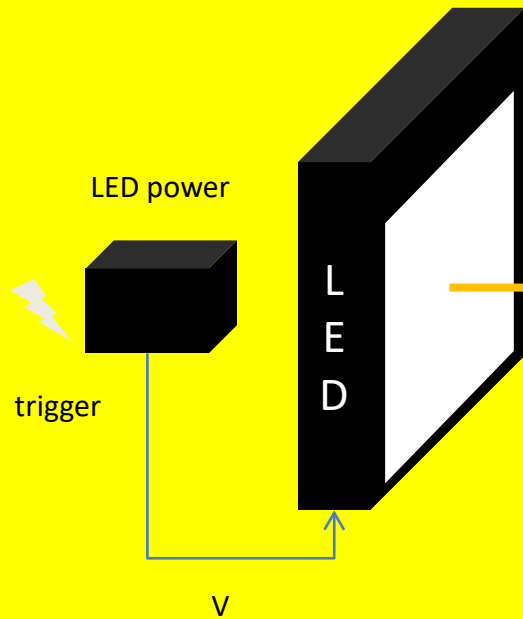


**Light illumination**

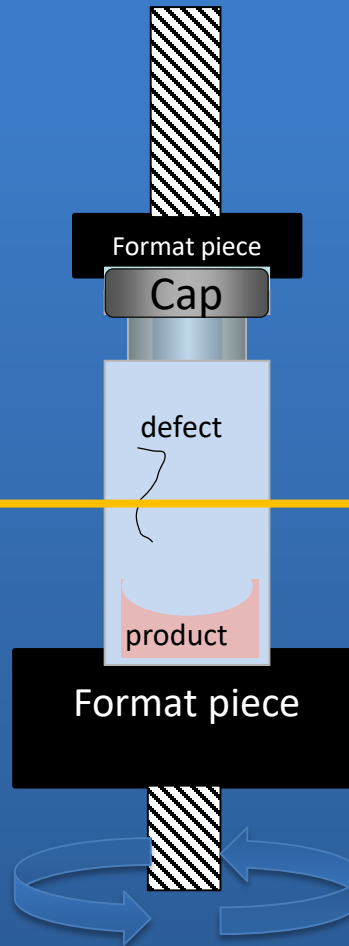


**Digital image processing**

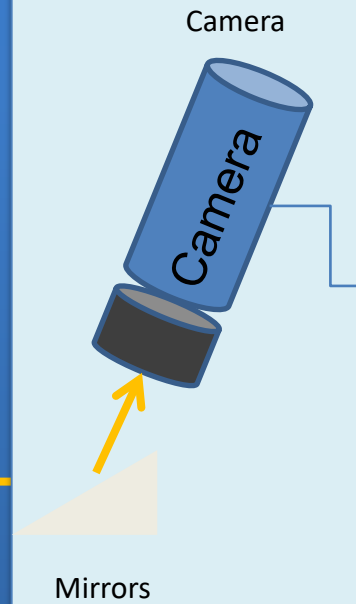
**Illumination**



**Unit Handling**



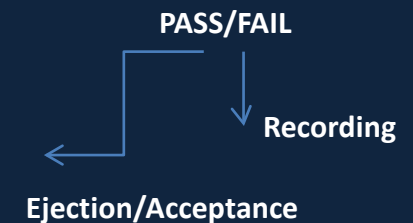
**Image Acquisition**



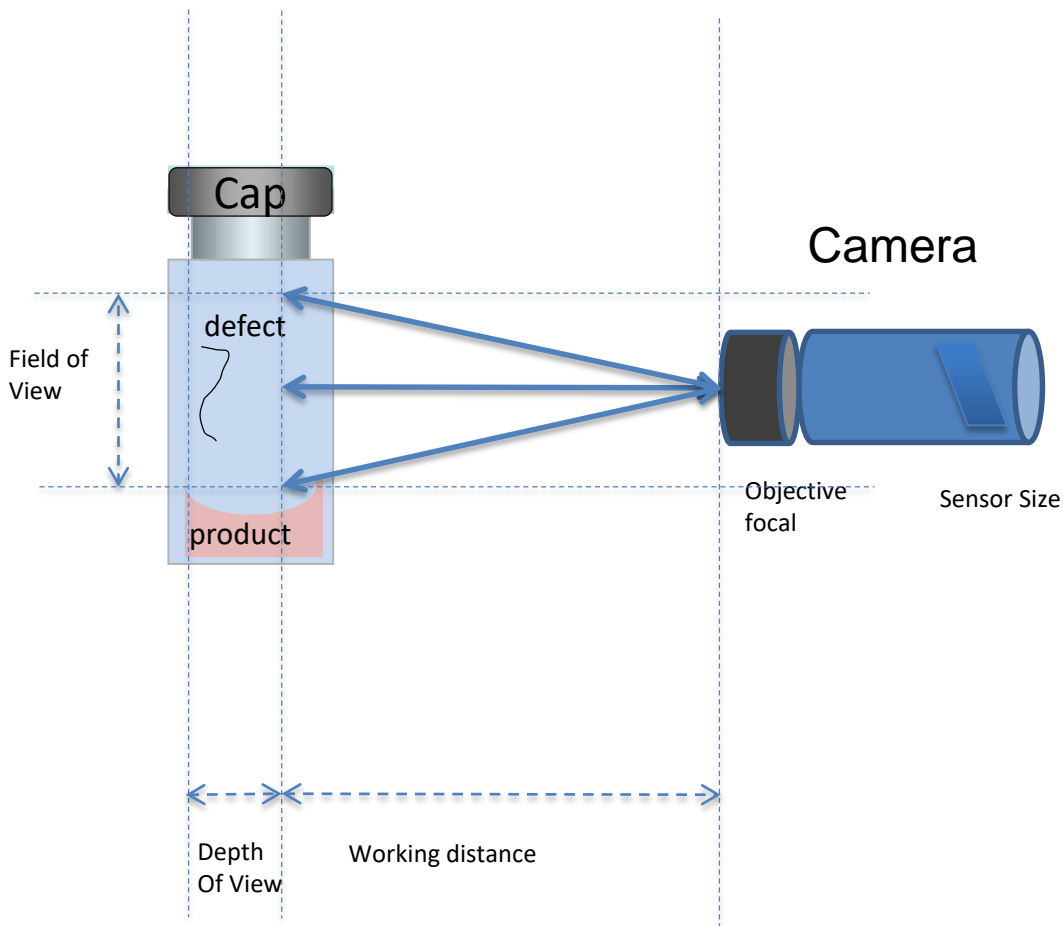
**Image Processing**



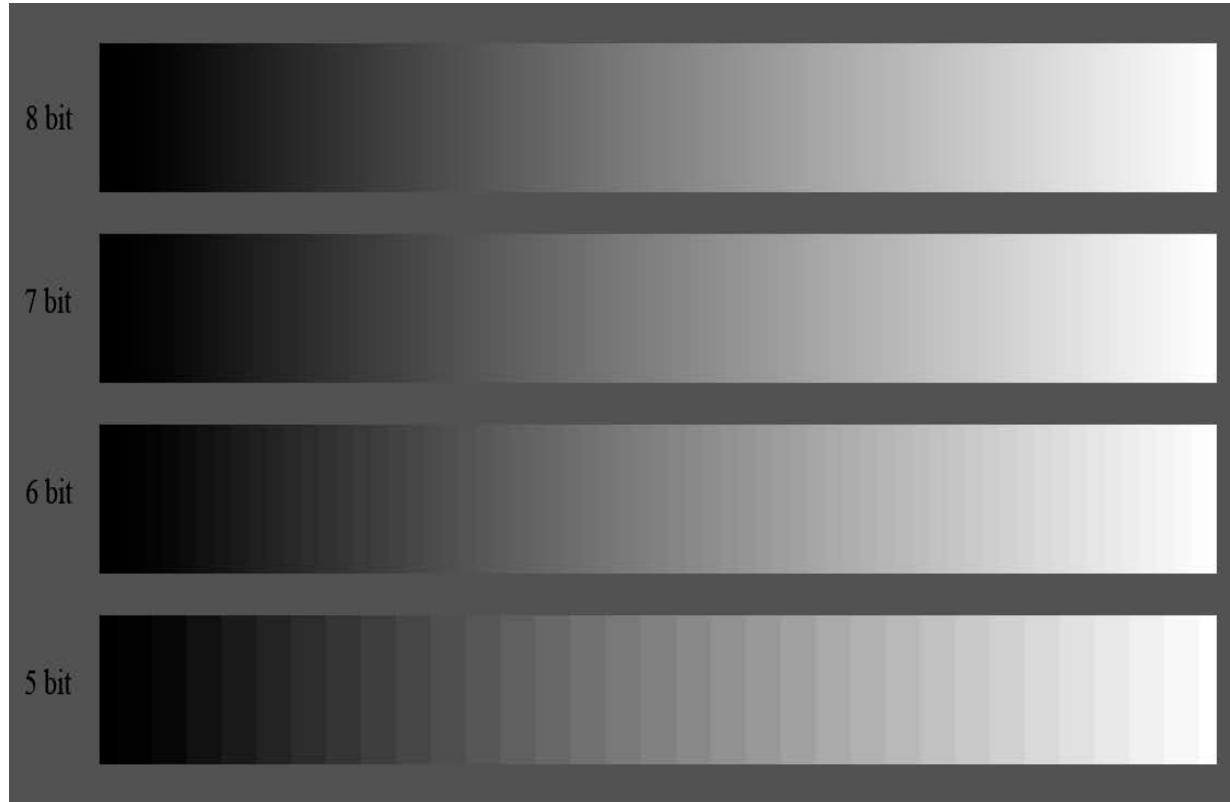
**Unit disposal**



### Image Acquisition

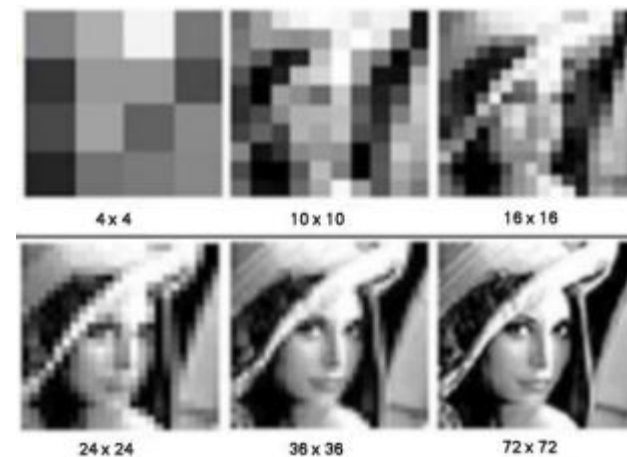


tonal resolution



**Key learning:**  
Tonal resolution  
Spatial resolution / Size sensor

Spatial resolution

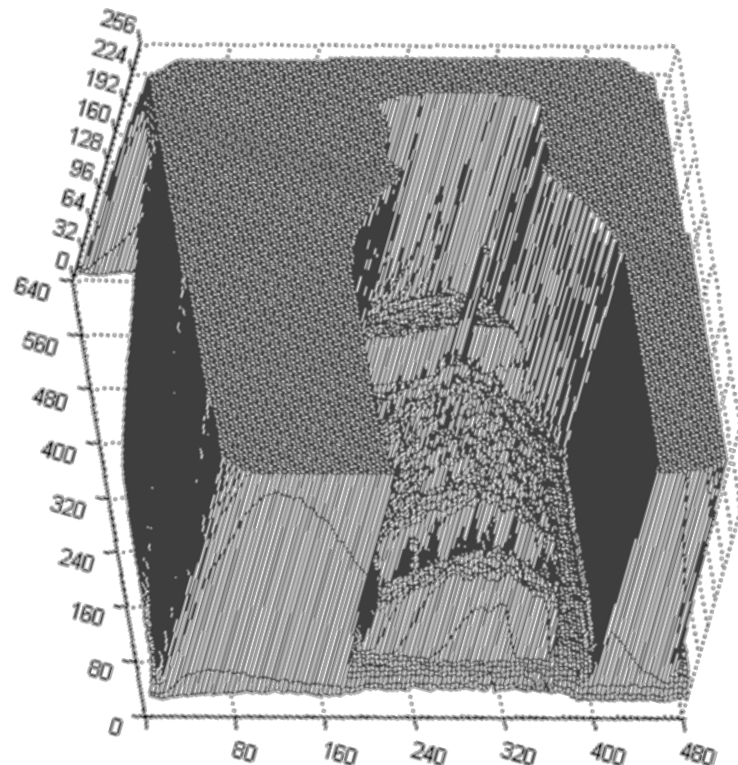
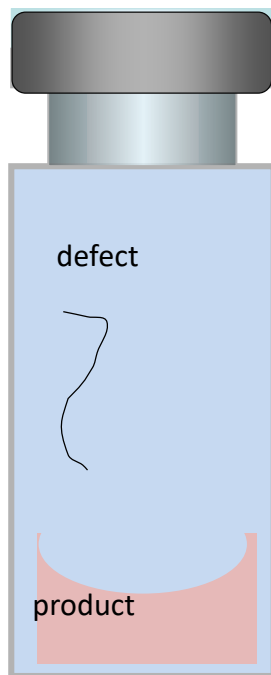


# What a machine really sees, what is DIP?

**Key learning:** AVI sees only a matrices of discrete information in X Y and Z for grey levels

## Variable:

- discrete spatially
- discrete quantitatively



Map here different ways of conveying

⇒ Suckers

⇒ Gripper

⇒ Rotation

⇒ Vial base holders

Those are pieces with ageing / regular  
checks / changes

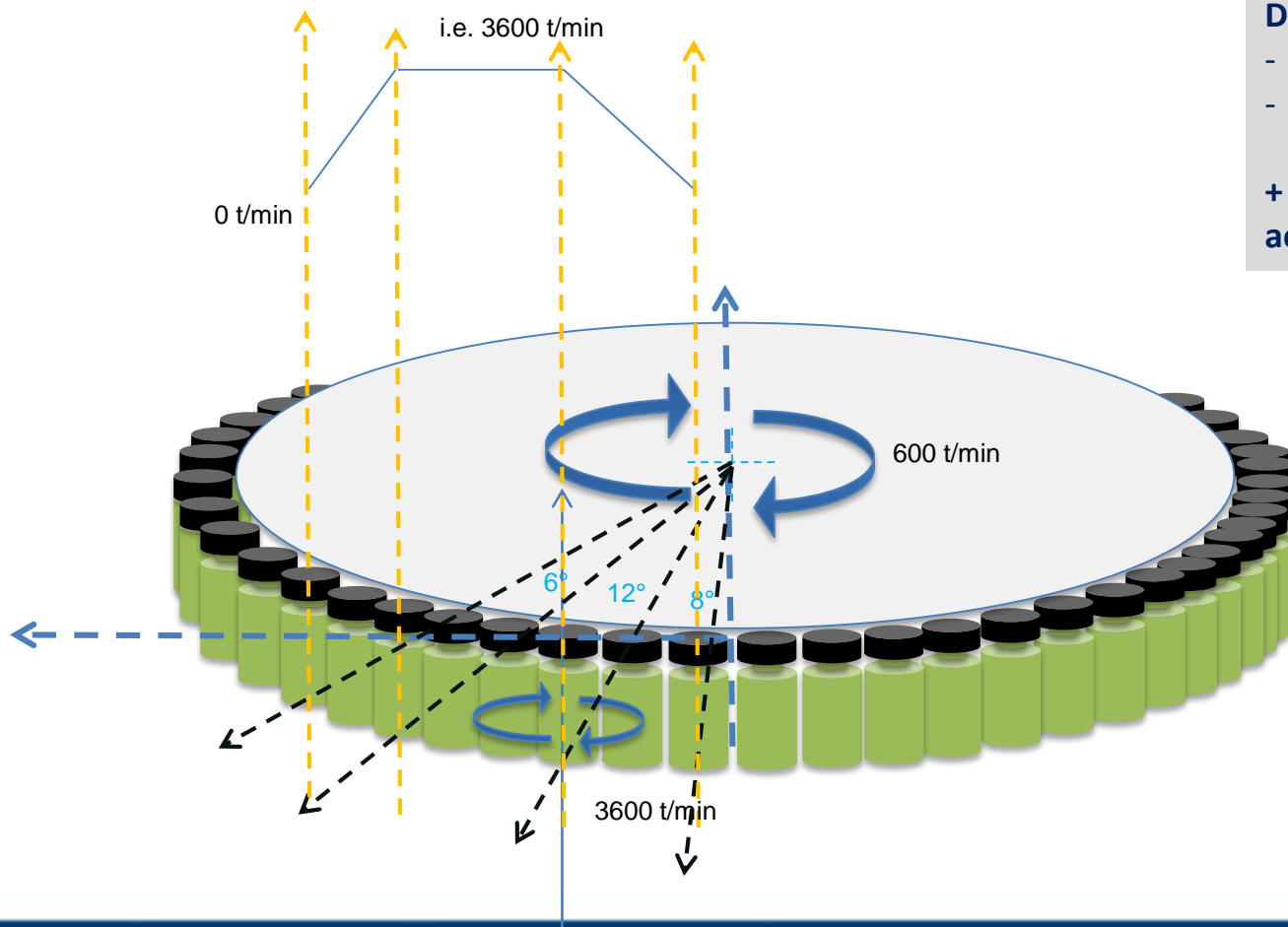


**Key learning:** Modern AVI machine is very complex in term of unit motion;

**Double motion main**

- carousel rotation
- each unit individual fast rotation

+ all synchronized to image acquisition every few ms





How to inspect Automatically a suspension that has a high optical density + scattering?

= Fast rotation To present liquid in thin layer

- ⇒ Lower optical path (density beer lambert)
- ⇒ Minimized scattering effect



0 t/min



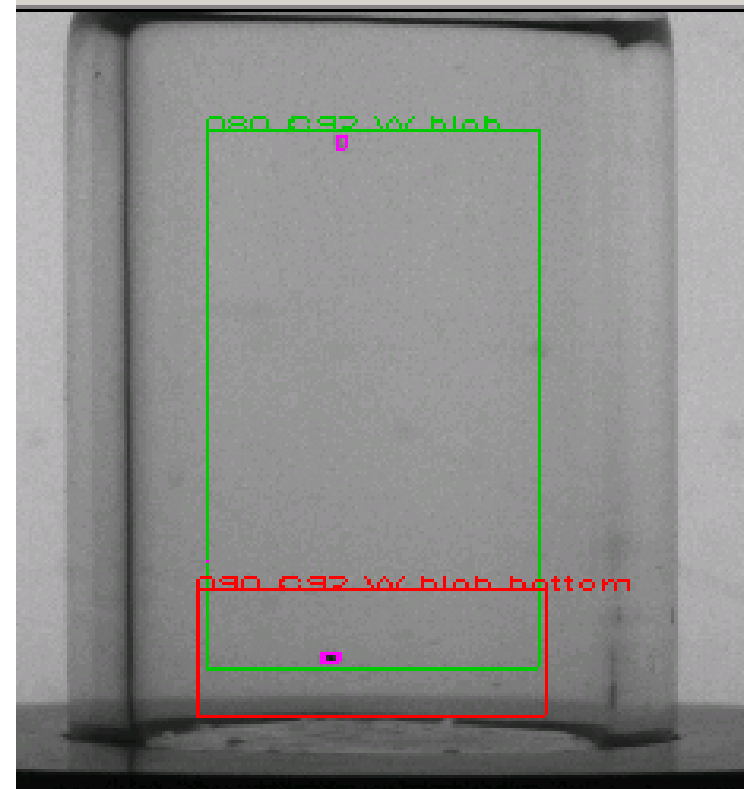
600 t/min



1800 t/min

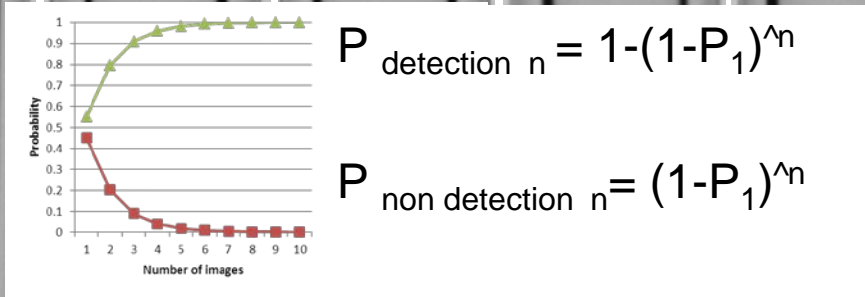
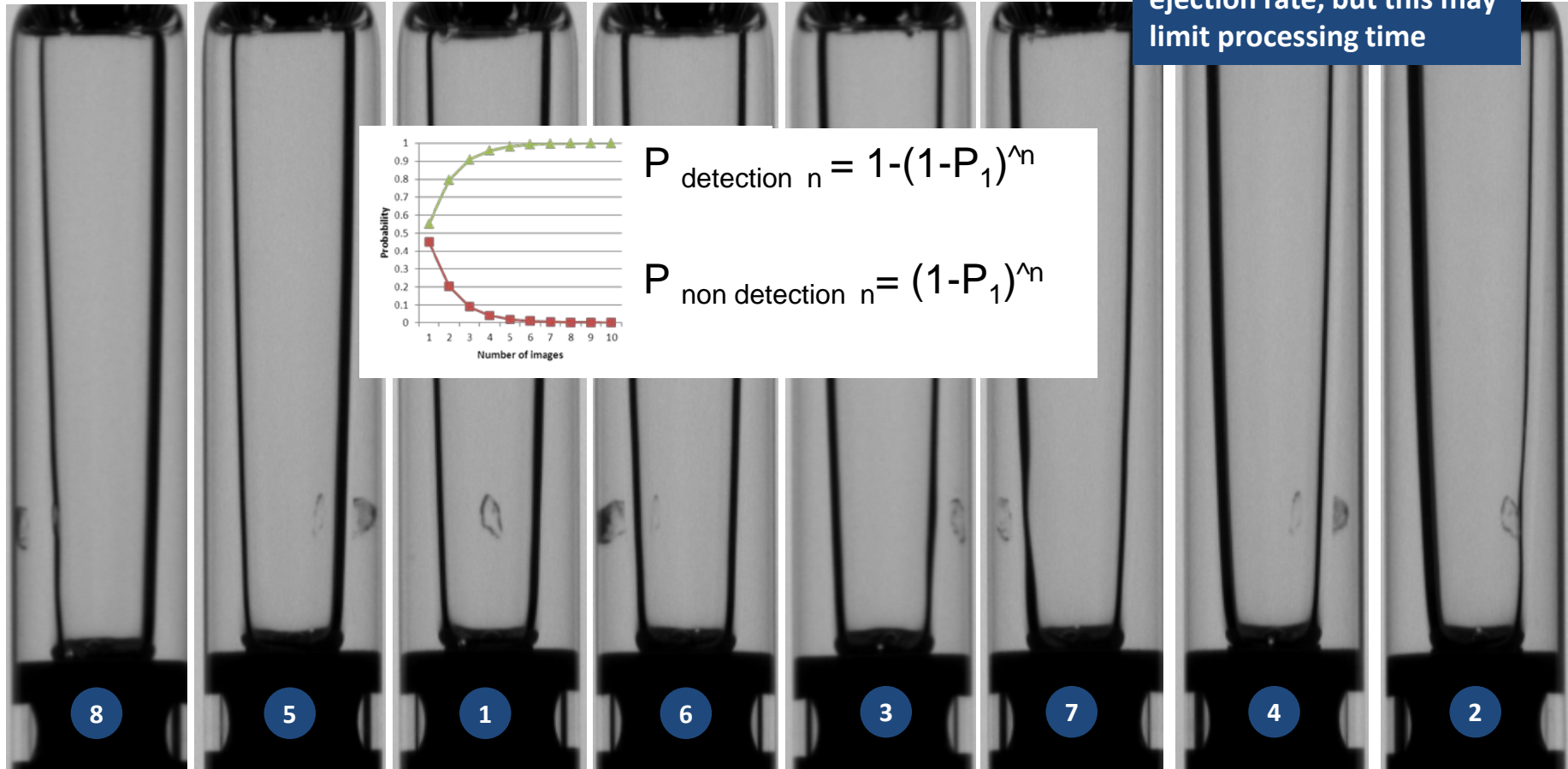


3600 t/min



- Unit rotation

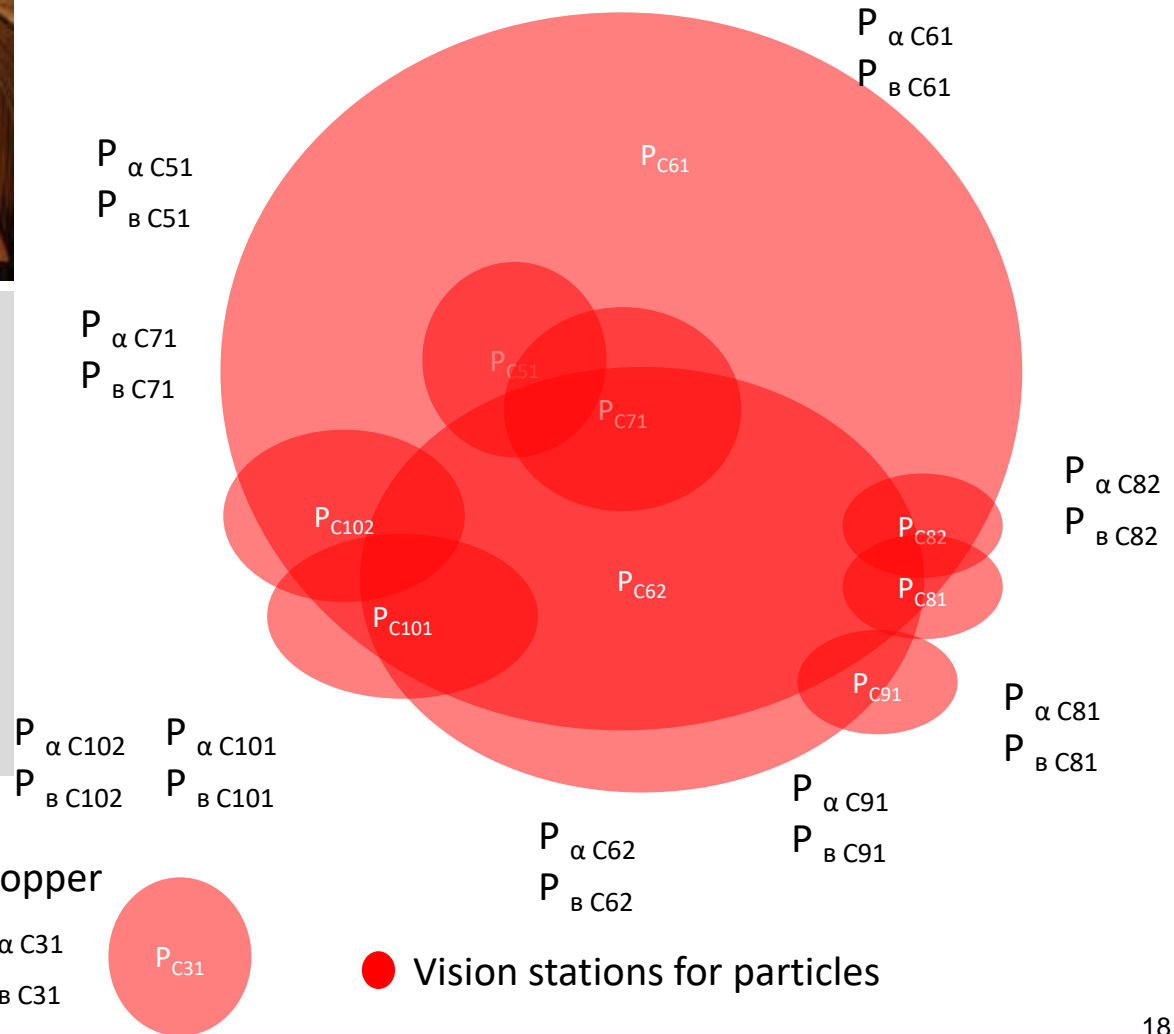
**Key learning:** more images per unit is better for detection rate and for ejection rate, but this may limit processing time





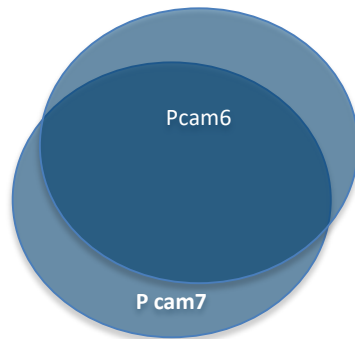
**Key learning:** Automated Inspection machine may be compared to an orchestra:  
each camera may be compared to an instrument group contributing to an overall particle detection.  
Each image may be compared to a individual player.  
We have up to 15 cameras and from 32 images to 150 images per unit

Venn diagram for detection probability



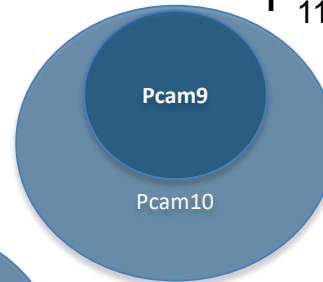
- Multiple camera on AVI machines**

2 collaborative  
 Cameras for a  
 specific area  
 i.e. = Syr. flange

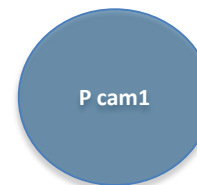
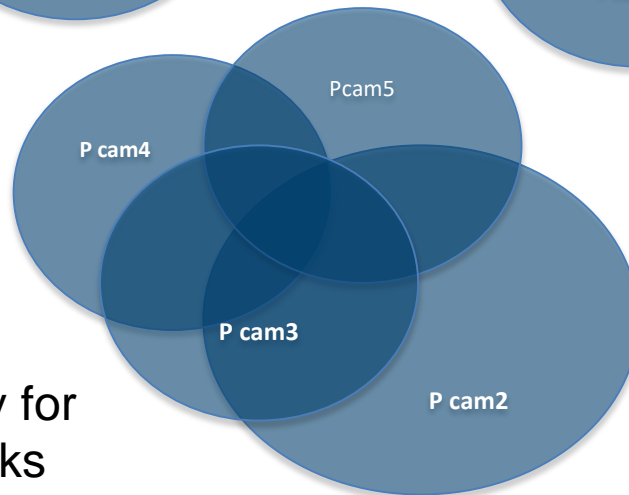


A & B mutually exclusive  
 $P_{11+12} = P_{11} + P_{12}$

2 Camera specific  
 for a defect area  
 i.e. = Syr. closure

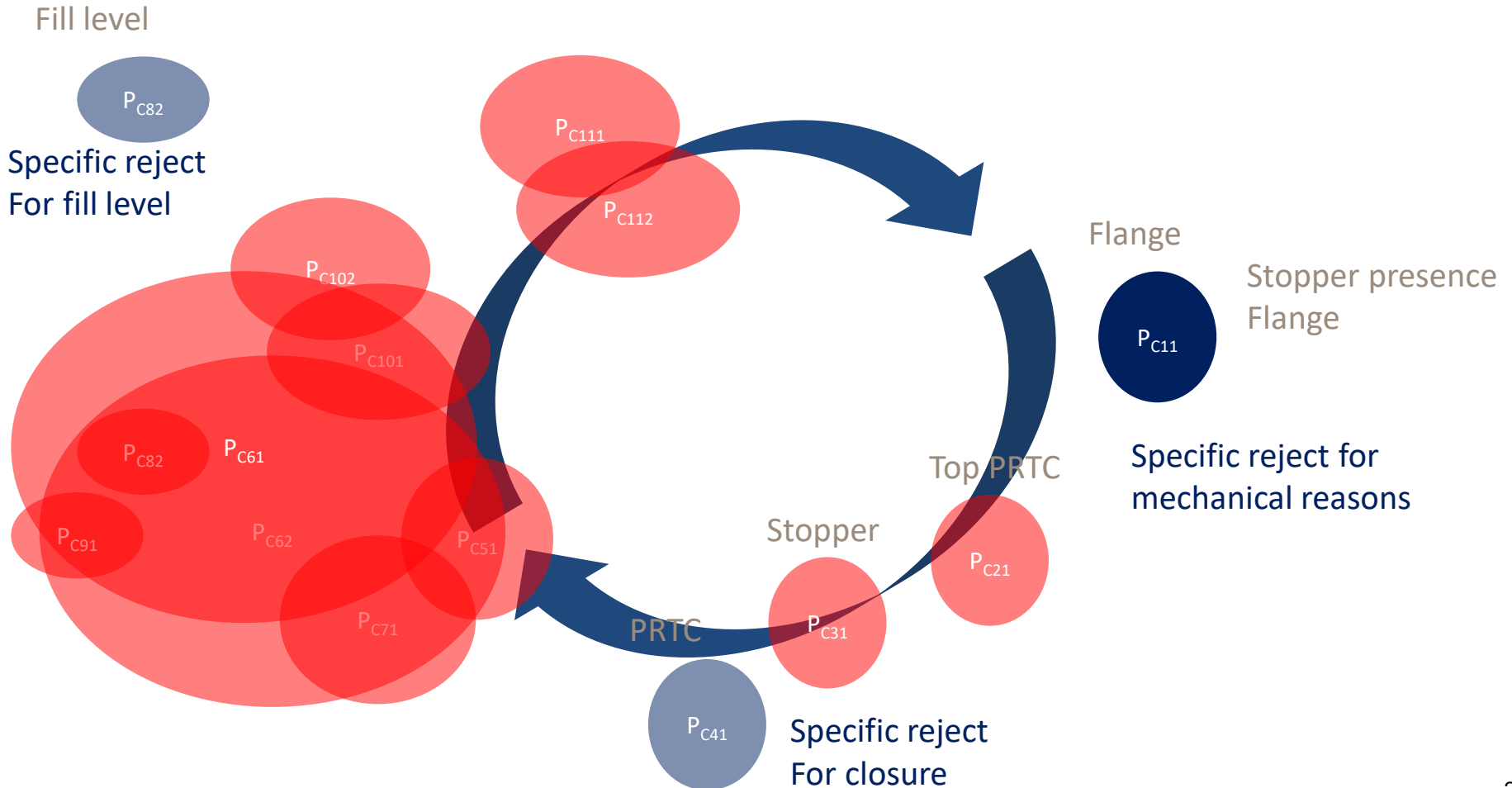


4 collaborative  
 Cameras for a  
 specific area  
 i.e. = Syr. Body for  
 particle or cracks



Camera specific  
 for a defect family  
 i.e. = Fill level

Venn diagram for detection probability



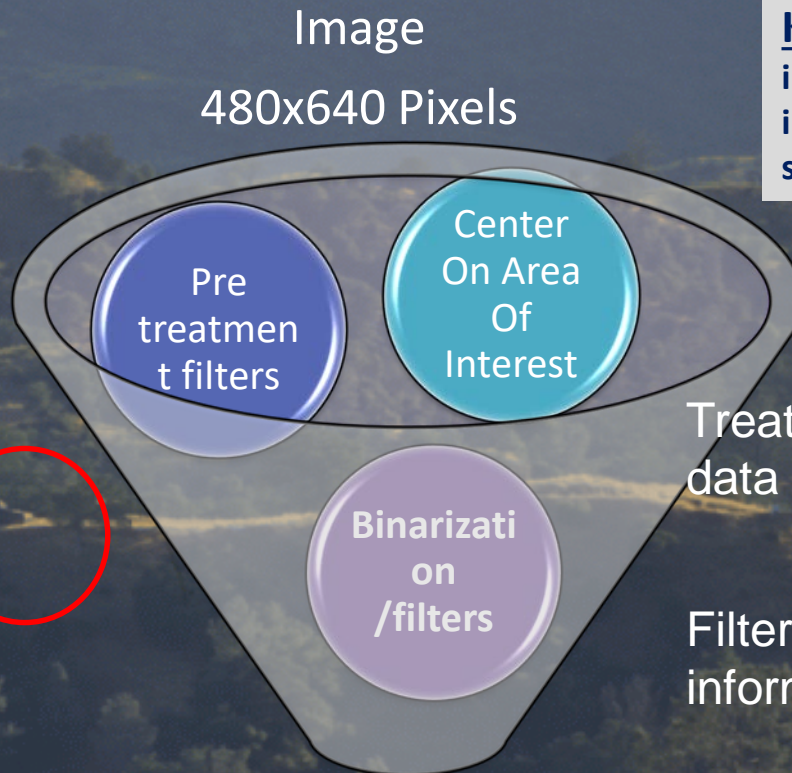


# What is the goal of image processing ?

Why ? Image = too much information

**Key learning:** an image has too much information need some data reduction...

A car is very difficult to see first....image treatment will help

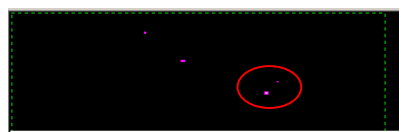
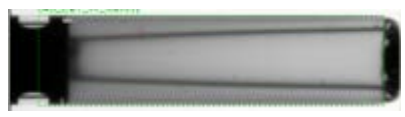
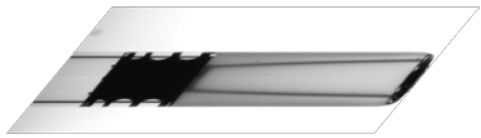
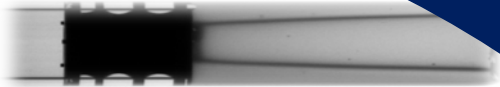


Treatment = reduce data information

Filter relevant data information

Take decision on relevant information

- 1 3D Object presented
- 2 2D image
- 3 Area Of Interest (=AOI)
- 4 Binarization
- 5 Object detection

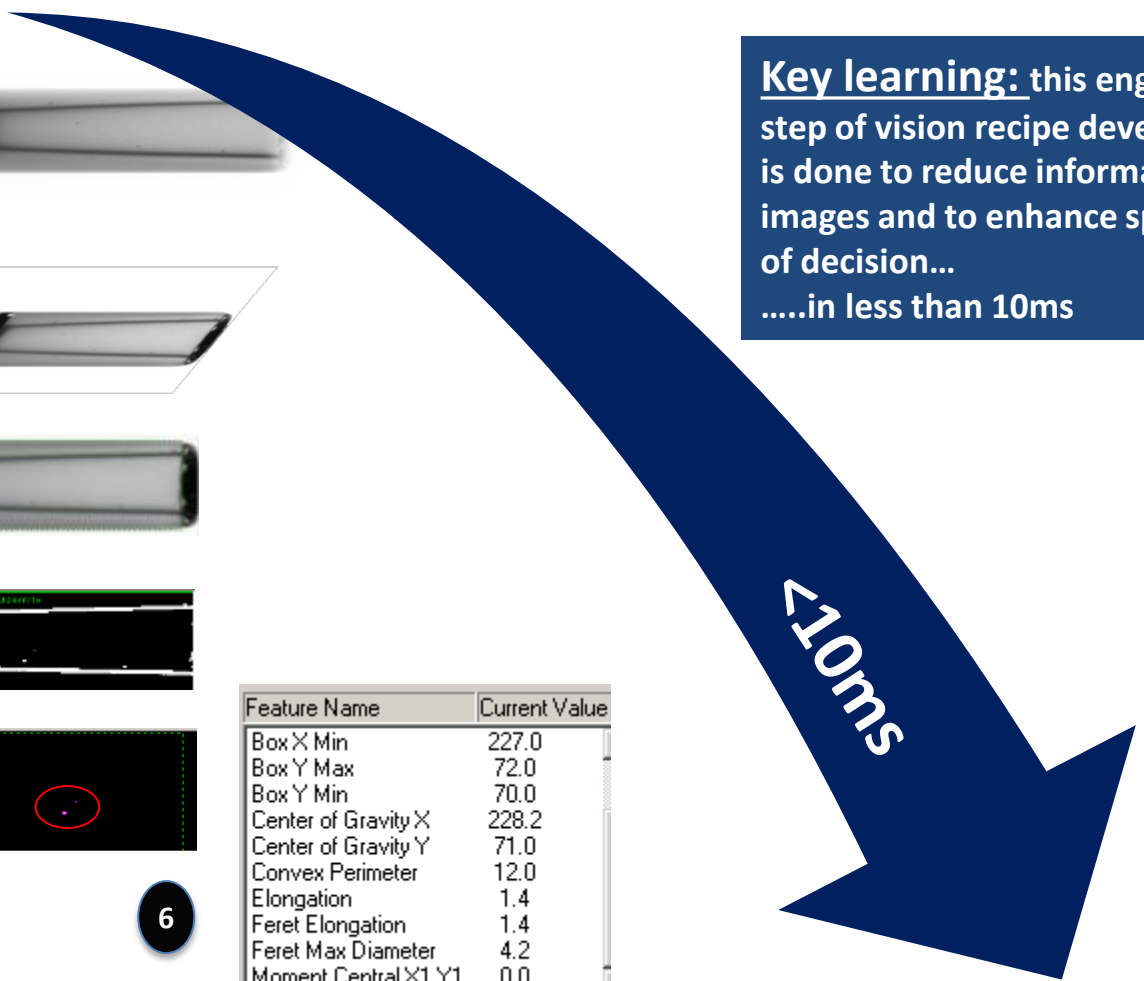


Feature Name	Current Value
Box X Min	227.0
Box Y Max	72.0
Box Y Min	70.0
Center of Gravity X	228.2
Center of Gravity Y	71.0
Convex Perimeter	12.0
Elongation	1.4
Feret Elongation	1.4
Feret Max Diameter	4.2
Moment Central X1 Y1	0.0

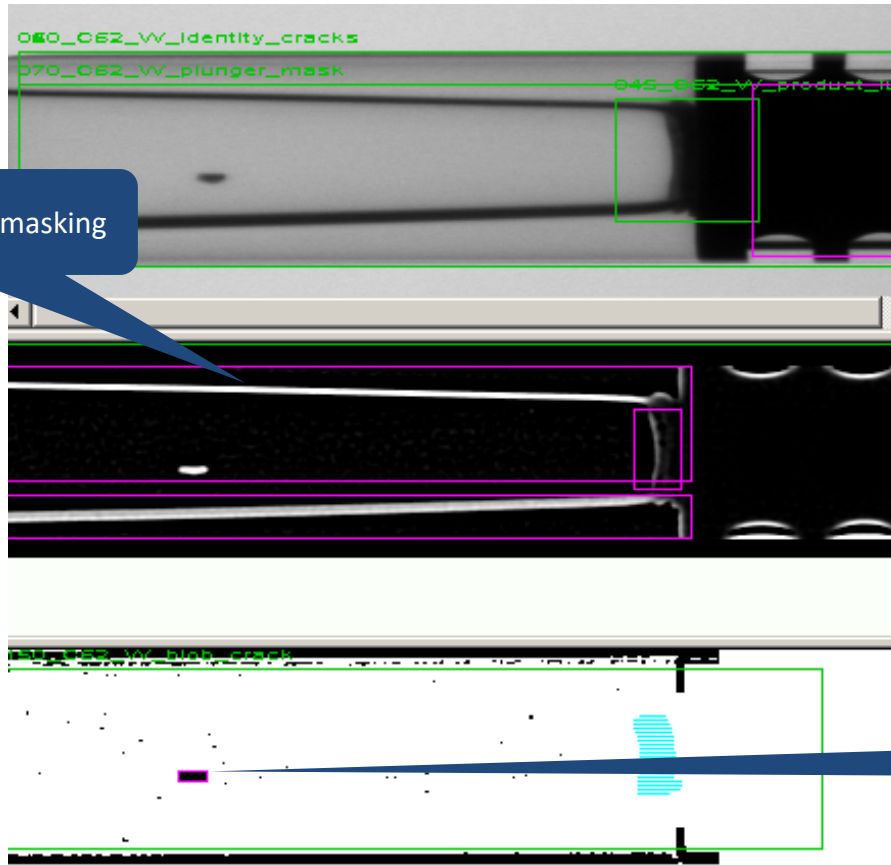
Image feature

- 7 Image understanding
- 8 Pass / Fail

**Key learning:** this engineering step of vision recipe development is done to reduce information of images and to enhance specificity of decision...  
.....in less than 10ms



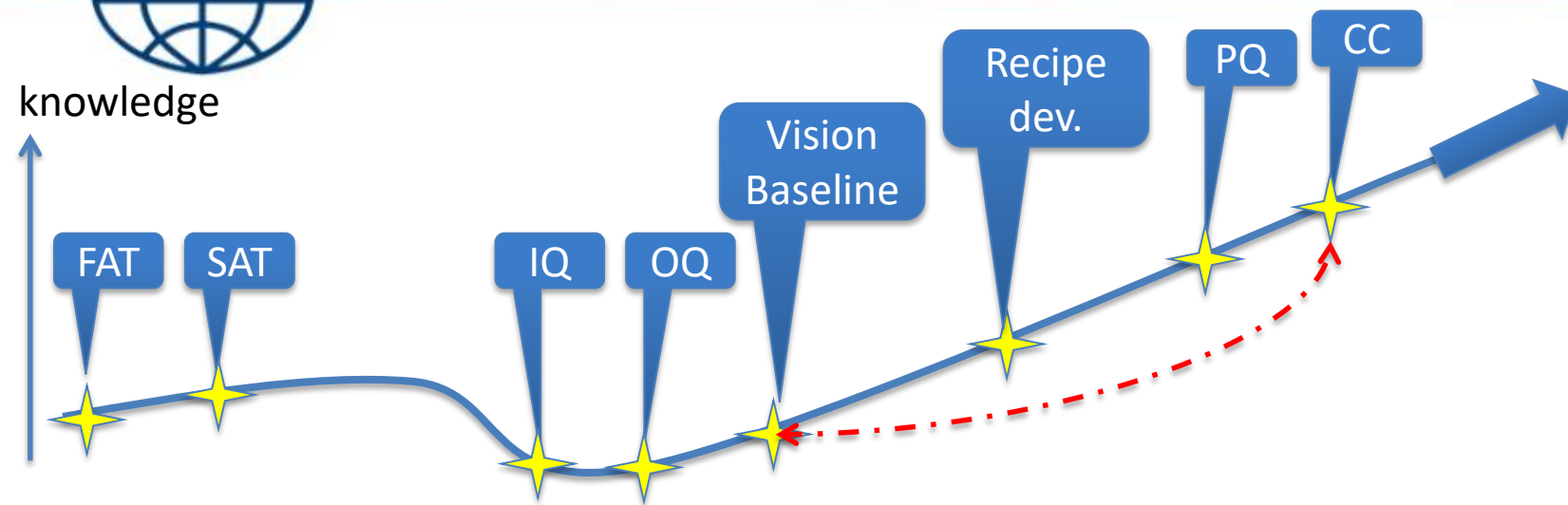
1 meniscus dynamic masking



2 Particle is localized

### Key learning:

Color / Shape / Position features can help to discriminate particle and bubbles



- = to comeback to initial state of PQ, what ever appends in life time (big machine breakage, power failure, camera replacement, or CC)

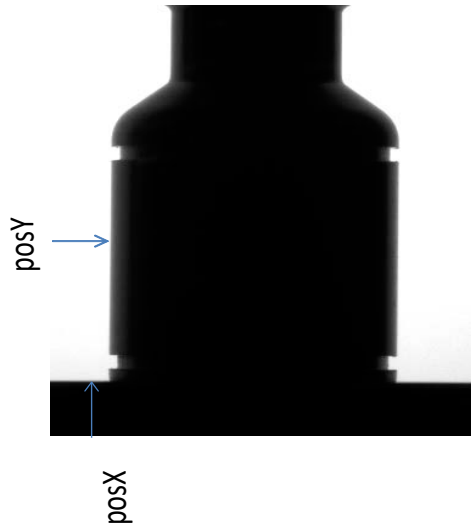
- Mechanical Zero piece
- Encoder Zero
- Vision Zero





### Key learning:

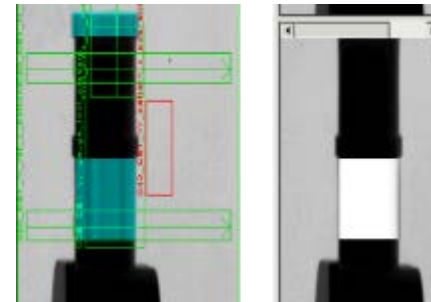
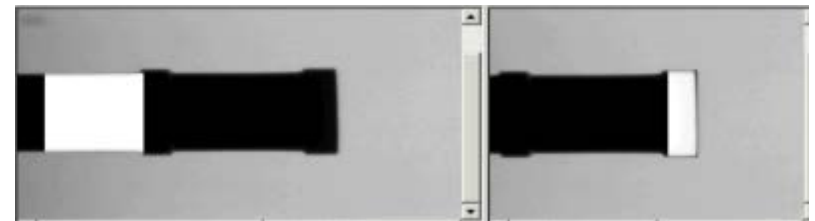
There should be tools to control vision alignment to document that vision tools remains within range from initial baseline corresponding to initial PQ



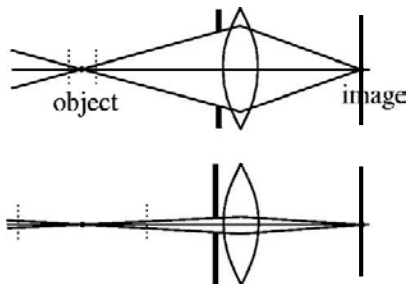
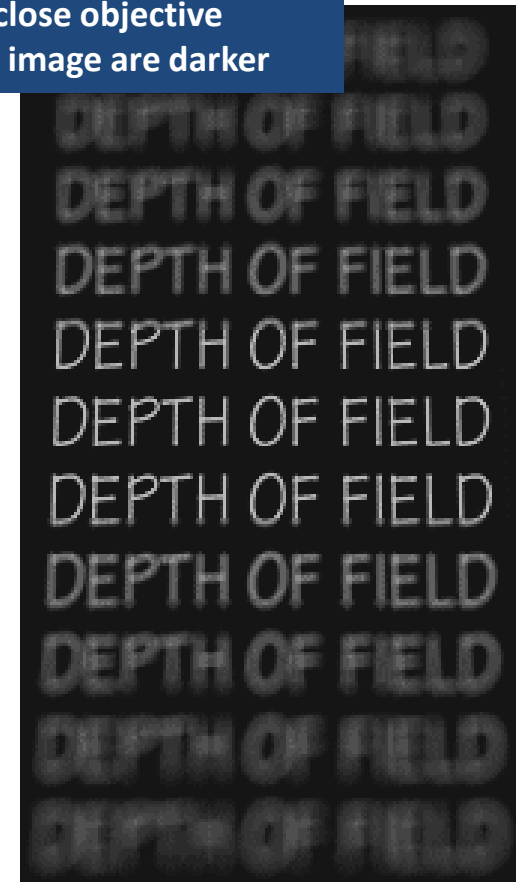
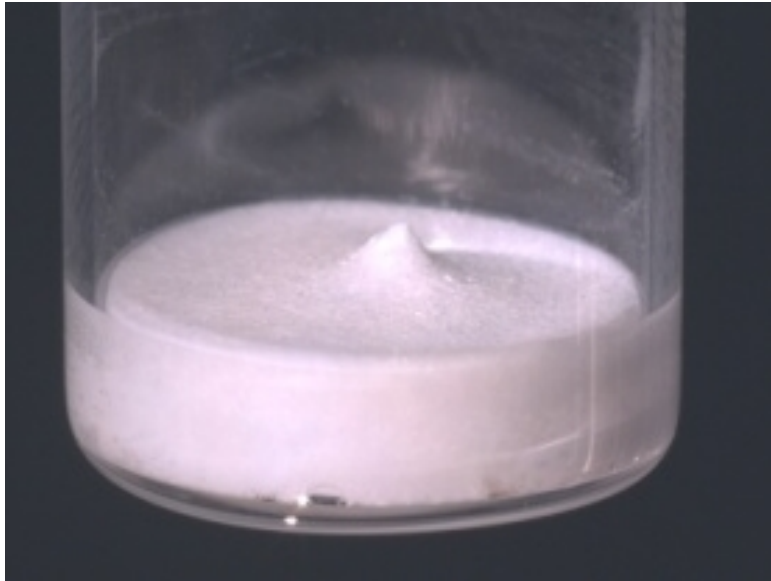
Dummy vial



Dummy syringe

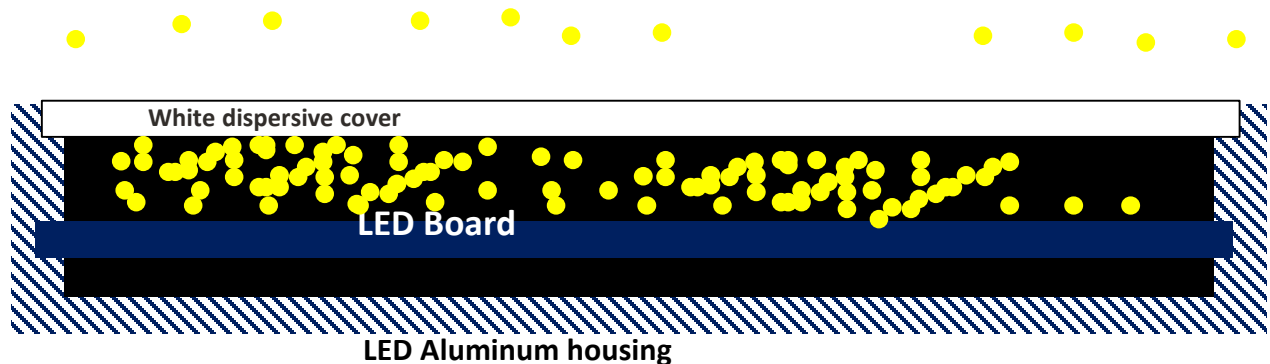
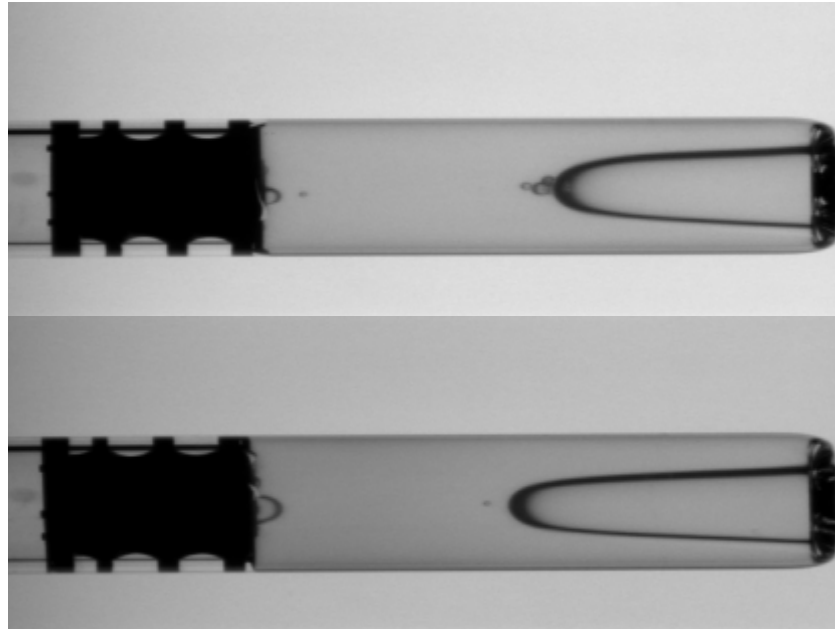


**Key learning:** High Depth of Field can allow to see defect from front and back of unit at same time.  
To do so we close objective aperture but image are darker





LED are more stable but .....beware of heat dissipation

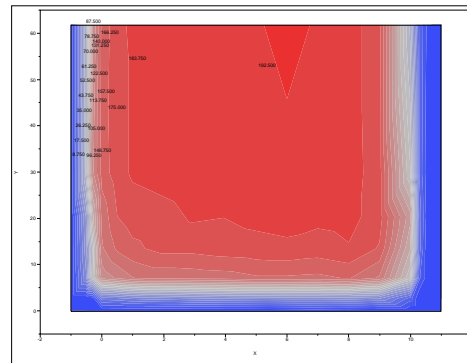


LED are more stable but .....beware of boarder effect

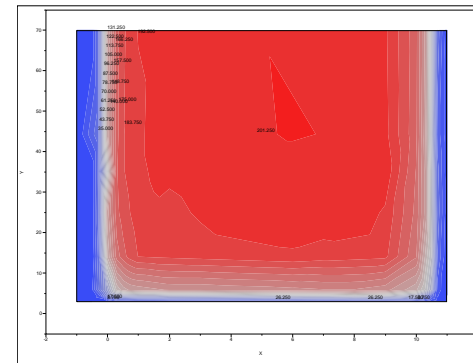
- Practical Examples of key parameters ctrl:  
=> opportunity for knowledge improvement : spacial homogeneity of LED in 3D

Mapping of  
Luminance  
Level in X and Y  
position  
And Z position

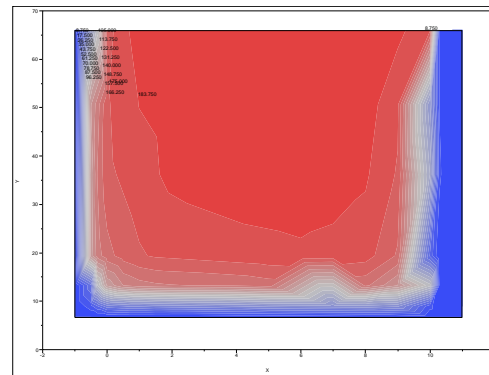
=> Very  
Homegeneous  
in area of use



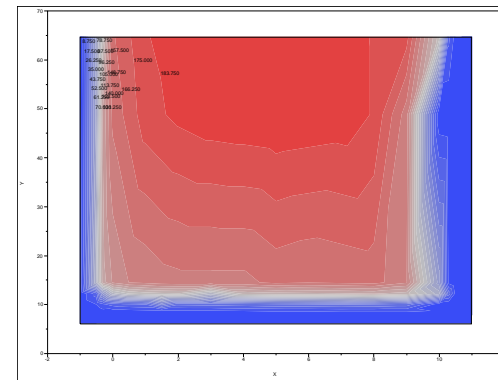
z =53.42mm



z =98.1mm

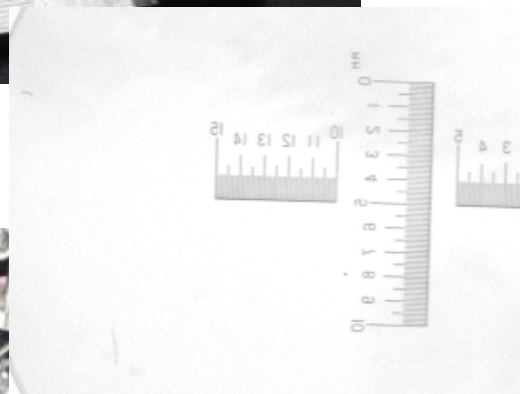
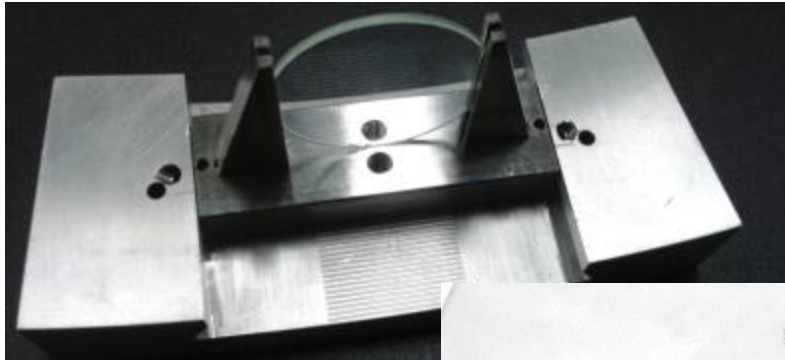


z =134.5mm

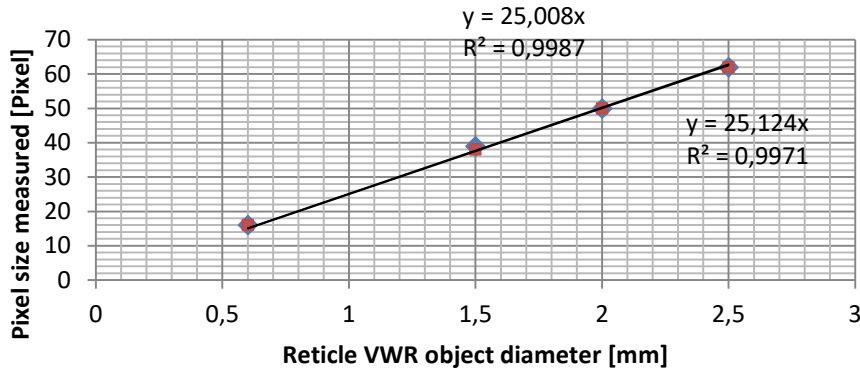


z=178mm

Bad focus



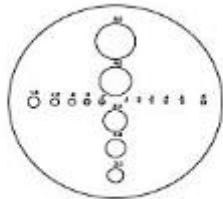
### C91 machine B



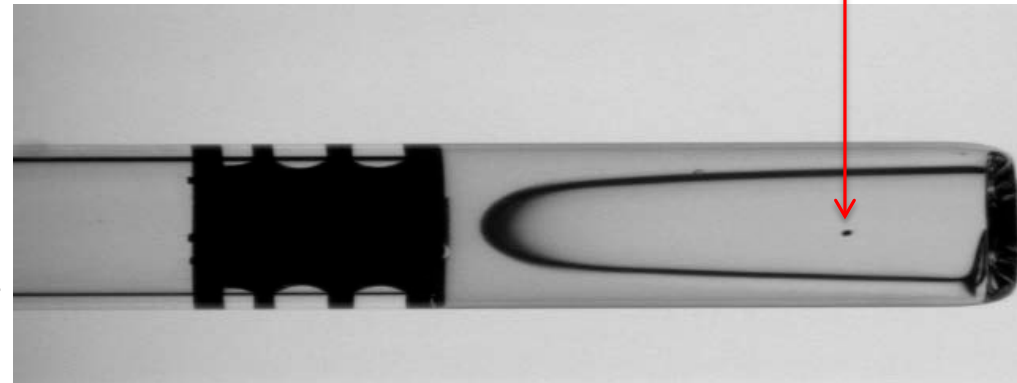
- ◆ Size X
- Size Y
- Linear (Size X)
- Linear (Size Y)

1.1 mm = 5,3 pixel

640 pixels = 134 mm (in this picture)



240 pixels = 50 mm

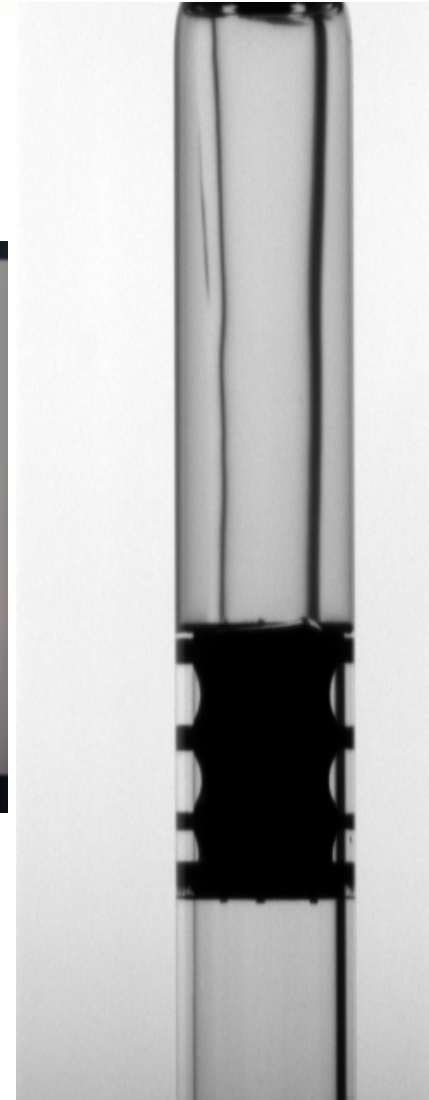
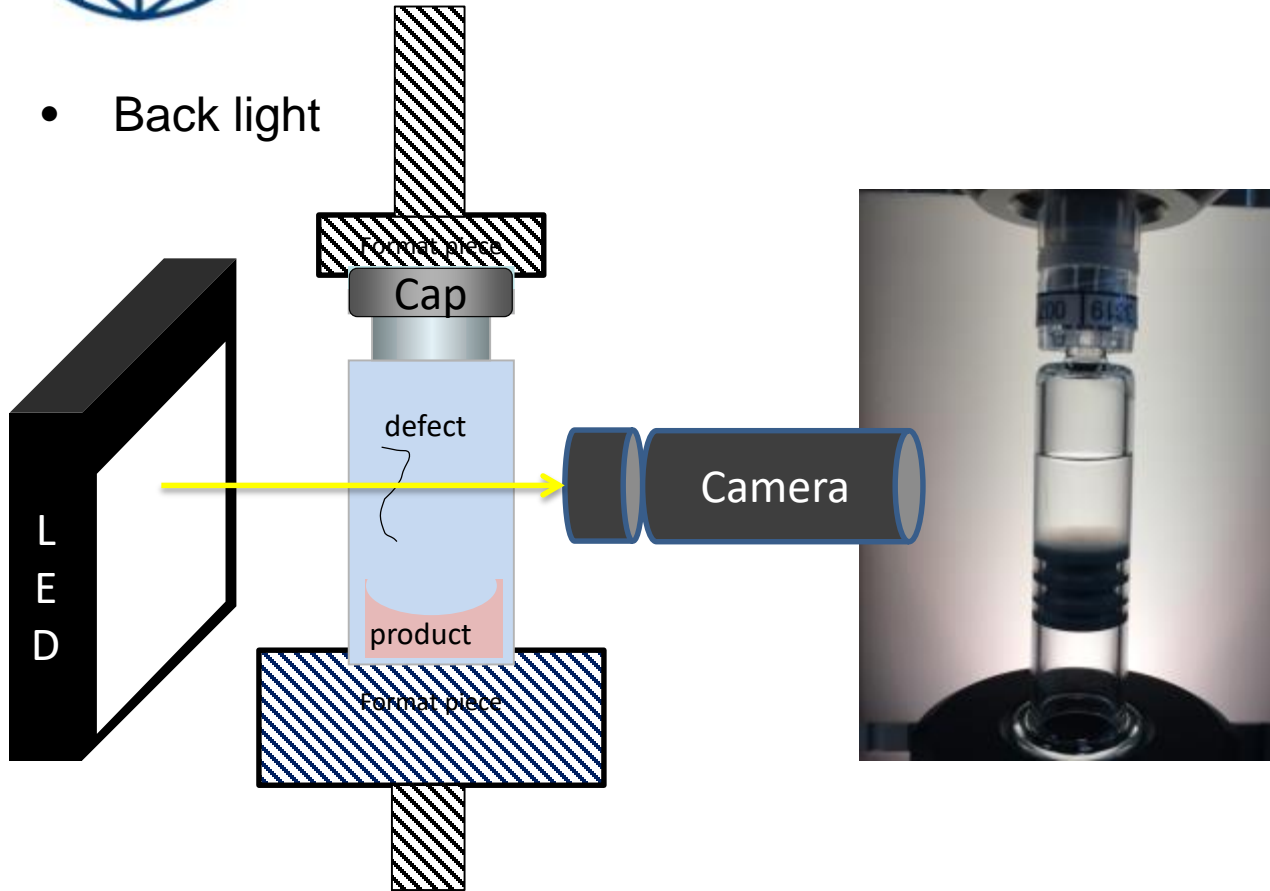


Camera C61 resolution: 0.05 mm per pixel or 5,3 pixel = 0,27 mm

- Add couples of slides of all illumination
  - (syr vials)
- ➔ Play with light
- ➔ Combination of light
- ➔ Add a foreword on compensation of light with different product families (opacities)

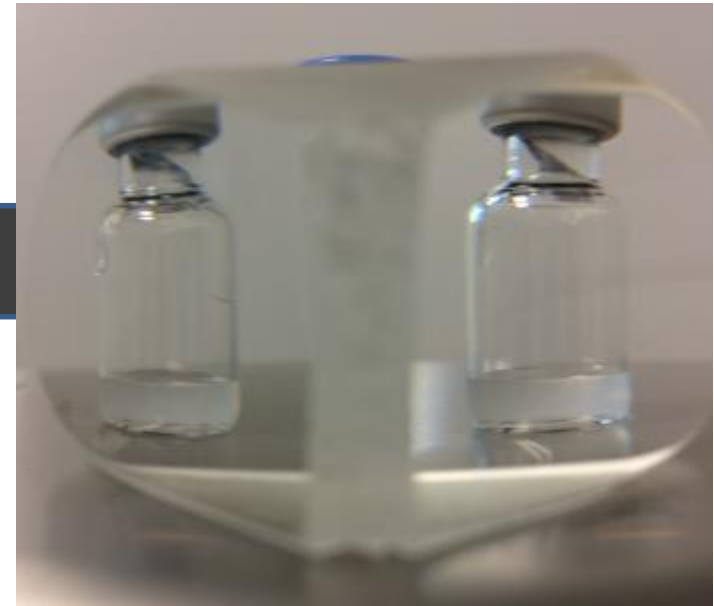
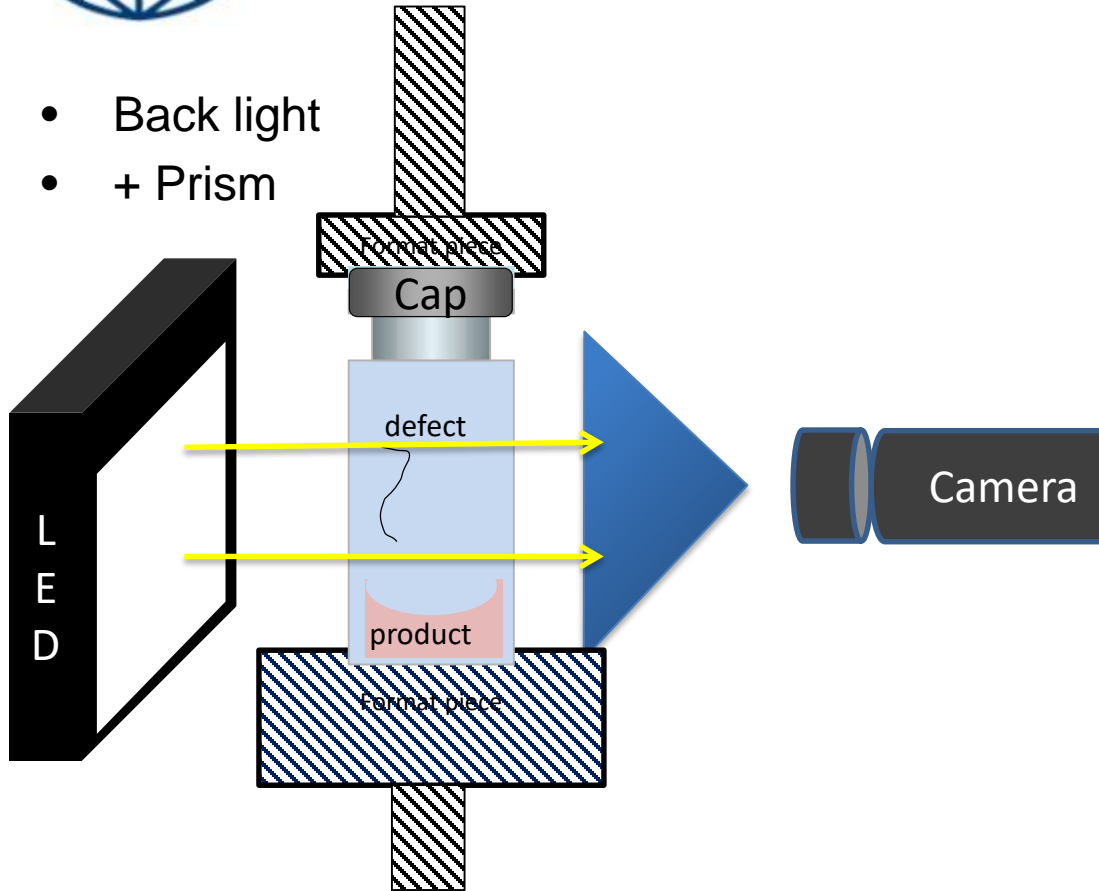


- Back light

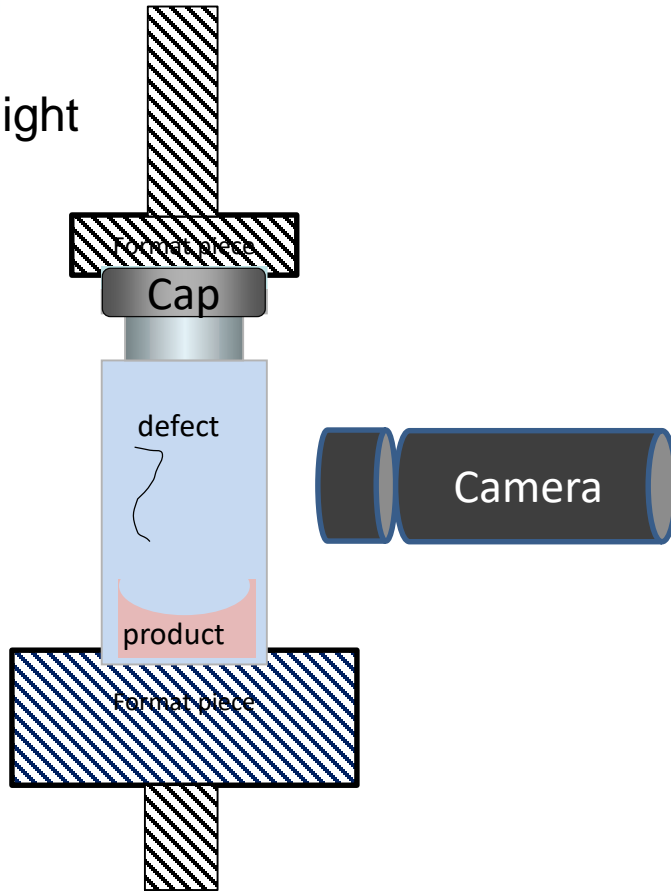




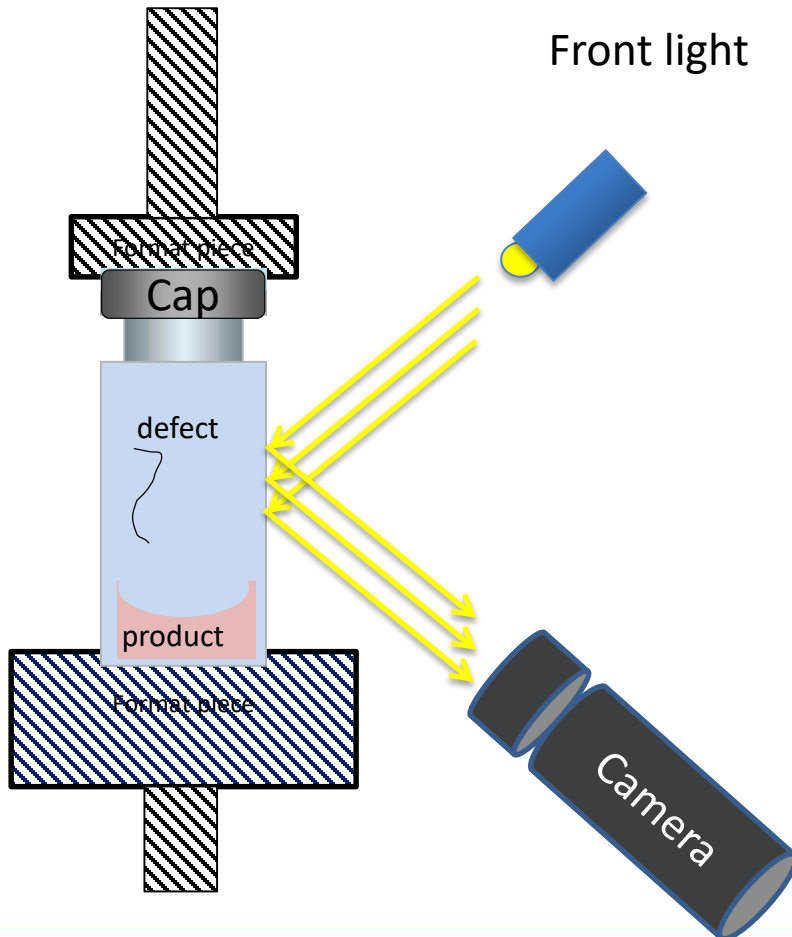
- Back light
- + Prism



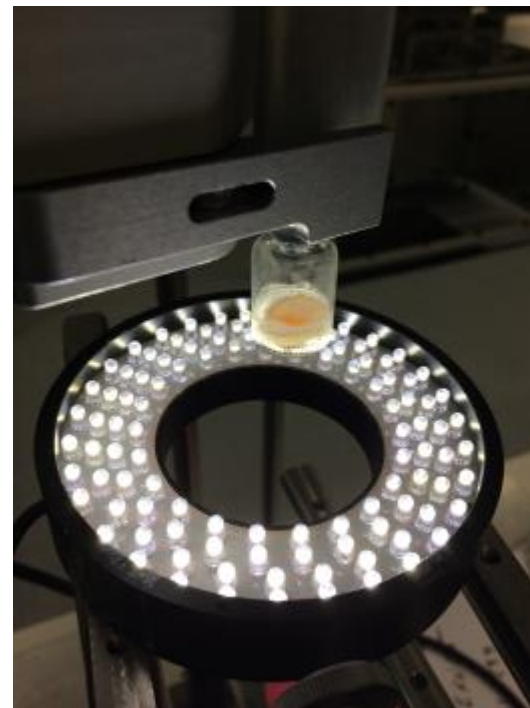
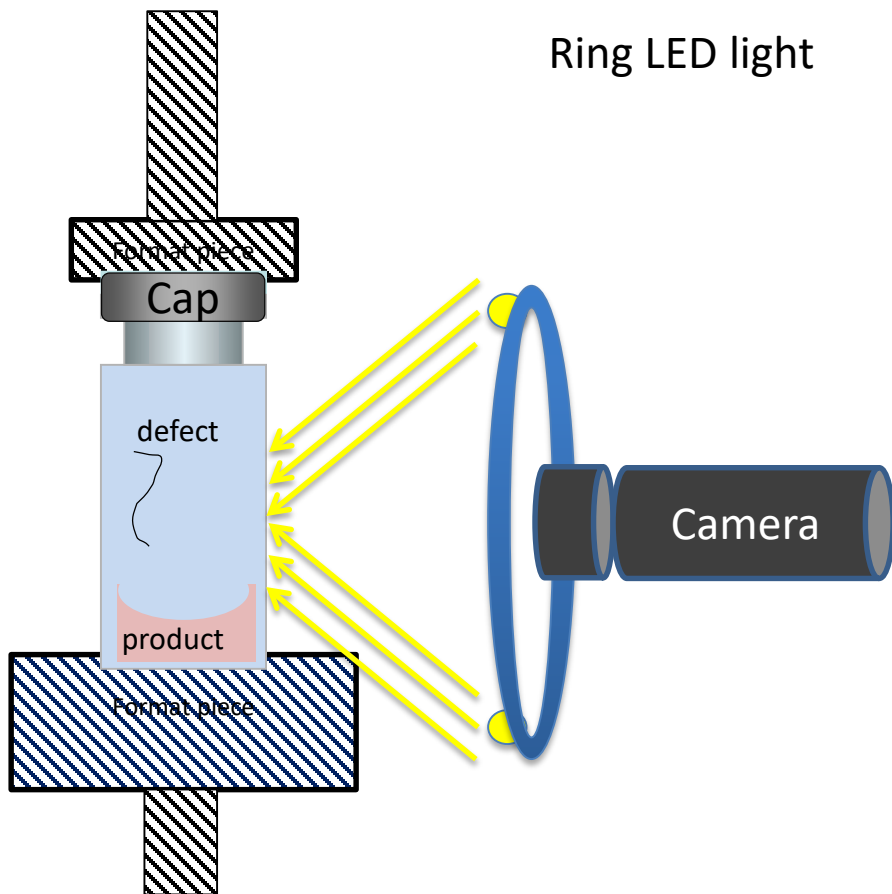
- Front light



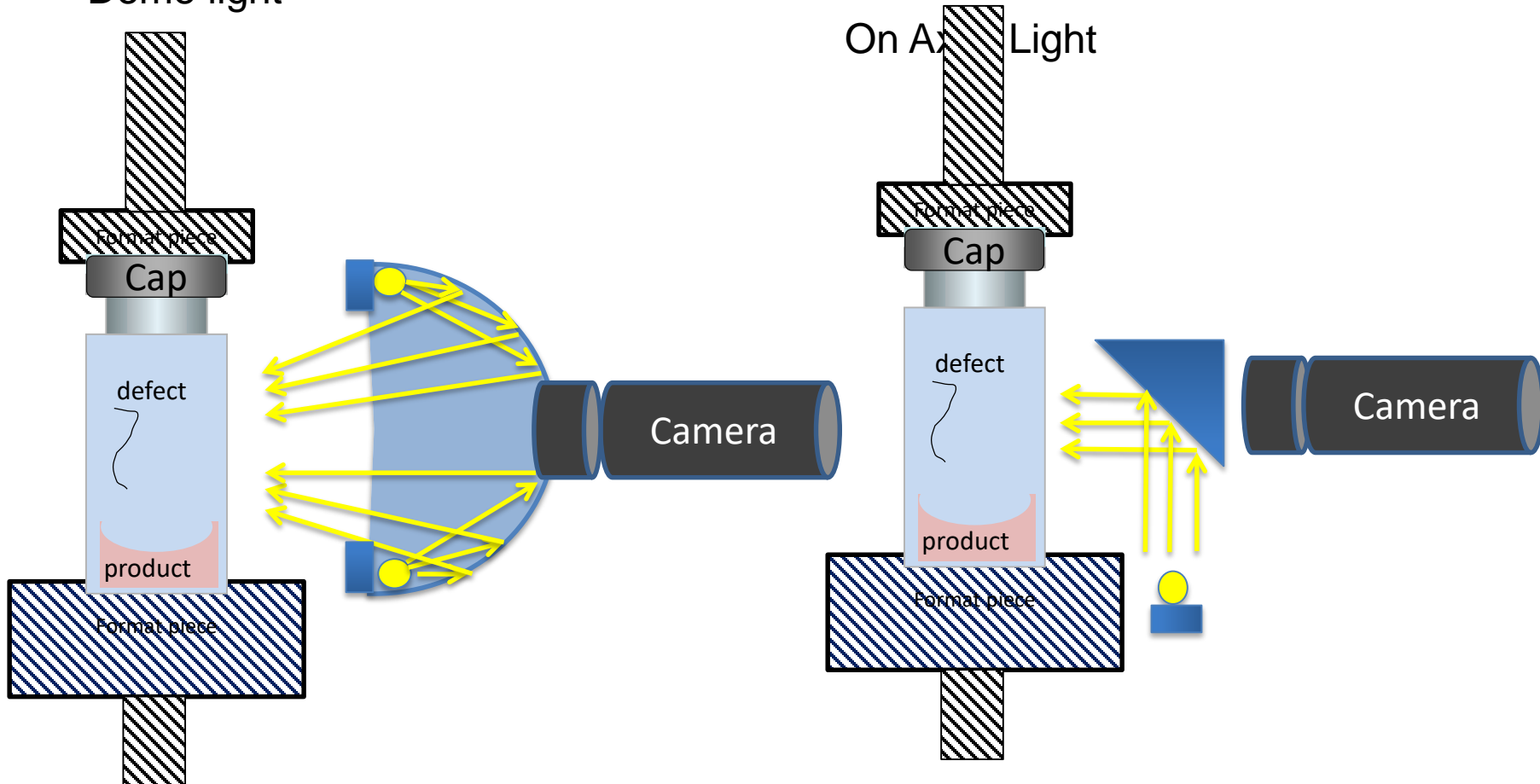
- reflectance light



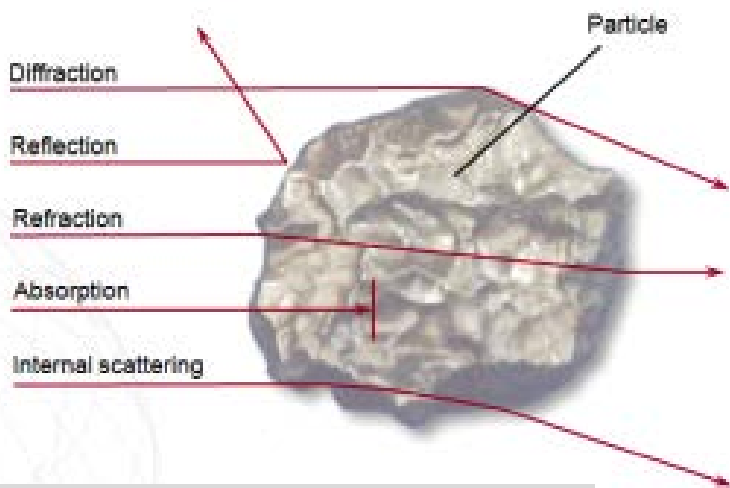
- reflectance light



- Dome light



3ml vial with  
Tap Water



**Key learning:** with transparent liquid solution Light obscuration techniques may be sensitive but more suitable for bench characterization purpose (PDA 2014)



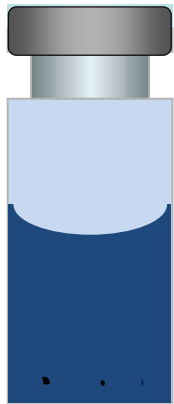
Red Laser  
beam

Visible and Sub visible  
particle are detected

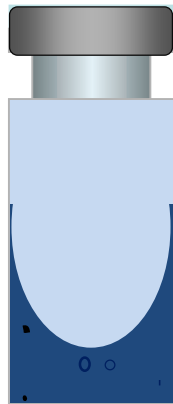




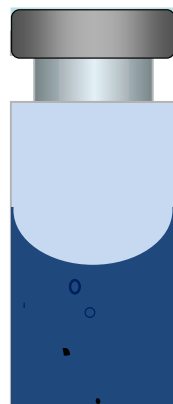
Vial with 3 particles



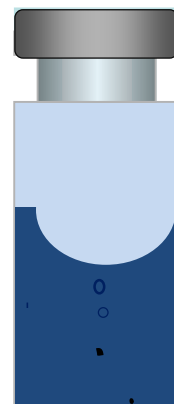
Rotation 600t/min 2 bubbles



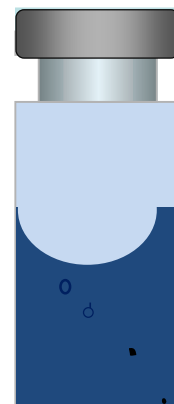
Stop 1<sup>st</sup> Image



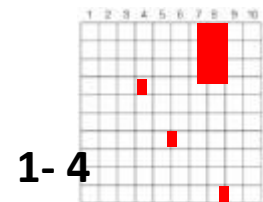
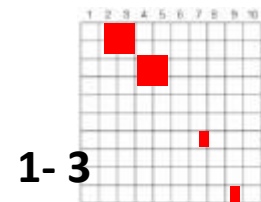
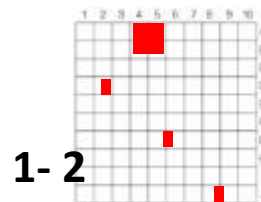
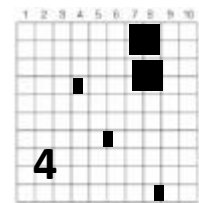
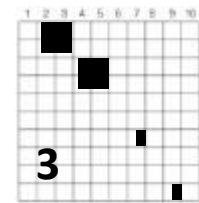
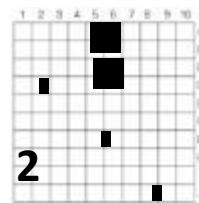
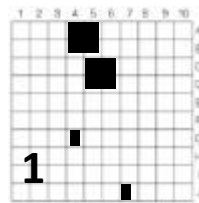
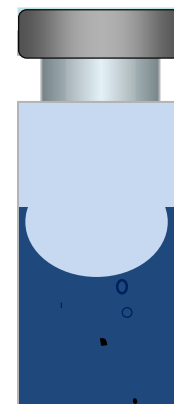
Stop 2<sup>nd</sup> Image



Stop 3<sup>rd</sup> Image



Stop 4<sup>th</sup> Image



**Key learning:** Image Subtraction is not very sensitive for particle detection in small suspension unit + no detection above liquid + no detection of fixed particles

**NOT SENSITIVE TO FIXED PARTICLES + Above liquid**





How to inspect Automatically a suspension that has a high optical density + scattering?

= Fast rotation To present liquid in thin layer

- ⇒ Lower optical path (density beer lambert)
- ⇒ Minimized scattering effect



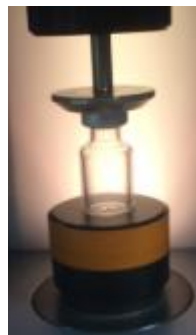
0 t/min



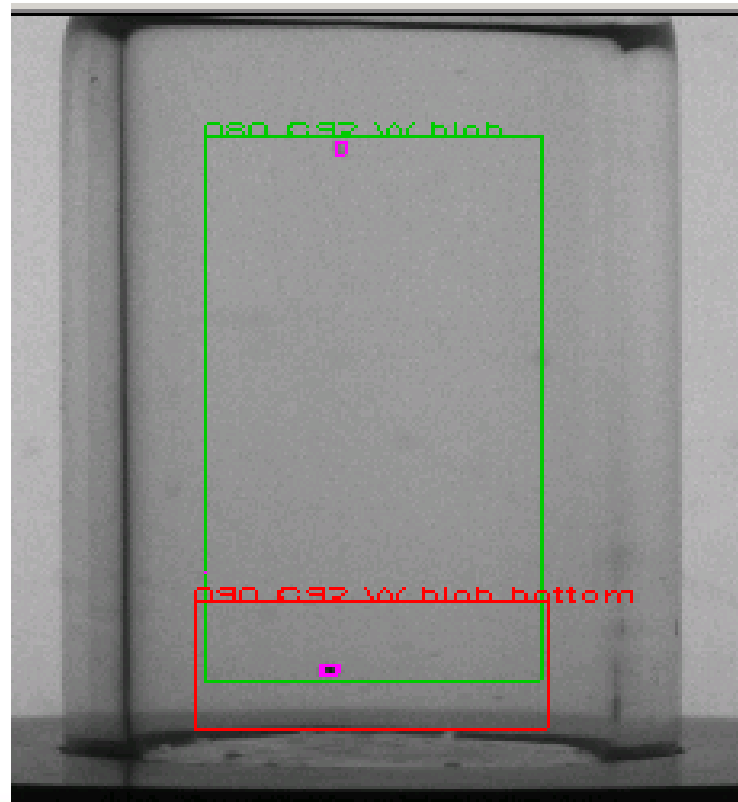
600 t/min



1800 t/min

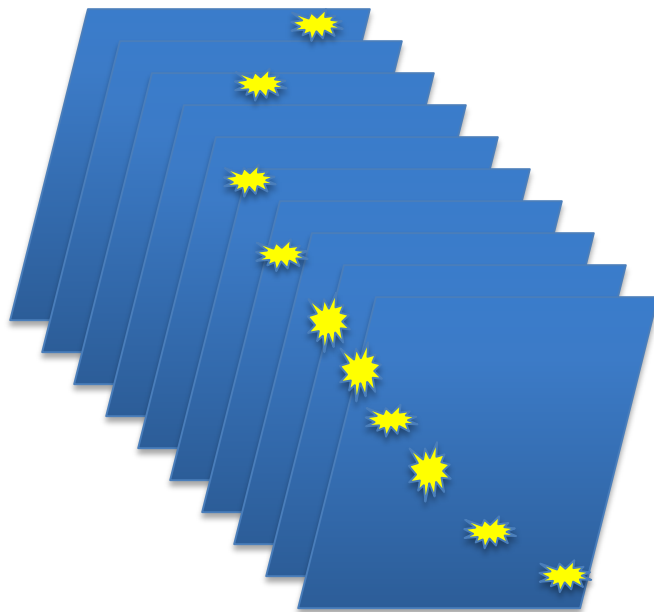


3600 t/min



## Particle Detection strategies : Particle tracking

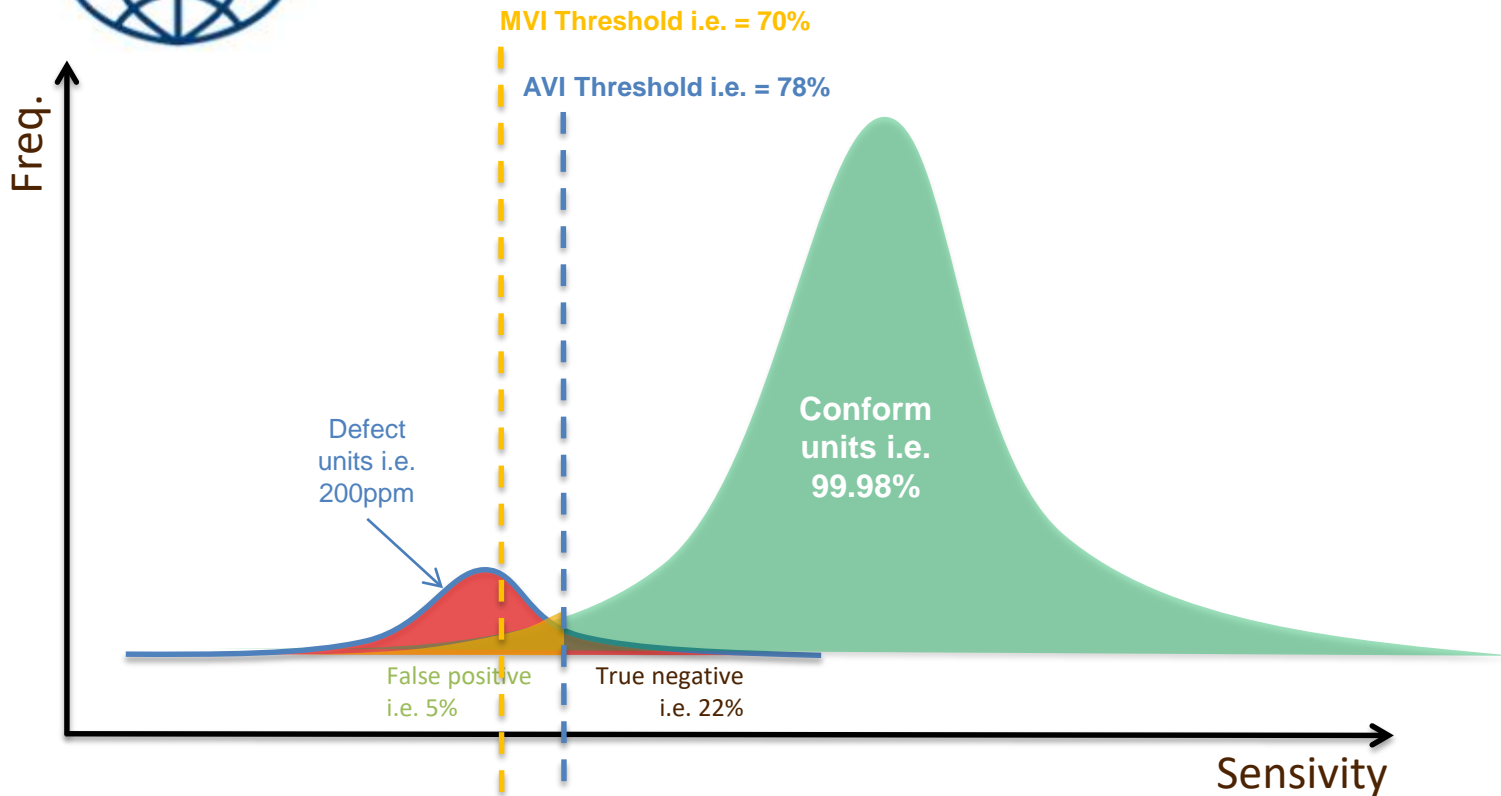
- With modern vision machine more images are available
- Images can be treated not only 1 by 1 individually but in stack of images
- Rendering particle trajectories analyzed
- And differentiation to artifacts like bubbles



Analyze of 1  
stack of 10 to 60  
images all at  
once to track  
particle  
trajectories

# Theory 2: Introduction to technical principles of automated inspection machines

## False reject / balance patient vs business risk



Defect

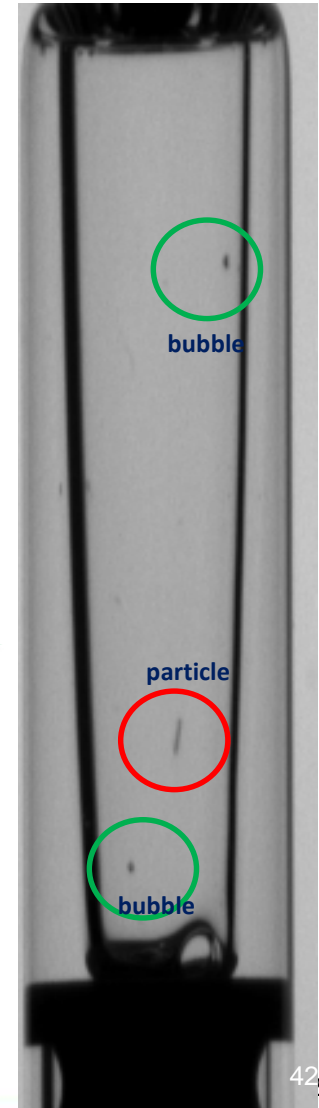


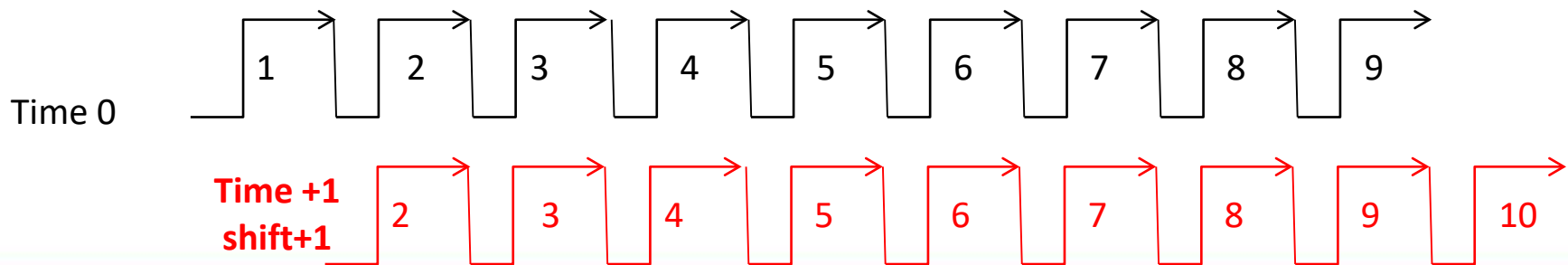
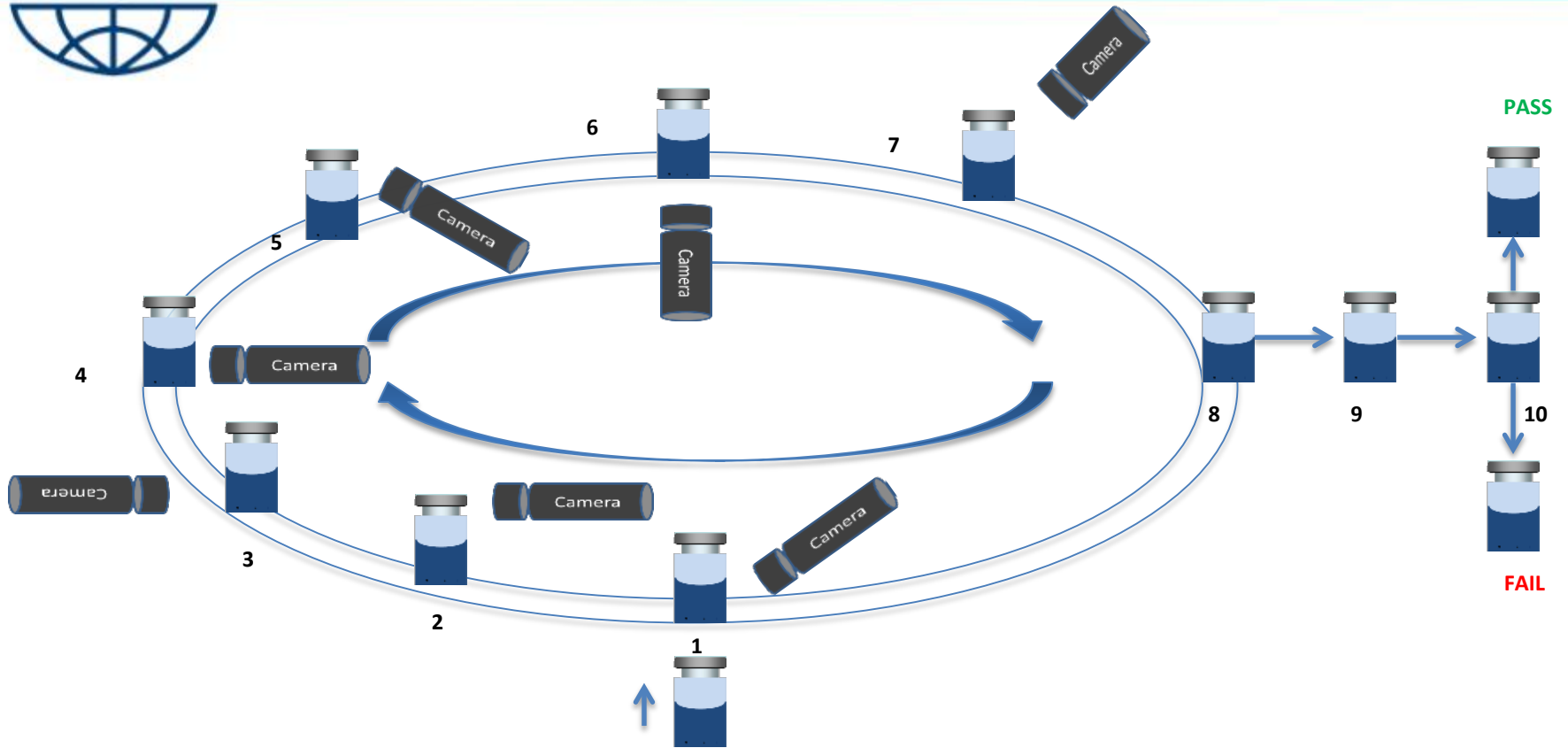
Conform



Inherent part.

**Key learning:** Automated Inspection tuning is a balance between patient risk (Beta) and business risk (Alpha)





- In this section you have learnt:

## AVI

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Long way

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Equipment / Process / ctrl strategy design

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Parts of AVI equipment

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Image processing steps

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Critical parameters

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Illumination sources

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False reject / true detection

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Automation concept

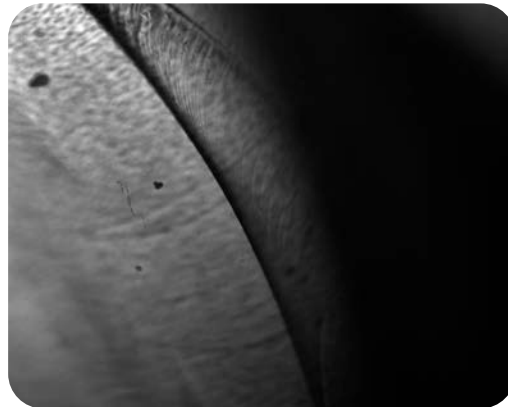
---

- Leak Detection

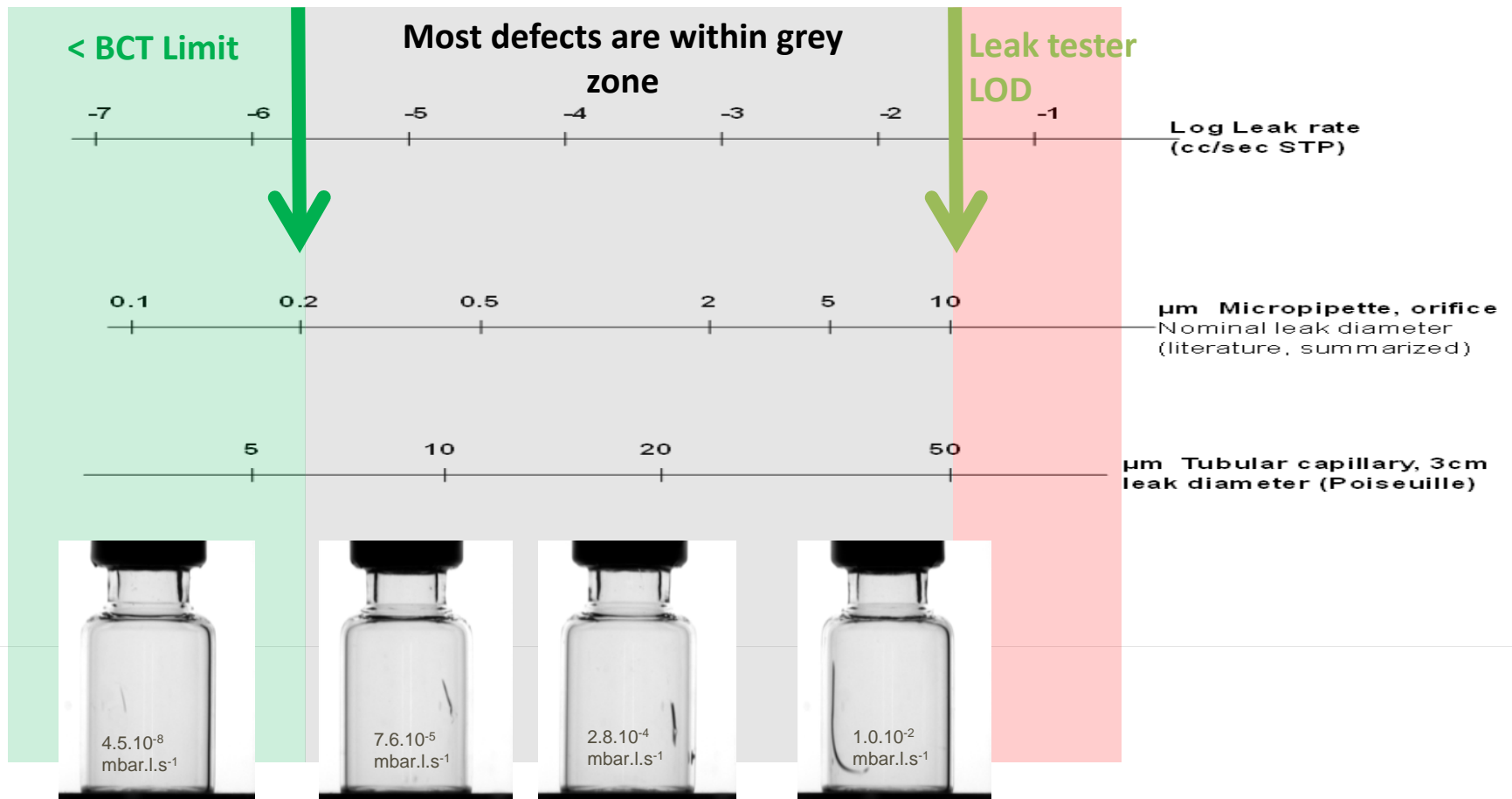


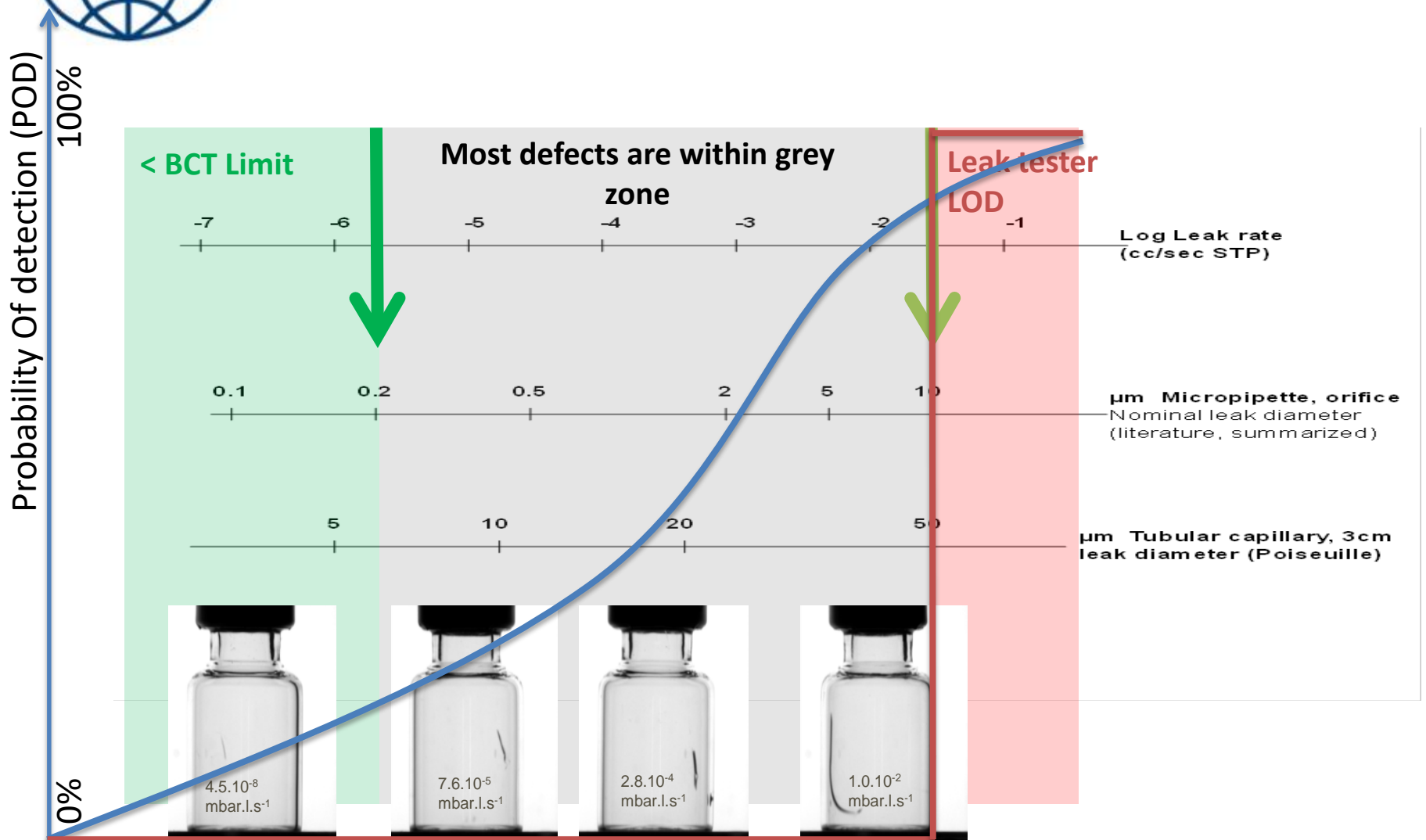


A leak can be described as a breach in a package wall, or a gap between package components capable of permitting the passage of gas or liquid. Leaks in glass are complex, multi-cavity tortuous paths. Associated risks to a leak can be potential loss of sterility, oxidation, hydrolysis, loss of vacuum affecting reconstitution of lyos, discoloration.



## Helium test can measure Leak Rate of CCIT defects





### Regulatory Landscape

**EP Annex1 Clause 117 -123**, Eur. Pharm. is prescriptive for leak Detection on 2 presentations; sealed containers and packaging sealed under vacuum (lyo vials)

- **Clause 123**: containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period (Lyophilized vials to maintain vacuum).
- **Clause 117**: for sealed containers Leak Detection is mandatory (Tubes, BFS).

**Annex 1 Revision is on-going**, first draft is expected in Q2 2017,

**USP<1207.1>** was revised in February 2016 and released in Aug 2016. This gives an overview of CCIT control strategy and validation. The subchapter **USP<1207.2>** PACKAGE INTEGRITY LEAK TEST TECHNOLOGIES presents a catalogue of leak detection or testing methods for offline and on line detection. But no Leak Detection 100% is mandatory for US, USP rather prone integrated holistic approach from development to validation and commercial use. USP opposes the deterministic methods (100% Detection) versus probabilistic methods (<100% Detection).




Also, in compendia there is not limit of detection a leak detection equipment should reach (hole size).

# Leak Detection Equipment

**Current Technology Mapping available as Leak Detection Equipment (YES= available / NO = not available)**



Leak Detection Technology	AVI/MVI or SAVI	Pressure Decay	Vacuum Decay	High Voltage	Head space
Liquid Syringe	Yes	No	No (Limited to bench)	Yes	No (Limited to inerted gas)
Liquid Vial	Yes	Yes	Yes	Yes	No (Limited to inerted gas)
Lyo Vial	Yes	Yes	Yes	No	Yes
Ampule	Yes	No	Yes	No	No
BFS	No	No	Yes	No	No
Cartridge	Yes	No	No (Limited to bench)	Yes	No (Limited to inerted gas)

## Pro & Cons for each LD technologies

Leak Detection Technology	Principle	Advantage	Limitation
<b>AVI / MVI</b> (Seidenader, Brevetti, Bosch, Innoscan.....)		<ul style="list-style-type: none"> <li>- Only technology to detect leaks in grey zone (&gt;BCT but lower than 10µm)</li> <li>- Can detect liquid leaking cracks but also gas leaking cracks (very sensitive)</li> </ul>	<ul style="list-style-type: none"> <li>- Remains probabilistic (&lt; 100% detection rate for small cracks)</li> <li>- Limited specificity (generates false rejects)</li> <li>- Low sensitivity for Lyo</li> </ul>
<b>Pressure Decay</b> (Wilco/Bonfig.)		<ul style="list-style-type: none"> <li>- Deterministic method 100% Detection for leaks &gt; 10µm</li> <li>- Can only be used for Lyo and overfilled liquid vials</li> </ul>	<ul style="list-style-type: none"> <li>- Can only detect leak &gt; 5-10µm (5% of cracks in our defect library)</li> </ul>
<b>Vacuum Decay</b> (Wilco/Bonfig.)		<ul style="list-style-type: none"> <li>- Deterministic method 100% Detection for leaks &gt; 10µm</li> <li>- Can be used for Lyo and liquid vials (partial fill)</li> <li>- Can be used for tubes and BFS</li> </ul>	<ul style="list-style-type: none"> <li>- Can only detect leak &gt; 5-10µm (5% of cracks in our defect library)</li> <li>- For Syringe there is only offline benchtop not yet industrial machine</li> </ul>



## Pro & Cons for each LD technologies

Leak Detection Technology	Principle	Advantage	Limitation
<b>High Voltage</b> (Seidenader/ Brevetti / Bosch / ....)	 <p>High voltage detection of current shift with conductive liquid through cracks</p>	<ul style="list-style-type: none"> <li>- Deterministic method 100% Detection for liquid leaks</li> <li>- Can be used for syringe and liquid vials</li> </ul>	<ul style="list-style-type: none"> <li>- Ozone generation that require product impact validation + Stability study per product</li> <li>- Limited added value to AVI for small crack detection (&lt;30% DR cracks in liquid when AVI DR&gt;80%) can see only liquid leaks</li> <li>- Hardlly correlated to leak size (only liquid leaks)</li> </ul>
<b>Head Space</b> (Wilco / Bonfig. / Seidenader / Bosch Lighthouse/ Brevetti)	 <p>Measure Oxygen ingress in leaking vials</p>	<ul style="list-style-type: none"> <li>- Deterministic method 100% Detection for gas leaks</li> <li>- Very sensitive method down to 1µm with holding time XX days product dependent</li> <li>- As it test Oxygen ingress it is a good control for sensitive to oxidation products (Zoster Metox)</li> </ul>	<ul style="list-style-type: none"> <li>- Limited to Lyo vials (inerted)</li> <li>- GSK Vaccines are worst case (high pressure/low volume), lower sensitivity</li> <li>- Requires holding time product dep</li> <li>- On line machine require space/complexity</li> <li>- 2 in 1 machine (AVI + headspace) are not yet mature (slow/lead time before insp.)</li> </ul>

# Key take away:

- In this section you have learnt:

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Leak

Leak definition

Testing

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Leak range

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Deterministic vs probabilistic

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Mapping technologies

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Advantage / Inconvenient

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