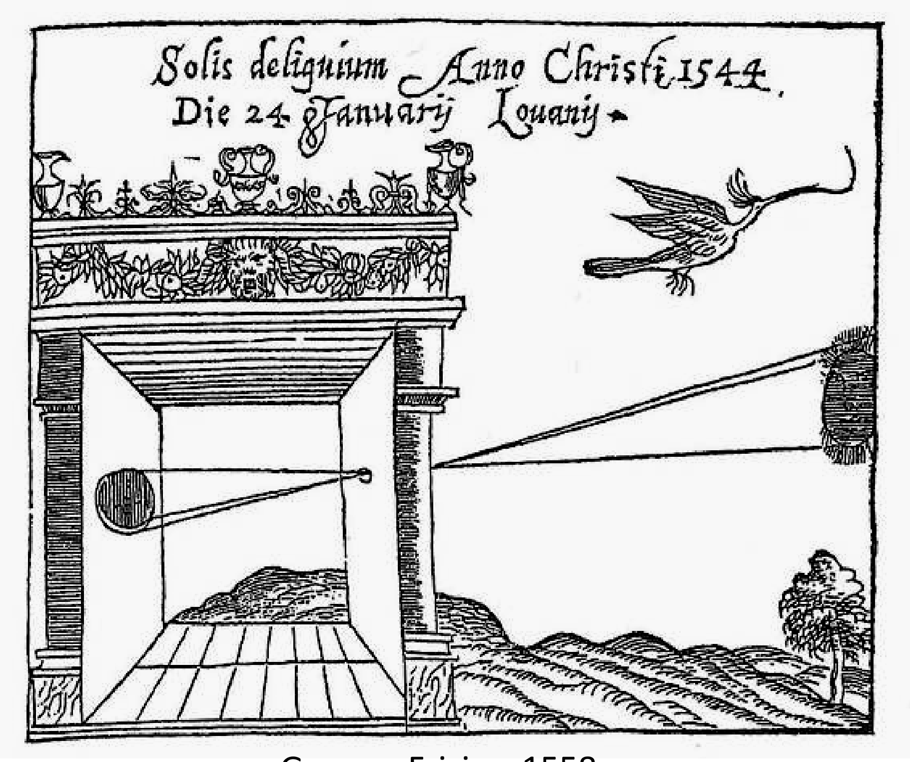
PDA® Parenteral Drug Association

• 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

Some milestones



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

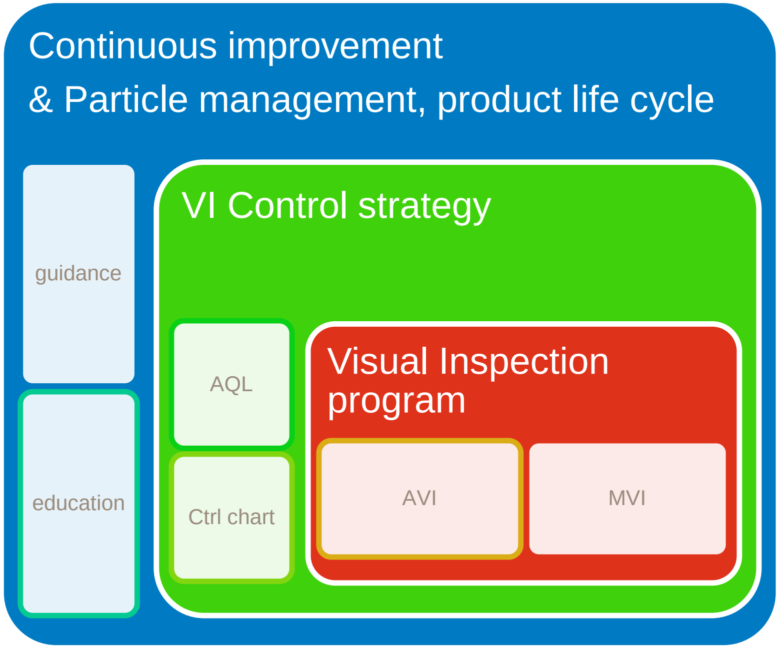
- Basic principle Aristotle (384-322 BCE)
- Drawing aid for artists: described by Leonardo da Vinci (1452-1519)
- …..first industrial CCD camera 1975
- 2017 AVI

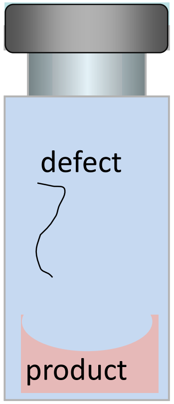
Control strategy is also key with AVI

- AVI basic description

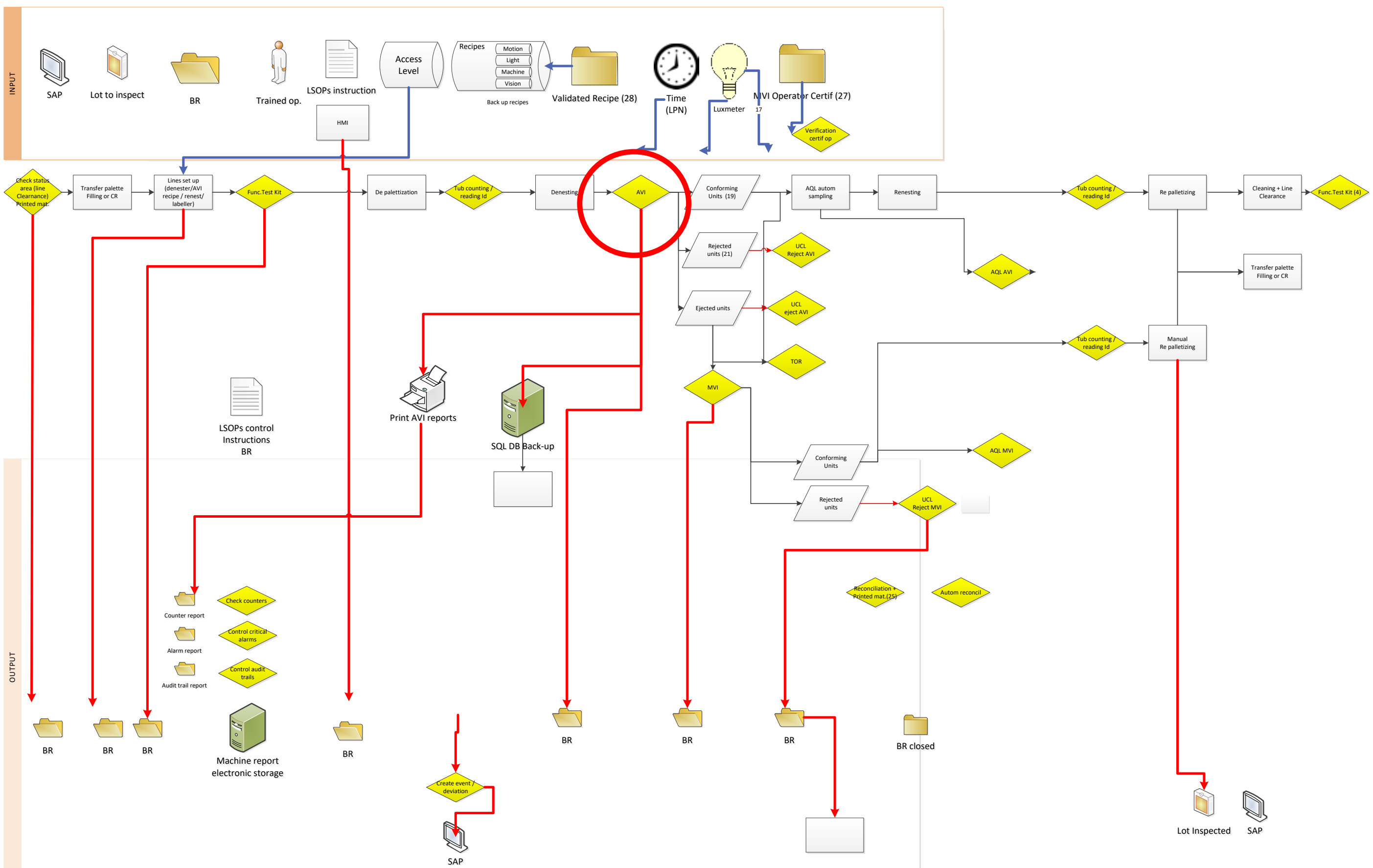
Visual inspection program in 3 layers:

- -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





- AVI Equipment is part of an overall VI process



- what are your CQAs / CPPs for VI process ?

Can you list some of them ?

- CQAs:

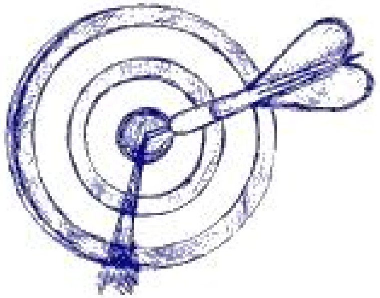
=> think about USP<1790>….

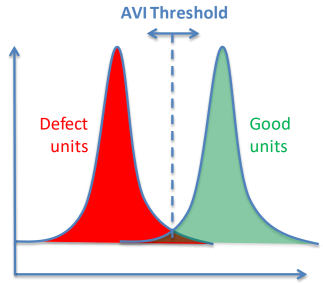
- CPPs:

Mastering Automated Visual Inspection

Theory 2: Introduction to technical principles of automated inspection machines

- 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





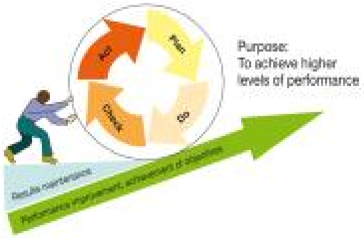
Theory 2: Introduction to technical principles of automated inspection machines
For AVI mastery ….People mgnt is a key !

Best in class organisation for VI (People mngt)
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



Theory 2: Introduction to technical principles of automated inspection machines
AVI improvement last 2 decades, soon matching Human Eyes

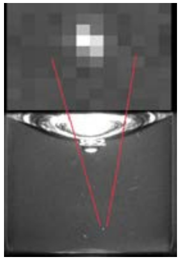
MVI

11µm per cone/6^{E6} Cones/ LOD 50-150µm particle

Image resolution trend

=> better detection + lower false reject

AVI



First machines with diode array detectors No camera — 1976

First machines with Cameras — 1981

640x480 Pixels 6 images / vials — 2008

640x480 Pixels 8 images / Syr. — 2010

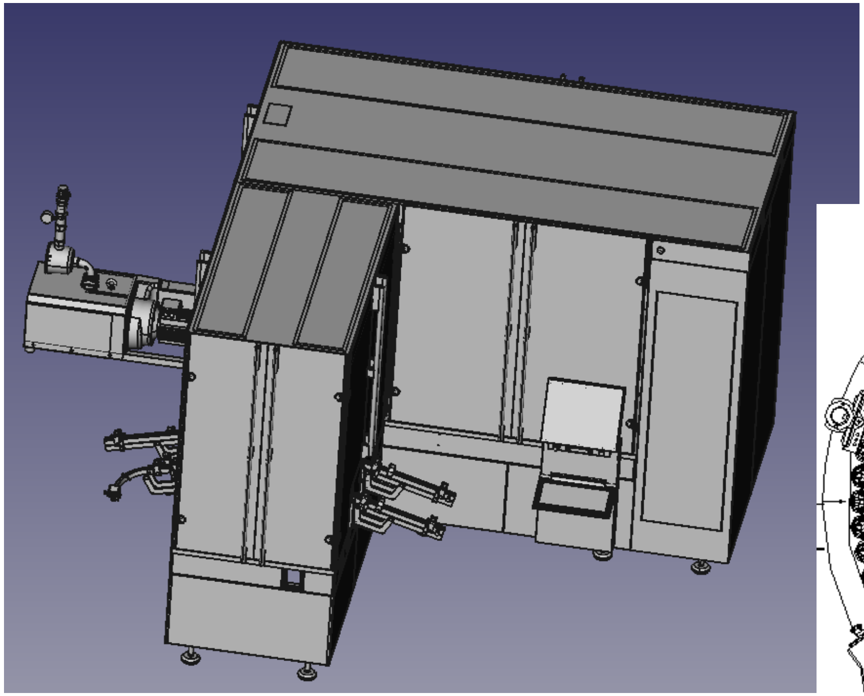
x4

1024x1024 Pixels 10 images / vial. — 2014.

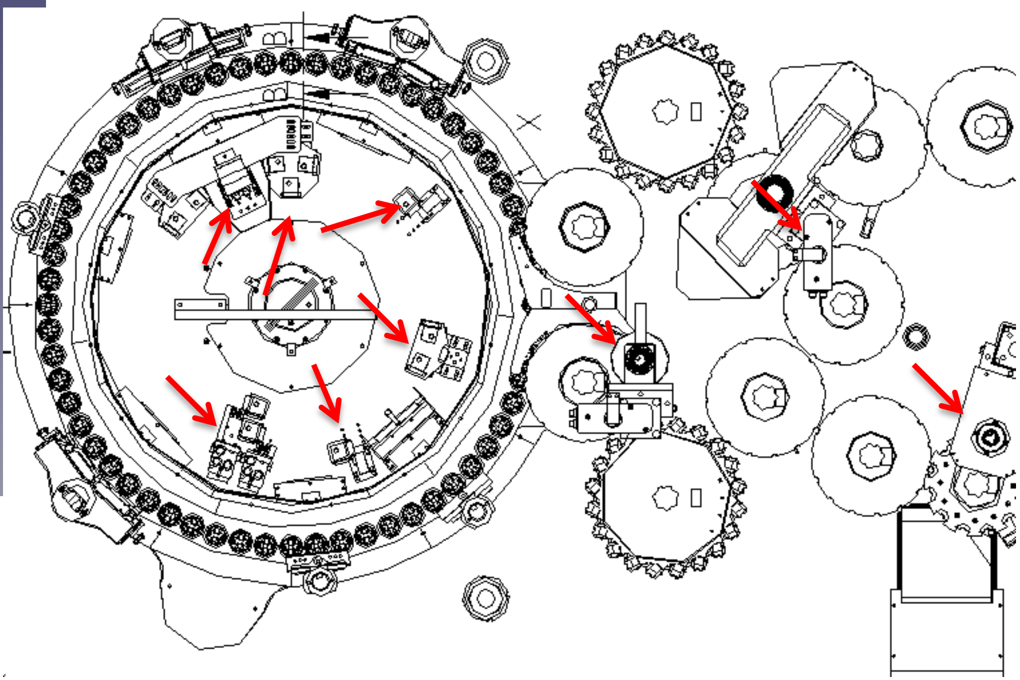
2016

x72

12MPixels 60 images / vial. — 2017

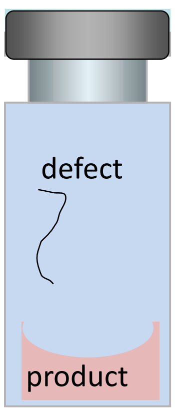


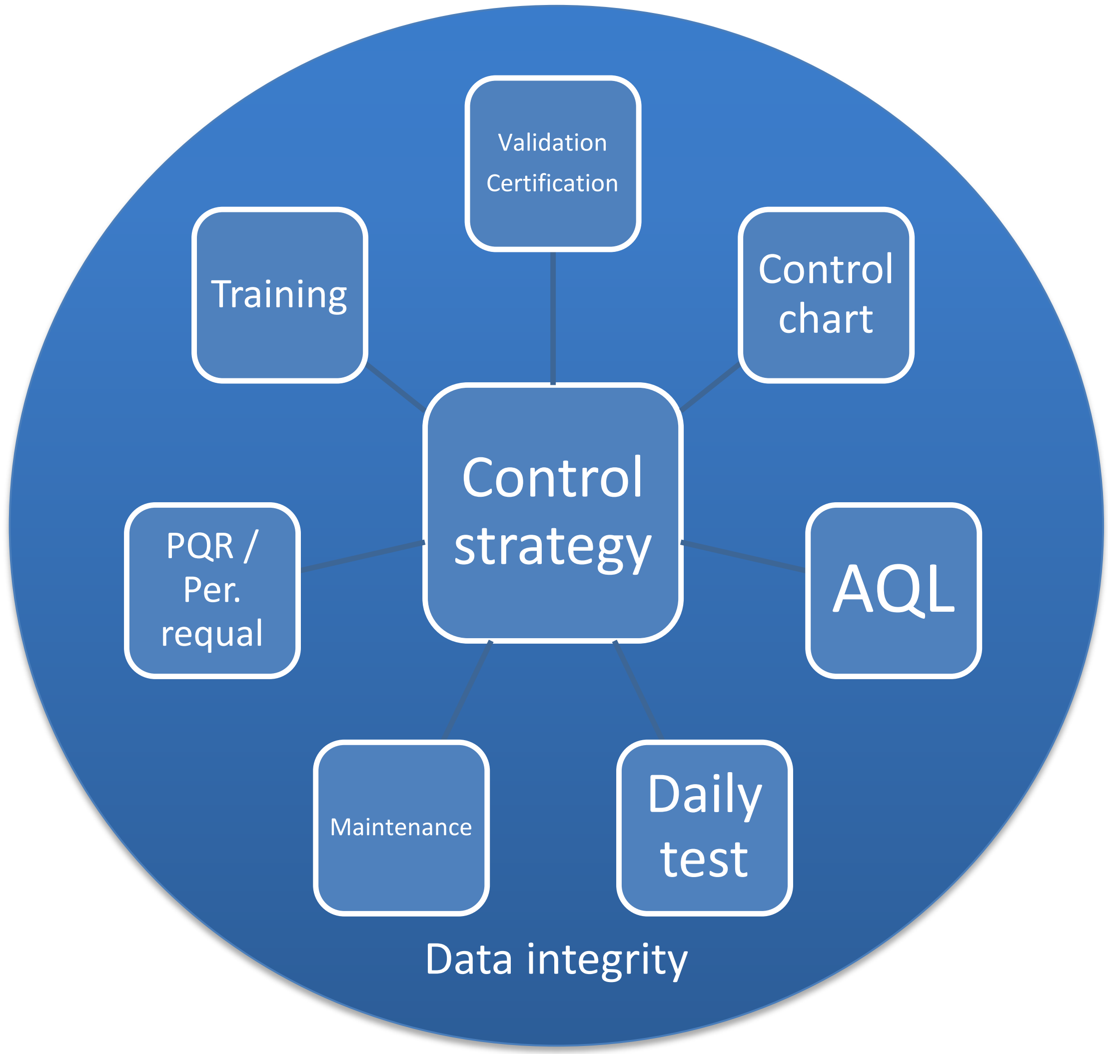
Just a black box



Key element of a control strategy

- Control Strategy





AVI Main functions

- Motion of units
- Light illumination
- Digital image processing

AVI Main functions

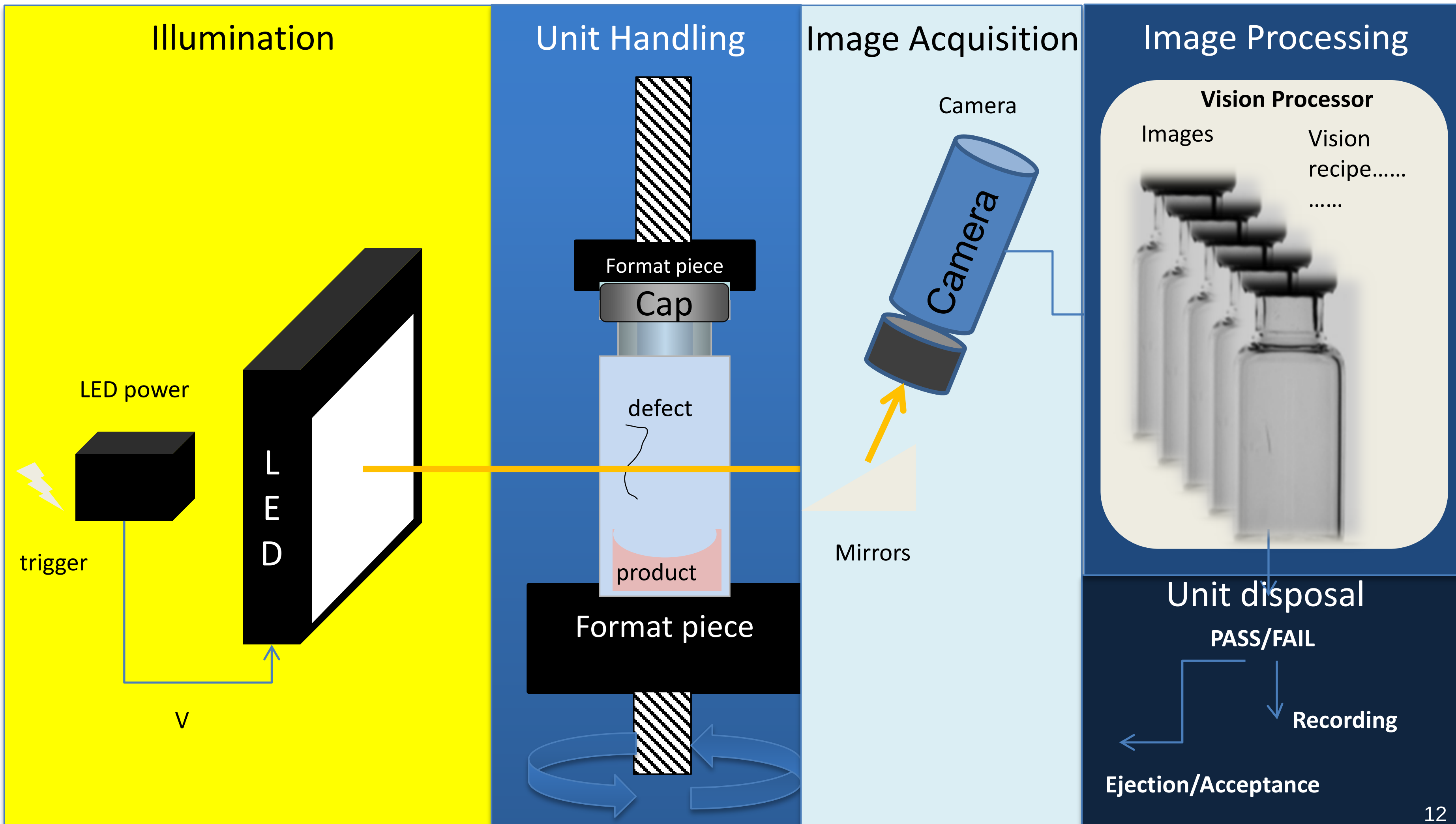


Image Acquisition

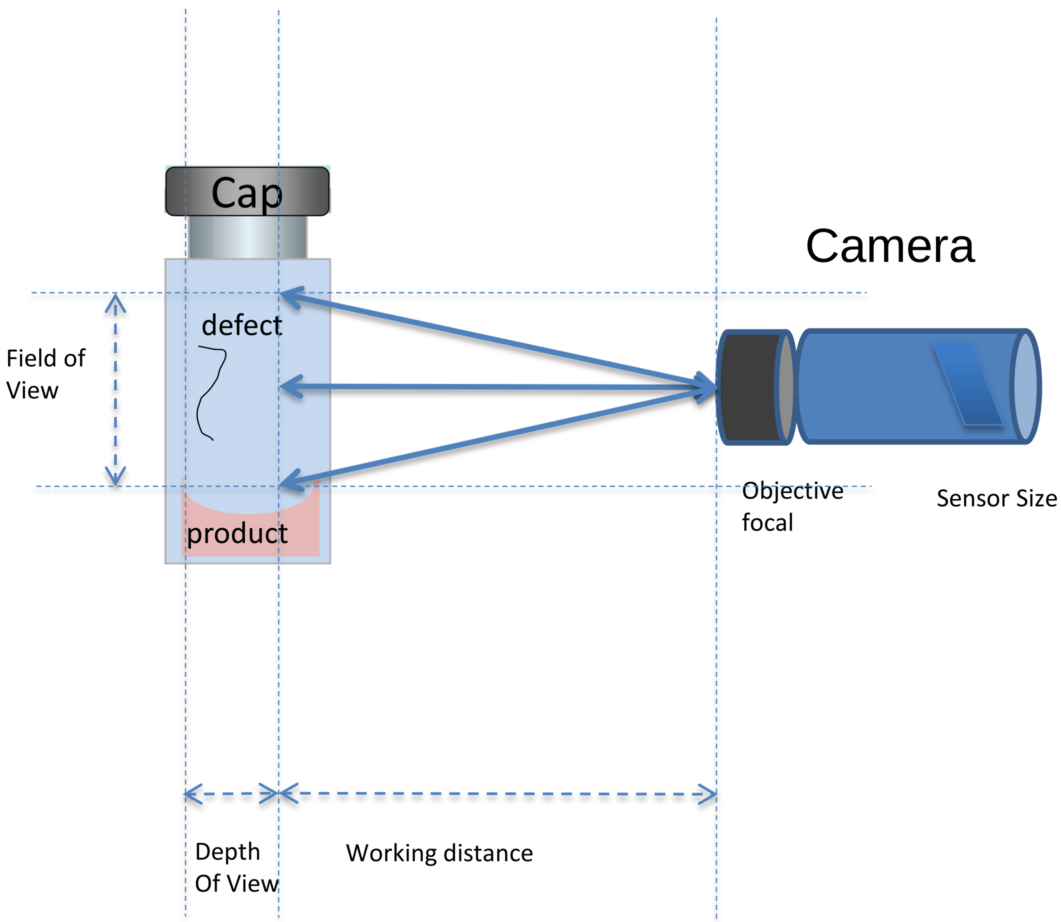


Image Acquisition

Camera

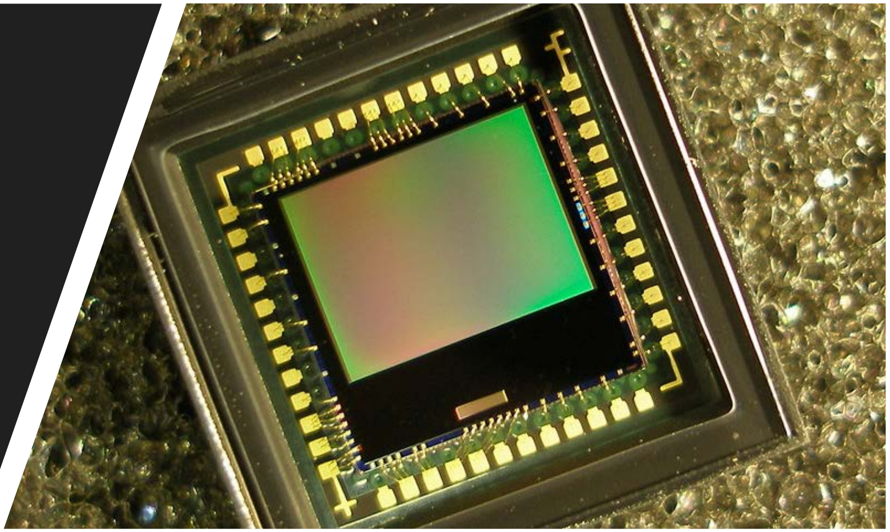
Photon → Photosite → Electron

- Integration
- Transfert
- Amplification

Theory 2: Introduction to technical principles of automated inspection machines

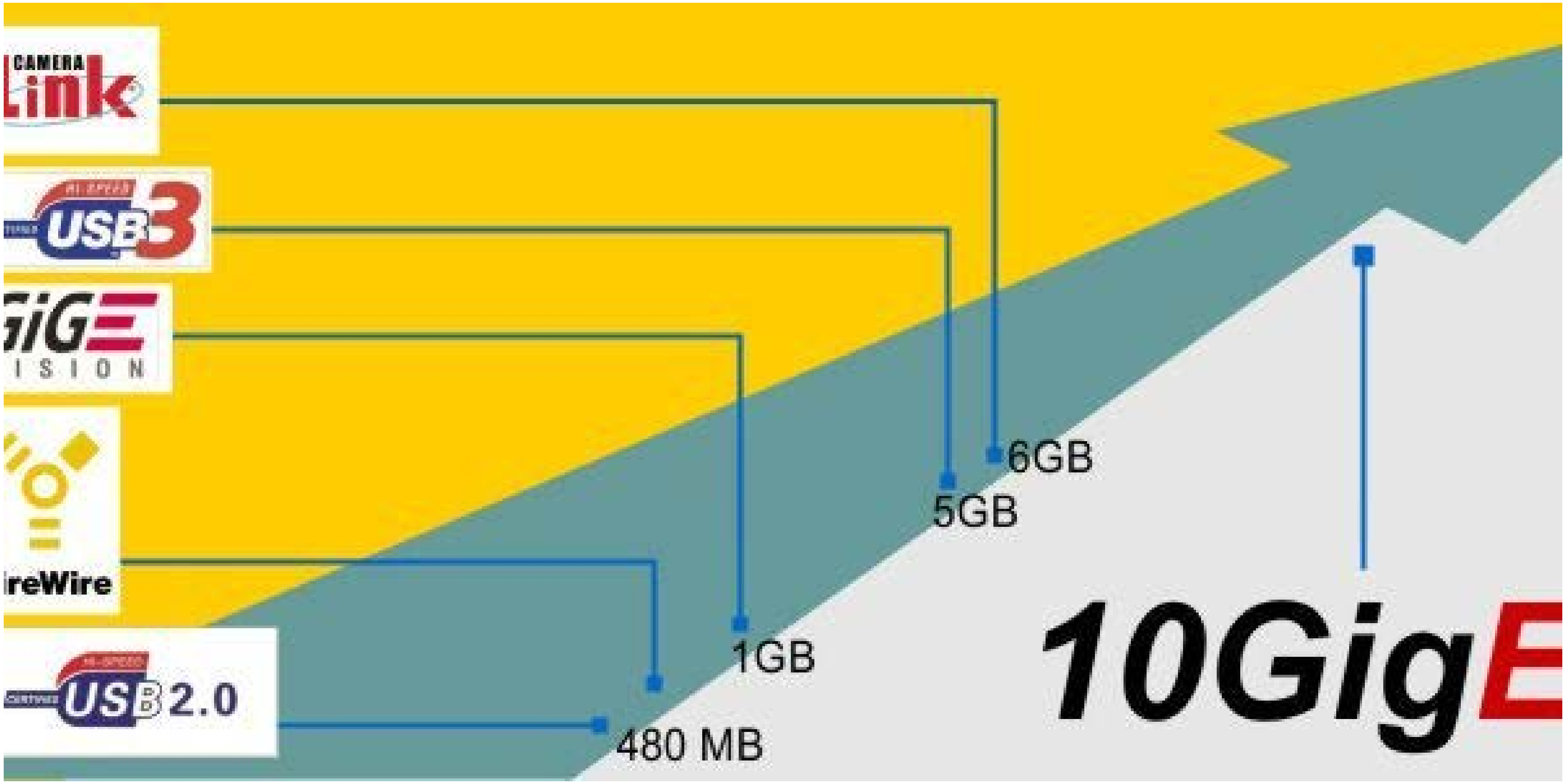
Camera

- Matricial Sensor : CCD or CMOS



- Linear Sensor = Line Scan

Camera transfer protocols



Tansfer of electron on a CCD

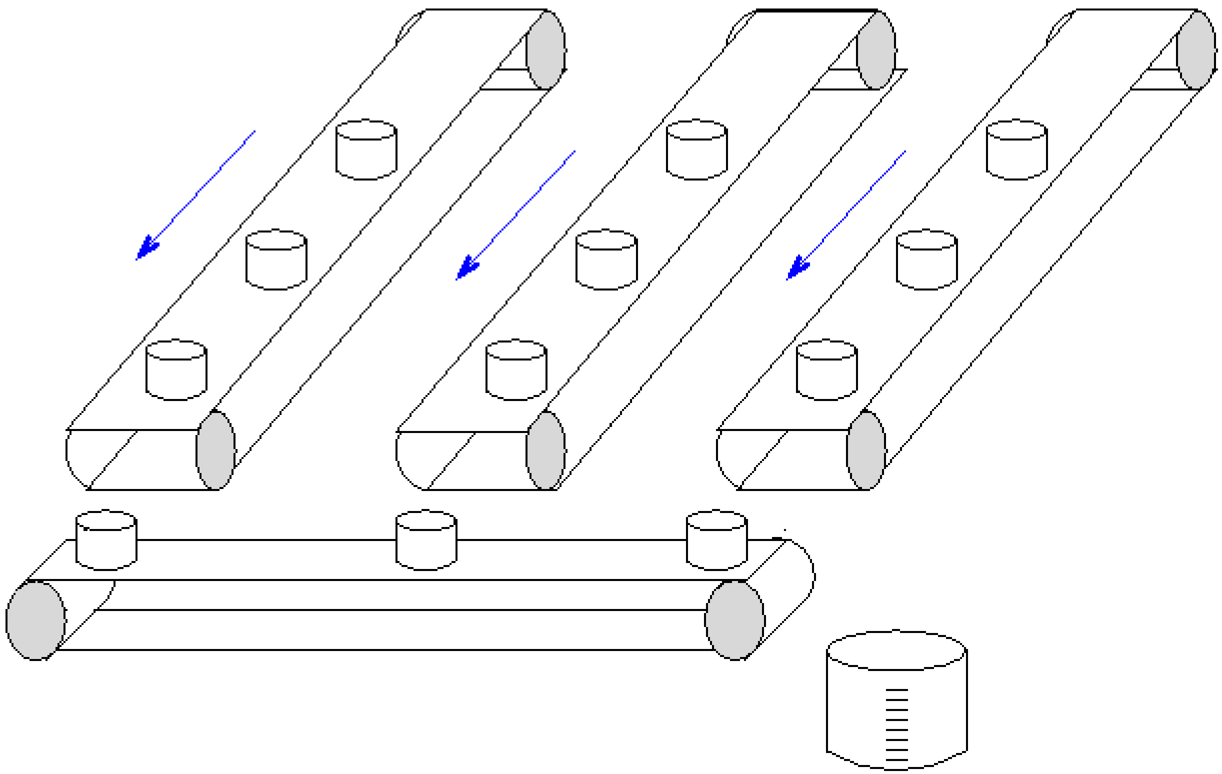


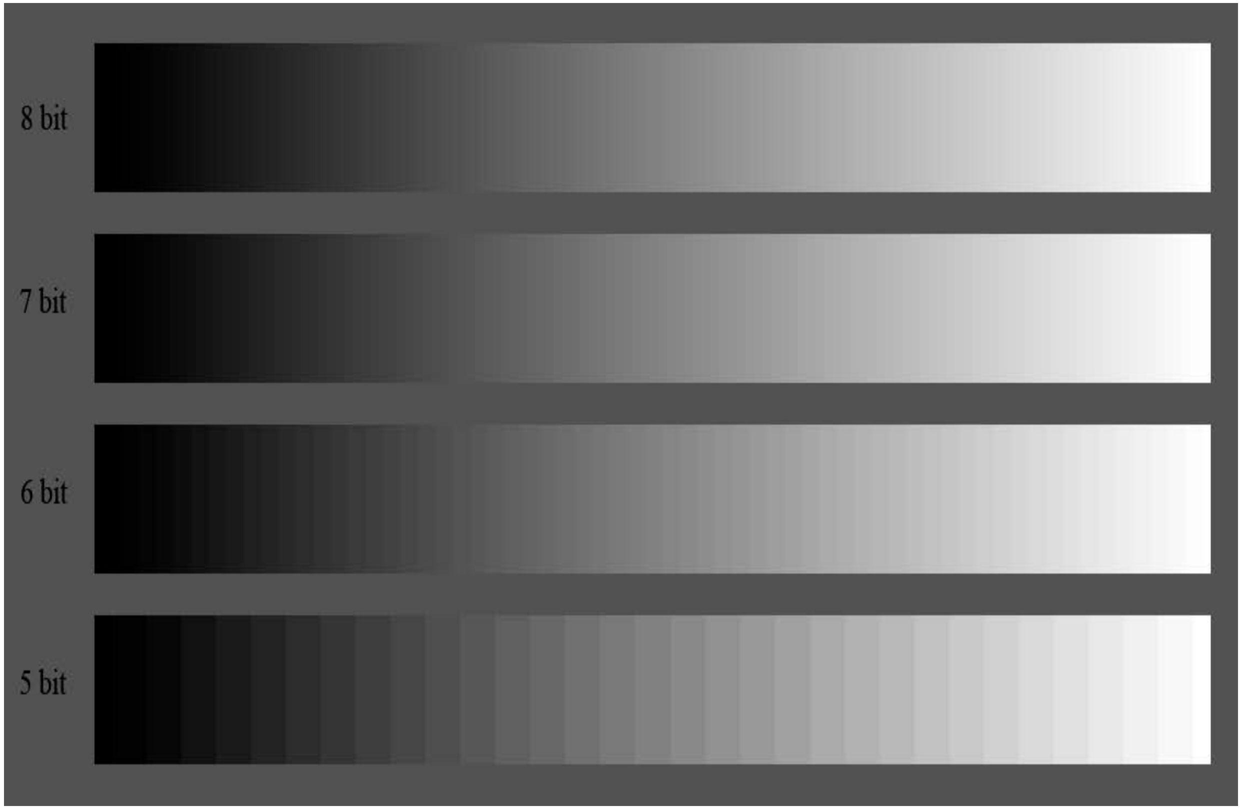
Image resolution

Key learning:

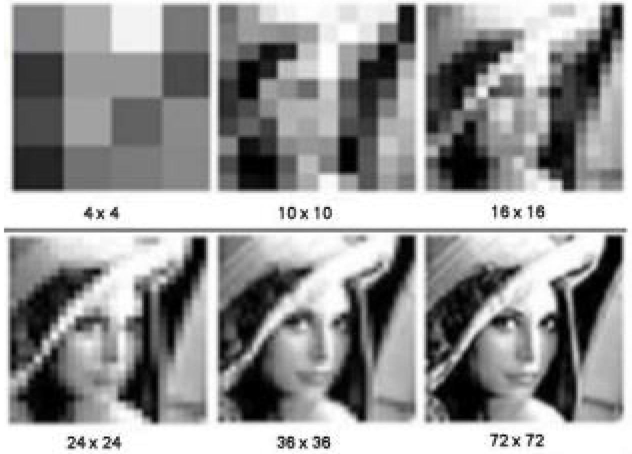
Tonal resolution

Spatial resolution / Size sensor

tonal resolution



Spatial resolution

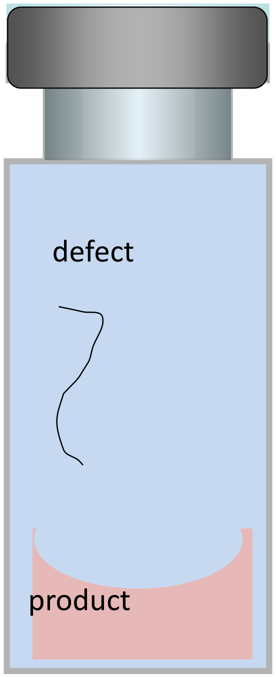


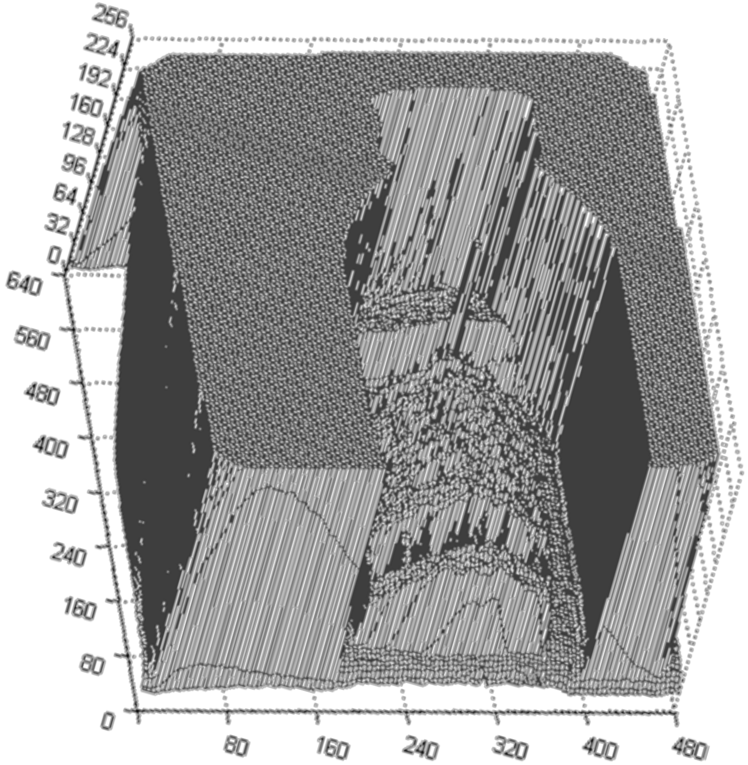
What a machine really sees, what is DIP?

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

Variable:

- discrete spatially
- discrete quantitatively





Unit presentation to camera

Map here different ways of conveying

⇒ Suckers

⇒ Gripper

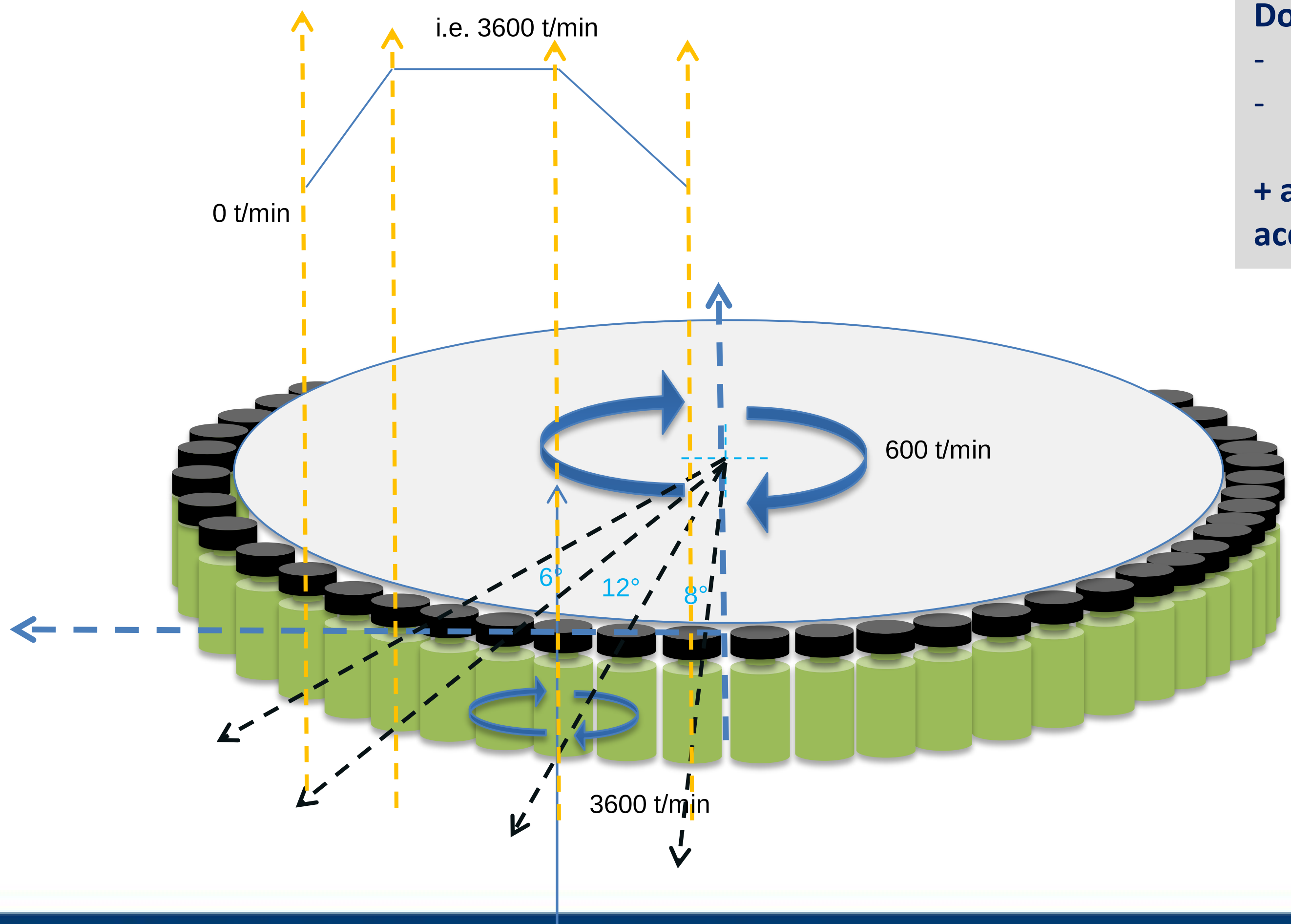
⇒ Rotation

⇒ Vial base holders

Those are pieces with ageing / regular checks / changes

Unit presentation to camera

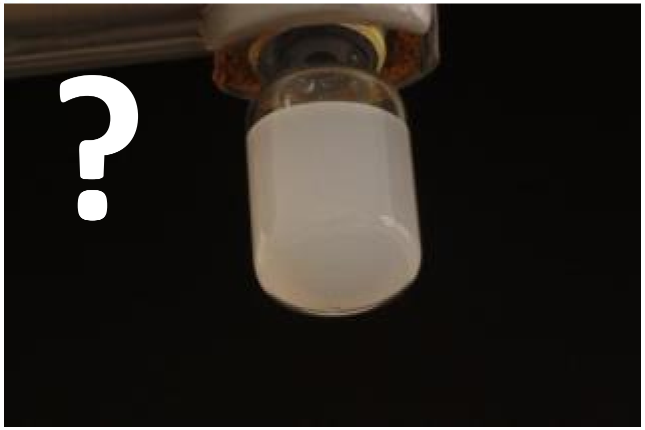
-



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

Unit presentation to camera => rotation



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

= Fast rotation To present liquid in thin layer

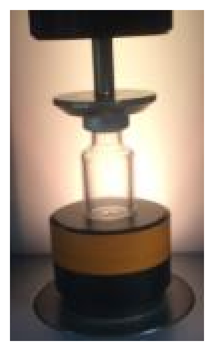
⇒ Lower optical path (density beer lambert)

⇒ Minimized scattering effect

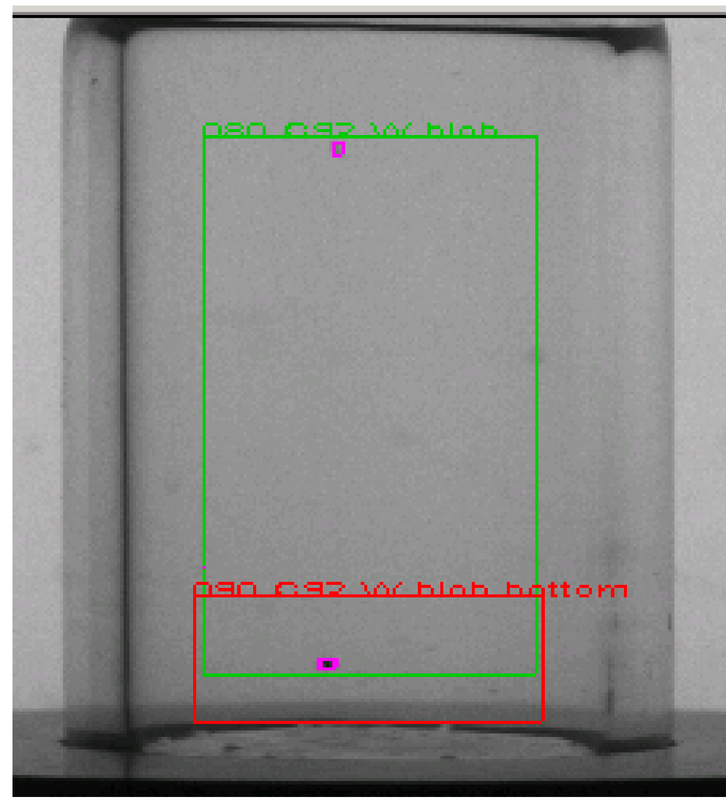
0 t/min

600 t/min

1800 t/min



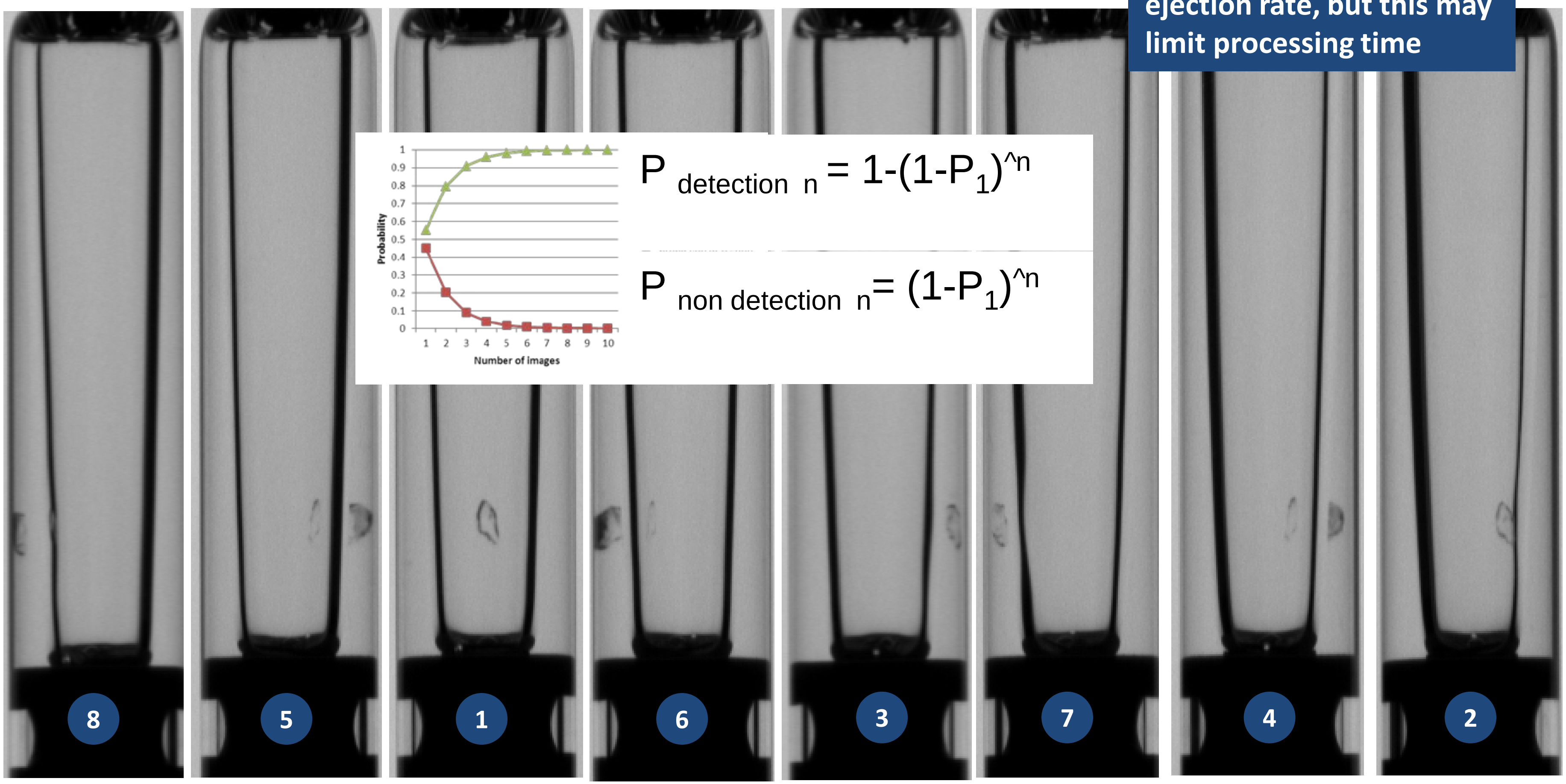
3600 t/min



Unit presentation to camera=> multiple images

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

- **Unit rotation**



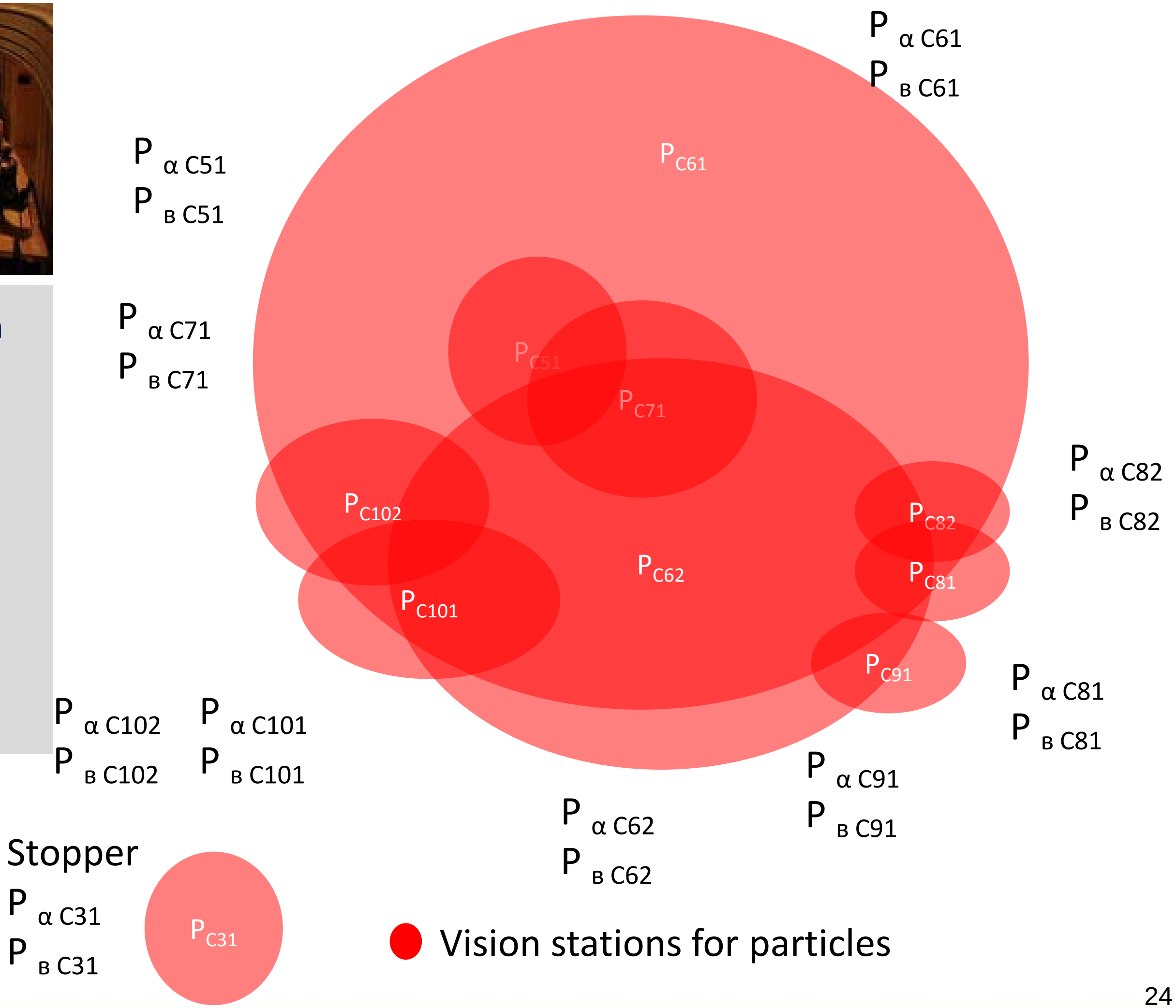
$$P_{\text{detection } n} = 1-(1-P_1)^{\wedge n}$$

$$P_{\text{non detection } n} = (1-P_1)^{\wedge n}$$

multiple images, multiple cameras => probabilistic

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

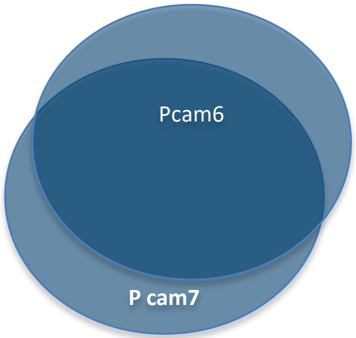


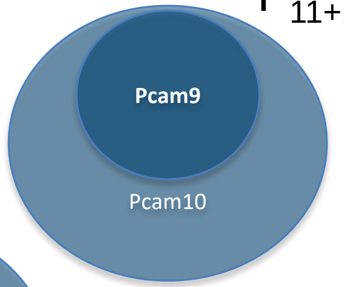
multiple images, multiple cameras => probabilistic

- **Multiple camera on AVI machines**

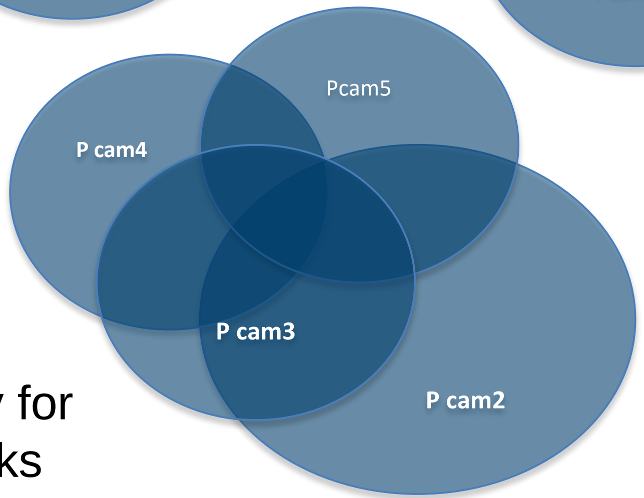
A & B mutually exclusive
$P_{11+12}=P_{11}+P_{12}$

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

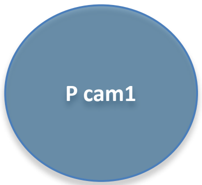




2 Camera specific
for a defect area
i.e. = Syr. closure



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

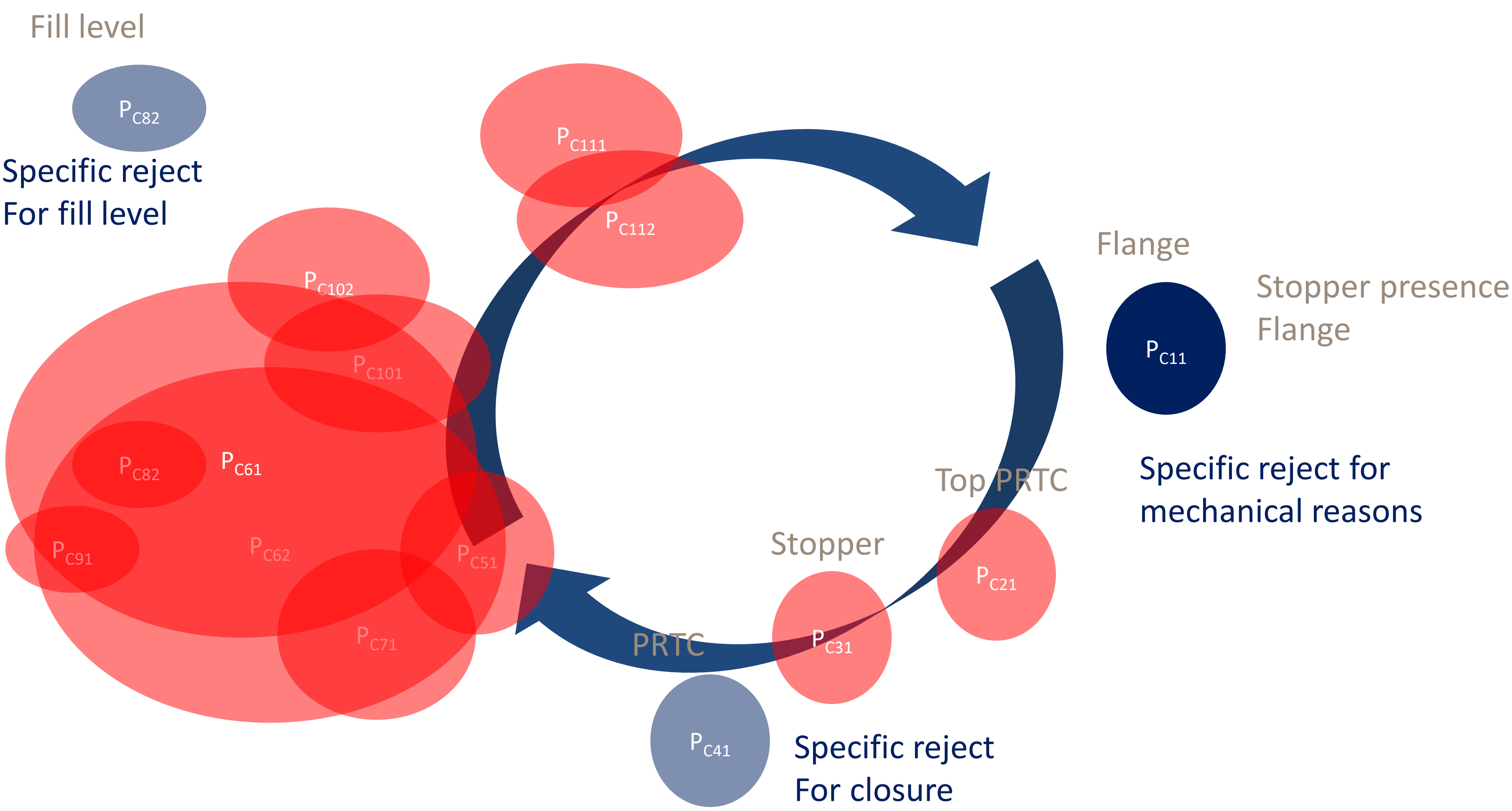


Camera specific
for a defect family
i.e. = Fill level

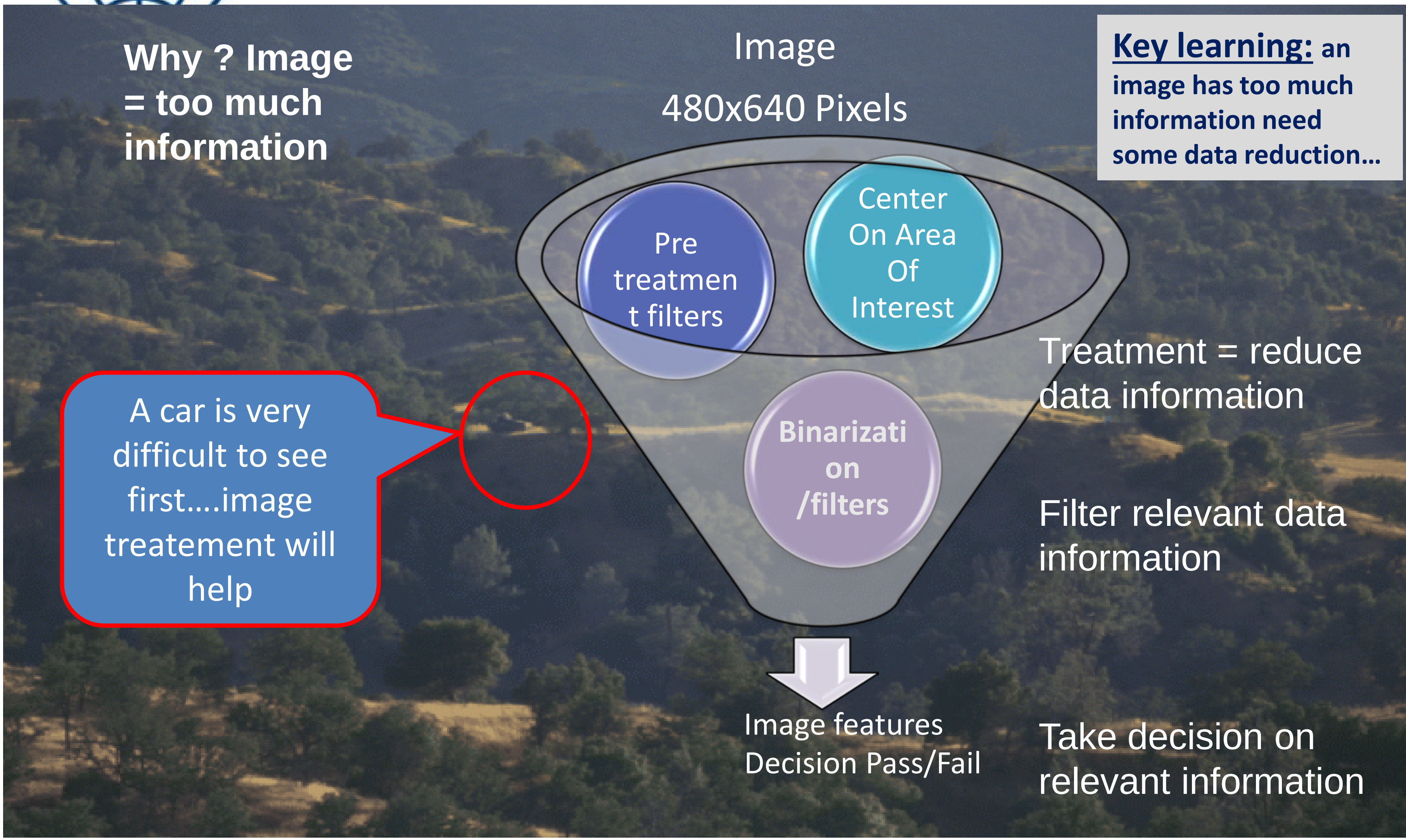
Theory 2: Introduction to technical principles of automated inspection machines

multiple images, multiple cameras => probabilistic

Venn diagram for detection probability



What is the goal of image processing ?



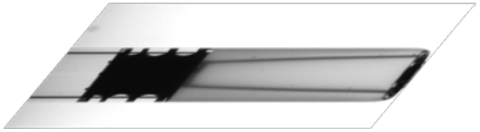
Main steps in image processing

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

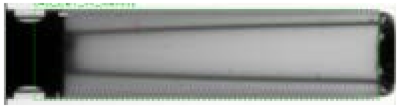
<10ms

1 3D Object presented

2 2D image

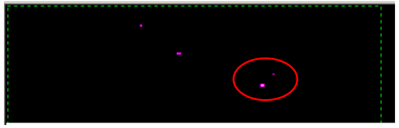


3 Area Of Interest (=AOI)



4 Binarization

5 Object detection



6 Image feature

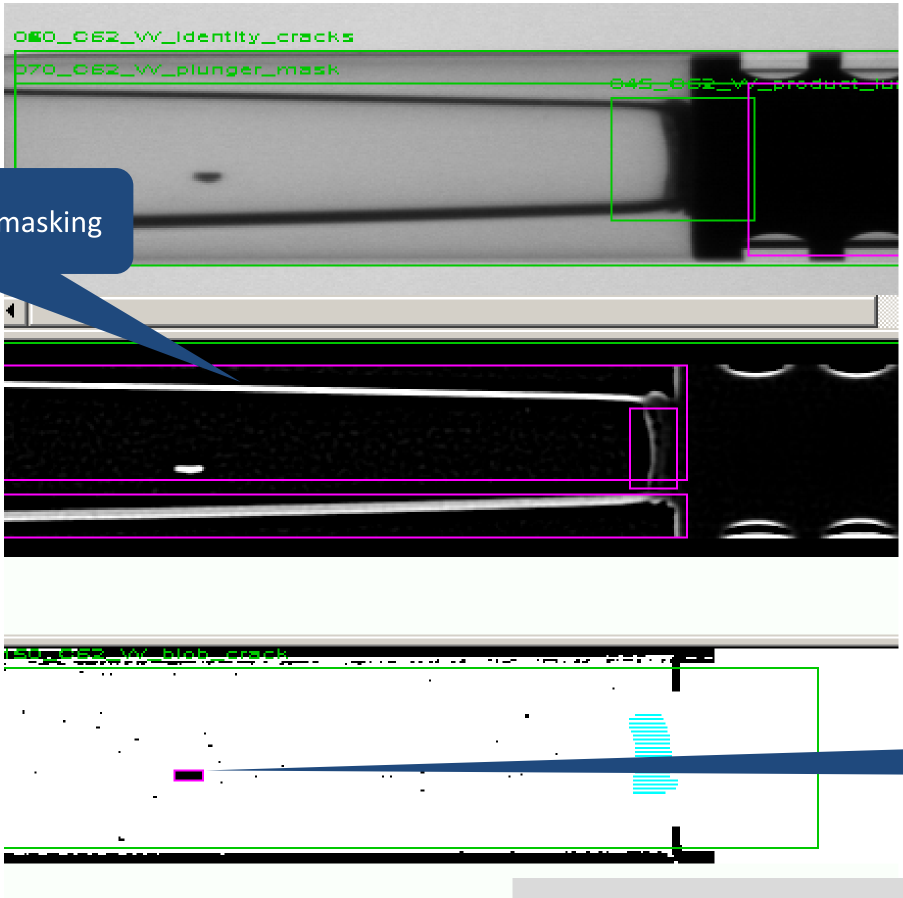
Feature Name	Current Value
Box X Min	227.0
Box Y Max	72.0
Box Y Min	70.0
Center of Gravity X	228.2
Center of Gravity Y	71.0
Convex Perimeter	12.0
Elongation	1.4
Feret Elongation	1.4
Feret Max Diameter	4.2
Moment Central X1 Y1	0.0

7 Image understanding

8 Pass / Fail

Image processing example

1 meniscus dynamic masking

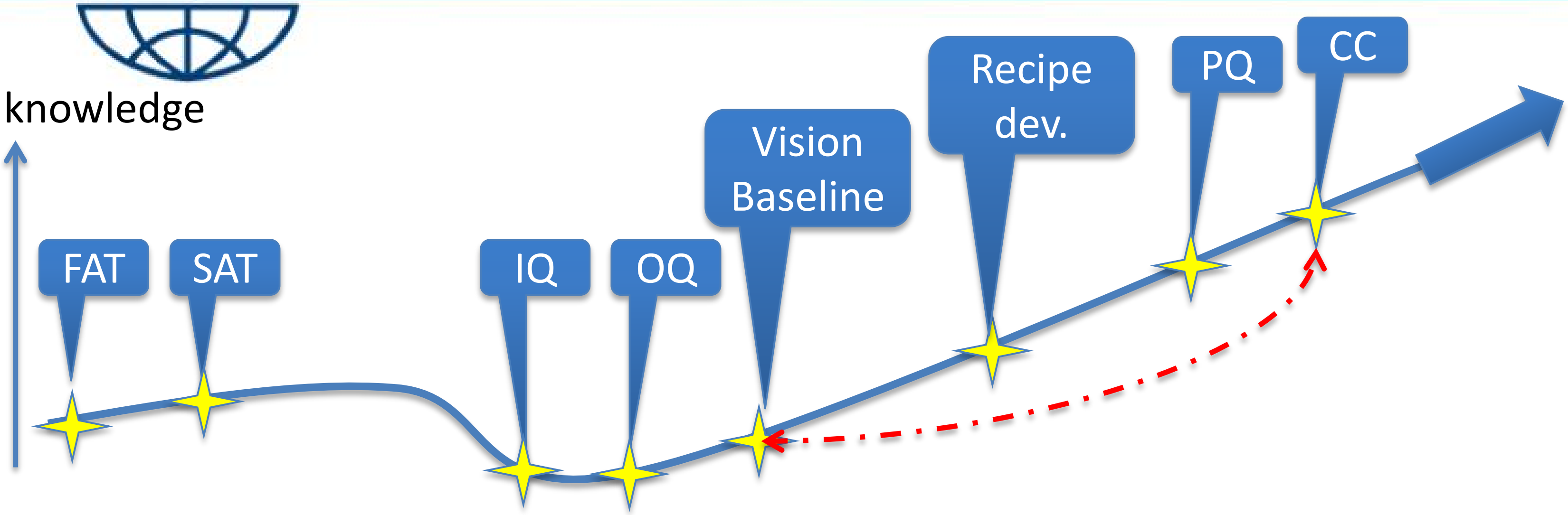


2 Particle is localized

Key learning:

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

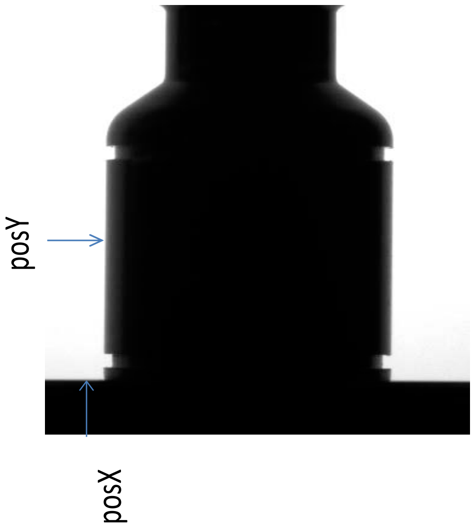
Baseline definition



- = 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

Vision mechanical alignment

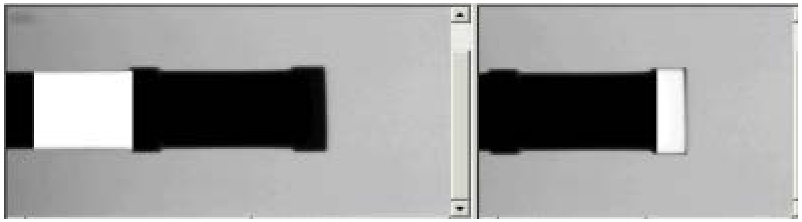


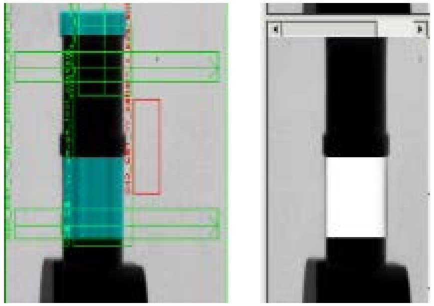
Dummy syringe

Dummy vial

Key learning:

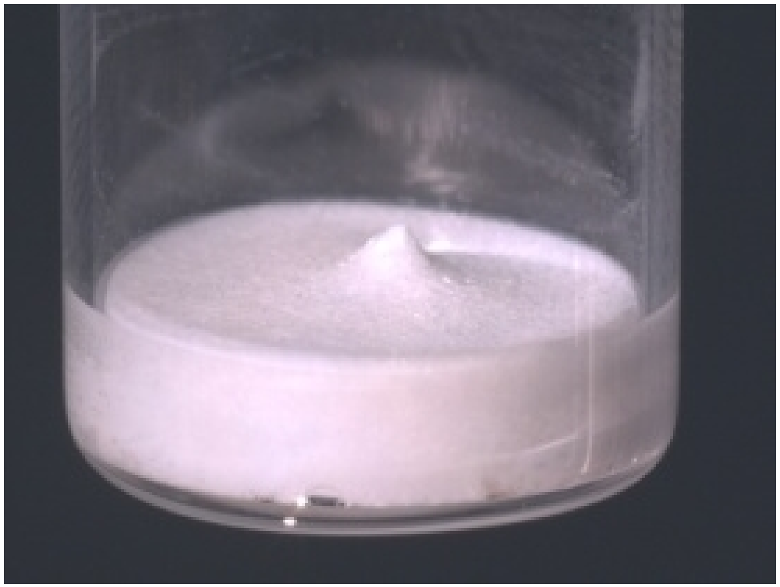
There should be tools to control vision alignment to document that vision tools remains within range from initial baseline corresponding to initial PQ

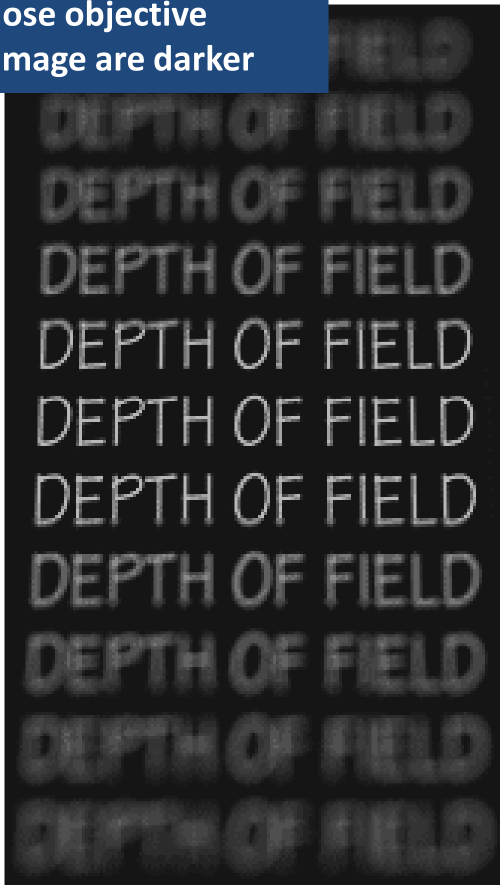


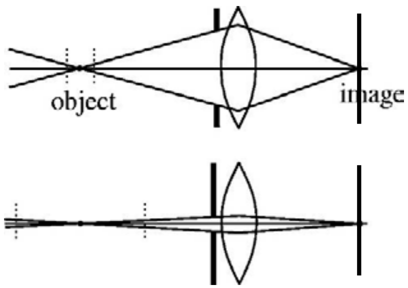


Depht of field

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

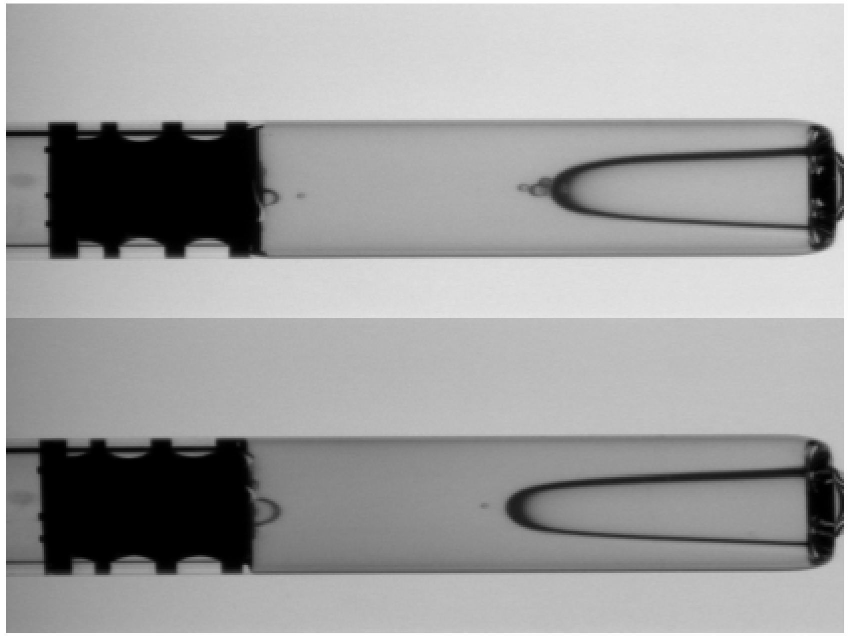


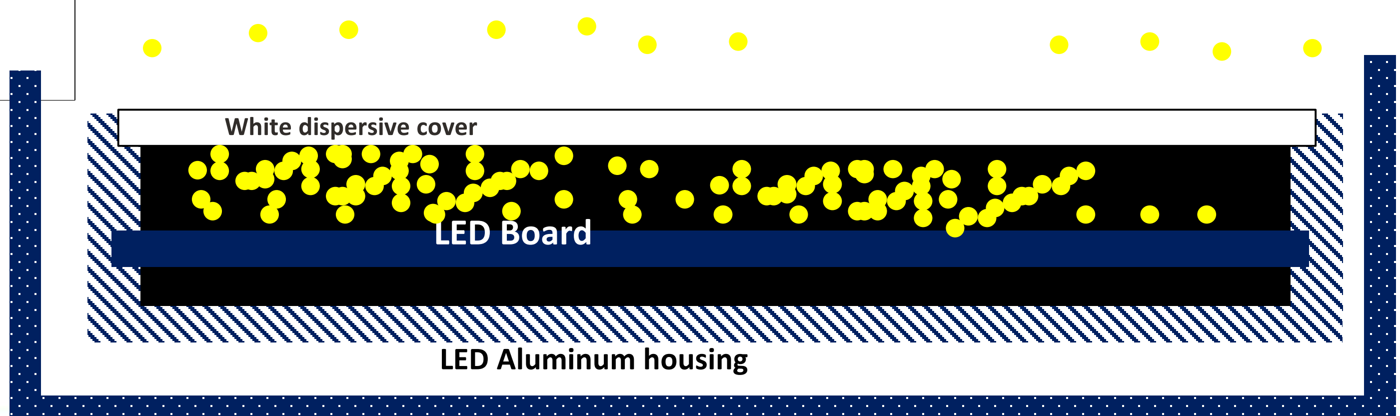




Light stability

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





Light spatial homogeneity

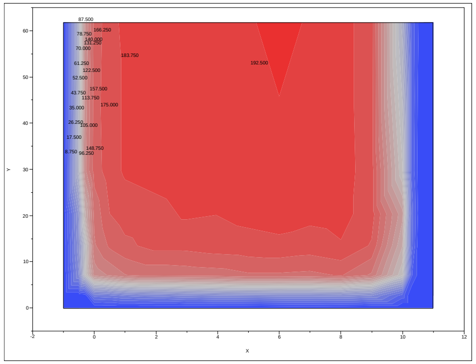
LED are more stable but …….beware of boarder effect

- Practical Examples of key parameters ctrl:

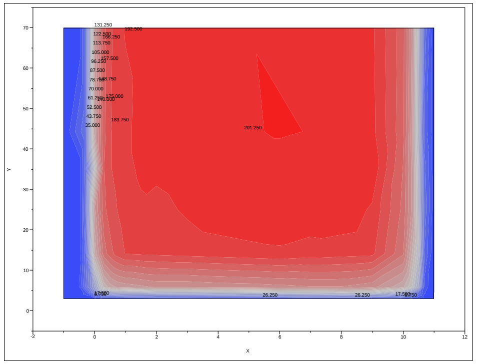
=> opportunity for knowledge improvement : spacial homogeneity of LED in 3D

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

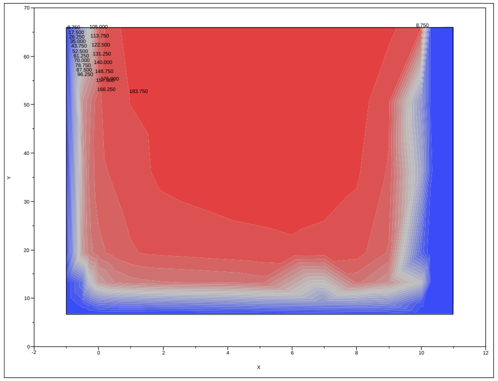
=> Very Homegeneous in area of use



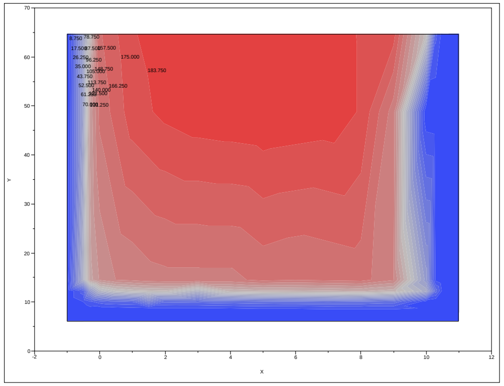
z =53.42mm



z =98.1mm



z =134.5mm



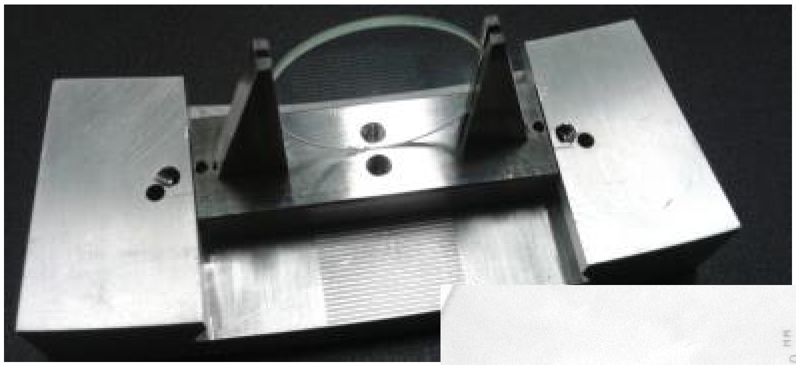
z=178mm

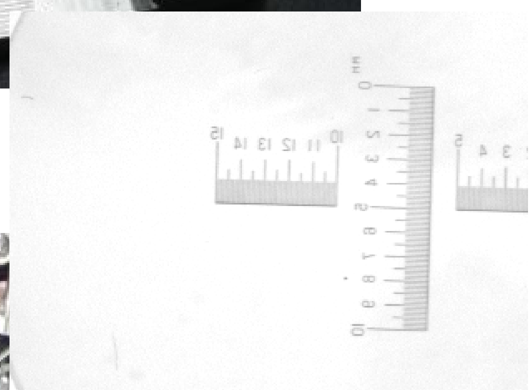
Heat dissipation and possible impact to consider

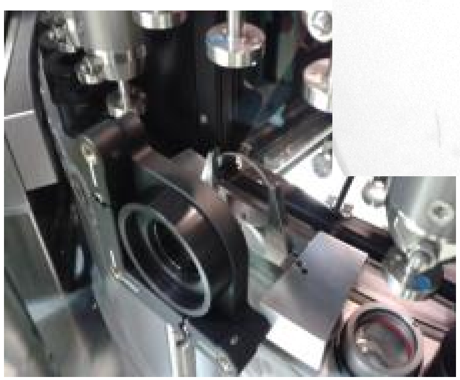
Luminance over 3.5 hours

	Initial	End	Delta
C21	164	162	2
C41	96	87	9
C51	179	167	12
C61	197	192	5
C62	183	176	7
C71	189	178	11
C81	174	167	7
C82	191	180	11
C101	175	165	10
C102	203	190	13
C111L	133	132	1
C111R	127	126	1
C112L	115	115	0
C111R	121	121	0

Image Focus

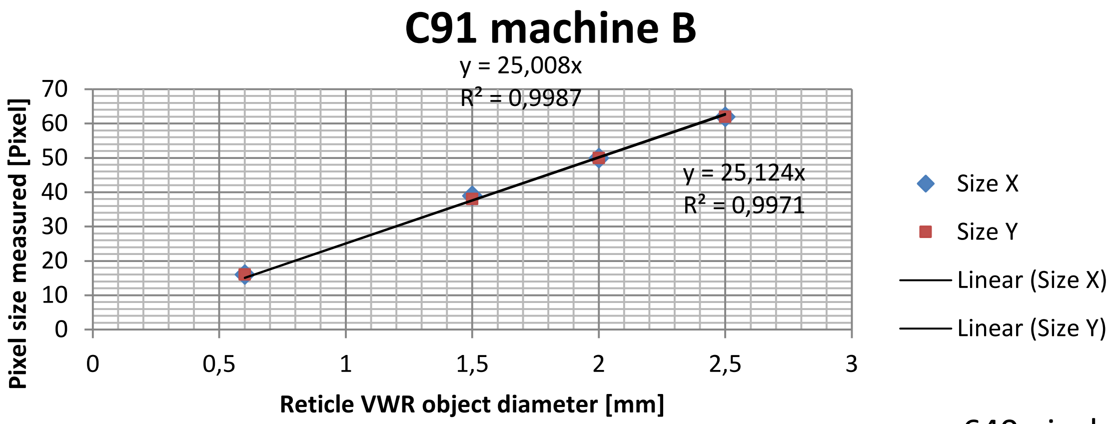






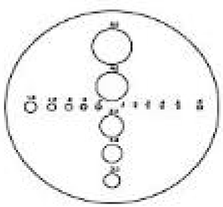
Bad focus

Image correlation pixel to size

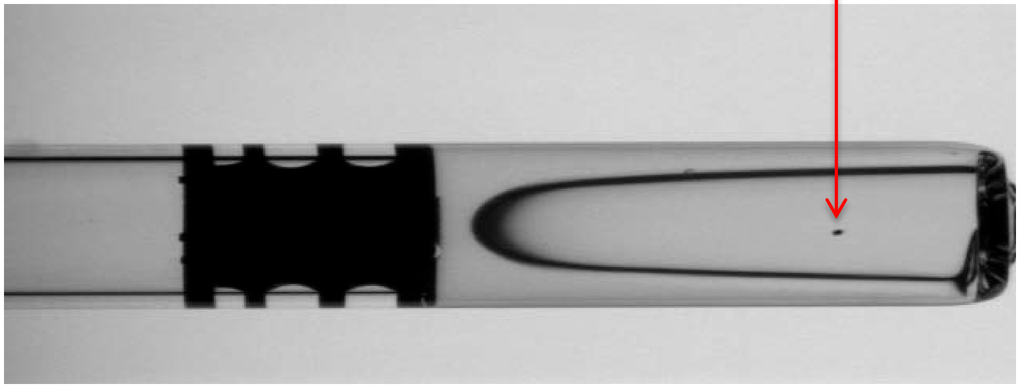


1.1 mm = 5,3 pixel

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

Light source

- Add couples of slides of all illumination
- (syr vials)

➔ Play with light

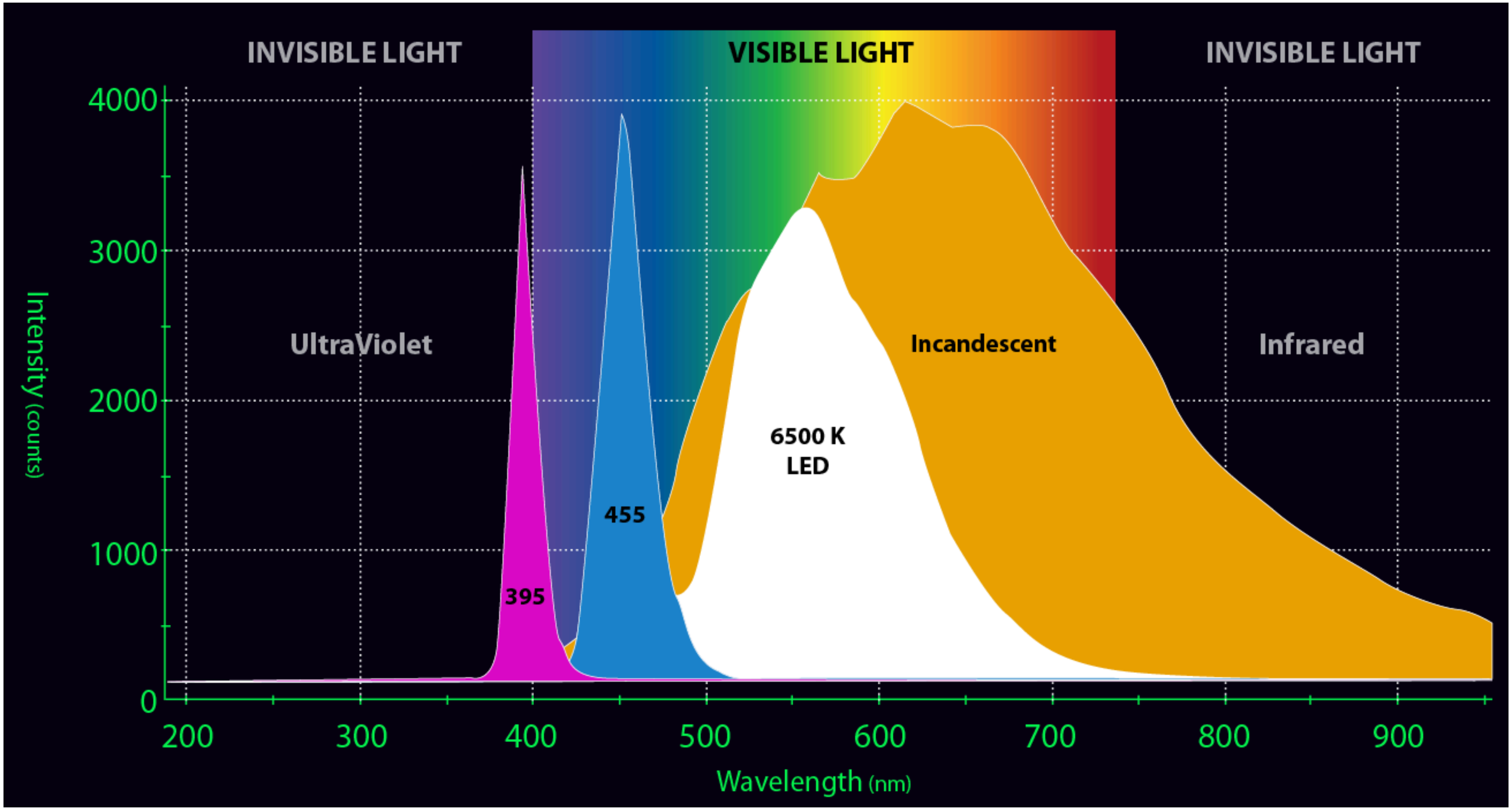
➔ Combination of light

➔ Add a foreword on compensation of light with different product families (opacities)





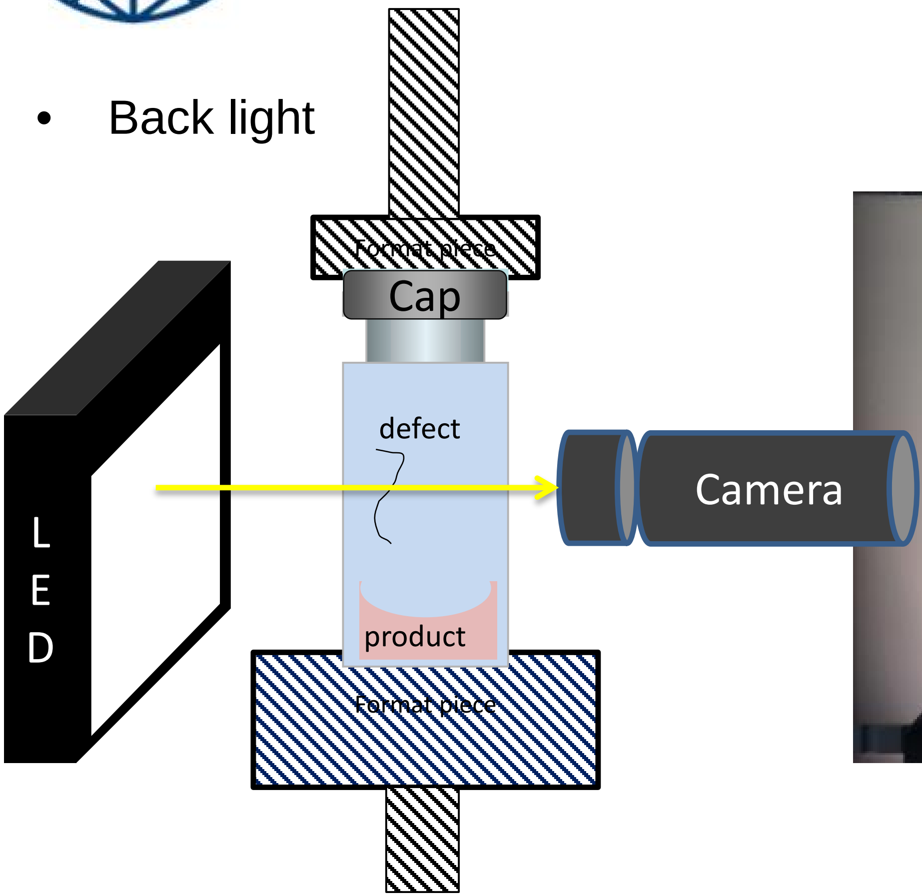

Light source

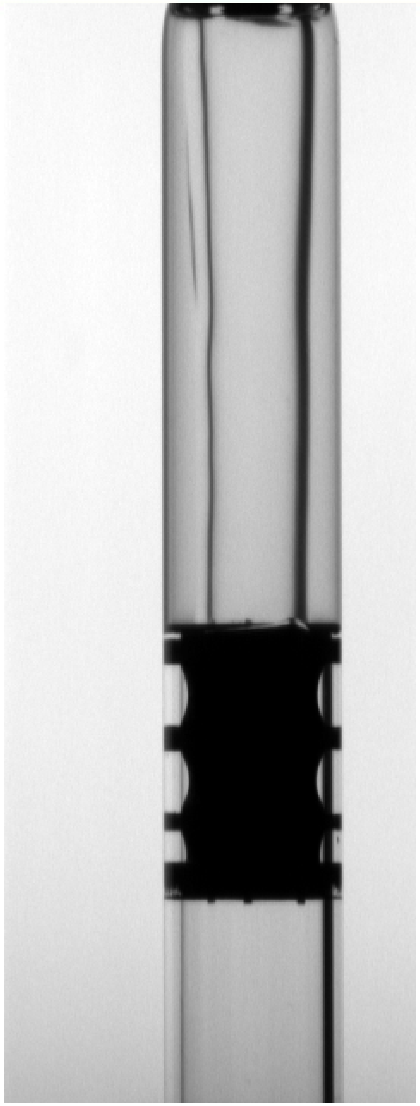


Theory 2: Introduction to technical principles of automated inspection machines

Light source

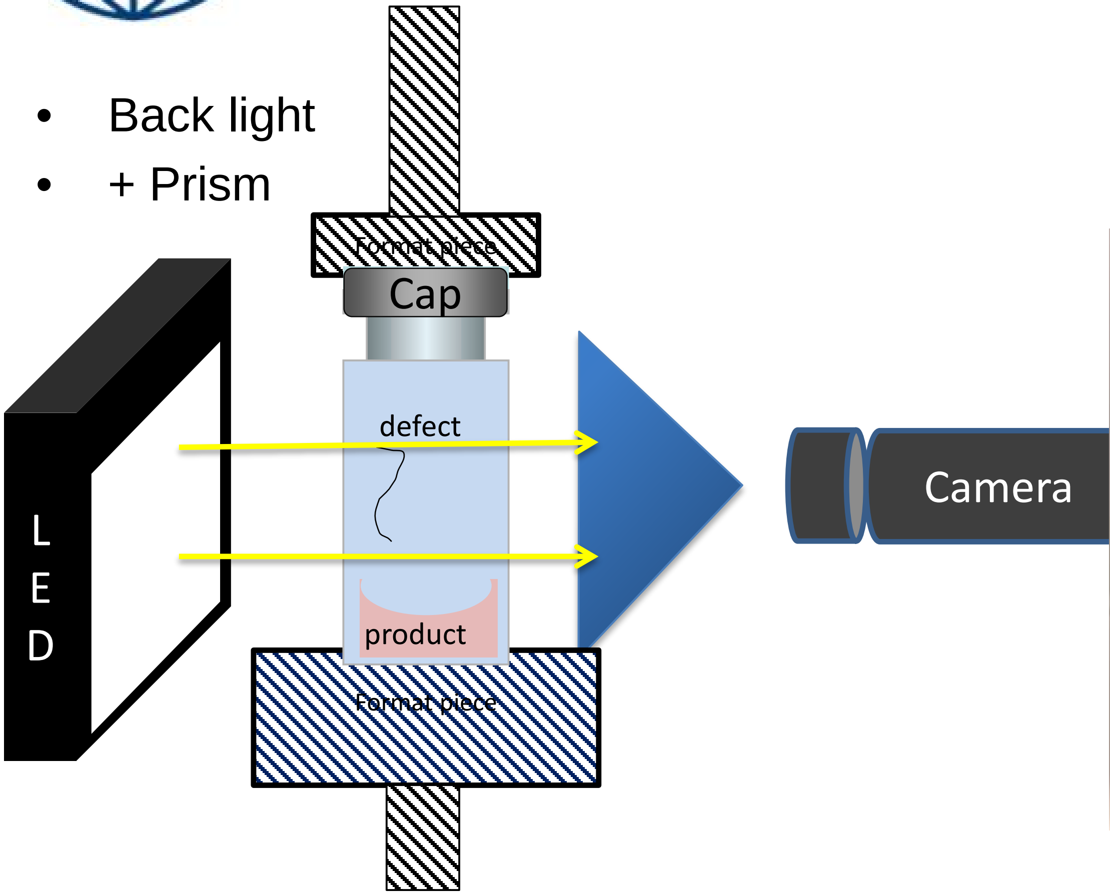
- Back light

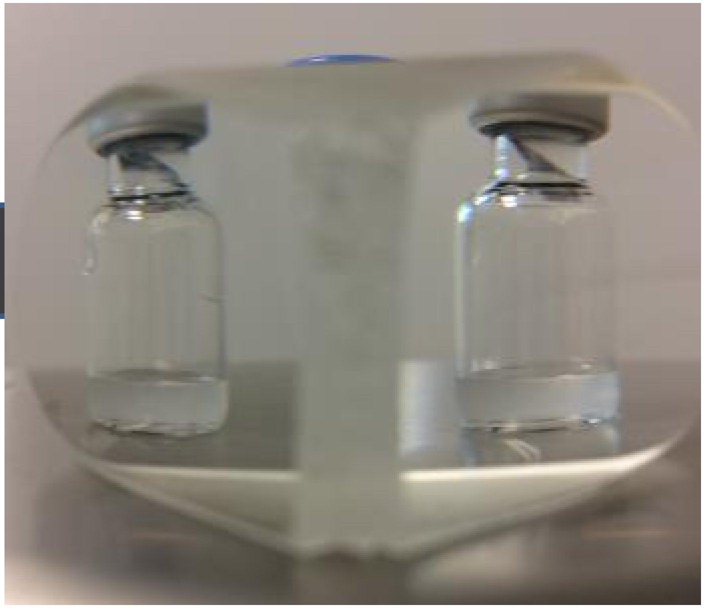




Light source

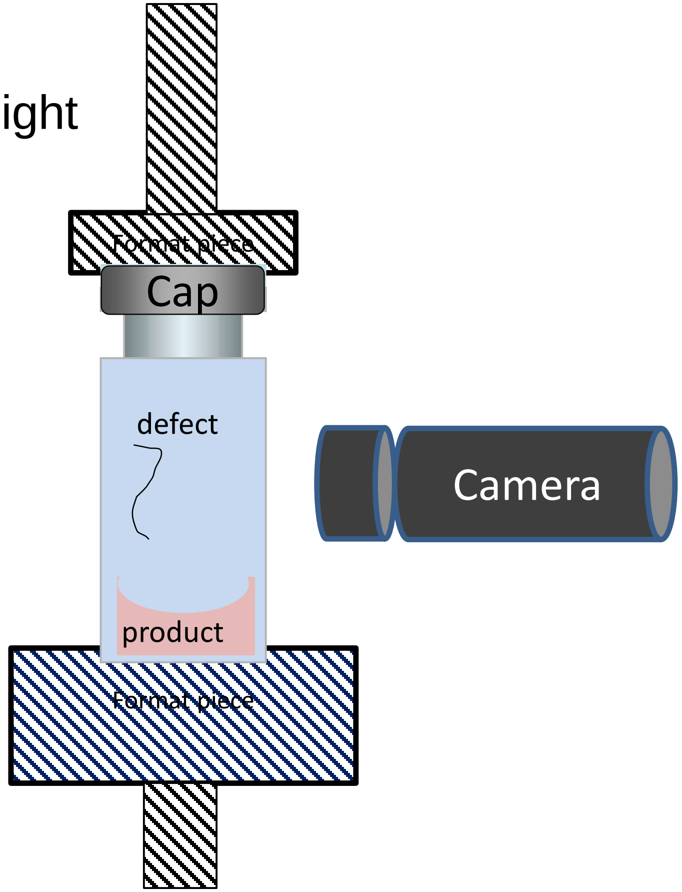
- Back light
- + Prism





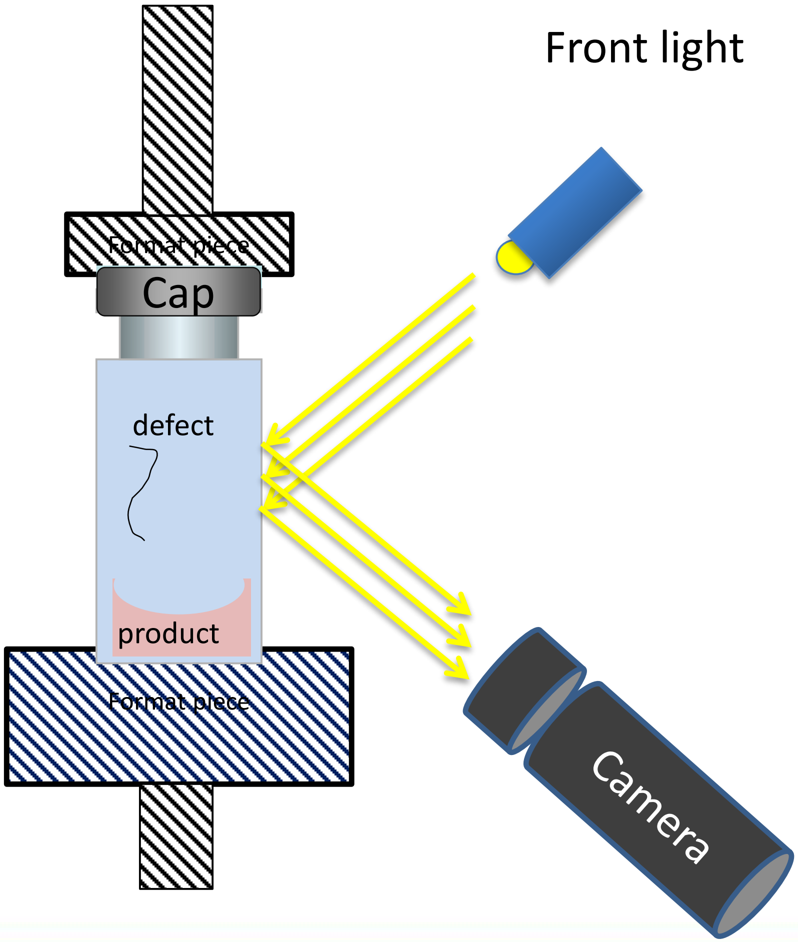
Light source

- Front light



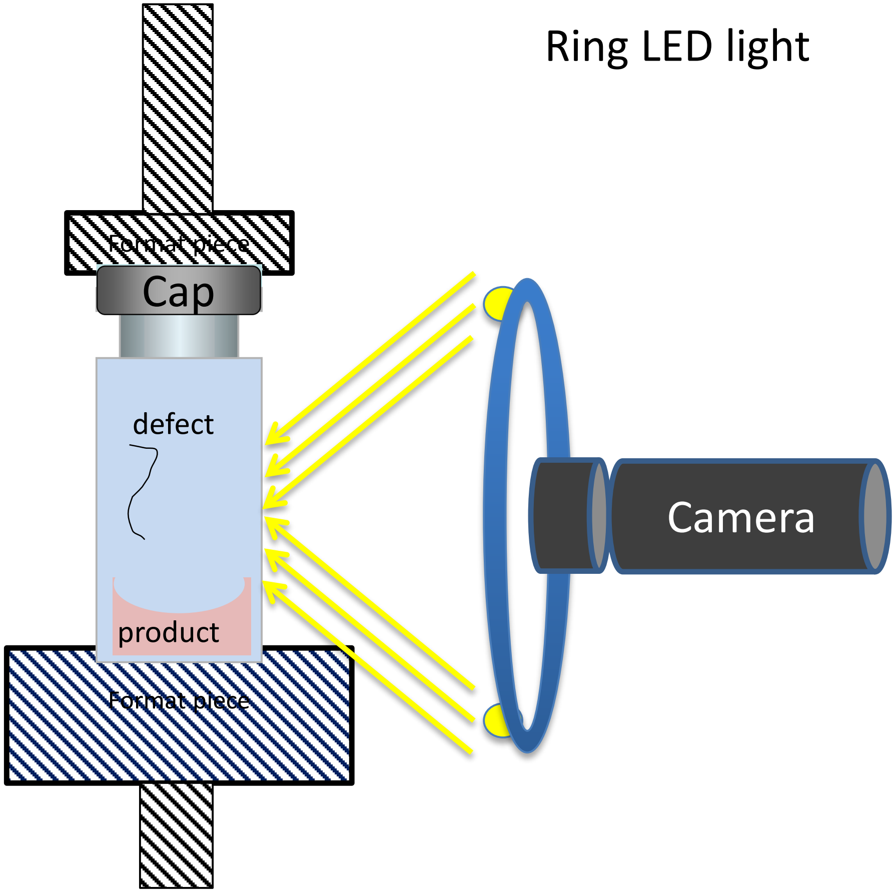
Light source

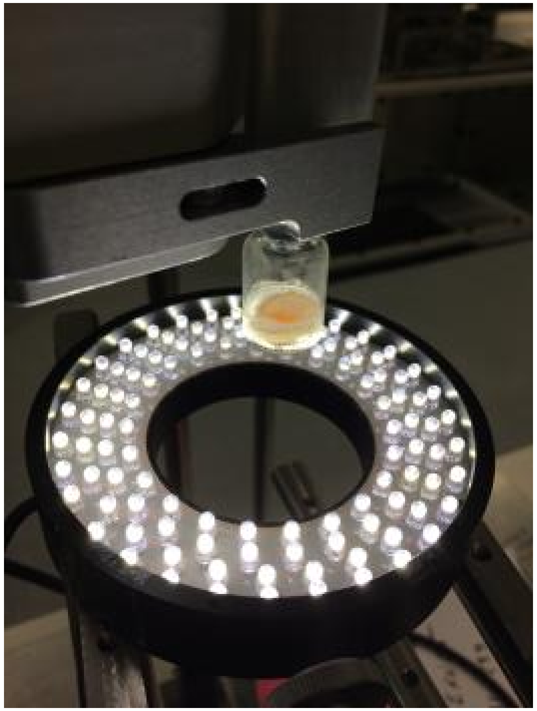
- reflectance light



Light source

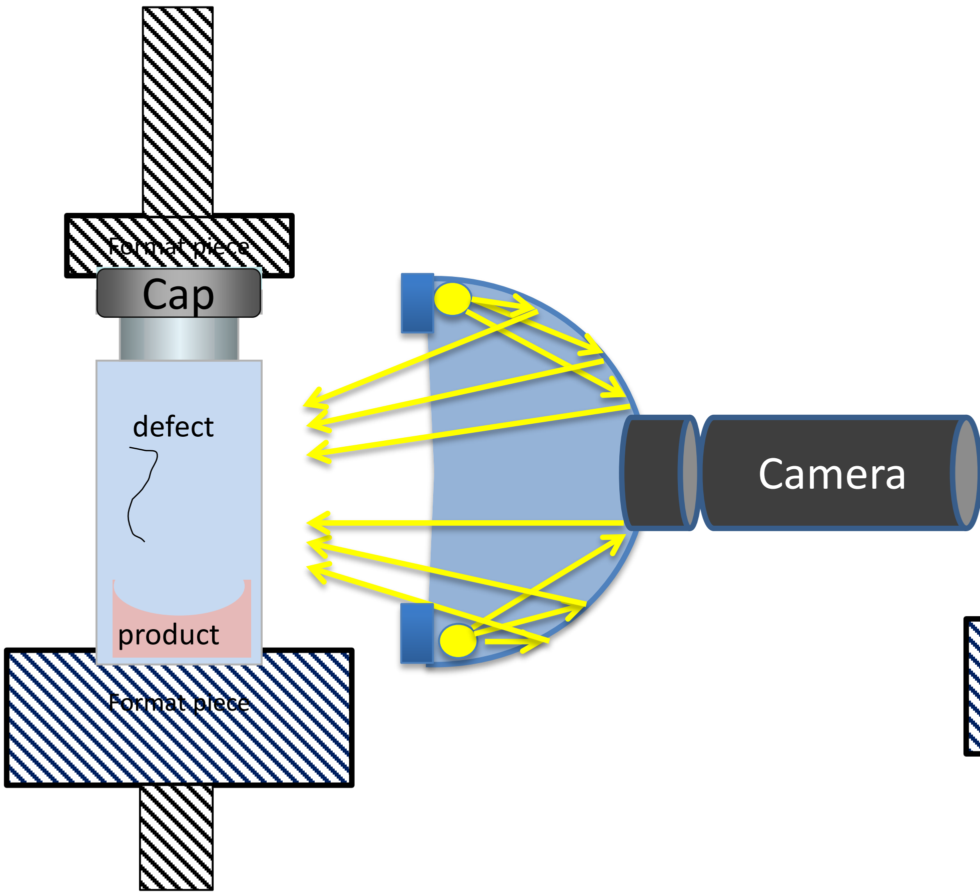
- reflectance light



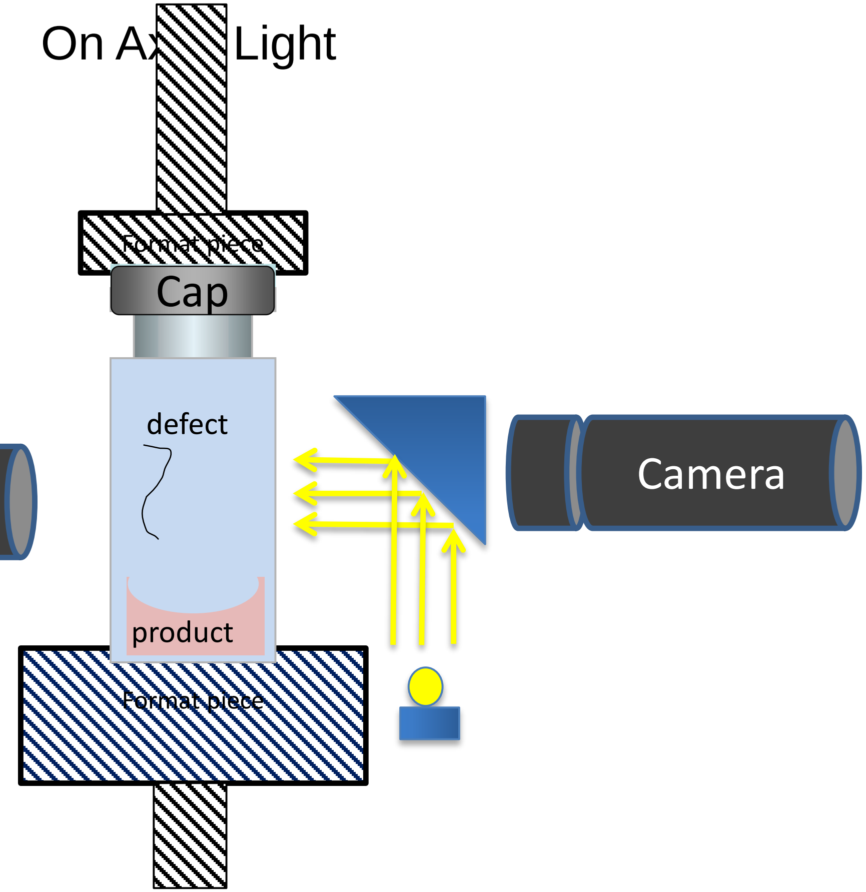


Light source

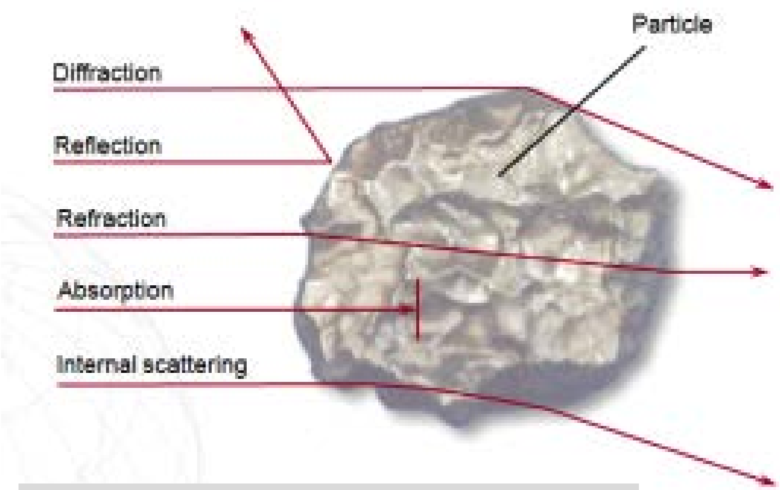
- Dome light



On Axis Light



Particle Detection strategies : Light obscuration



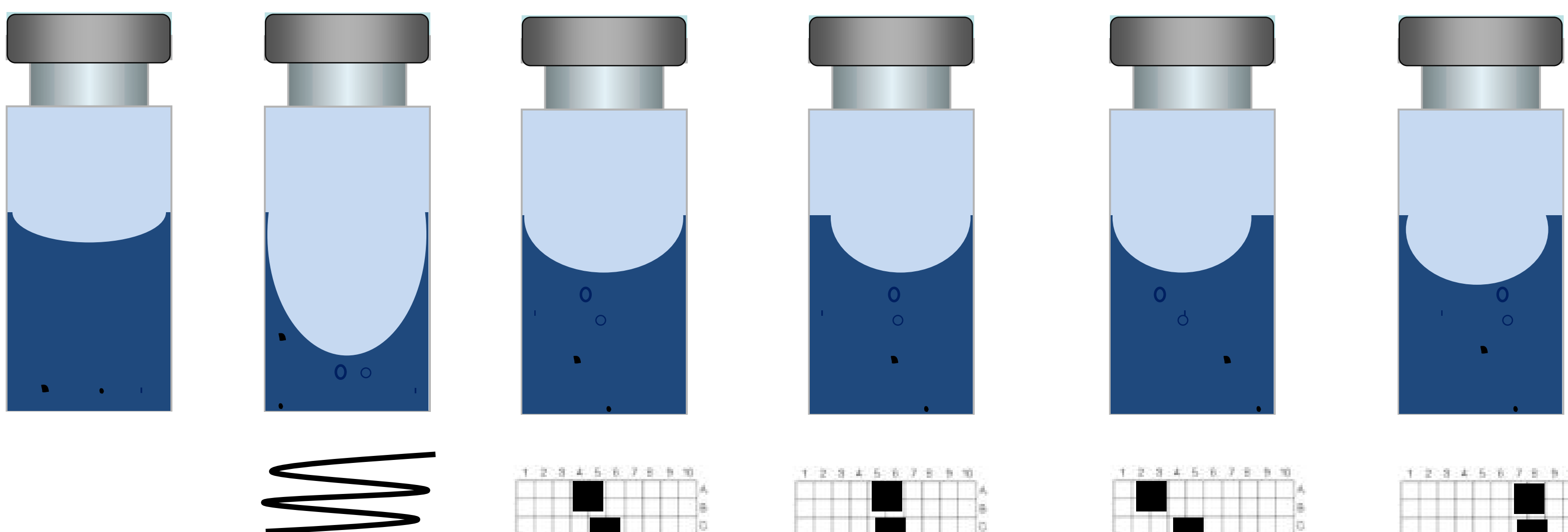
3ml vial with Tape Water

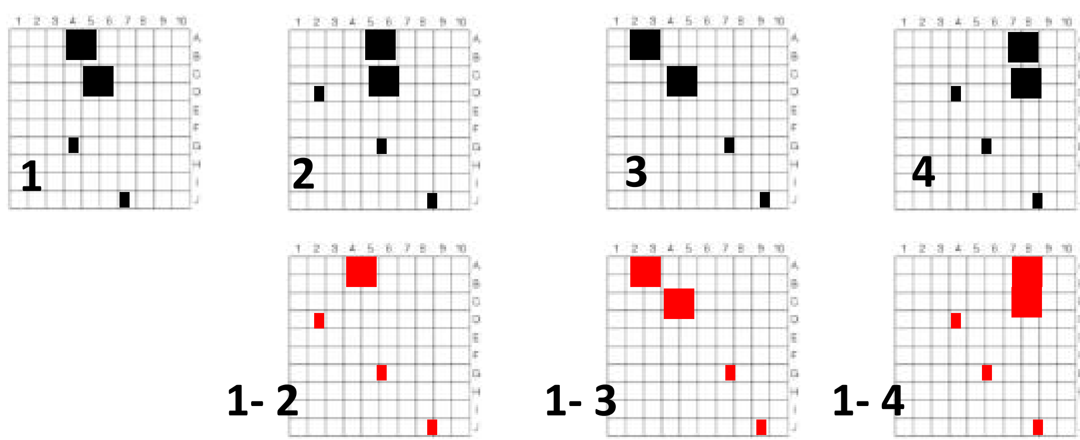
Red Laser beam

Visible and Sub visible particle are detected

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

Particle Detection strategies : image subtraction





NOT SENSITIVE TO FIXED PARTICLES + Above liquid

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

Particle Detection strategies : Fast rotation

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

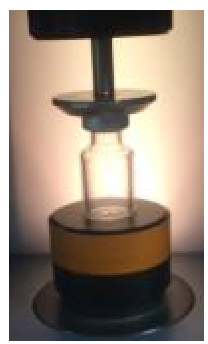
= Fast rotation To present liquid in thin layer

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

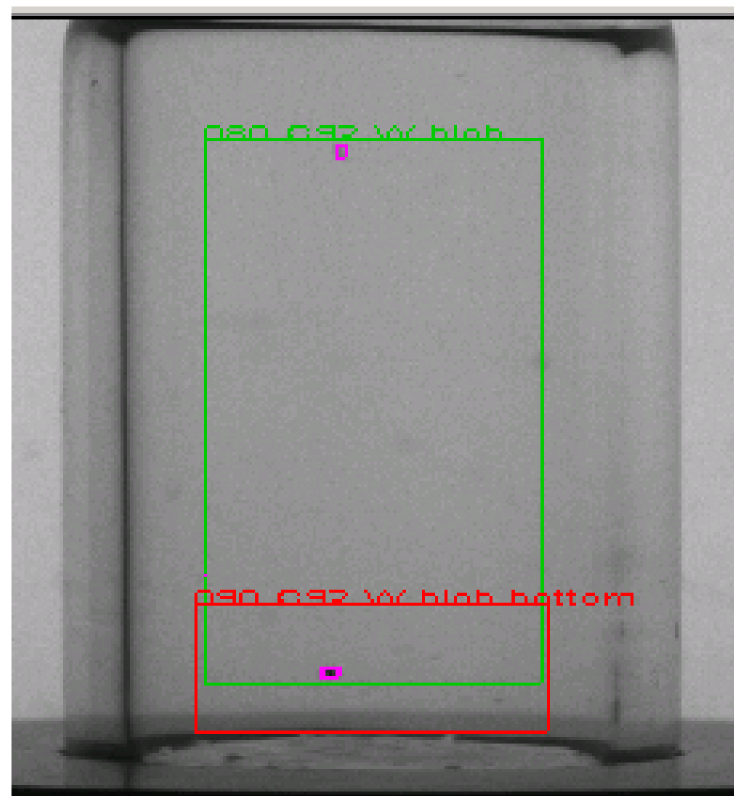
0 t/min

600 t/min

1800 t/min

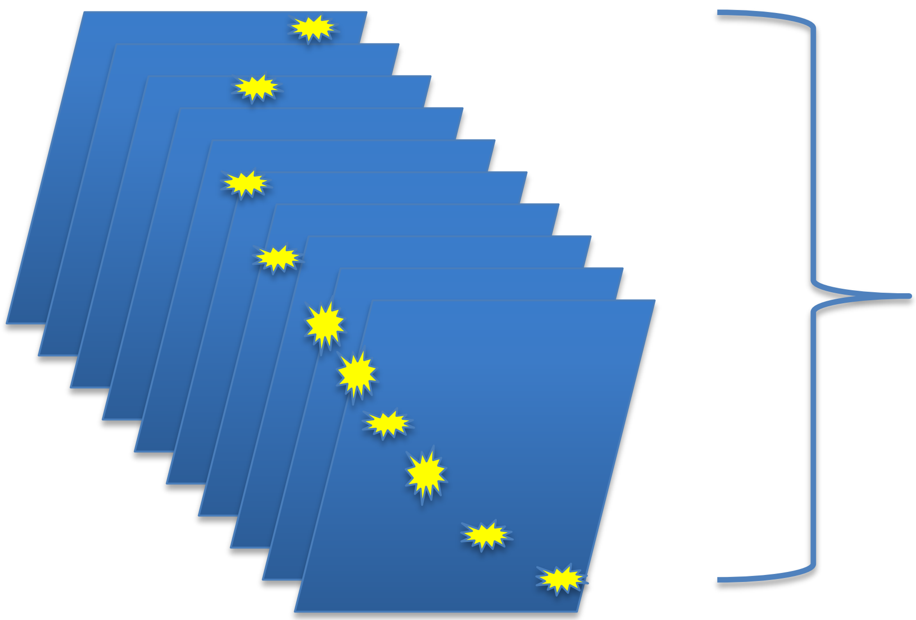


3600 t/min



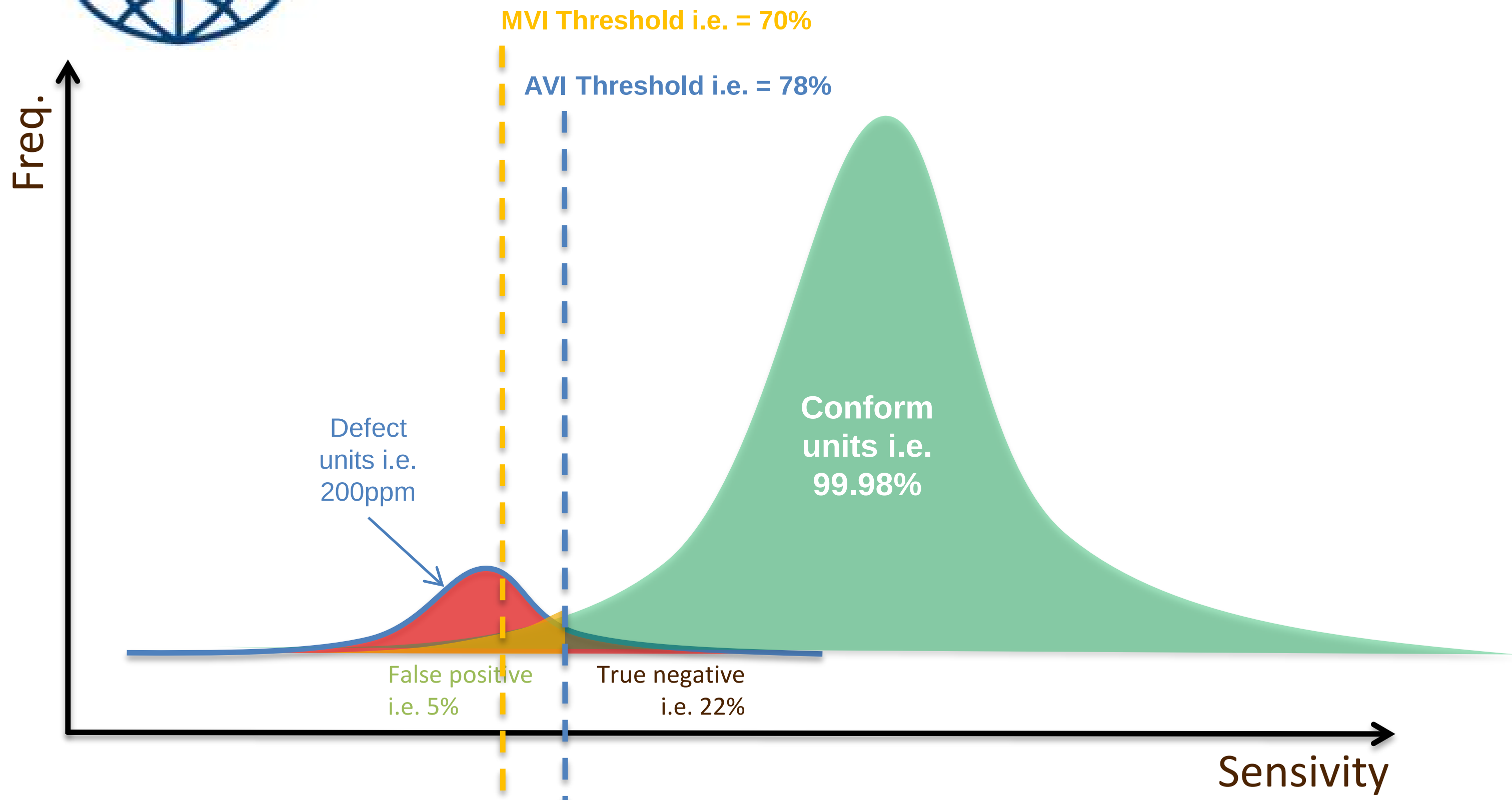
Particle Detection strategies : Particle tracking

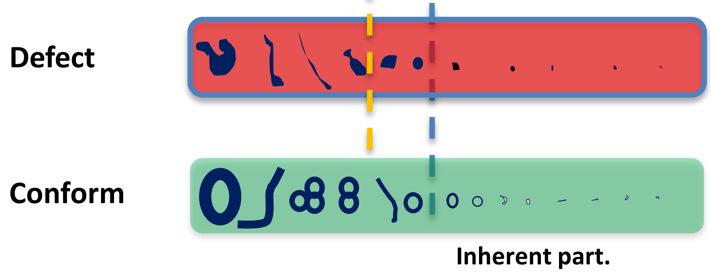
- With modern vision machine more images are available
- Images can be treated not only 1 by 1 individually but in stack of images
- Rendering particle trajectories analyzed
- And differentiation to artifacts like bubbles

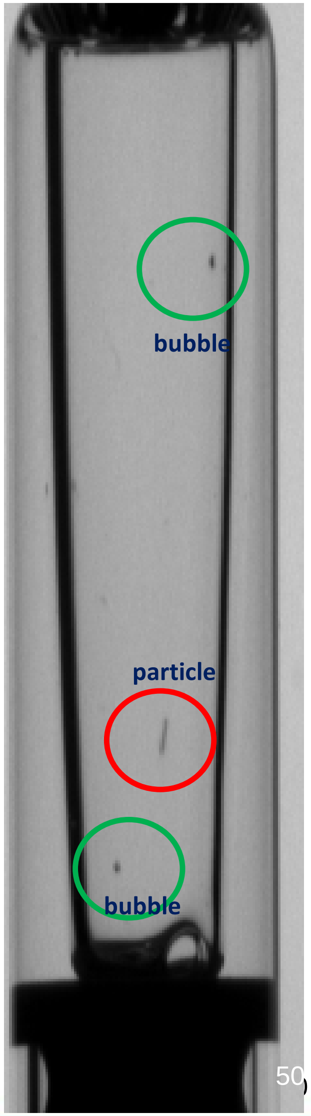


Analyze of 1 stack of 10 to 60 images all at once to track particle trajectories

False reject / balance patient vs business risk

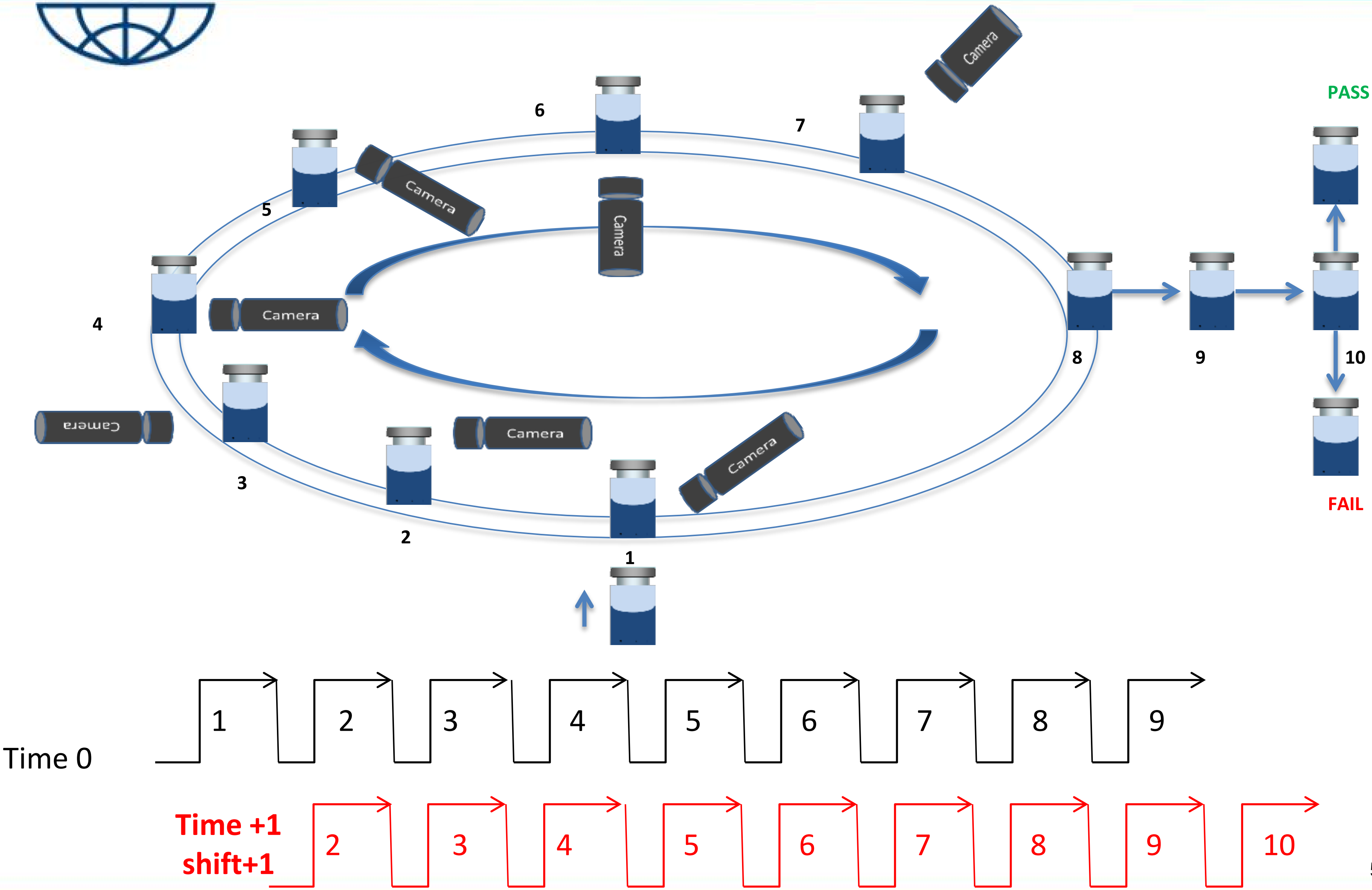






Key learning: Automated Inspection tuning is a balance between patient risk (Beta) and business risk (Alpha)

Automation concept / shift register



Key take away:

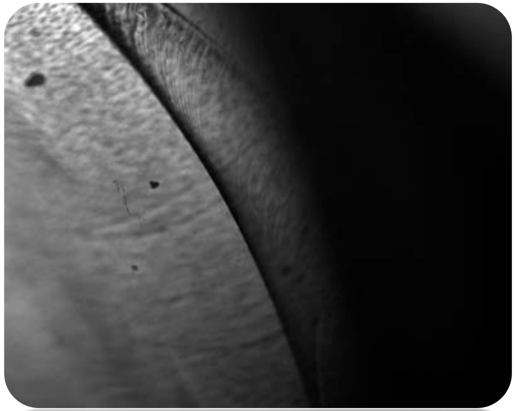
- In this section you have learnt:

AVI	Long way
	Equipment / Process / ctrl strategy design
	Parts of AVI equipment
	Image processing steps
	Critical parameters
	Illumination sources
	False reject / true detection
	Automation concept

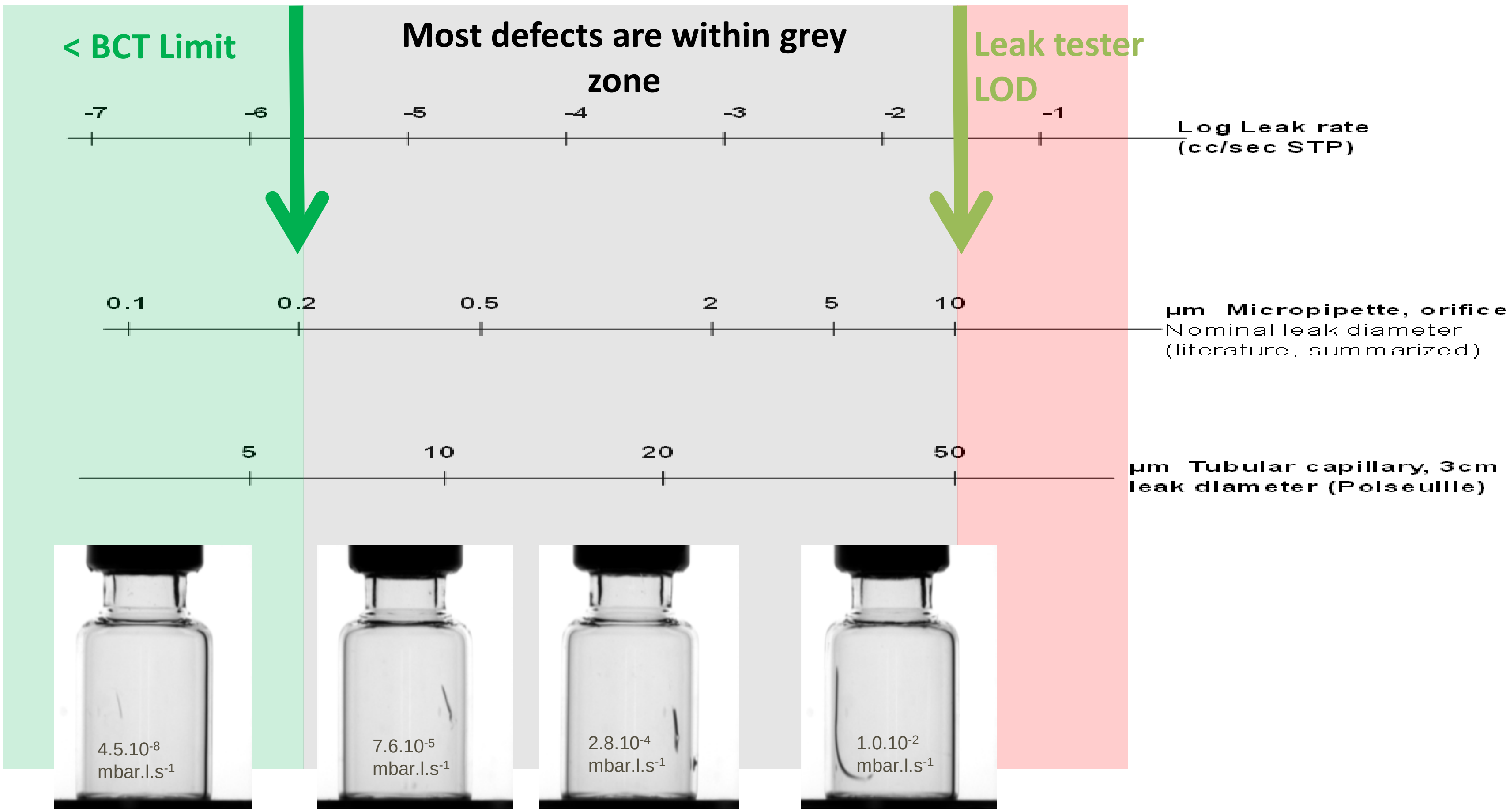
- Leak Detection

What is a Leak ?

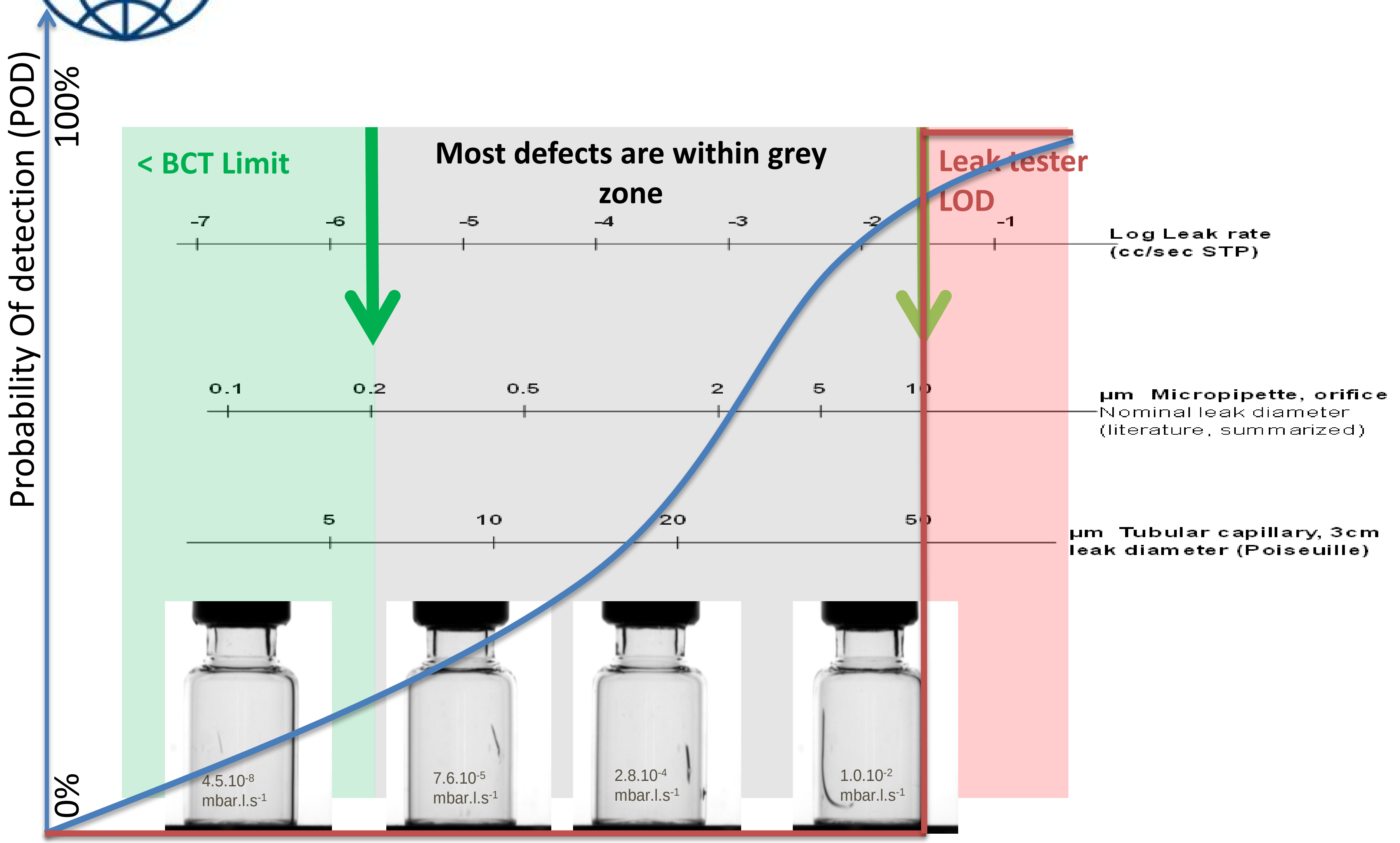
A leak can be described as a breach in a package wall, or a gap between package components capable of permitting the passage of gas or liquid. Leaks in glass are complex, multi-cavity tortuous paths. Associated risks to a leak can be potential loss of sterility, oxidation, hydrolysis, loss of vacuum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



Helium test can measure Leak Rate of CCIT defects



Probabilistic vs Deterministic Detetection



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	No	Yes	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
AVI / MVI (Seidenader, Brevetti, Bosch, Innoscan……)		- Only technology to detect leaks in grey zone (>BCT but lower than 10µm) - Can detect liquid leaking cracks but also gas leaking cracks (very sensitive)	- Remains probabilistic (< 100% detection rate for small cracks) - Limited specificity (generates false rejects) - Low sensitivity for Lyo
Pressure Decay (Wilco/Bonfig.)		- Deterministic method 100% Detection for leaks> 10µm - Can only be used for Lyo and overfilled liquid vials	- Can only detect leak > 5-10µm (5% of cracks in our defect library)
Vacuum Decay (Wilco/Bonfig.)		- Deterministic method 100% Detection for leaks> 10µm - Can be used for Lyo and liquid vials (partial fill) - Can be used for tubes and BFS	- Can only detect leak > 5-10µm (5% of cracks in our defect library) - For Syringe there is only offline benchtop not yet industrial machine

Pro &Cons for each LD technologies

Leak Detection Technology	Principle	Advantage	Limitation
High Voltage (Seidenader/ Brevetti / Bosch / …..)	 High voltage detection of current shift with conductive liquid though cracks	- Deterministic method 100% Detection for liquid leaks - Can be used for syringe and liquid vials	- Ozone generation that require product impact validation + Stability study per product - Limited added value to AVI for small crack detection (<30% DR cracks in liquid when AVI DR>80%) can see only liquid leaks - Hardlly correlated to leak size (only liquid leaks)
Head Space (Wilco / Bonfig. / Seidenader / Bosch Lighthouse/ Brevetti)	 Measure Oxygen ingress in leaking vials	- Deterministic method 100% Detection for gas leaks - Very sensitive method down to 1µm with holding time XX days product dependent - As it test Oxygen ingress it is a good control for sensitive to oxidation products (Zoster Metox)	- Limited to vials that are inerted - GSK Vaccines are worst case (high pressure/low volume), lower sensitivity - Requires holding time product dep and thus inline machine is not possible - 2 in 1 machine (AVI + headspace) up to 400/min offline is possible

60

Key take away:

- In this section you have learnt:

Leak Testing	Leak definition
	Leak range
	Determistic vs probabilistic
	Mapping technologies
	Advantage / Inconvenient