THE THEORY BEHIND AUTOMATIC INSPECTION TECHNOLOGIES

FOR SUBVISIBLE-TO-VISIBLE PARTICLE DETECTION AND CONTAINER CLOSURE INTEGRITY

Edwin Martinez
Senior Engineering Manager
Baxter Healthcare
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Speaker Bio

Thien Pham

Pfizer

Principle Engineer

More than 20 years of manufacturing operations experience in Electronic Manufacturing Services and Pharmaceuticals and Medical Device Manufacturing in combination with a Bachelor of Science in Electrical and Computer Engineering. This includes production, maintenance, and engineering. This also includes most phases of manufacturing including filling, sterilization, visual inspection, packaging, and utilities.

For the past 10 years, he has designed, developed, implemented, and managed multiple major capital projects at different facilities. The projects included a new packaging facility, multiple automated visual inspection lines, a SCADA system for product autoclaves, a steam plant, and a new sterile filling facility.

Edwin Martinez

Baxter Healthcare

Sr. Engineering Manager

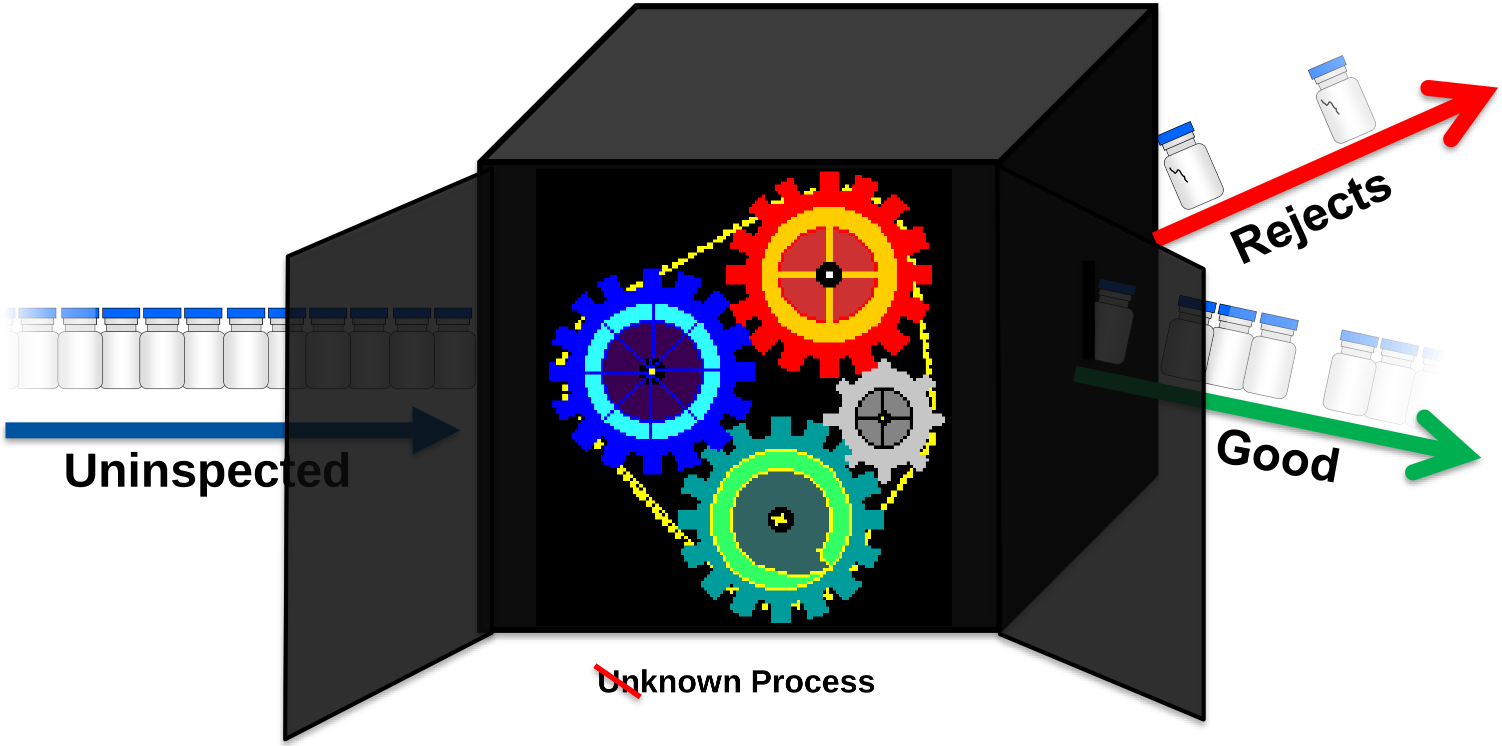
Subject matter expert on automated manufacturing systems, with more than 20 years of manufacturing operations experience; in the design, development, integration and support of various automated processes, in combination with his BS on Electrical Engineering with a concentration on automated controls, vision systems and mechatronic.

Experienced managing numerous projects at several worldwide locations for the deployment and qualification of new advance automated systems, applied to most of the phases of the manufacturing process; filling, sealing, inspection, serialization and packaging.

Disclaimer

The views expressed in this presentation come from our participation in the industry technical roundtables, field interaction with equipment manufacturers and from my personal interpretation. It do not reflect the views, strategies, preferences or official policy or position of any of my employers.

Inspection Equipment Black Box Paradigm



Agenda

- Particle Inspection Methods
    - Particle Matter
    - Principles of the Static Division (SD) Detection
    - Particle Detection using Camera Charge Coupled Device (CCD) X-Ray Inspection
- Leak Inspection Methods
    - High Voltage Leak Detection (HVLD)
    - Pressure & Vacuum Leak Detection
    - Liquid Filled Container (LFC)
    - Head Space Analysis (HSA)
    - Tracer gas (vacuum mode)
- Qualification Strategies
- Summary

Visual Inspection

U.S. Pharmacopeial Convention

All products intended for parenteral administration ***must be visually inspected*** for the presence of ***particulate matter*** as specified in Injections and Implanted Drug Products.

ECA

World Health Organization

Filled containers of parenteral products ***should be inspected individually*** for ***extraneous contamination or other defects***... the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Visual Inspection

The USP: ⟨790⟩ Visible Particulates in Injections

Inspection Procedure

Used along with ***100% inspection*** during the manufacturing process, this procedure is sufficient to demonstrate that the batch is ***essentially free of visible particulates***. A complete program for the control and monitoring of particulate matter remains an essential prerequisite.

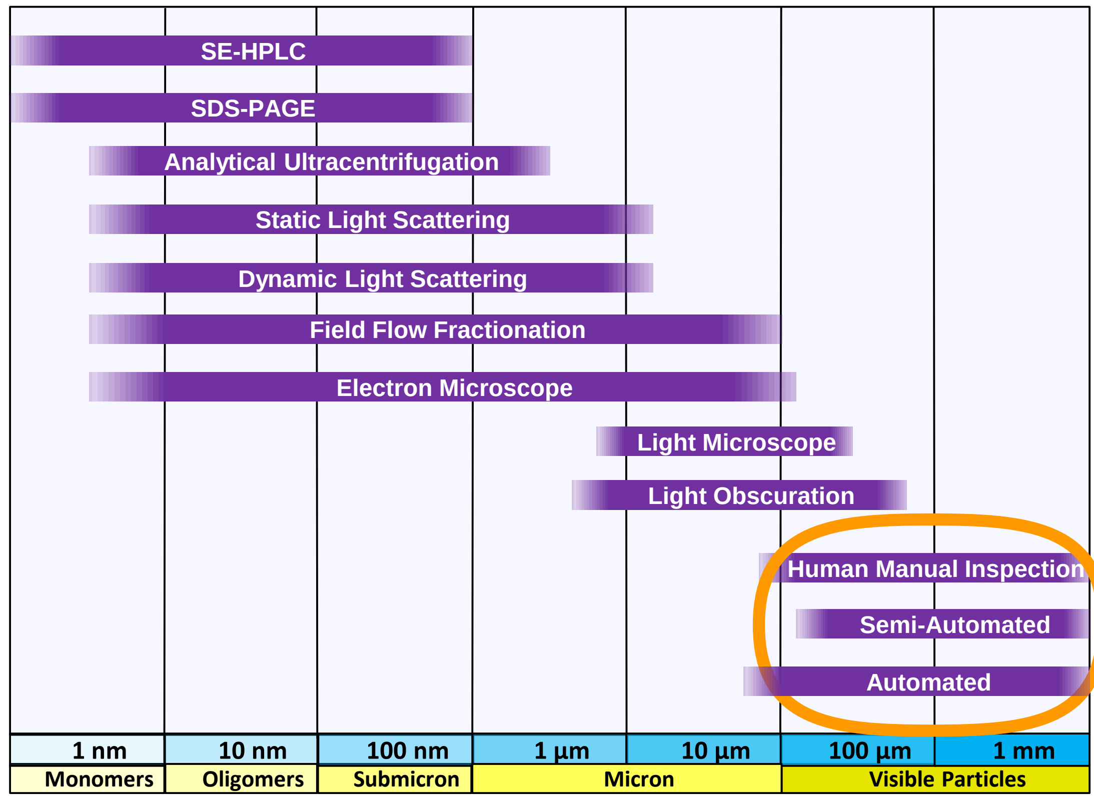
Qualification of the inspection process should be performed with reference to particulates in the ***visible range*** and those particulates that might emanate from the manufacturing or filling process. Every container in which the contents show evidence of visible particulates ***must be rejected***. The inspection for visible particulates may take place during examination for other critical defects such as ***cracked or defective containers or seals*** or when characterizing the appearance of a lyophilized product

Particle Matter

USP ⟨788⟩ Particulate Matter in Injection

Particulate Matter in Injections extraneous **mobile** undissolved particles, other than gas bubbles, unintentionally present in solutions.

Adapted from John G. Shabushnig, Ph.D, Insigth

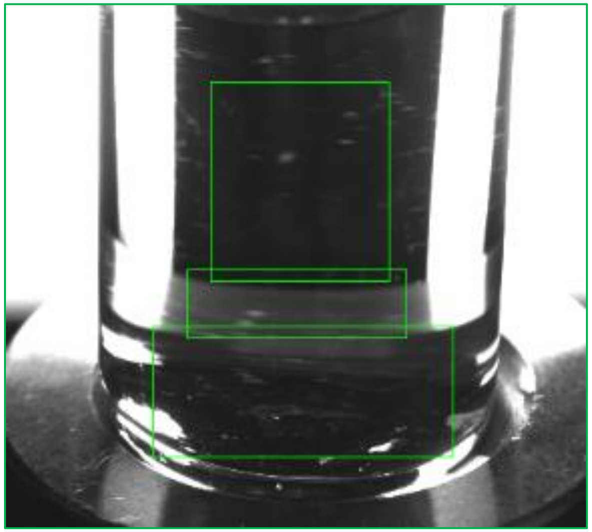


Adapted from Michael Wiggenhorn, Coriolis

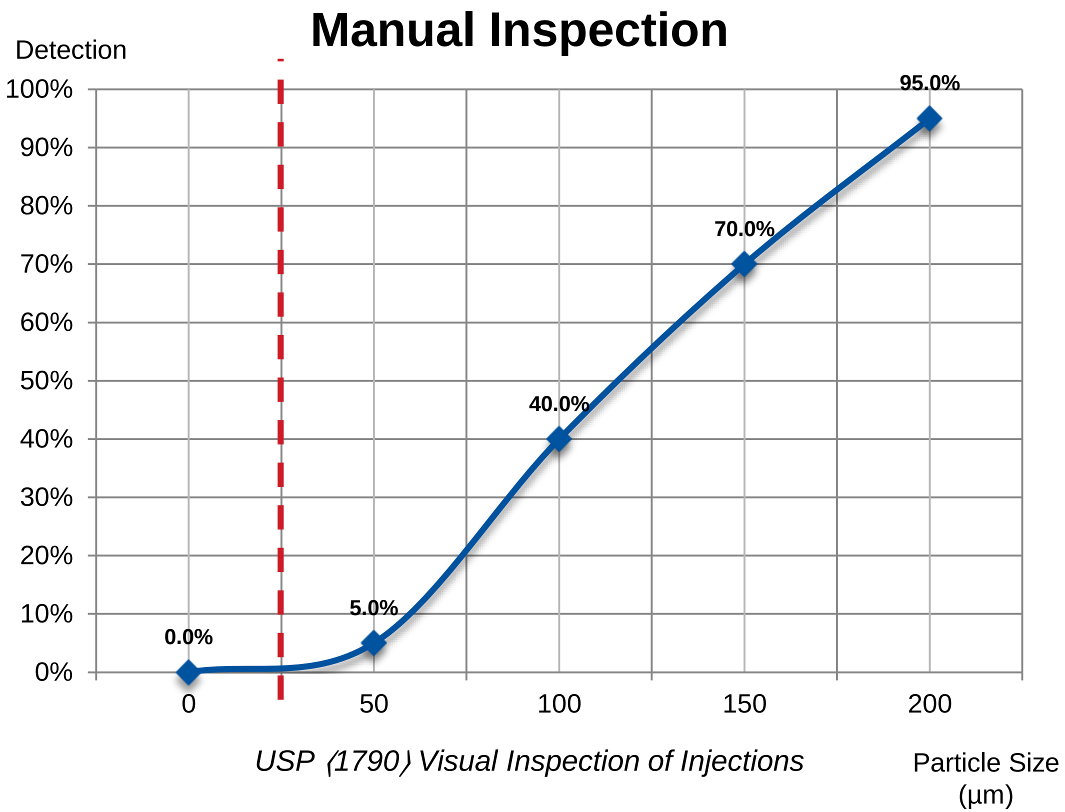
Find additional information on inherent, intrinsic, and extrinsic particulates. Subvisible Particulate Matter in Therapeutic Protein Injections ⟨787⟩

Human Performance

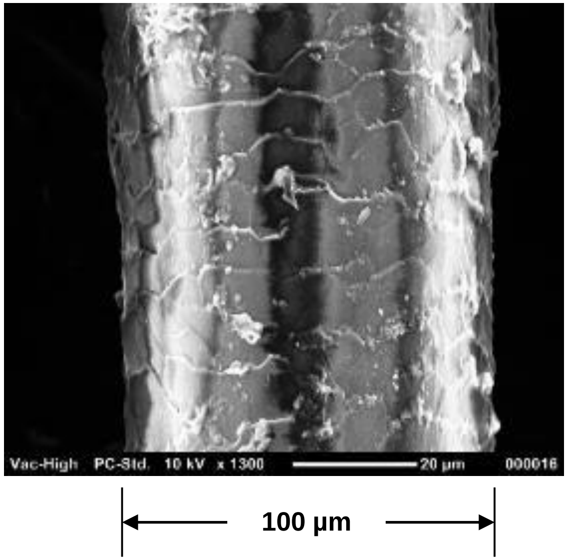
<u>USP ⟨1790⟩ Visual Inspection of Injections</u> The threshold for human vision is generally accepted to be ***50 µm***. Individual receptors in the eye have a resolution of ***11 µm***, but typical resolving power is reported as ***85–100 µm***



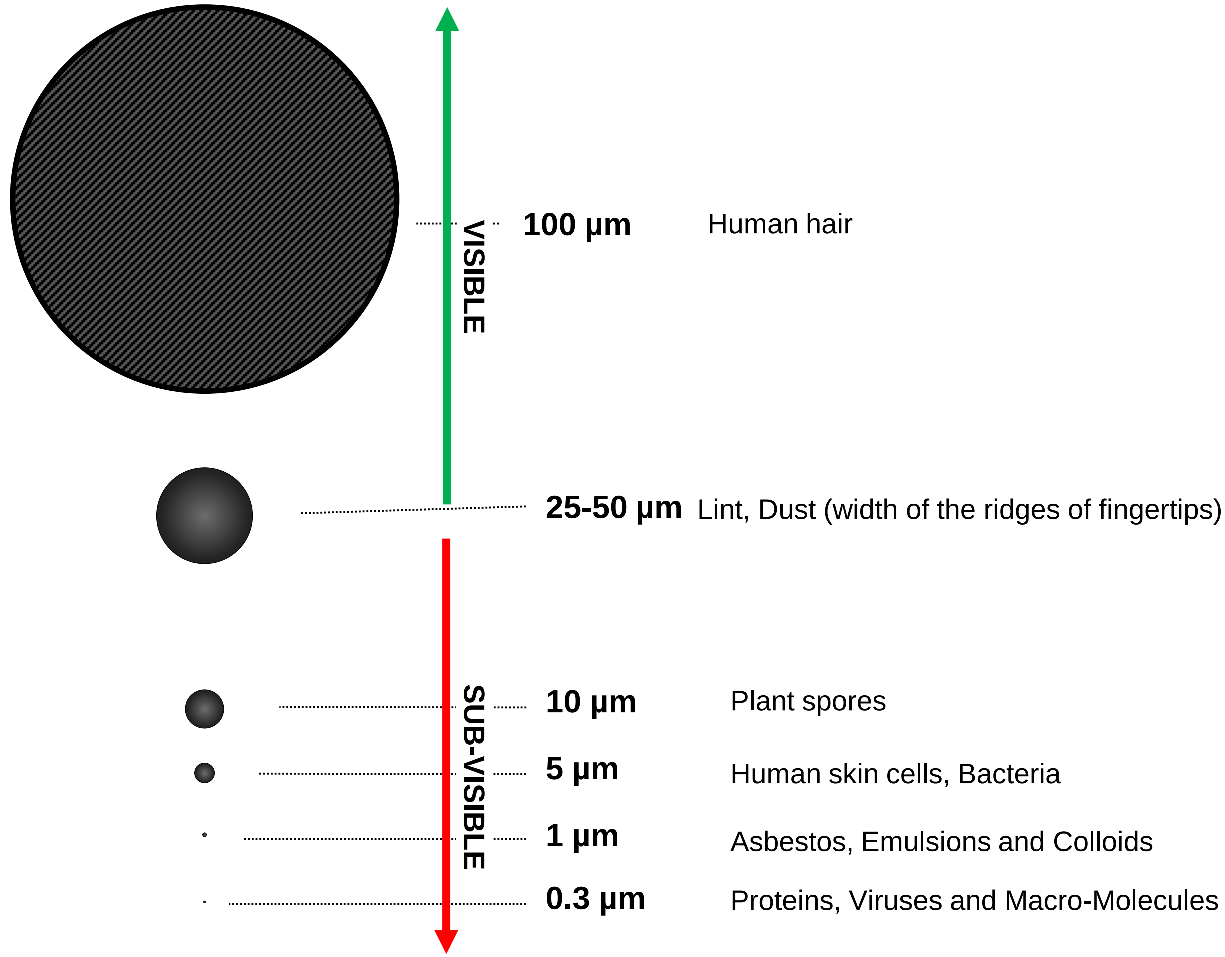
The detection process is **probabilistic**: the likelihood of detection is a cumulative function of visible attributes such as particle ***size, shape, color, density, and reflectivity***.



Particle Matter



Mert Keçeli, Joanne Wen, Sara Saad, Glenn Elert. Midwood Science (7 November 2011).



*The diameter of human hair ranges from **17 to 181 µm**. Ley, Brian (1999). "Width of a Human Hair". The Physics Factbook.*

Machine vs Humans

- **Automated**

- **Better sensitivity** for some type of defects
- More **repeatable** process
- Better **efficiency**, higher **throughput**
- Reduced **ergonomic** injury risk
- Often higher false **reject rate**
- **High** initial **cost** (0.7 MM to 3.0 MM)

- **Human** (Manual or Semi-automated)

- More **flexible**
    - New products and packages
- Quicker **response** to new defect types
- **Cost effective** for small batches slow rates
- Reference **standard** for all compendia
- **Low** initial **cost**

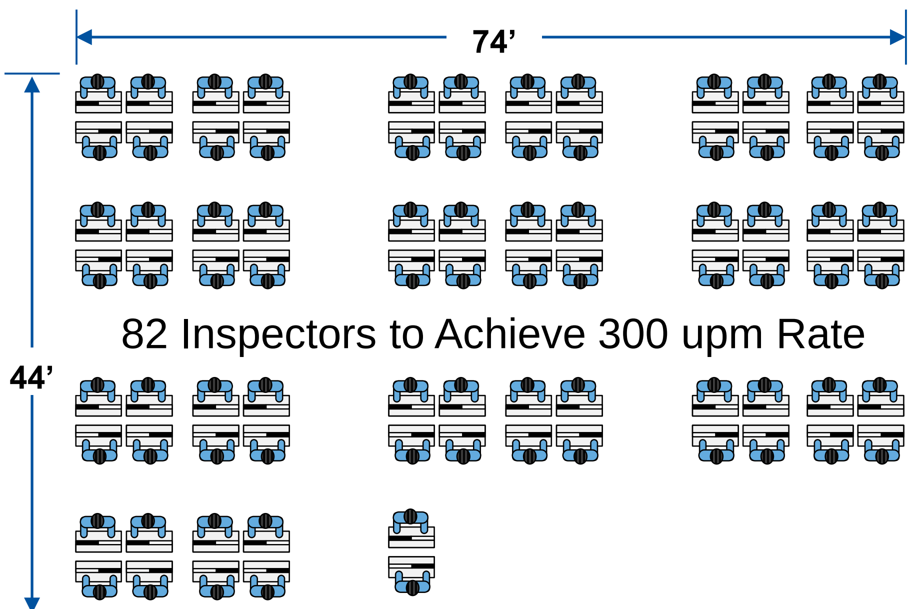
Adapted from John G. Shabushnig, Ph.D, Insigth

Machine vs Humans

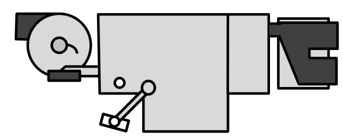
There are workforce and floor space requirements to be considered as a result of the average rate of a manual inspection.

Average Rate: 3.67 upm

Average Rate: 300 upm



3,256 sq. feet

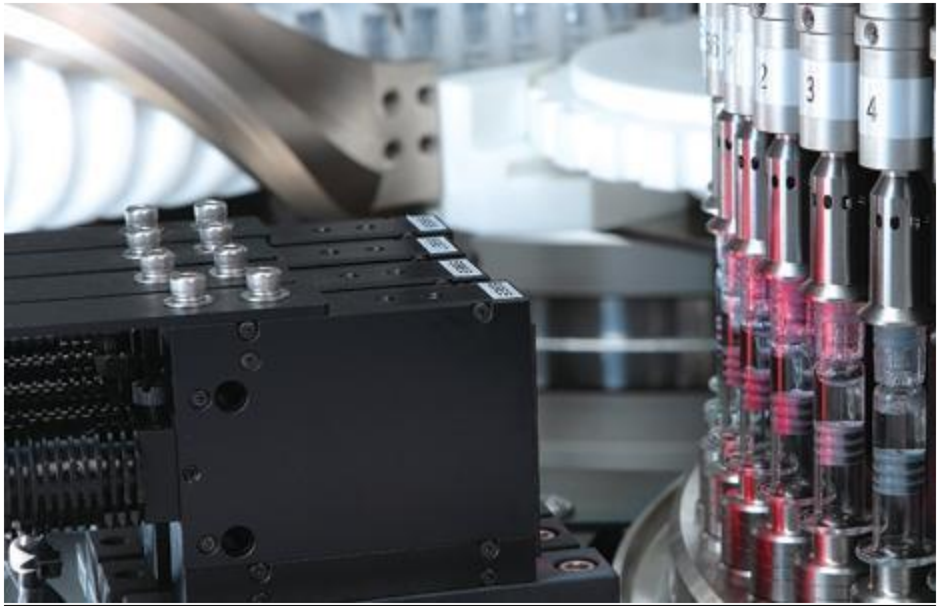


Average Size: 15'x7'

105 sq. feet

Based on 1 Shift volume.

Particle Inspection Methods



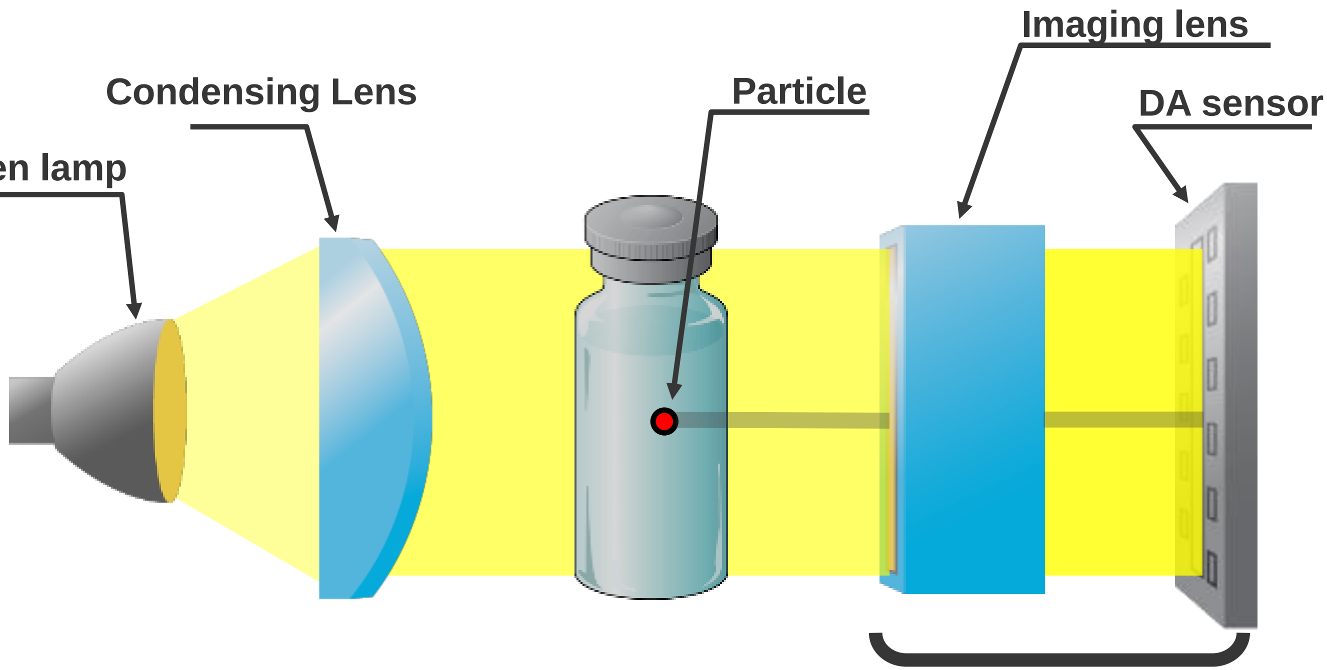
Static Division (SD) Particle Detection

Defect Inspection using Camera (CCD)

PARTICLE INSPECTION METHODS

PRINCIPLES OF THE STATIC DIVISION (SD) DETECTION

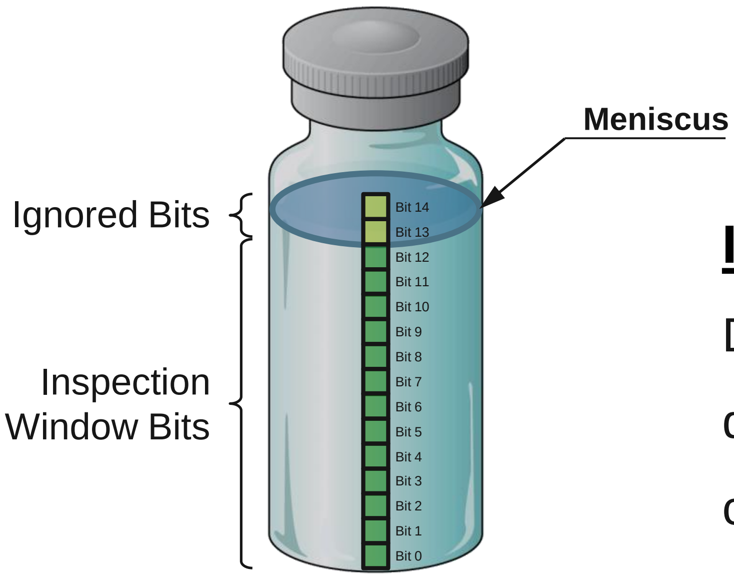
Static Division (SD) Detection Principle



The moving particles create a difference in light intensity while passing the (DA).

The shadow created by particle causes the difference in light intensity reaching to Diode Array (DA) sensor, which is converted to an electric current signal.

Detection System Block Description



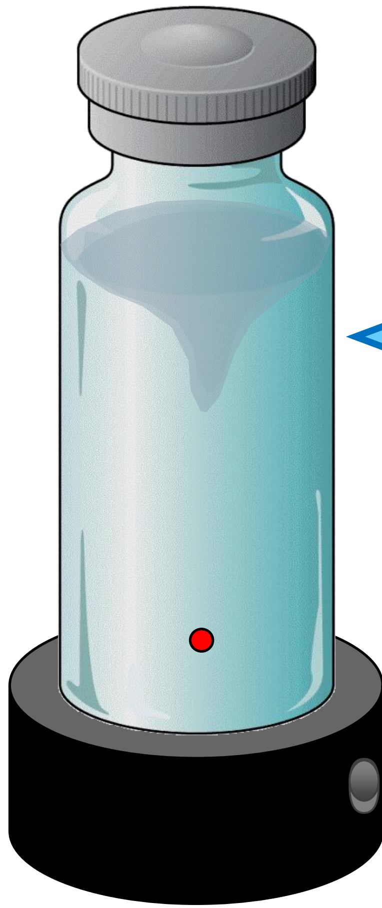
Inspection View Selection

DA sensor is made up an array of small photo diodes that are piled up in vertical direction to cover the required inspection view.

Each photo diode of DA sensor is called "Bit"

Particle Movement

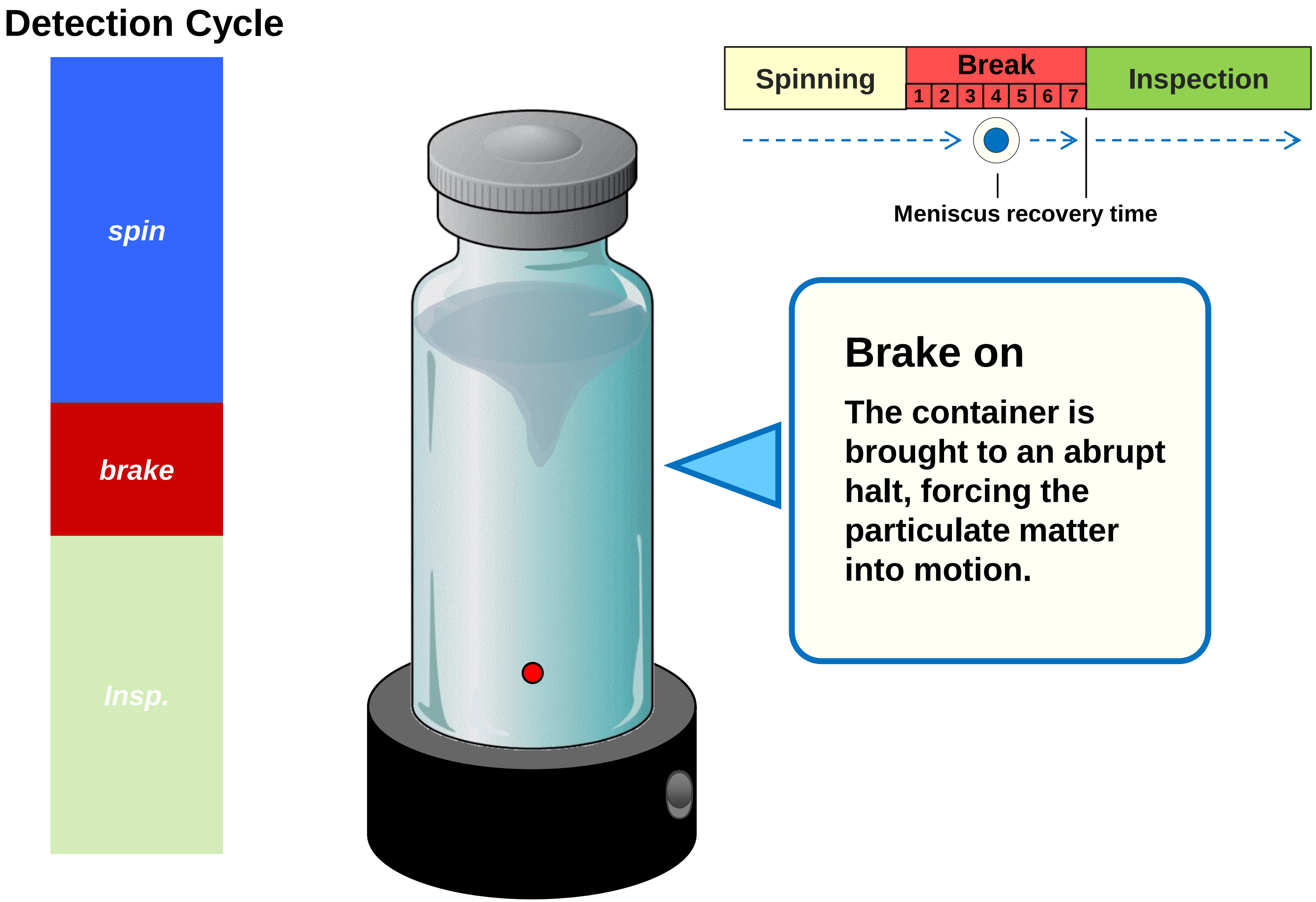
Detection Cycle



Spin Container

The container is spun, which pushes the contents up the wall of the vial, lowering the level of the meniscus of the solution inside.

Particle Movement

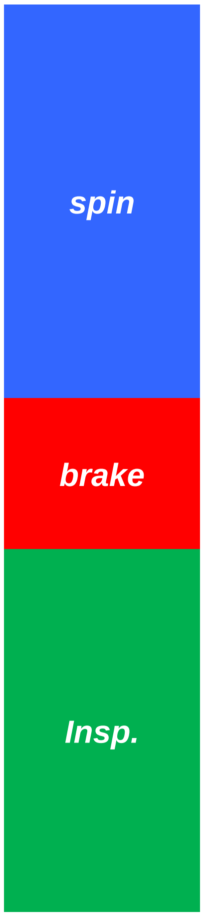


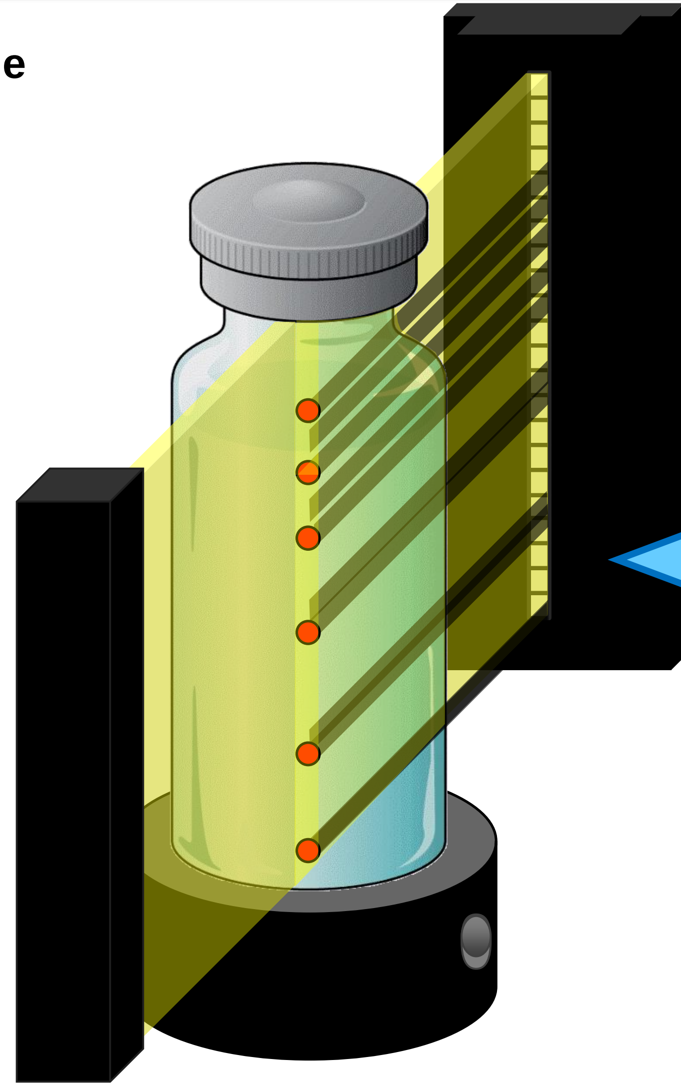
Brake on

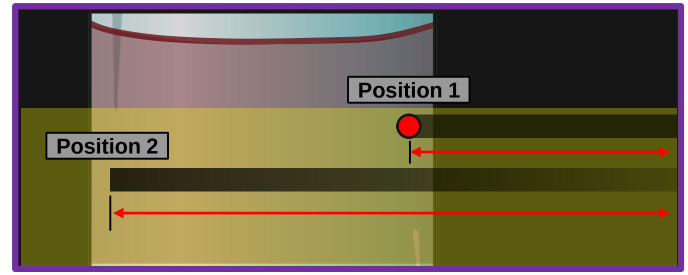
The container is brought to an abrupt halt, forcing the particulate matter into motion.

Particle Movement

Detection Cycle



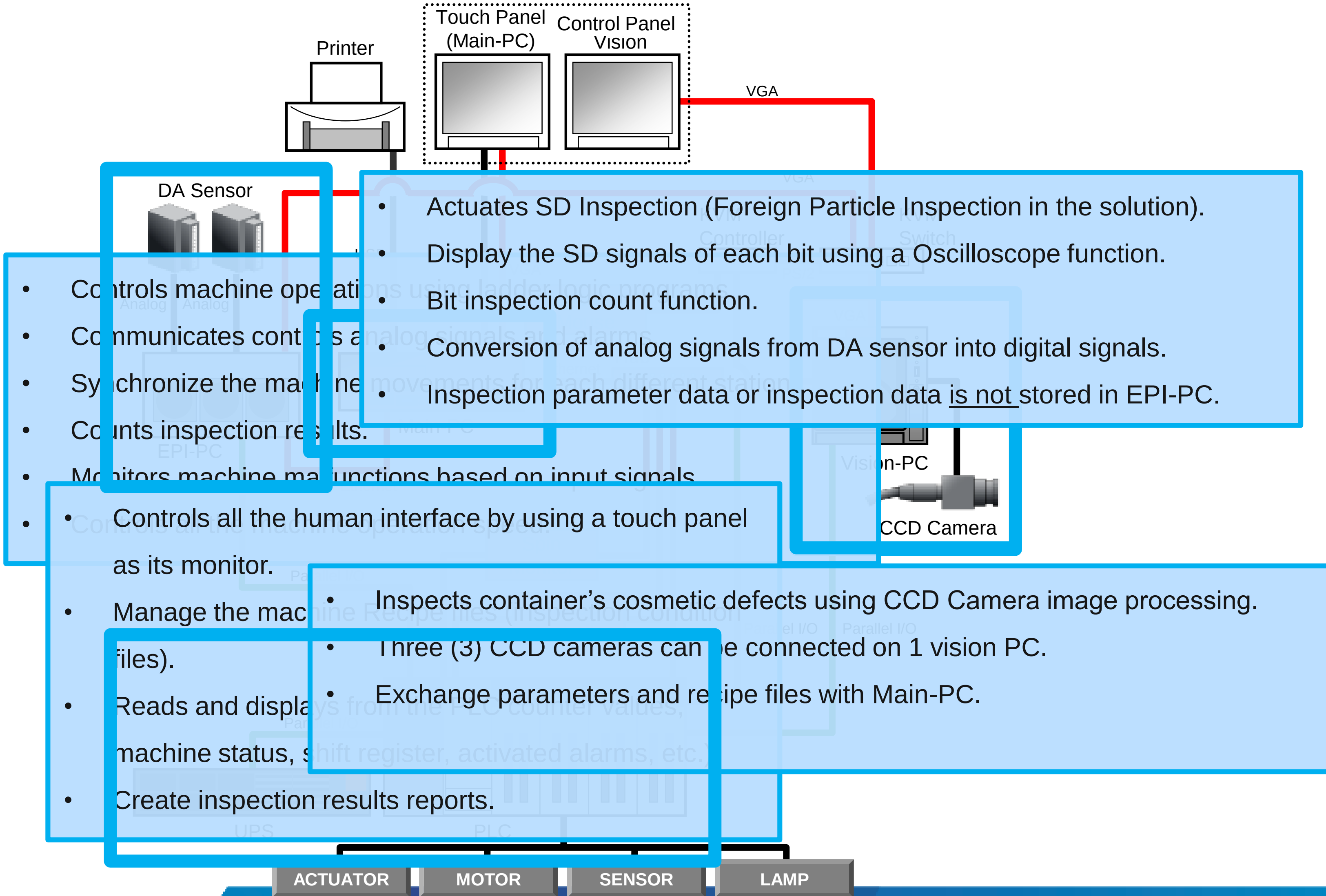




Inspection

The particulate in motion a cast shadow which moves across the DA sensor, detecting fluctuations of the light intensity by the photodiodes

System Block Diagram



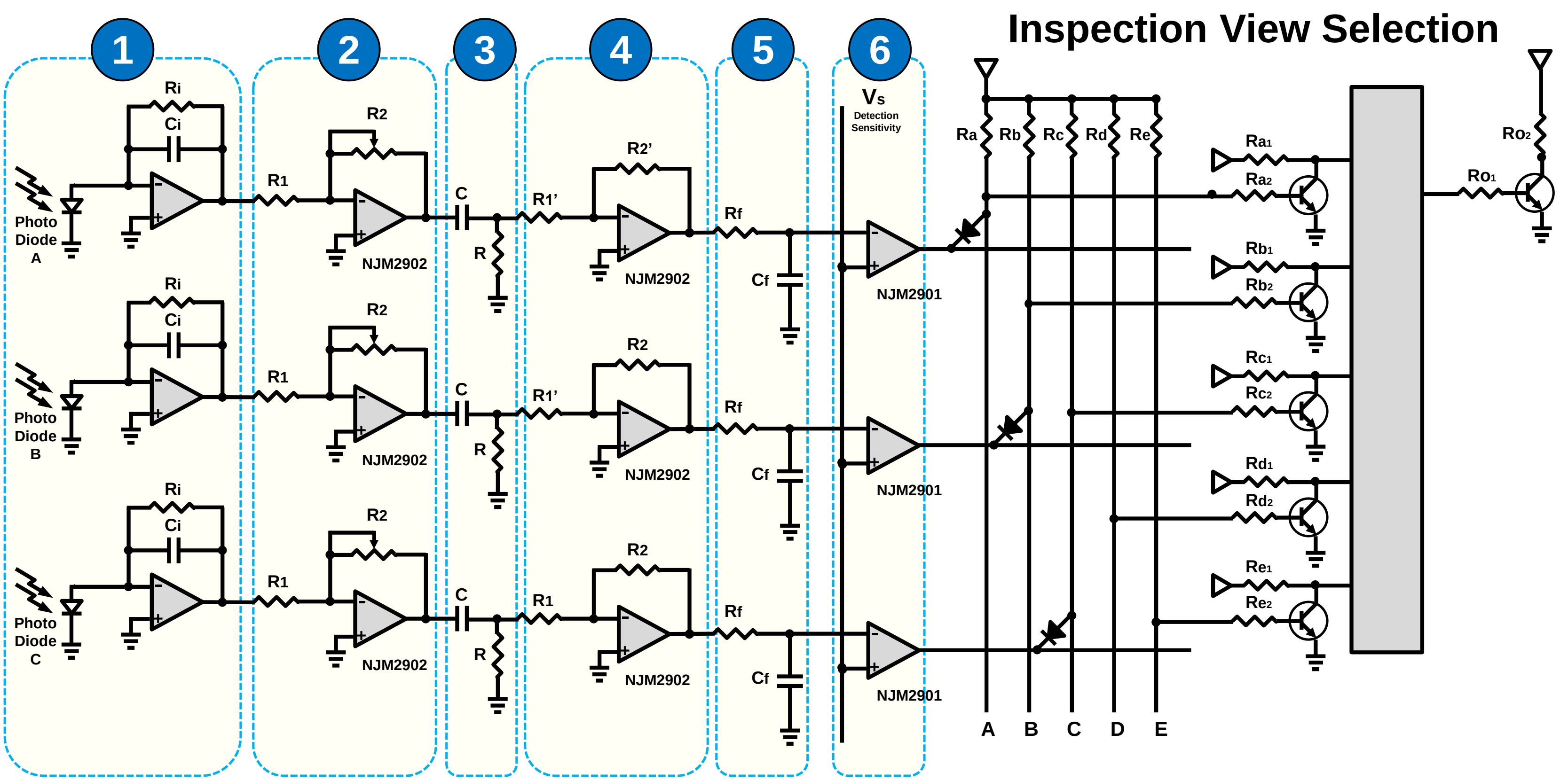
- Actuates SD Inspection (Foreign Particle Inspection in the solution).
- Display the SD signals of each bit using a Oscilloscope function.
- Bit inspection count function.
- Conversion of analog signals from DA sensor into digital signals.
- Inspection parameter data or inspection data <u>is not</u> stored in EPI-PC.

- Controls machine operations using ladder logic programs.
- Communicates controls analog signals and alarms.
- Synchronize the machine movements for each different station.
- Counts inspection results.
- Monitors machine malfunctions based on input signals.
- Controls all the machine operation speed.

- Controls all the human interface by using a touch panel as its monitor.
- Manage the machine Recipe files (inspection condition files).
- Reads and displays from the PLC counter values, machine status, shift register, activated alarms, etc.
- Create inspection results reports.

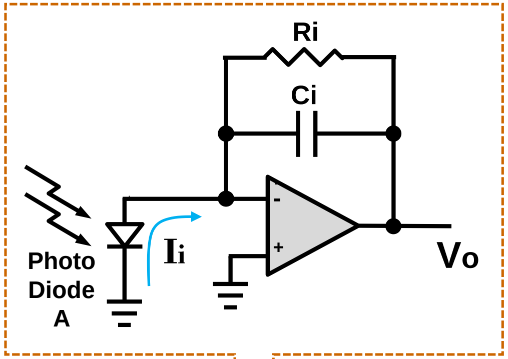
- Inspects container's cosmetic defects using CCD Camera image processing.
- Three (3) CCD cameras can be connected on 1 vision PC.
- Exchange parameters and recipe files with Main-PC.

Detection System Block Description



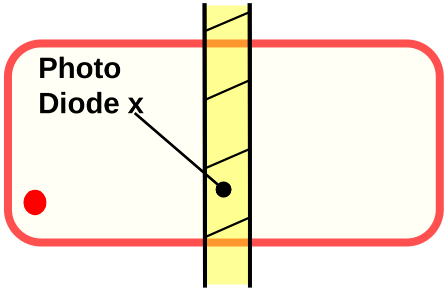
1 SD Head → 2 DC Amplifier → 3 Differential Circuit → 4 AC Amplifier → 5 Low Pass Filter → 6 Comparator

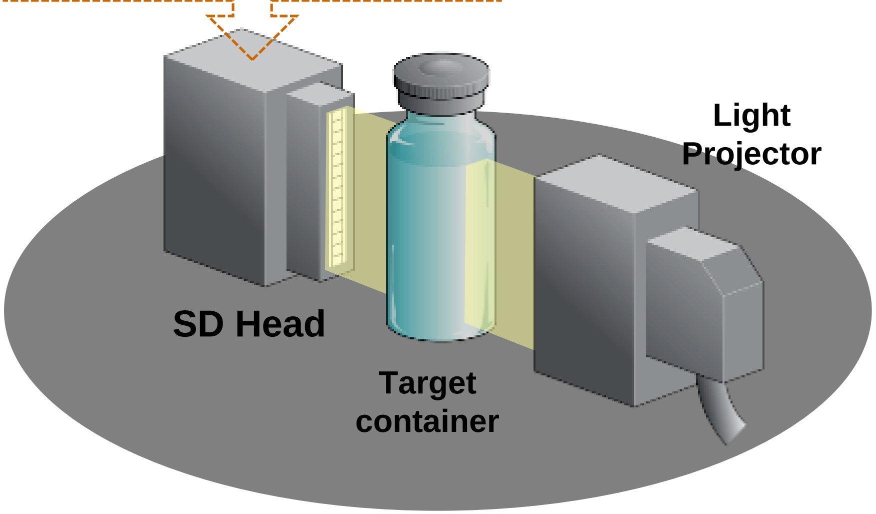
Detection System Block Description



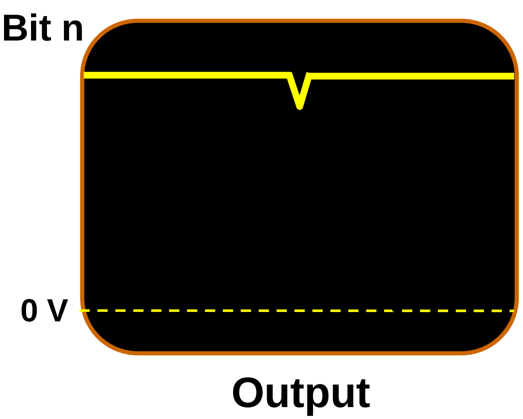
1) SD Head /Current-Voltage Conversion

Converts the light intensity into an electrical current signal using photo diodes, the operational amplifier converts then the current into a voltage output





With the optical path unblocked Vo = -1.5V, with a Lamp max voltage of 16V

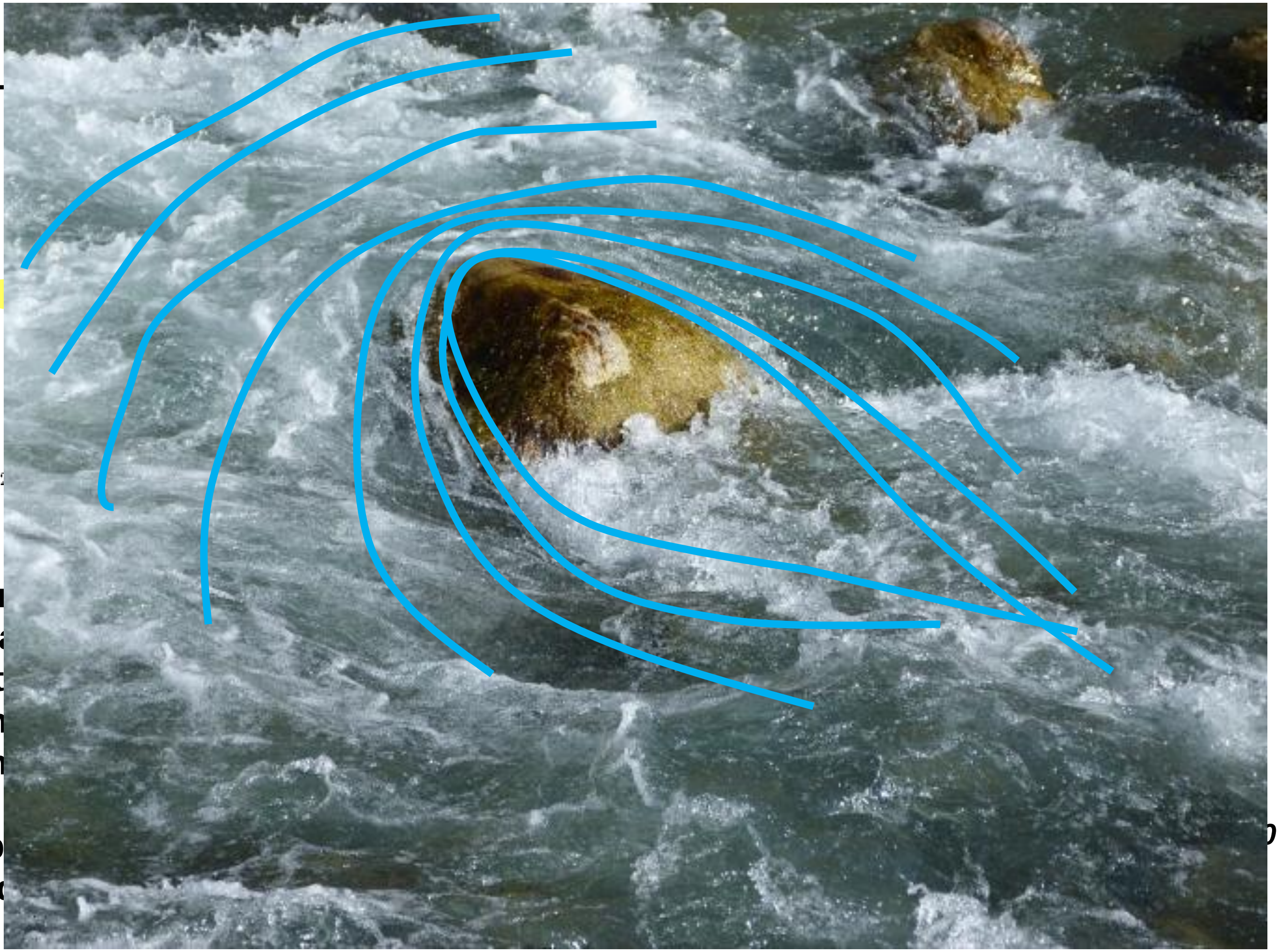


1 SD Head → 2 DC Amplifier → 3 Differential Circuit → 4 AC Amplifier → 5 Low Pass Filter → 6 Comparator

Particle Size Response

Particle

Halogen Light Source



$U(P_1) \propto \int_0$

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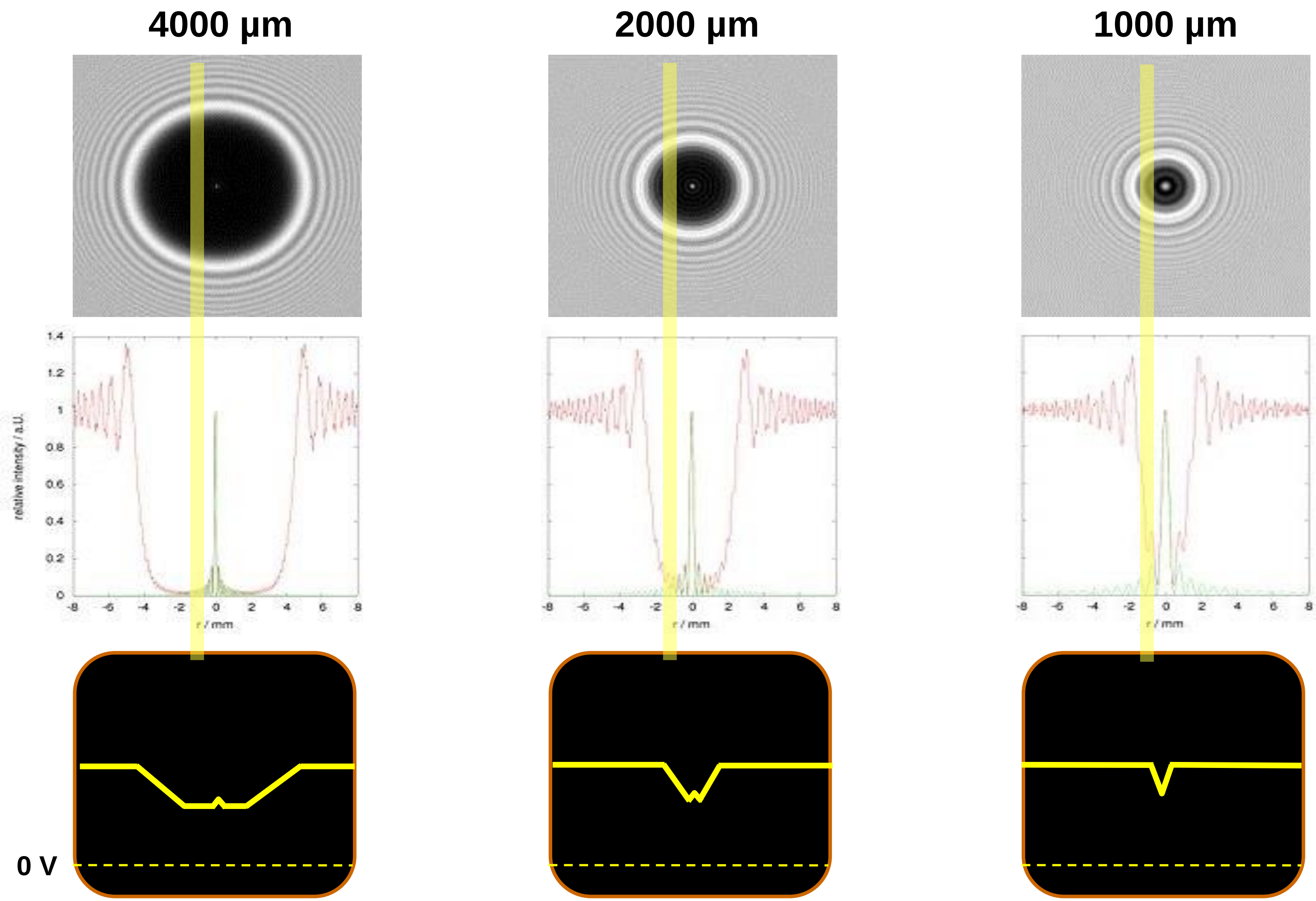
0 µm)

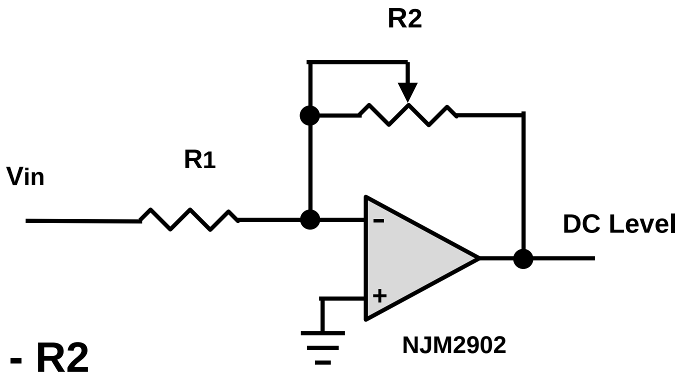
Particle Size Response



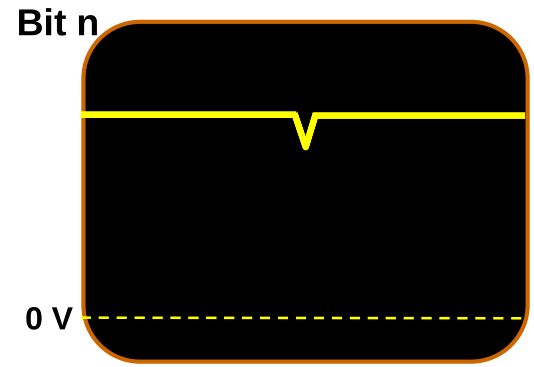
Detection System Block Description

2) DC Amplifier

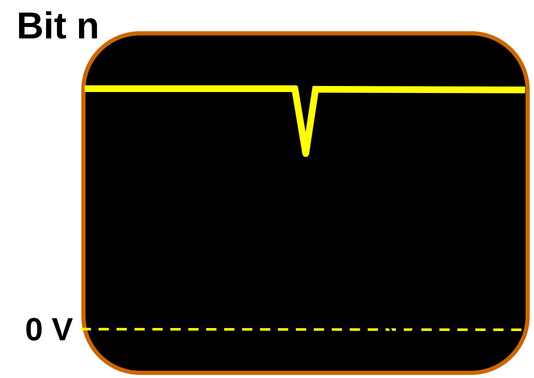
Currents converted by the current-voltage conversion circuit into voltage. Since the voltages from SD head my vary with bits, they must be adjusted to a fixed voltage value. The DC amplifier output is referred as the DC level.



$$\text{Gain} = \frac{-R2}{R1}$$



Input



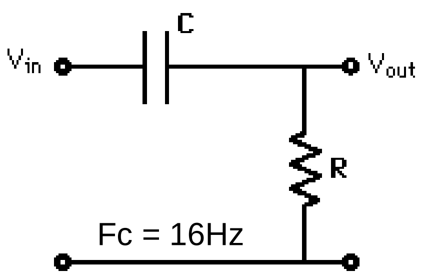
Output

1 SD Head → 2 DC Amplifier → 3 Differential Circuit → 4 AC Amplifier → 5 Low Pass Filter → 6 Comparator

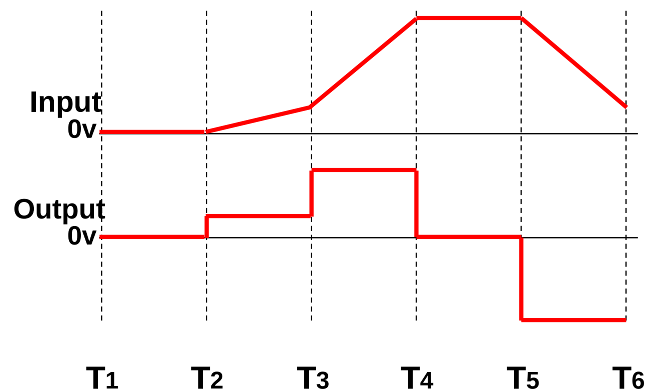
Detection System Block Description

3) Differential Circuit / High Pass Filter

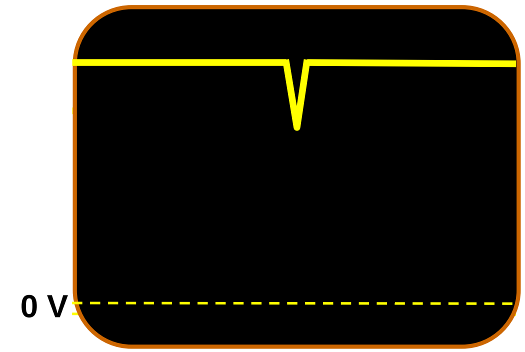
The reactance of the capacitor decreases with the increasing frequency. The output voltage is directly proportional to the derivative of the input voltage



$$X_C = \frac{1}{\omega C} = \frac{1}{2\pi f C}$$

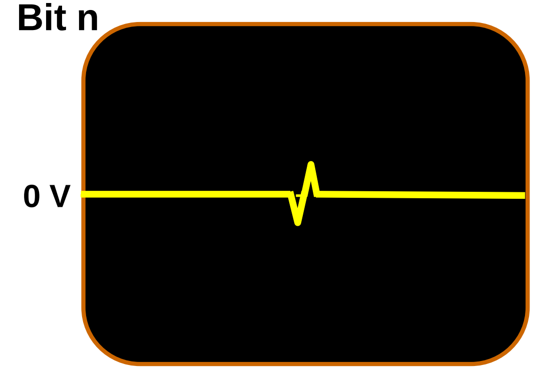


Circuit Response to Voltage changes

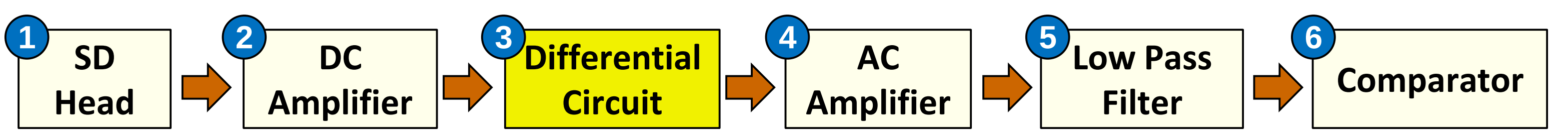


Input

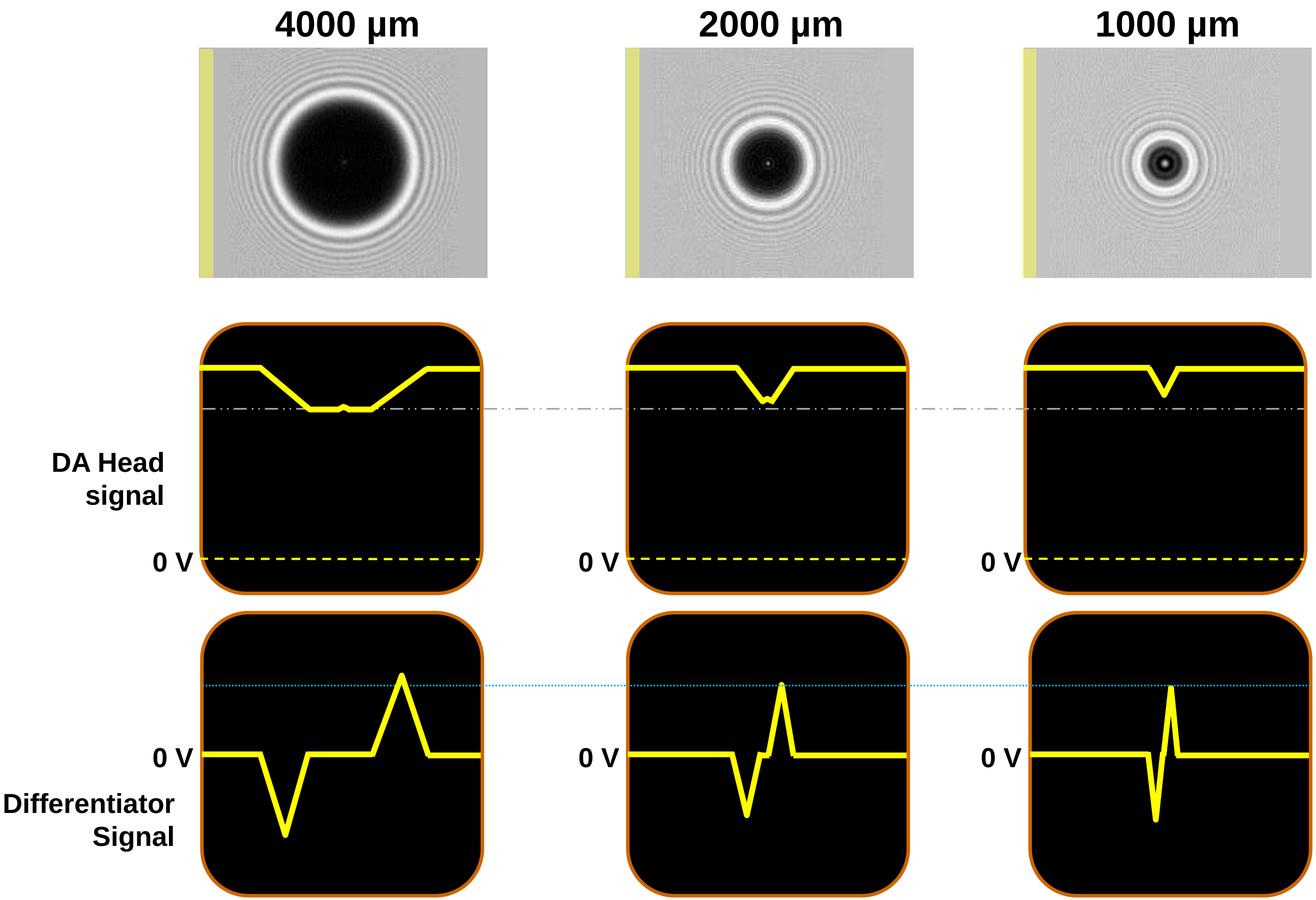
Bit n



Output



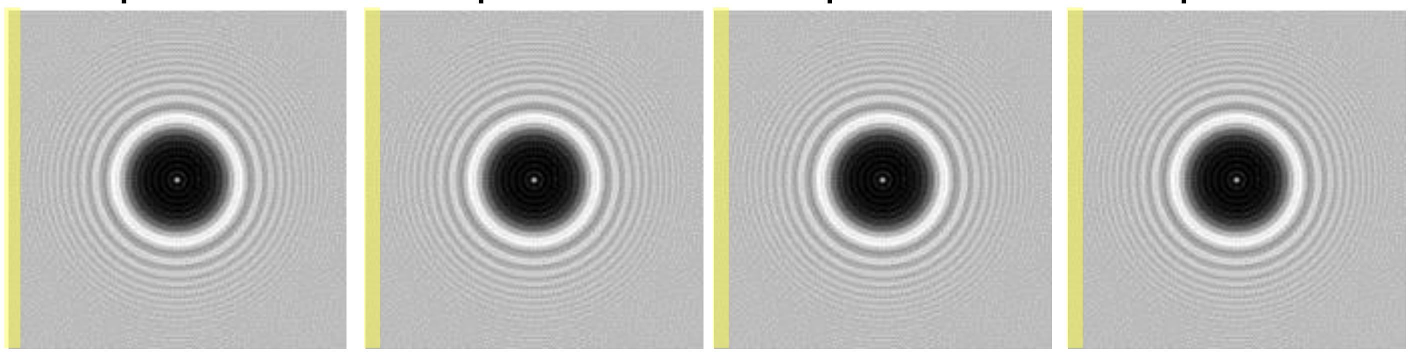
Particle Derivative Response: *Size*



Particle Derivative Response: *Speed*

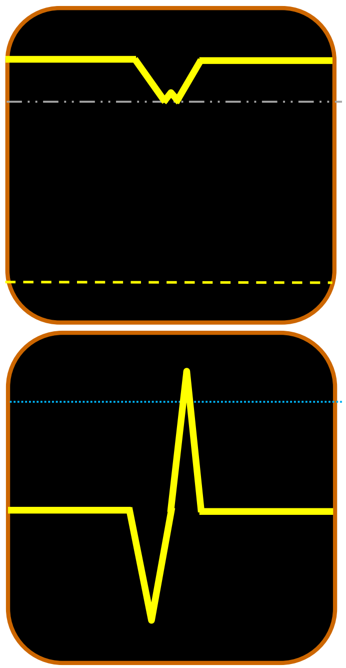
Speed 4X | Speed 3X | Speed 2X | Speed 1X

2000 µm



DA Head signal

Differentiator Signal

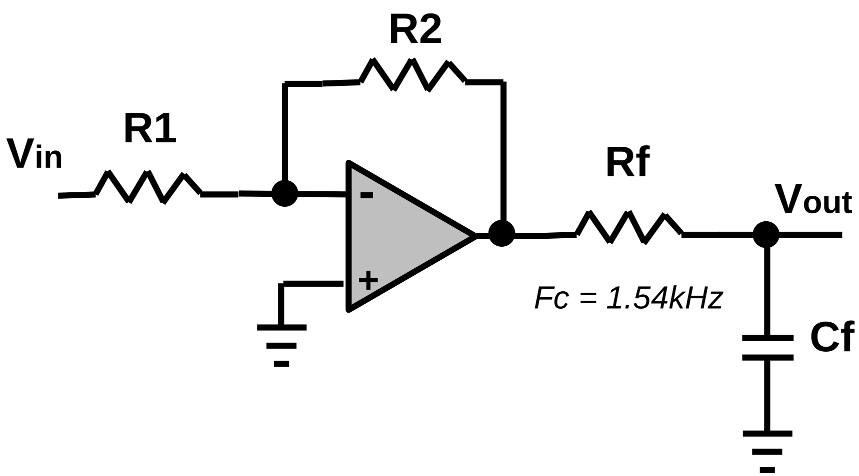


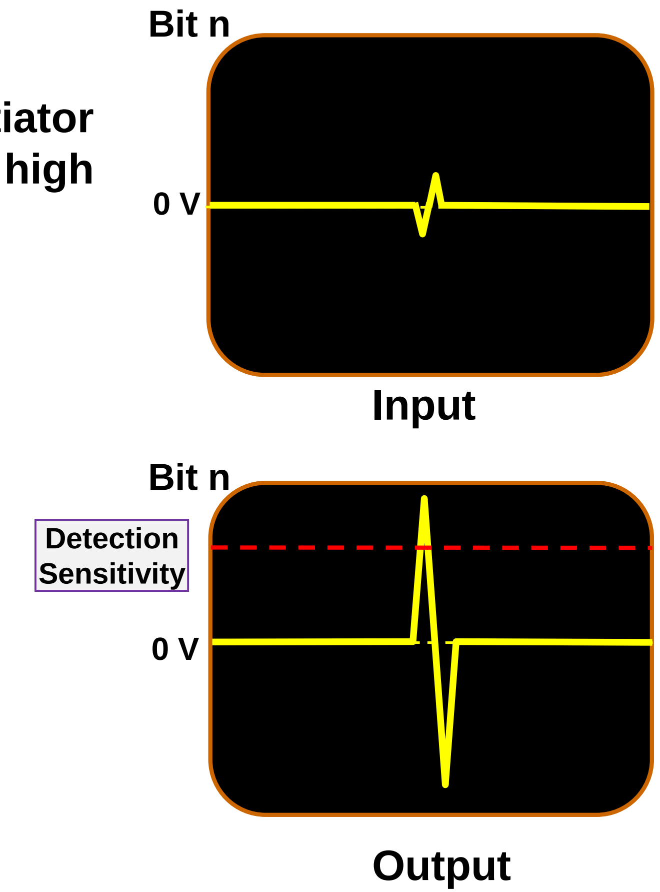
Note: This example simulates the response to different viscous solutions

Detection System Block Description

<u>4,5) AC Amplifier / Low Pass Filter</u>

Amplifies and inverts the output of the differentiator circuit with a known gain of –(R2/R1), and the high frequencies elements are eliminated.



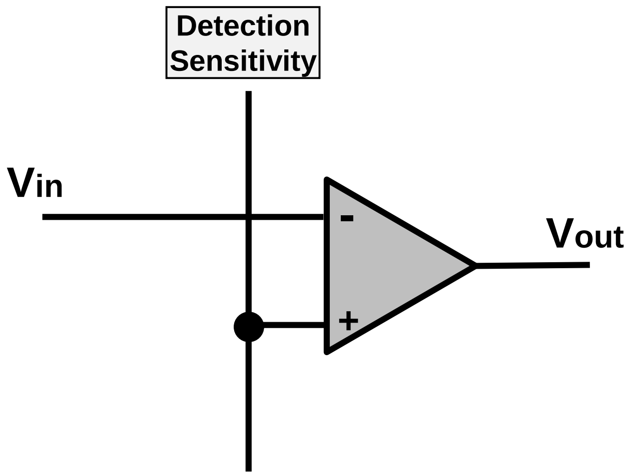


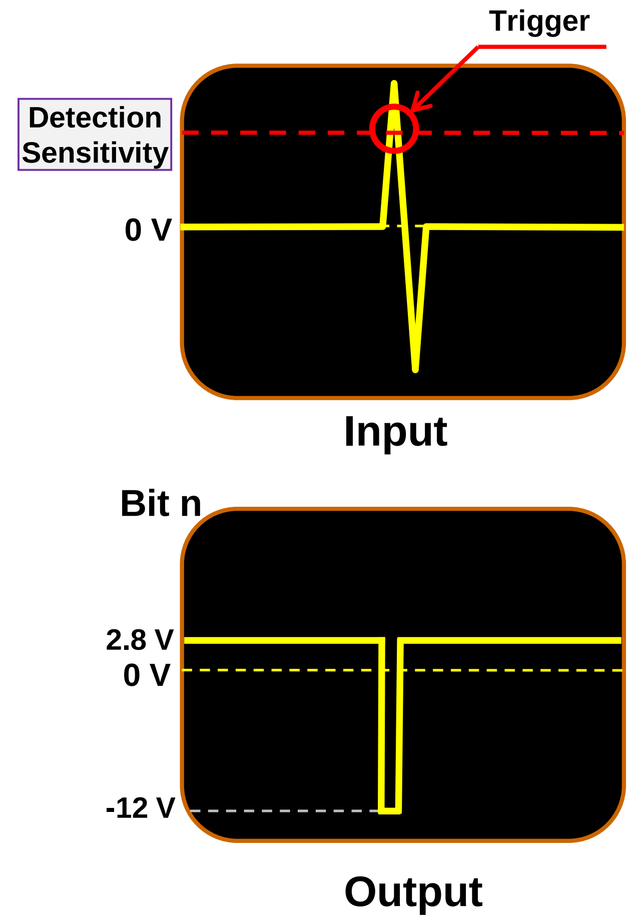
1 SD Head → 2 DC Amplifier → 3 Differential Circuit → 4 AC Amplifier → 5 Low Pass Filter → 6 Comparator

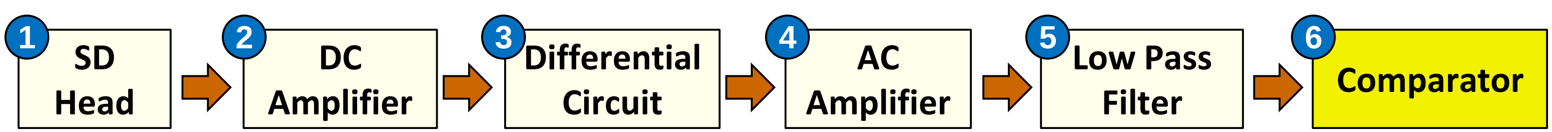
Detection System Block Description

4) Comparator

Any signals (Vin) that exceed the reference voltage (Detection Sensitivity) triggers an output.



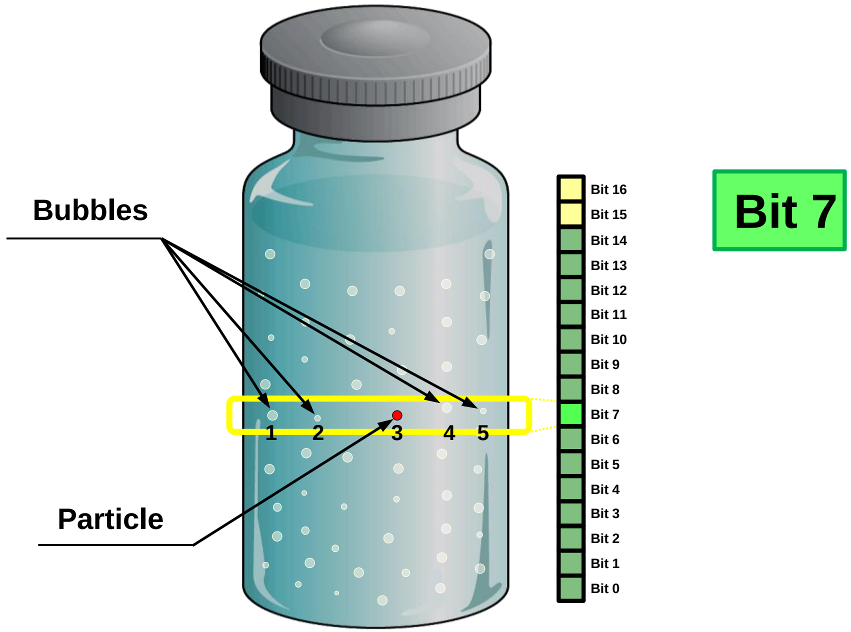


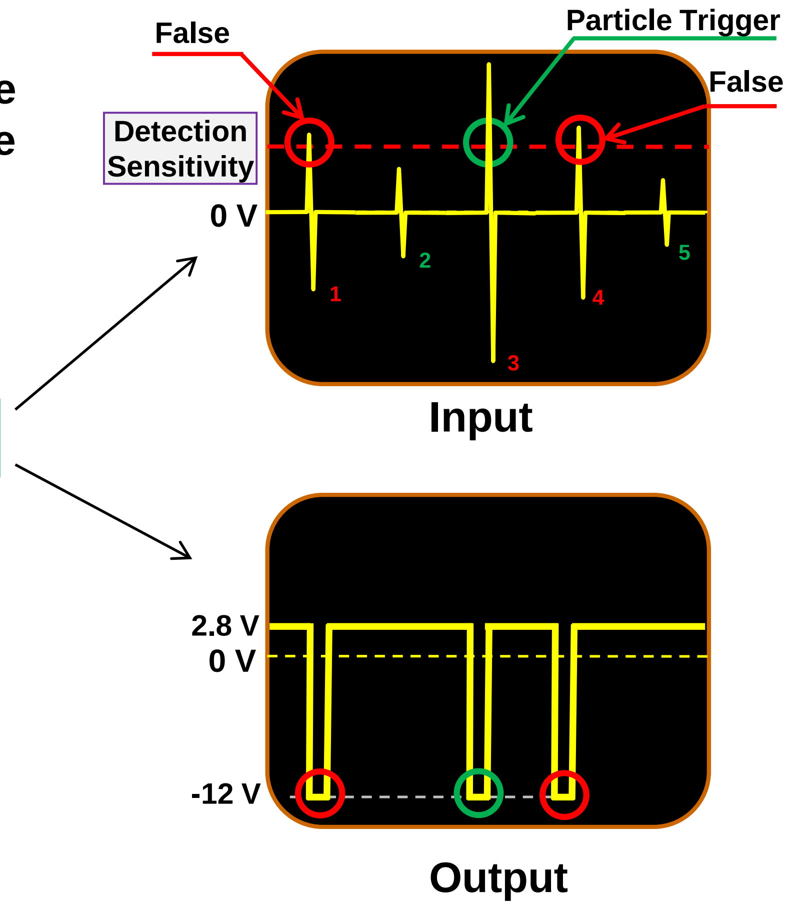


Detection System Block Description

Sensitivity Impact

Any presence of bubbles moving inside the solution can cast a shadow to the SD diode sensor, which could trigger a false reject.





1. SD Head → 2. DC Amplifier → 3. Differential Circuit → 4. AC Amplifier → 5. Low Pass Filter → 6. Comparator

Detection System Block Description

Sensitivity Impact

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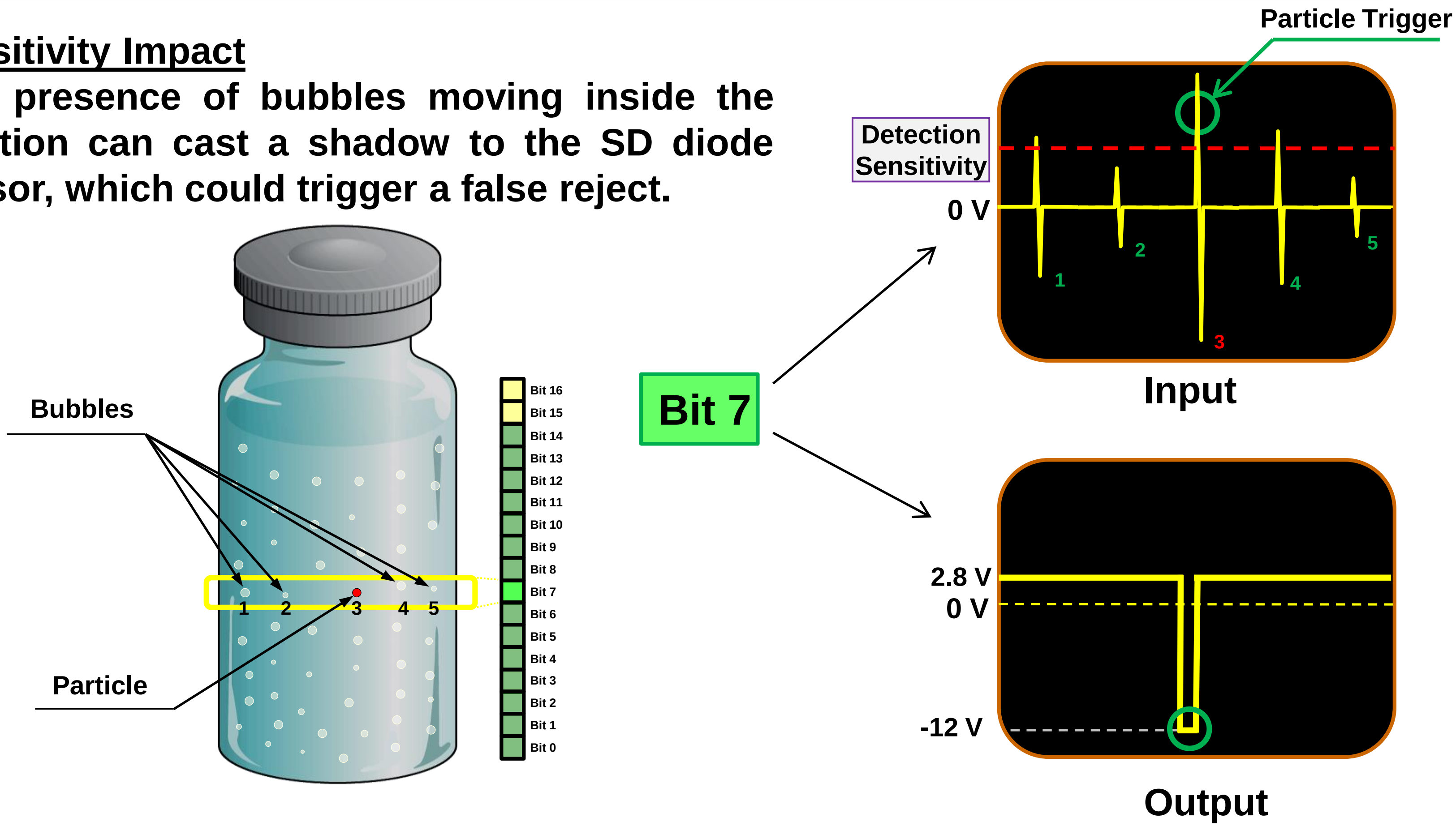
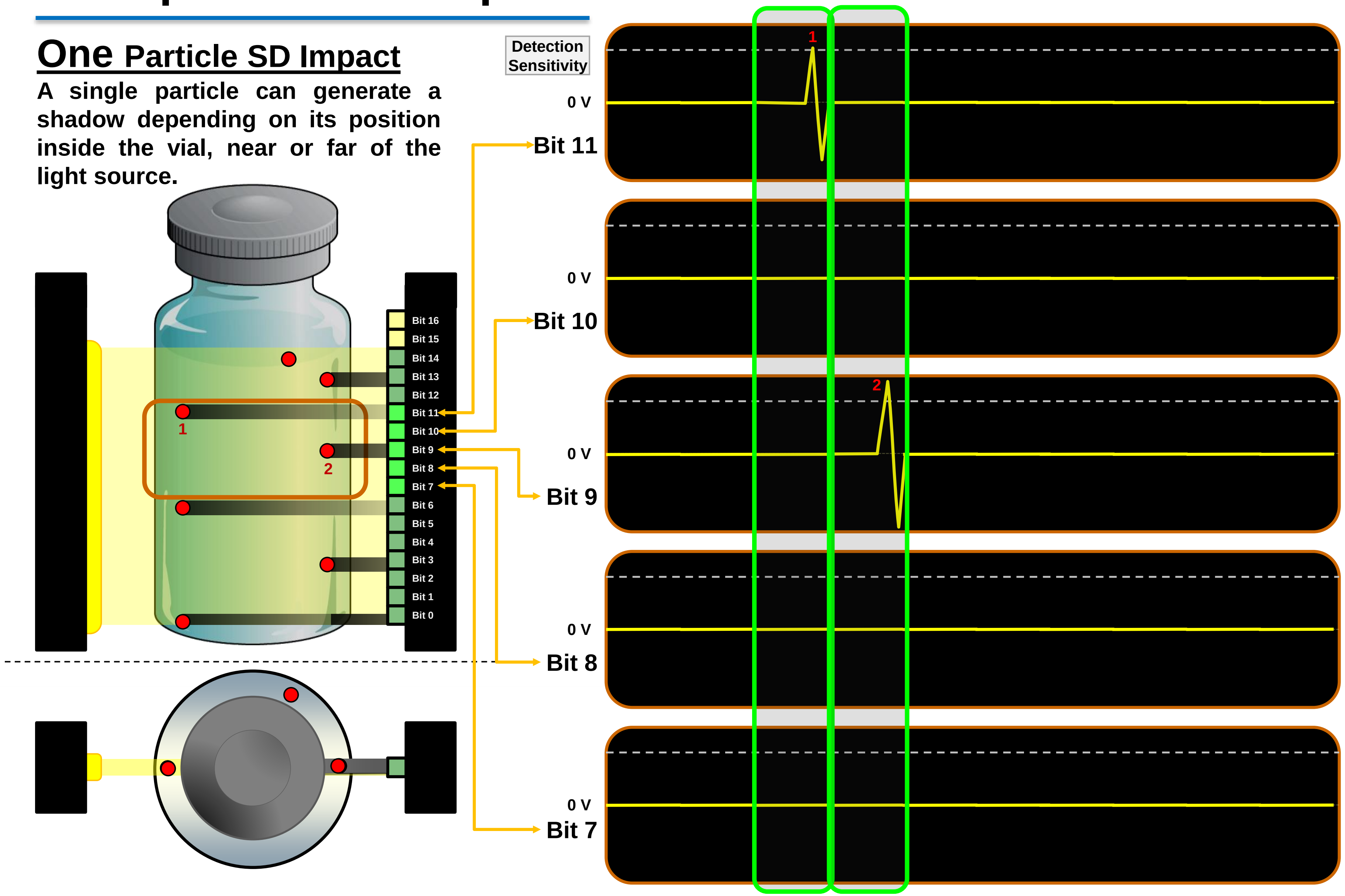


Multiple Particle Impact

One Particle SD Impact

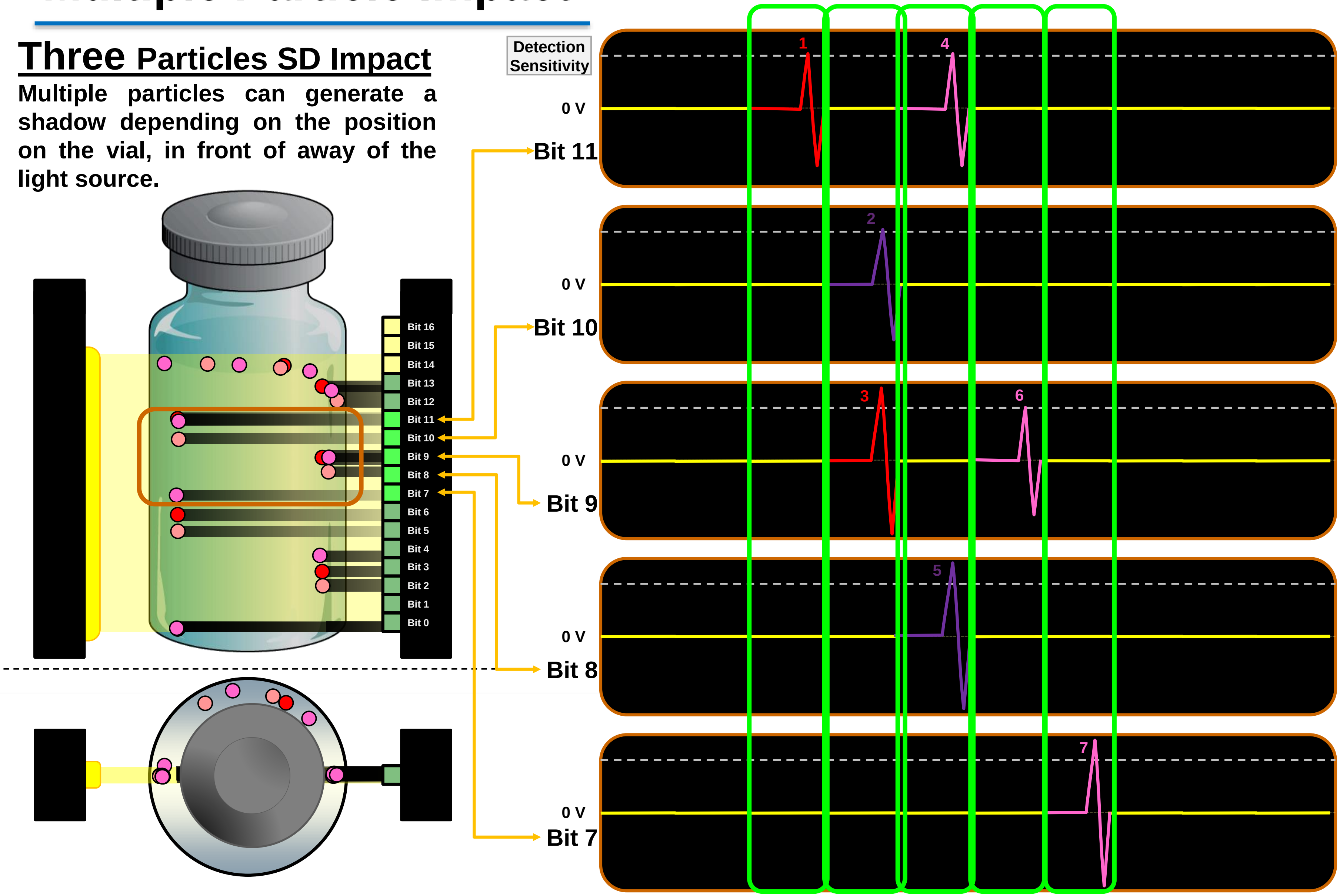
A single particle can generate a shadow depending on its position inside the vial, near or far of the light source.



Multiple Particle Impact

Three Particles SD Impact

Multiple particles can generate a shadow depending on the position on the vial, in front of away of the light source.



Multiple Particle Impact

Multi Particle Statistical Impact

The value of the detection Confidence level will be based on the conditions that we can’t control (value of uncertainty) which will be determined by the probability of the not detection (1- reliability of detection) and this value will be **exponentially increased depending on the amount of particles** included in the vial.

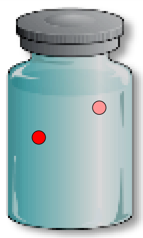
Confidence: 45%

Particles: 1

Y = 1 – (1 – 0.450)^1

Y = 1 – (0.550)^1

Y = 1 – 0.550 = 0.450 = 45.0%



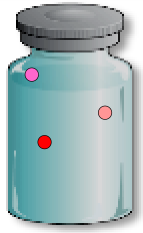
Confidence: 45%

Particles: 2

Y = 1 – (1 – 0.450)^2

Y = 1 – (0.550)^2

Y = 1 – 0.303 = 0.698 = 69.8%



Confidence: 45%

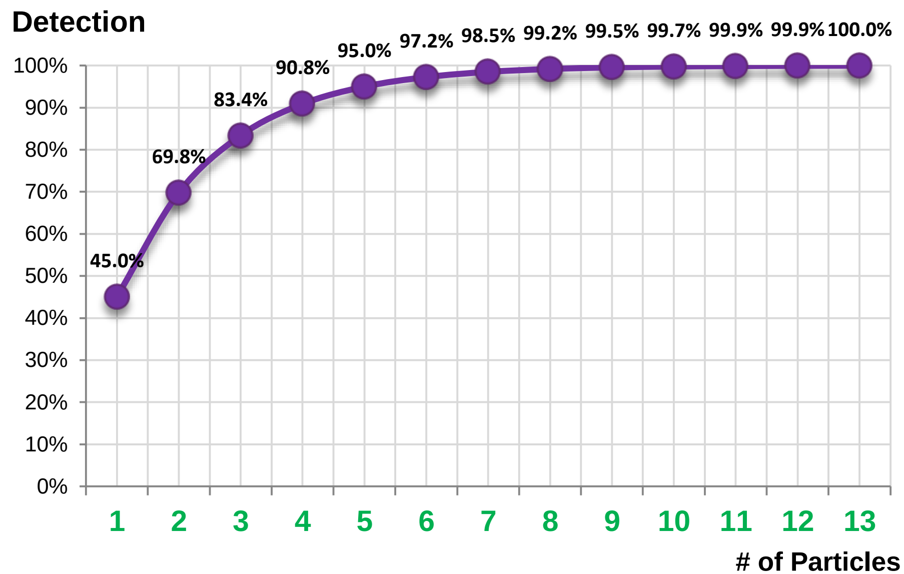
Particles: 3

Y = 1 – (1 – 0.450)^3

Y = 1 – (0.550)^3

Y = 1 – 0.166 = 0.834 = 83.4%

$$Y = 1 - (1 - \text{confidence})^n$$



Particle Detection Product Properties Impact

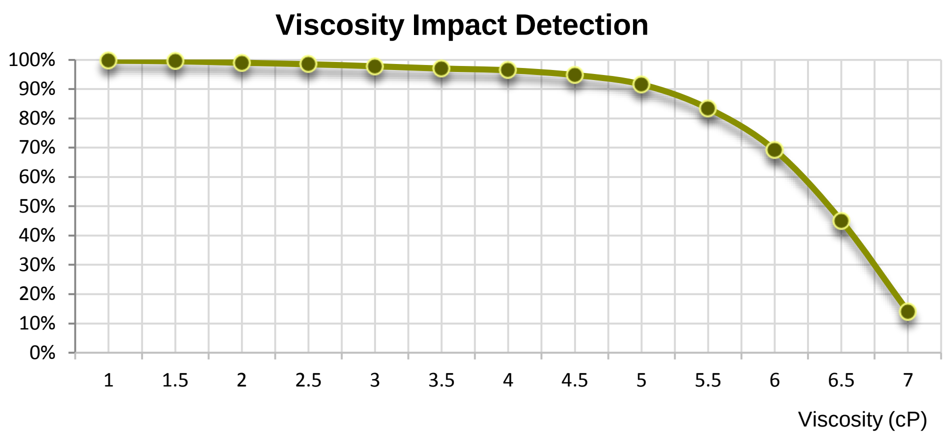
The particle detection its based in the detection of the **particle movement** during a **time lapse**. There are known product properties that directly affect the duration of **particle suspension**, and in consequence the detection performance:

- Viscosity
- Density
- Surface Tension

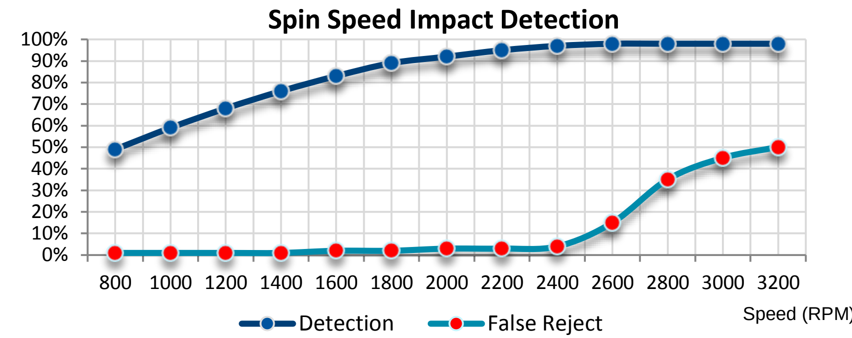
These properties also influence the probabilities of false rejections due to the generation of **bubbles**.

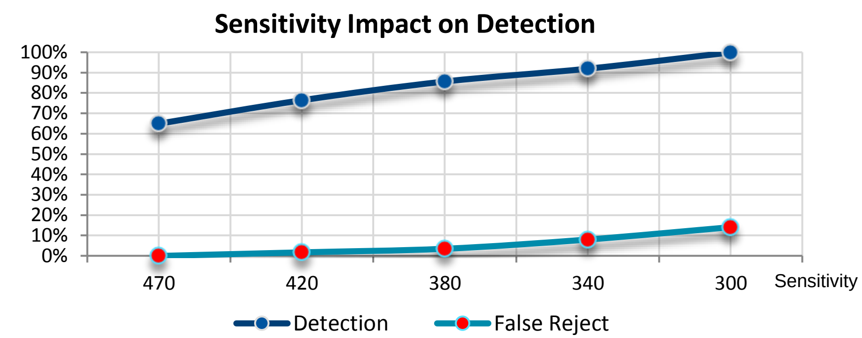
Any proper **recipe** development or **validation** process shall identify as **subgroups** any products with similar properties, and **bracket** those groups.

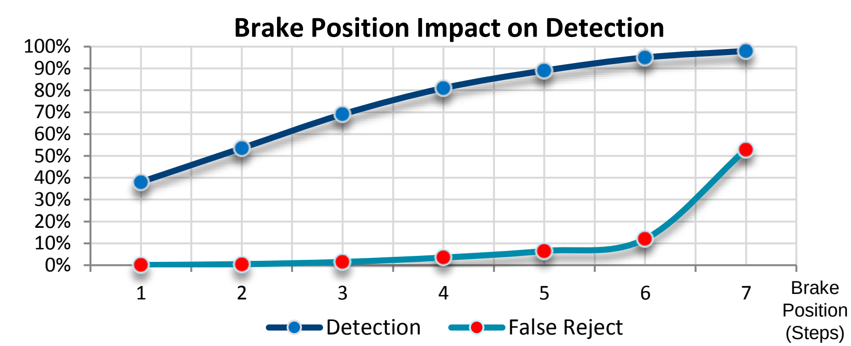
Particle Detection Parameters Impact



Parameter	Description
Spin	Number of complete rotations, revolutions, cycles, or turns per time unit (Minute), it can be adjusted for different viscous solutions. ***Range: (500 – 4,000 RPM)***
Sensitivity	Preset detection level against which the detection system compares the amount of light received. If the amount of light is lower than the preset level (sensitivity) the container will be rejected. ***Range: (0 – 1,000)***
Brake Position	Determine at what point of the cycle the container rotation will be halt, before getting in front of the SD sensor. This parameter will tuned in combination with the Spin value. ***Range: (1 – 7 steps)***
Light Intensity	Determine the percentage of electrical power applied to the halogen lamp, which represent the same percentage of the lamp full intensity. ***Range: (0 – 100%)***
Inspection View	Height of the inspection window. This helps to adjust the inspection window for the different container sizes and fill volume. ***Range: (1 – 81 Bits)***



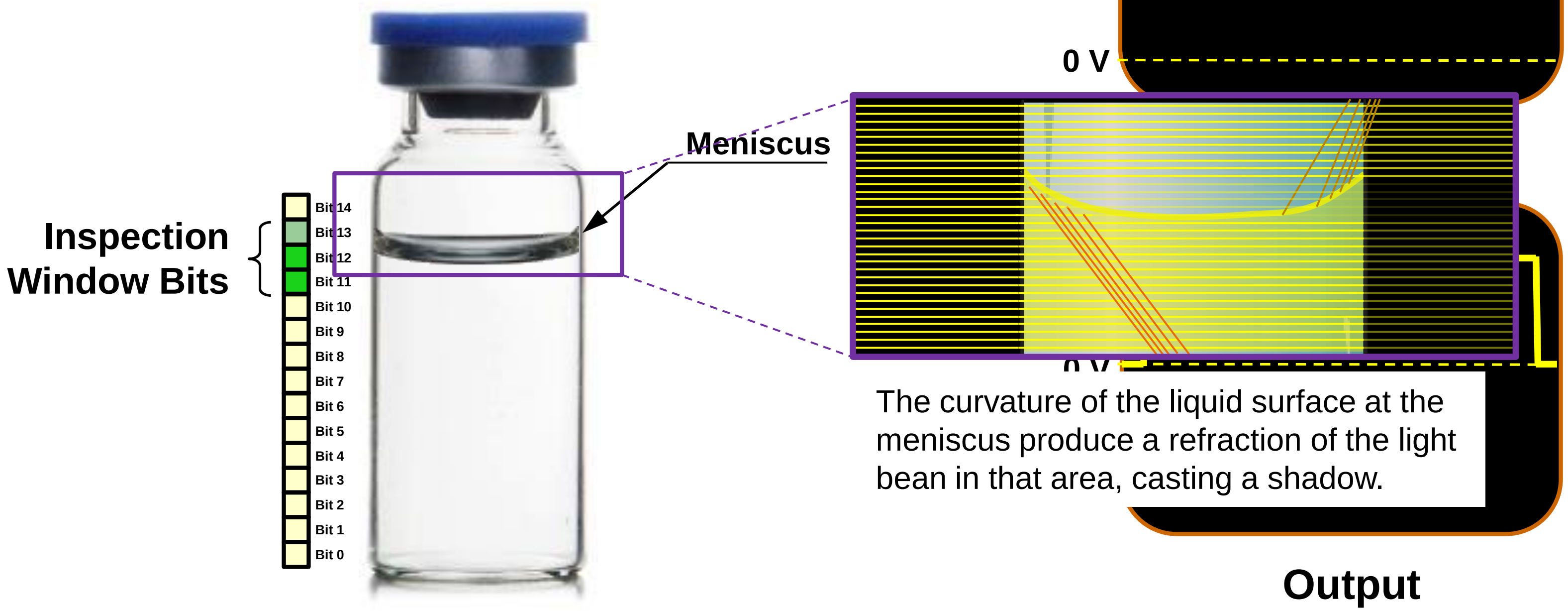




Fill Level Detection

Static Division (SD)

→Resolution will be based on the diode dimensions (0.5x0.5 mm or 1.0x0.5mm)



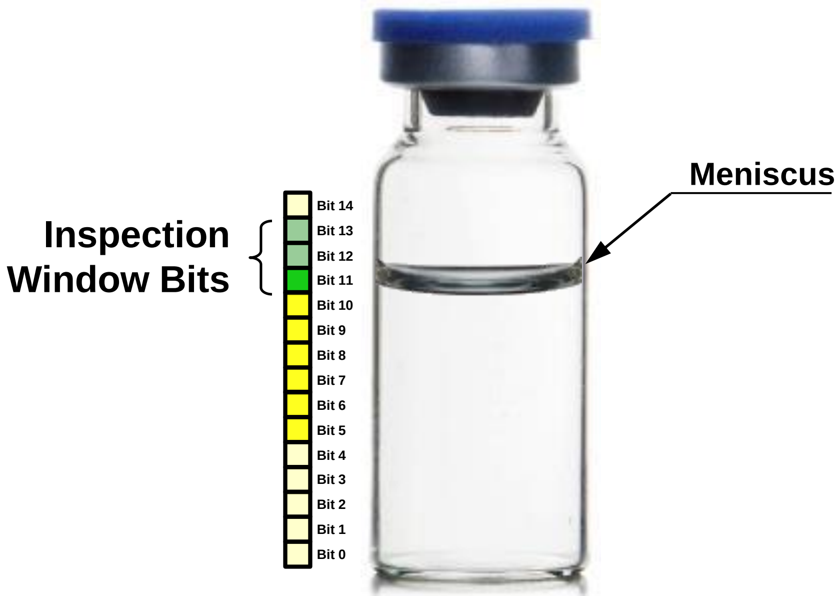
Rejects based on the light intensity reading of the meniscus shadow in the area of inspection.

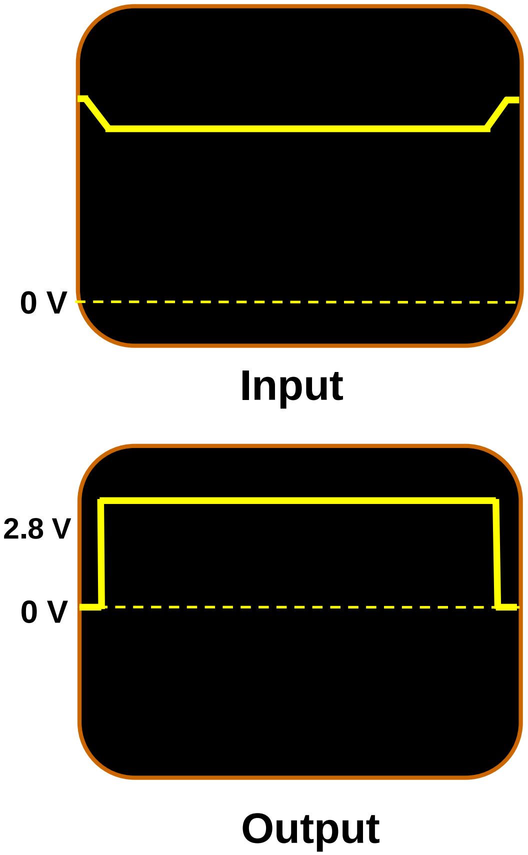
Inspection Window: Bits 11 – 13 (Only bits that will trigger an output)

Fill Level Detection

Static Division (SD)

➔Resolution will be based on the diode dimensions (0.5x0.5 mm or 1.0x0.5mm)





Rejects based on the light intensity reading of the meniscus shadow in the area of inspection.

Inspection Window: Bits 11 – 13 (Only bits that will trigger an output)

PARTICLE INSPECTION METHODS

PARTICLE DETECTION USING (CCD) CAMERA

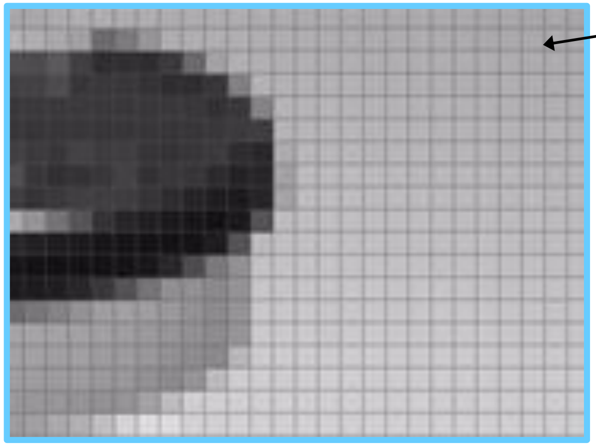
Content

- Particle Detection using Camera (CCD)
  - Raster Image
  - Vision Tools
  - Image Subtraction
  - Cosmetic Inspection using Cameras
  - Fill Level Detection

Camera Inspection

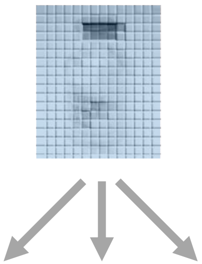
The digital raster images acquired by the digital camera have a finite set of pixels which are the smallest individual element in an image, holding quantized values that represent the brightness of a given color at any specific point. The pixels contain fixed number of rows and columns.

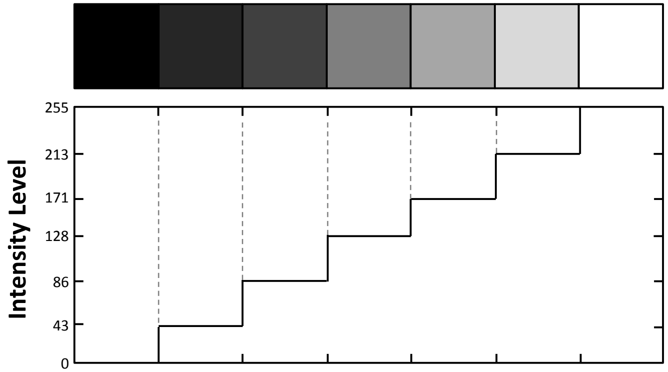
Raster Image
Vial



Pixels

Color Raster Image



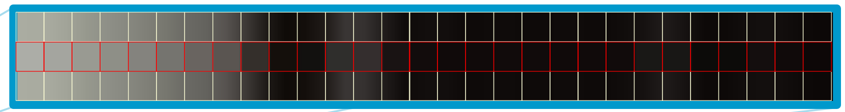


Each **pixel** use **8 bits** which have integer values from 0 to 255 for a total of 256 intensity levels.

In the **additive primaries and the RGB color model** each of the pixels in the **red**, **green** and **blue** channel images, uses 8 bits each, which makes 256*256*256 = **16,777,216** possible colors.

Vision Tools: Edge Detection

Edge detection is the name for a set of mathematical methods which aim at identifying points in a digital image at which the image brightness changes sharply or, more formally, has discontinuities.



28	28	28	27	27	27	26	26	14	14	14	19	19	1	1	1	1	1	1	1	1	3	4	4	0	0	0	0	0	**Pixel Intensity**
0	0	-1	0	0	-1	0	-8	0	0	5	0	-18	0	0	0	0	0	0	0	2	1	0	-4	0	0	0	0	0	**Pixel Gradient**

First Edge Found

$$\nabla f = \left[\frac{\partial f}{\partial x}, 0\right]$$

Edge Finding Tool Settings

Threshold 5 Edge Width 1

Transition
- ■ **Either**
- ☐ **Dark to Light**
- ☐ **Light to Dark**

Vision Tools: Edge Detection

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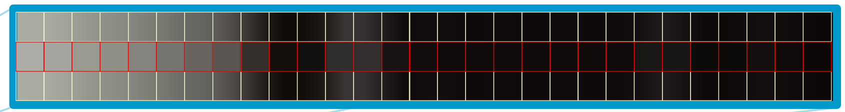


28	28	28	27	27	27	26	26	14	14	14	19	19	1	1	1	1	1	1	1	1	3	4	4	0	0	0	0	0	**Pixel Intensity**
0	0	-1	0	0	-1	0	-8	0	0	5	0	-18	0	0	0	0	0	0	0	2	1	0	-4	0	0	0	0	0	**Pixel Gradient**

$$\nabla f = \left[\frac{\partial f}{\partial x}, 0\right]$$

Edge Finding Tool Settings

Threshold: 5 | Edge Width: 1

Transition:
- ☐ Either
- ■ Dark to Light
- ☐ Light to Dark

Vision Tools: Blobs

Blob detection scans a regions inside a digital image finding a group of pixels that differ in intensity to the surrounding pixels in the region.

Blob Tool Settings

Threshold	20	Number	100

The pixel area needs to meet the criteria of the intensity threshold and the amount of **connected** pixels.

Vision Tools: Histogram

The histogram it's the intensity distribution of a region of a digital image. The graphical representation plots the number of pixels (y) for each tonal value (x).

Histogram Tool Settings

Threshold	230			Percentage	75%
Min	72	Max	246	Mean	193.2

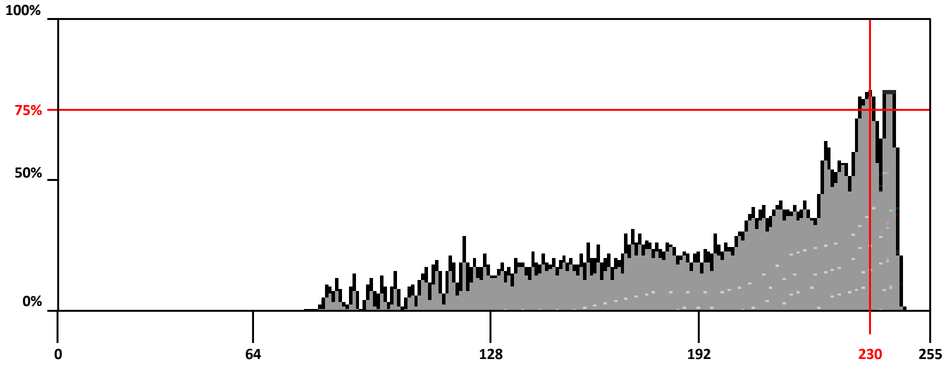
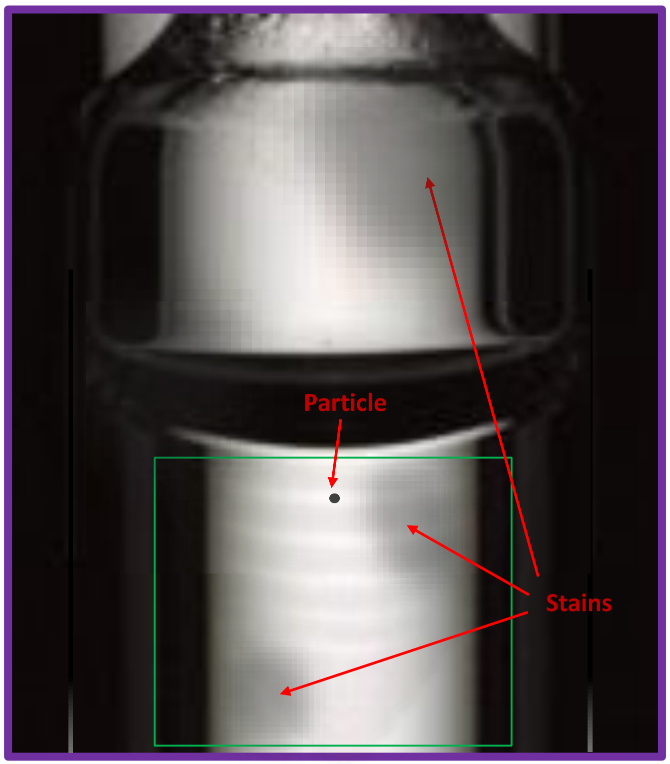
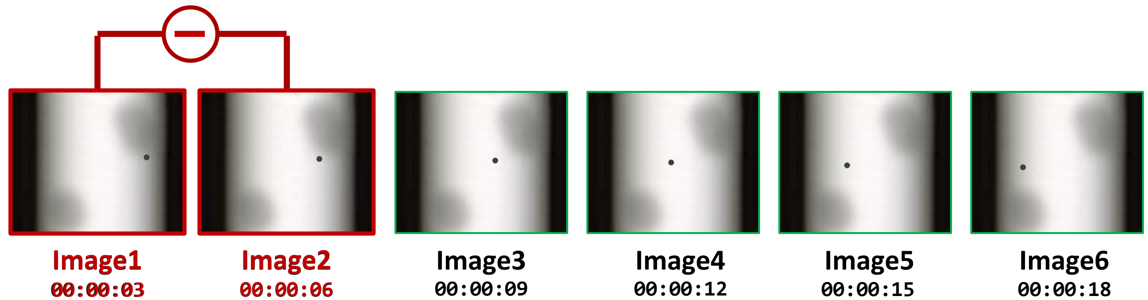


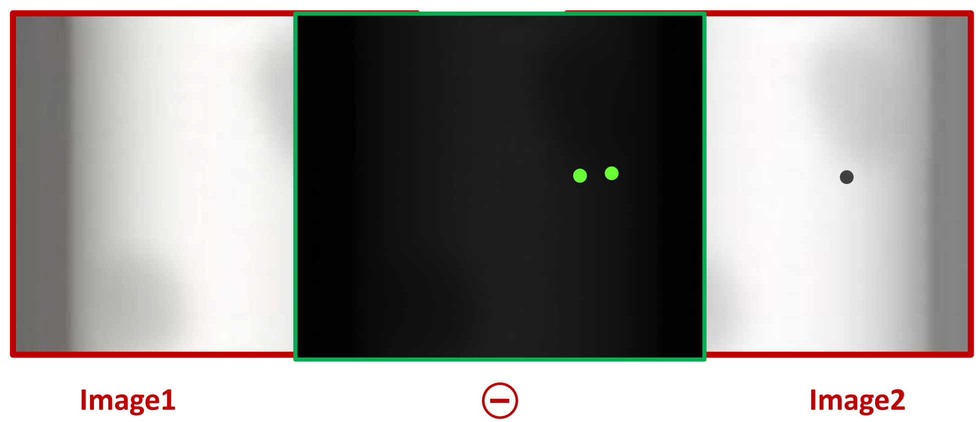
Image Subtraction (Differential Processing)

The result of the difference of the intensities of pixels from the same location in two images. Represent a movement or a difference between the images. And the rejects are based on a pixel count (contrast).

$$Q = \left| P_1(i,j) - P_2(i,j) \right|$$







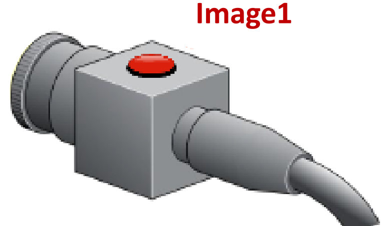


Image Acquisition

Image Subtraction (Differential Processing)

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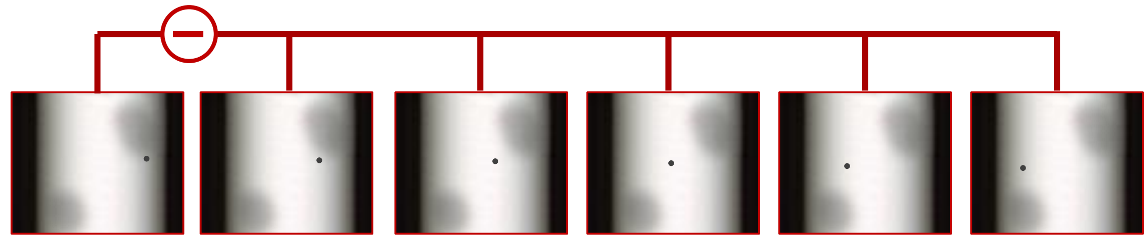
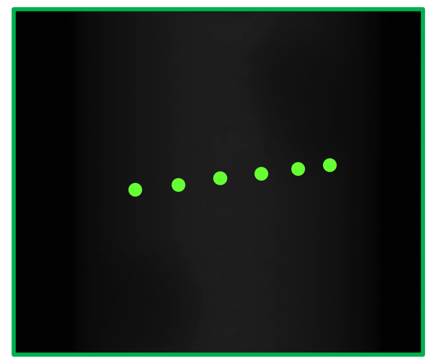
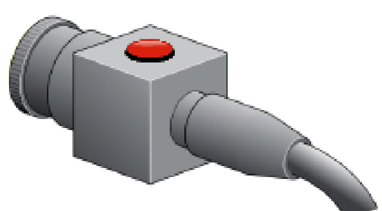




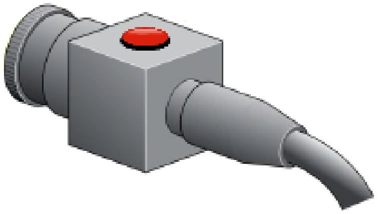


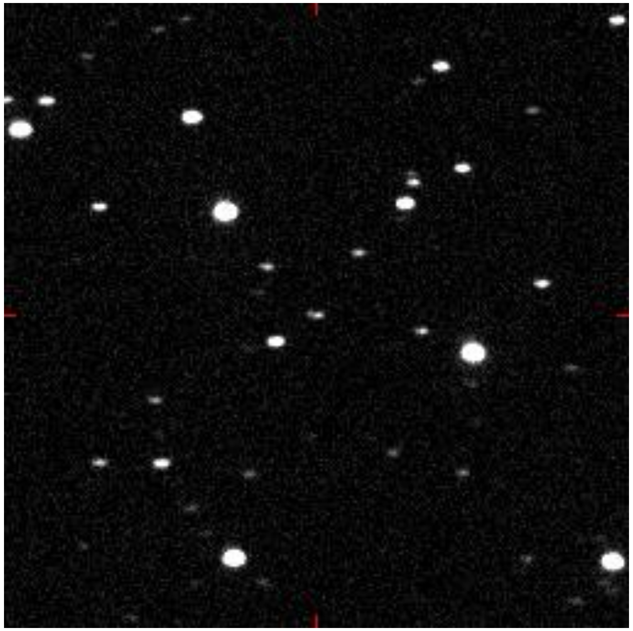
$$Q = \sum_{i=2}^{n} \text{Image1} - \text{Image(i)}$$

High definition cameras are required; the pixel size need to smaller or equal to the smallest particle size target to be detected.

Image Post Analysis

The resulting images are post-analyzed to ***filter*** and ***remove*** any **undesirable elements** from the resulting images. These computer based algorithm removes any objects that could produce traces like **bubbles, agglomerates, glares or marks** on the container while its vibrates.



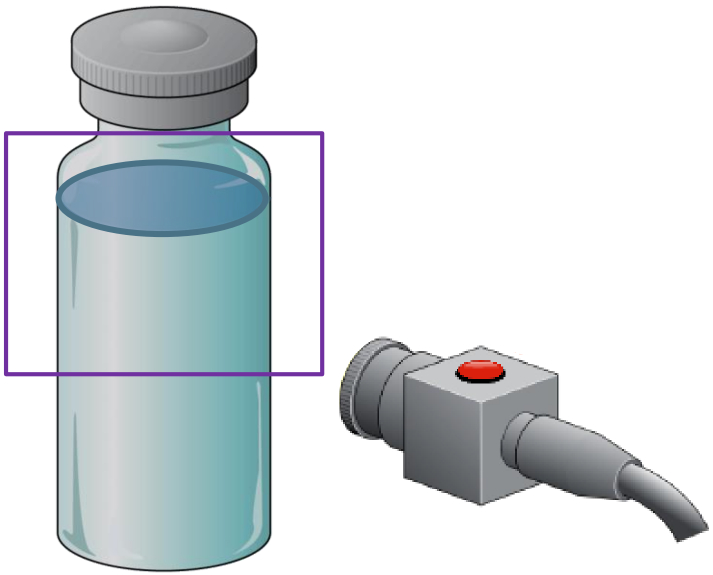


Method often used in Astronomy

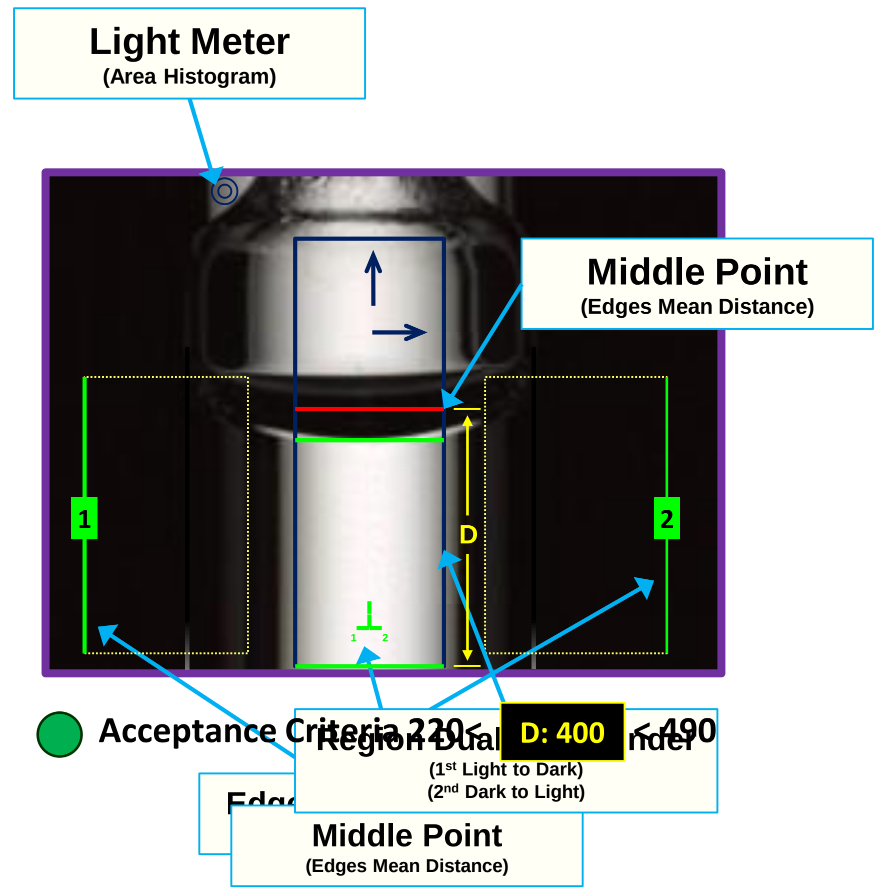
Fill Level Detection

Camera (CCD)

- Vision Tools as Edge Finder
- Higher Resolution than SD



Rejects based on pixel distance measurement.



Fill Level Detection

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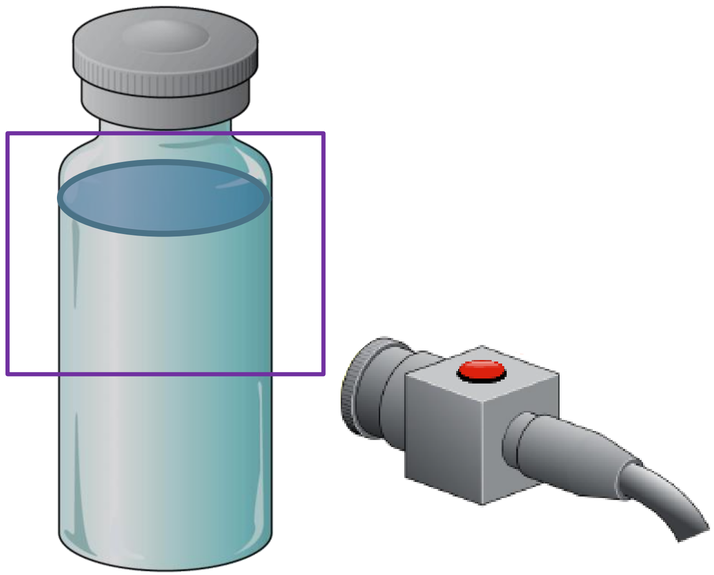
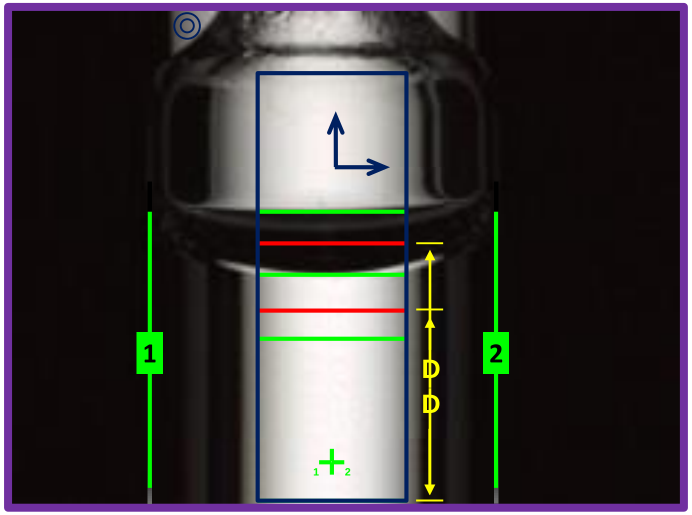




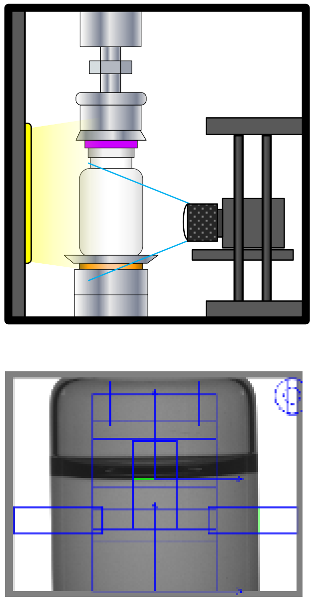
Acceptance Criteria 220< [redacted] < 490

Rejects based on pixel distance measurement.

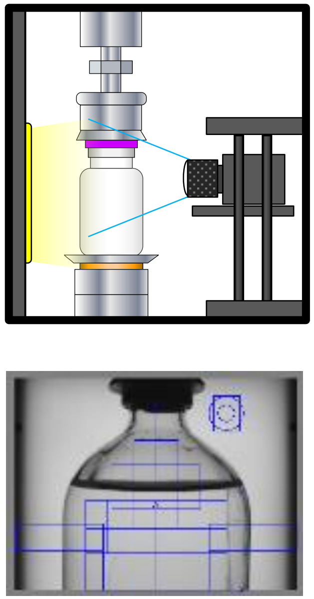
Cosmetic Inspection

The body of the container its divided in different zones, and independent cameras are dedicated to inspect these different areas. Using servo drives its possible to inspect a 360° of the body.

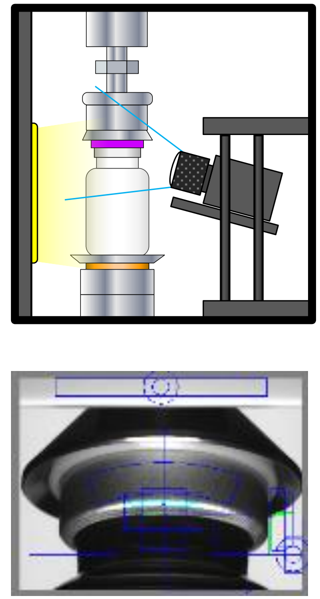
Lower Body



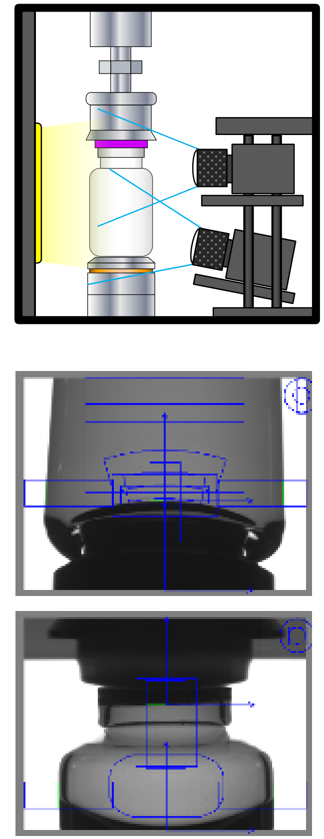
Higher Body



Crimp



Neck & Heel



Cap/Band Color

Flexible Containers Automatic Inspection: Challenges

Due to the container average volume, the nature materials of construction and its physical shape, creates a lot of challenges to automate the inspection.

Flexible body

Can generate false rejects produce by shadows and light variance.

Oval Shape

Spinning of the container don't produce a fluid vortex movement.

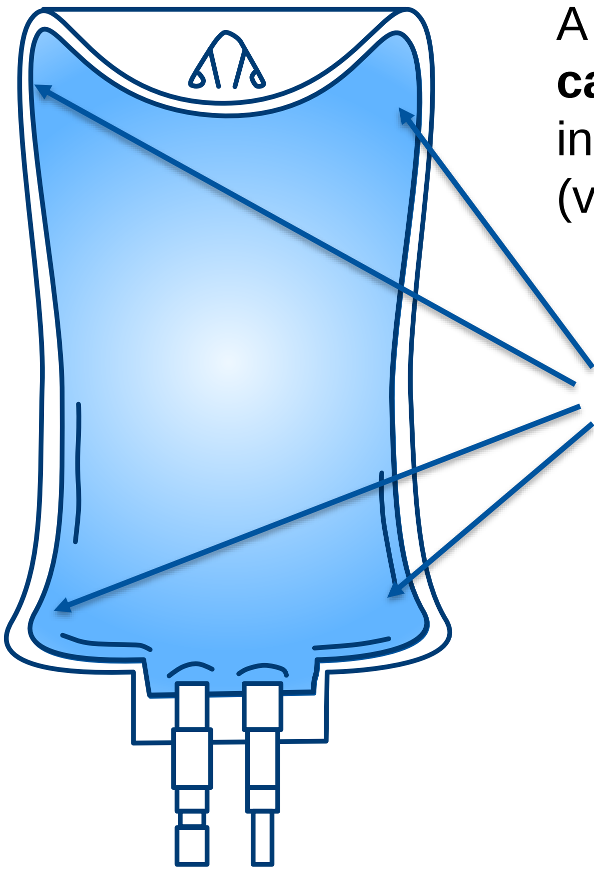
Pre-printed

The container normally has information printed which difficult the inspection process.

Large Volume

A large volume requires a bigger inspection area.

Flexible Containers Automatic Inspection: Challenges

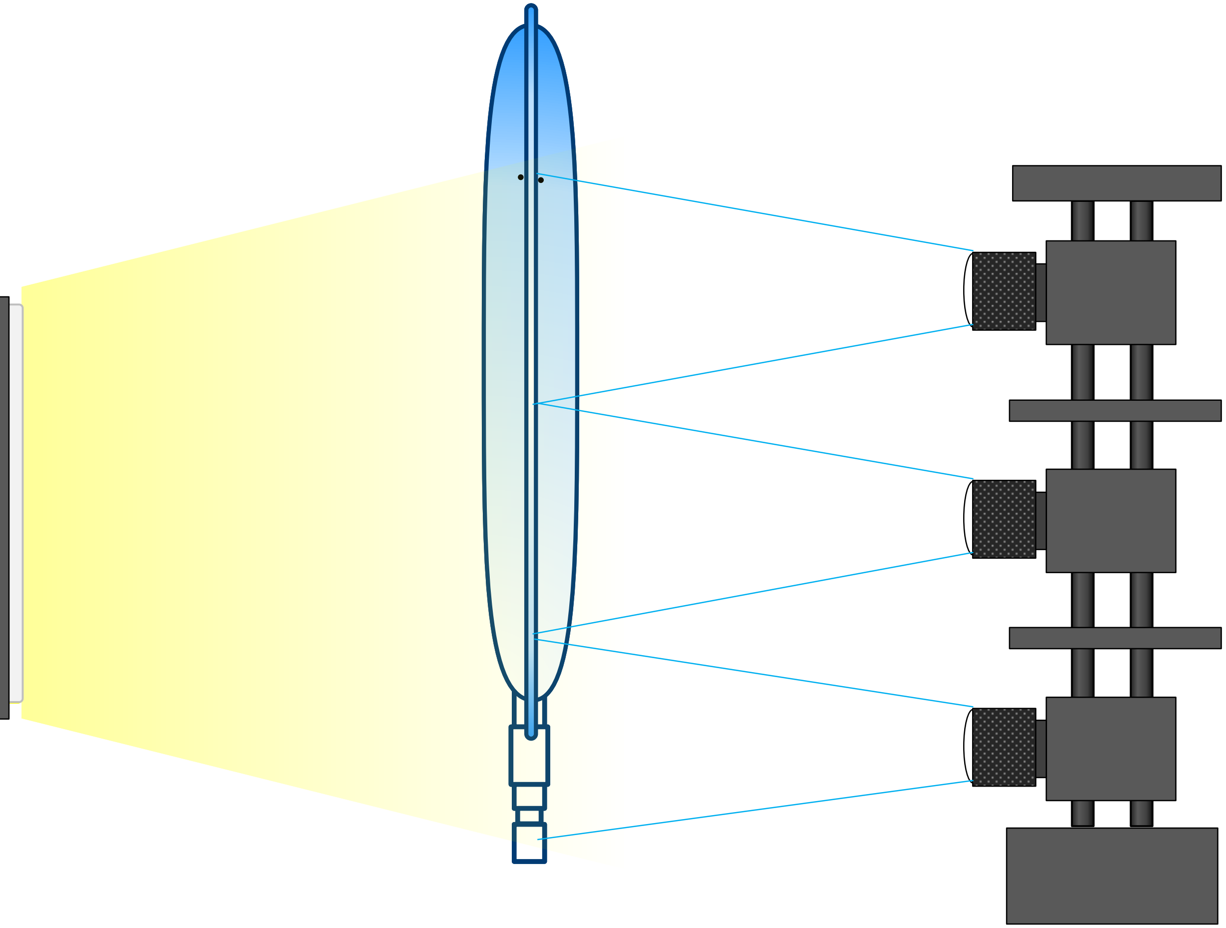


A consistent liquid vortex **cannot** be created as easy in the rigid tubular containers (vials, syringes, etc.)

Fluid slow moving areas.

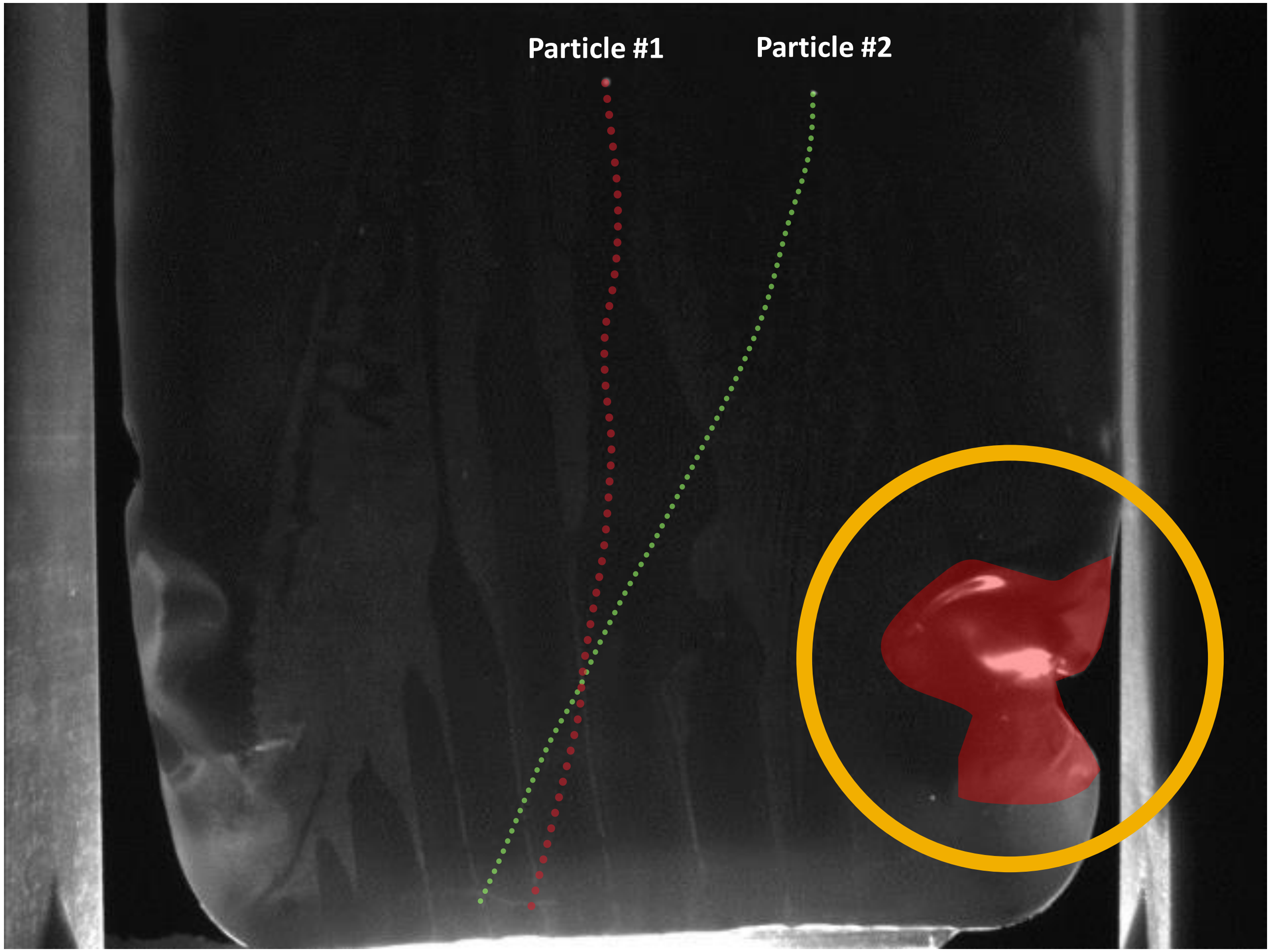
Revolving agitation do not produce a standard fluid movement.

Flexible Containers Automatic Inspection: Challenges



A flipping movement similar to the one done in the manual inspection process can provide particle movement. But it will also generate physical variability in the bag itself due to the solution mass movement, that can cause some inspection noise in the image subtraction process.

Flexible Containers Automatic Inspection: Challenges



Through the inspection any solution **movement** can produce light flares, shadows and/or changes on the physical dimensions on the container that could confuse the image substation algorithm.

Flexible Containers Automatic Inspection: Challenges

Printed information, makes it even more difficult to apply the **image substation**, and requires a lot of image **post processing** to filter or **mask** the printed information out.

Summary: Automated Visual Inspection Constraints

Types of Products that CANNOT be Inspected.

Products

- × Light Sensitive Products
- × Lyo Cake
- × Opaque Solutions
- × Extremely High Viscous Products
- × Agitation Susceptible (spin cycle)

Containers

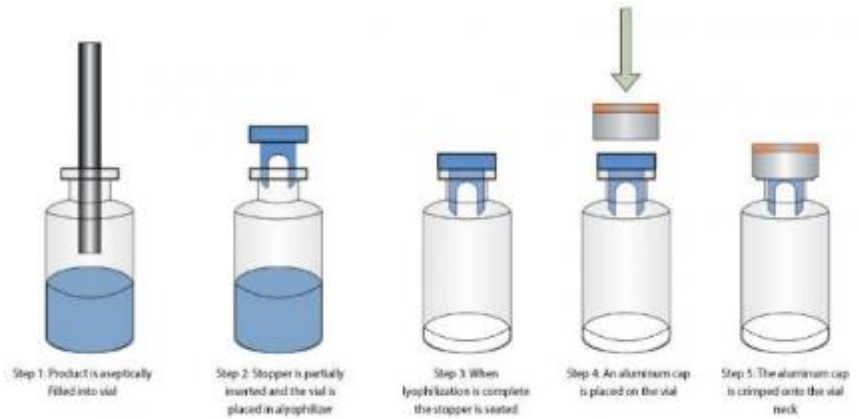
- × Metallic Containers
- × Opaque Container

Some biological products experience shear-induced agglomeration, so care should be taken with regard to agitation of these products.

Lyophilization: Particle Inspection Challenges

Lyophilization or freeze drying is a process in which **water is removed** from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from **solid to vapor** without passing through a liquid phase.

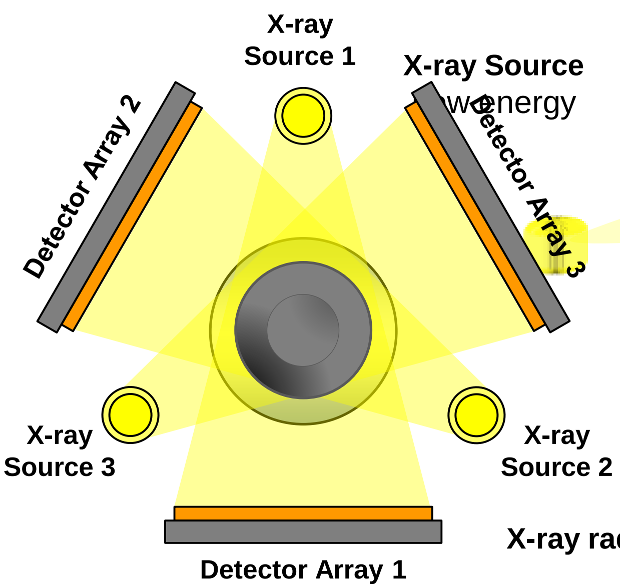
The moving particle detection is not possible in freeze-dried, lyophilized products, because the particulates are steady and hidden inside the solidified Lyo cake, in addition any high spinning cycle could damage the cake.

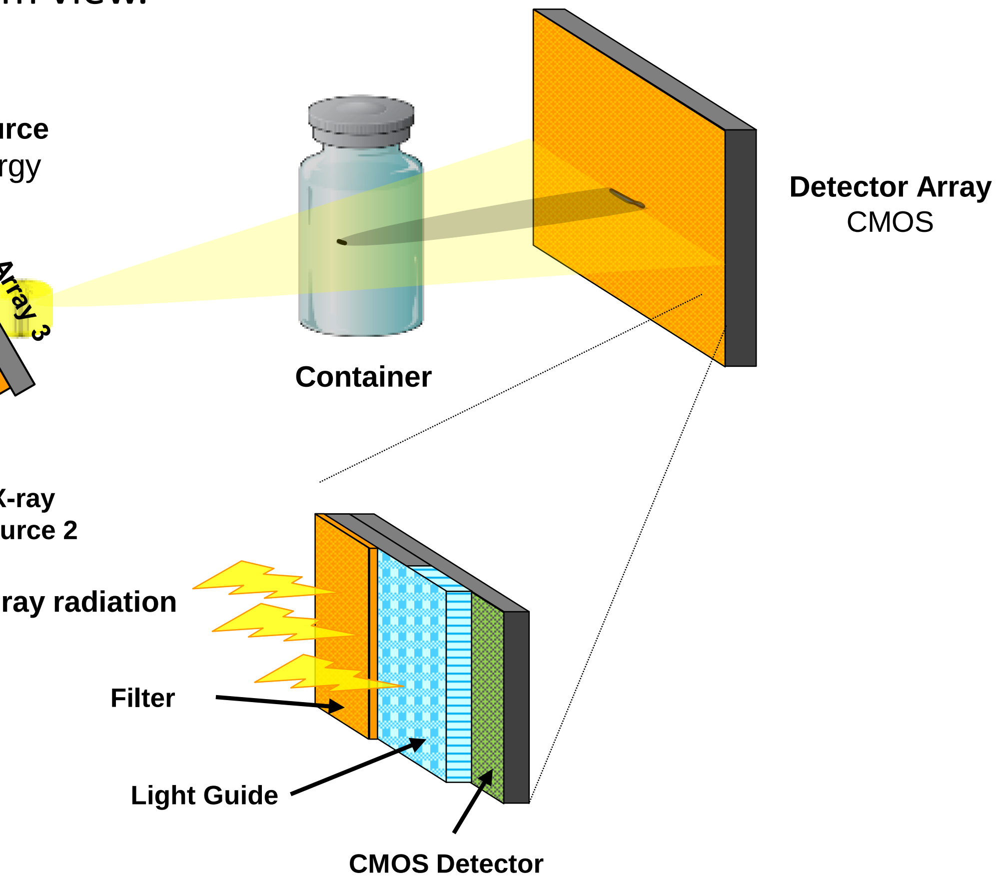


Inspection Guides > Lyophilization of Parenteral (7/93) - FDA

Automated X-Ray Inspection

Technology based on the same principles as vision automated inspection. But It uses X-rays as its source, instead of visible light, to automatically inspect features, which are typically hidden from view.





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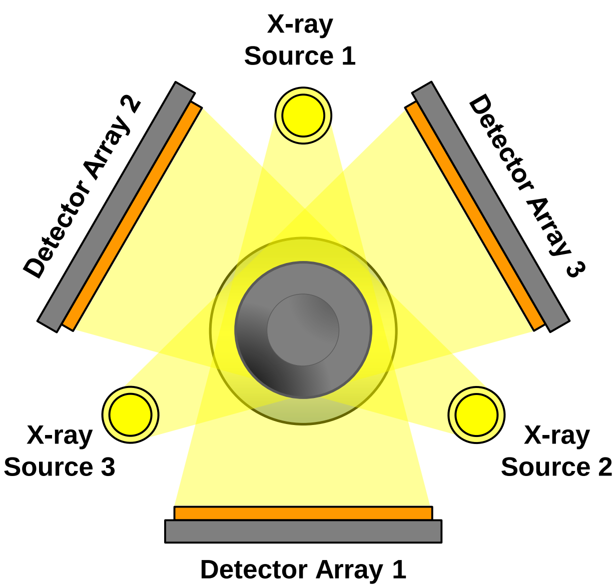
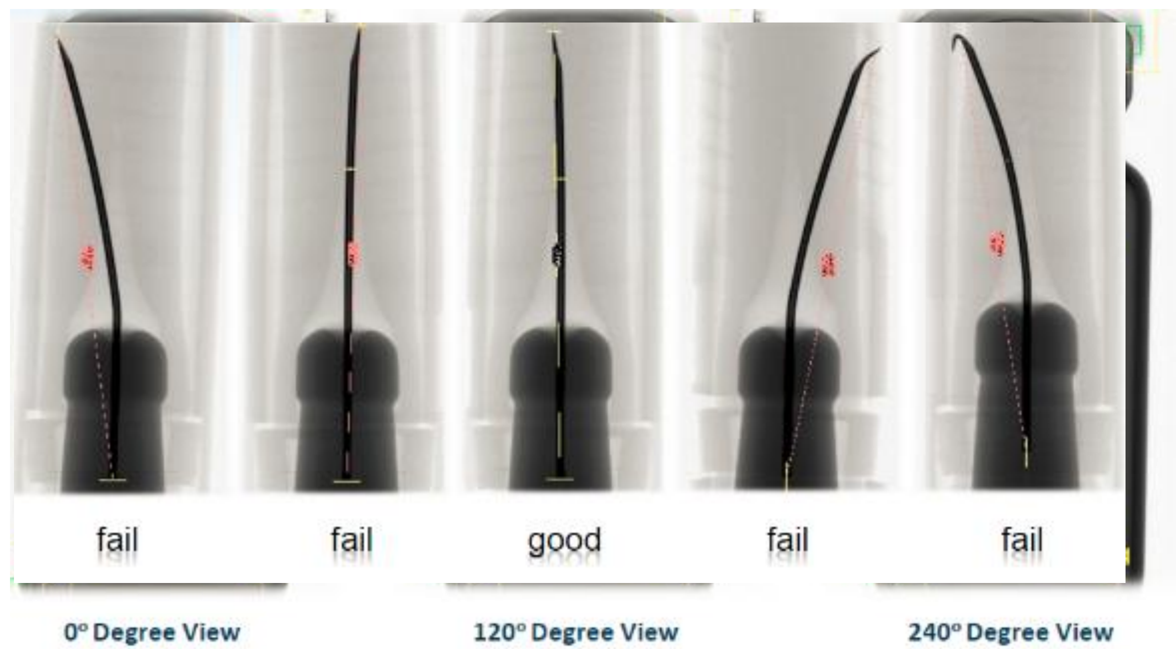


Verification of correct needle alignment

samples automatic detection results



Particles must be more dense than the container or medium inspected. Plastic, glass and fibers may not work.

CONTAINER INTEGRITY INSPECTION

Content

- Package Integrity
- Principles of High Voltage Leak Detection (HVLD)
- System Block Diagram
- Detection Process
- Voltage Reference Adjustment
- Buddy Reject Effect
- Detection Constraints

Package Integrity

Sterile Product Packaging – Integrity Evaluation <1207>

Package integrity is defined as a package's ability to ***prevent product loss***, maintain ***product sterility***, and in some cases, prevent oxygen ingress or maintain sub-atmosphere headspace pressures.

- **Leakage beyond inherent leakage rate is caused by:**
  - Poor assembly
  - Component defects

Maximum Allowable Leakage Limit (MALL)

is that smallest gap or leak rate that puts product quality* at risk

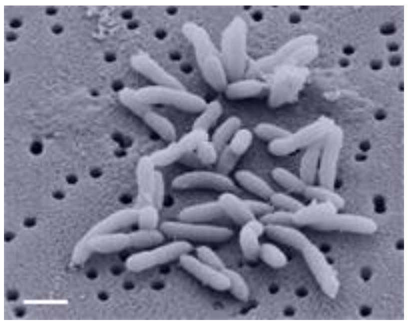
(sometimes called the 'critical leak')

Dana Guazzo, PhD, RxPax, LLC

Package Integrity

Smallest leak to allow ingress determination

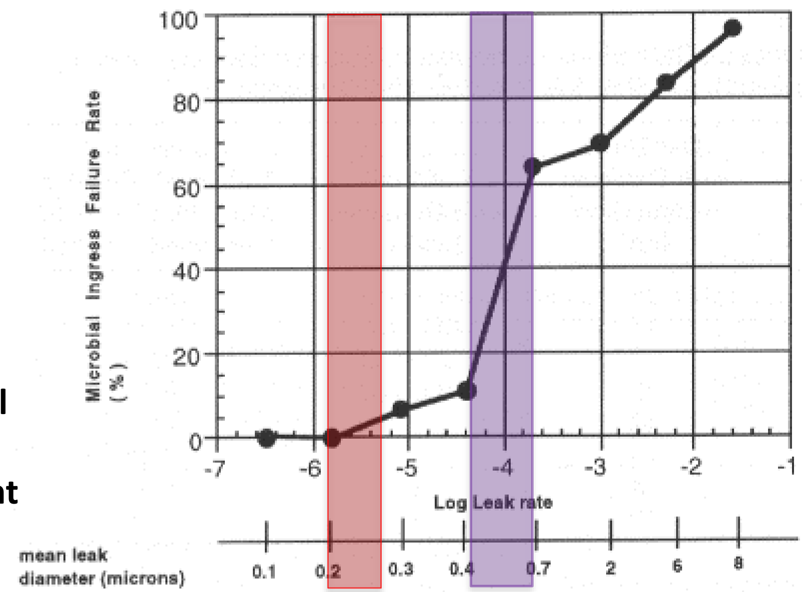
Lee Kirsch, et al, PDA J Pharm Sci & Technol, Vol. 51, No. 5, 1997



108 to 1010 P. diminuta
From: MicrobeWiki

E. Coli
From Wikipedia

- **Glass micro-pipettes through wall of stoppered glass vial**
  - **0.1 to 10µm diameter** (Sized via helium mass spec)
- **Microbial challenge by immersion + liquid tracer element**
- **Challenge conditions**
  - Water bath immersion 60ºC 2hr, then 25ºC 1hr
  - 24 hr immersion, ambient pressure



Most bacteria are **0.2 µm** in diameter and 2-8 µm in length. The three basic bacterial shapes are coccus (spherical), bacillus (rod-shaped), and spiral (twisted), however pleomorphic bacteria can assume several shapes.

Ingress Risk Dropped: Log -3.8 sccs (Leak < ~1µm)

No Ingress: Log -5 to -5.8 sccs (Leak ~0.3 to 0.2µm)

Package Integrity

Study Author	Challenge medium	Challenge microbe	Challenge path	Challenge conditions	Threshold path size
Kirsch JPDA '97-'99	Liquid	P. diminuta E. coli	Glass micro-pipette 0.3 µm	Airlock elimination step + 24 hr ambient	**0.3 µm**
Keller J Applied Pkgg Res 2006	Aerosol	P. Fragi	Nickel micro-tube	Varied: -20 kPato +20 kPa 4 to 37ºC	**5 µm**
Burrell JPDA 2000	Liquid	E. Coli	Poly-coated glass micro-tube	ISO closure reseal: 30 min 22"Hg + 30 min ambient	**10 µm**

"Critical leak" threshold ranged from 0.3 to 10µm

Dana Guazzo, PhD, RxPax, LLC

Package Integrity

Test Method

Deterministic: the leakage event is based on phenomena that follow a *predictable* chain of events, and leakage is *measured* using *physicochemical technologies* that are readily *controlled* and *monitored*, yielding objective *quantitative data*.

Probabilistic: its stochastic in nature in that it relies on a series of sequential and/or simultaneous *events* each associated with *uncertainties*, yielding *random outcomes* described by probability distributions.

Deterministic methods

- Electrical Conductivity and Capacitance (HVLD)
- Laser-Based Gas Headspace Analysis
- Mass Extraction
- Pressure Decay
- Tracer Gas Detection, Vacuum Mode
- Vacuum Decay

Probabilistic methods

- Bubble Emission
- Microbial Challenge, Immersion Exposure
- Tracer Gas Detection, Sniffer Mode
- Tracer Liquid

LEAK INSPECTION METHODS

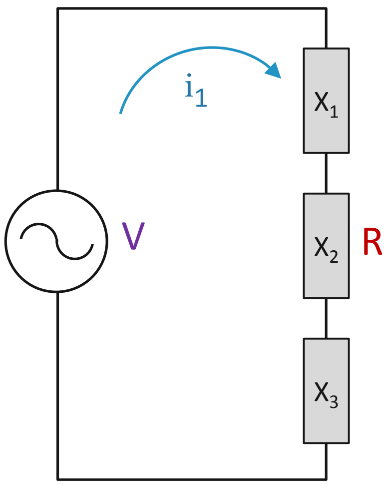
HIGH VOLTAGE LEAK DETECTION (HVLD)

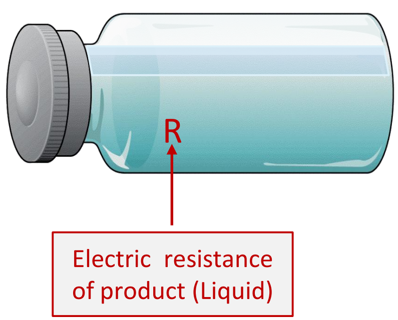
Principles of HVLD

Detection Circuit

The High Voltage Leak Detection (HVLD) is based on the Ohms Law and the principle of a high voltage spark-test system and is capable of handling any product as long as the container is made of electrically insulated material such as glass, rubber, plastic or plastic film, and contains an electrically conductive solution.

Note: V normally goes from 18 to 24 kV 500Hz



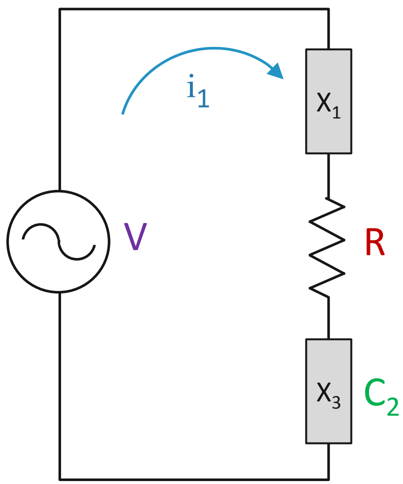


Principles of HVLD

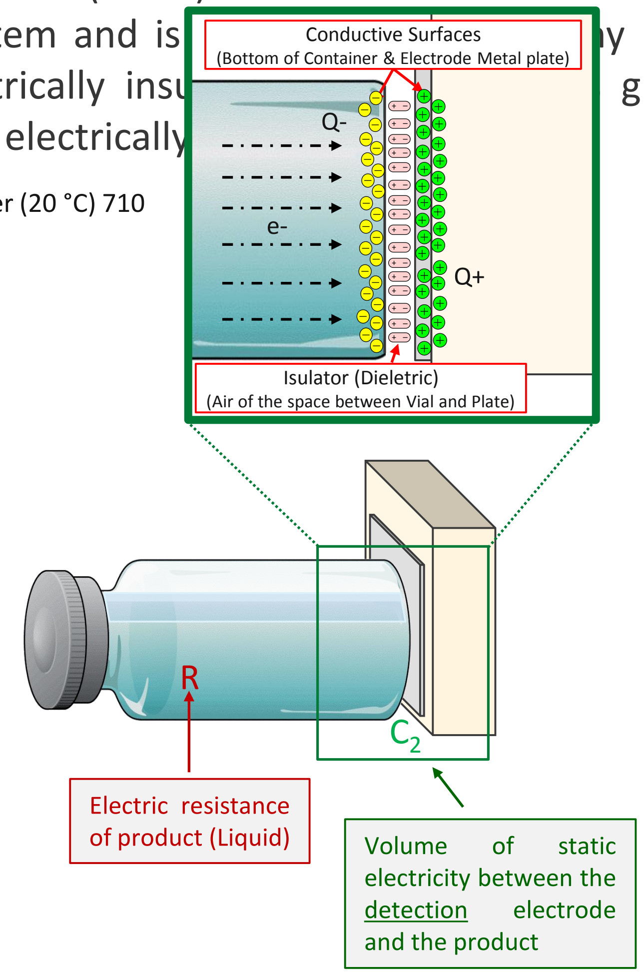
Detection Circuit

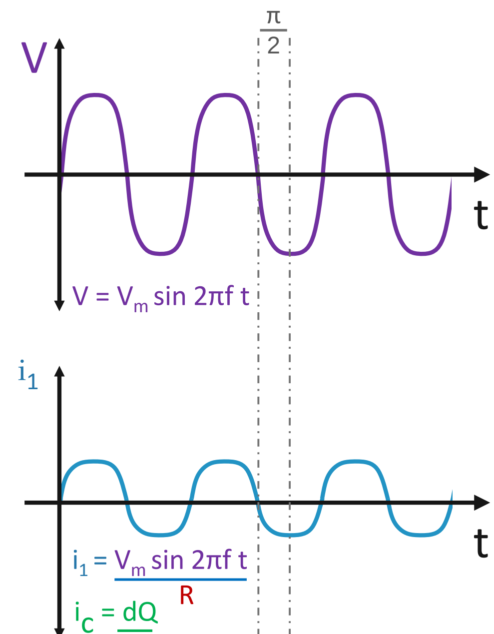
The High Voltage Leak Detection (HVLD) is based on the Ohms Law and the principle of a high voltage spark-test system and is ... y product as long as the container is made of electrically insu... glass, rubber, plastic or plastic film, and contains an electrically ...

Note: Permittivity of Air is 8.85 and Water (20 °C) 710



$$i_m = \frac{V}{X_1 + R + \frac{1}{2\pi f C_2}}$$





$$i_1 = \frac{V_m \sin 2\pi f t}{R}$$

$$i_C = \frac{dQ}{dt}$$

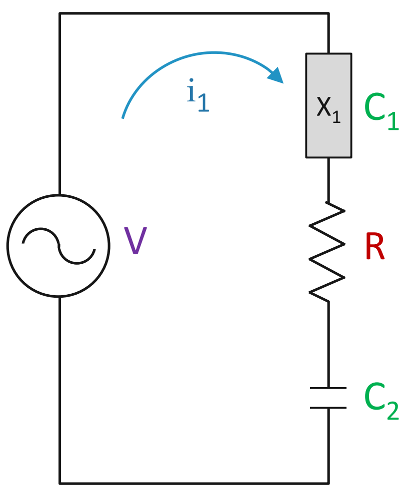
$$i_C = \frac{d}{dt} C V_m \sin 2\pi f t$$

$$i_1 = i_m \sin\left(2\pi f t + \frac{\pi}{2}\right)$$

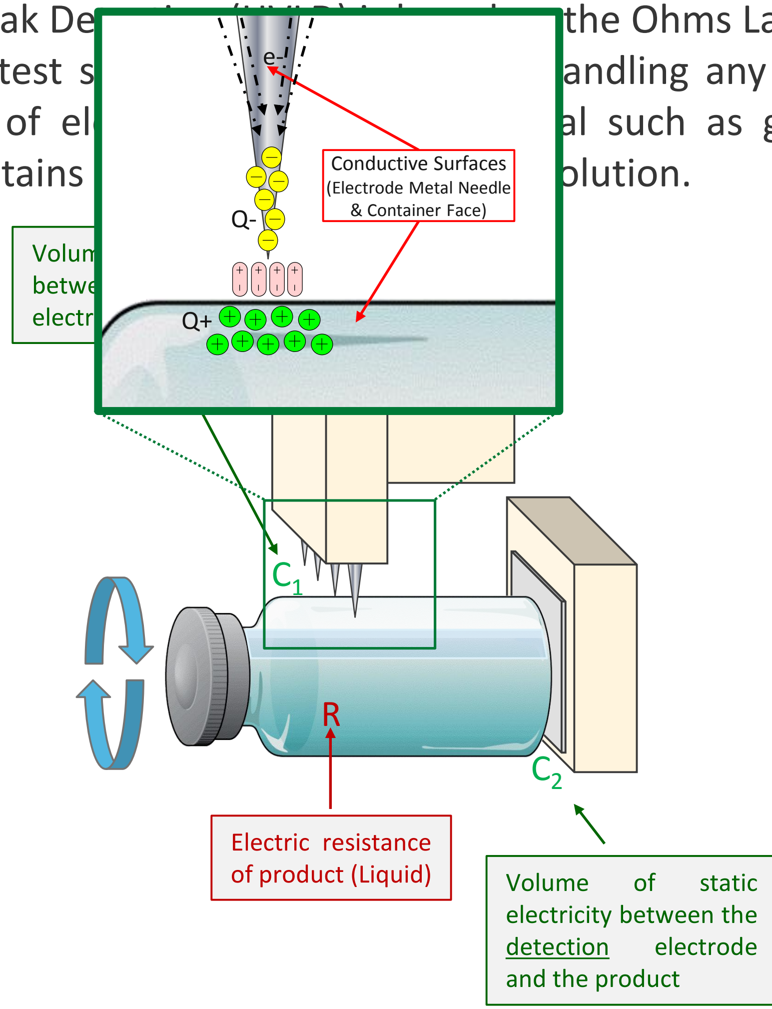
Principles of HVLD

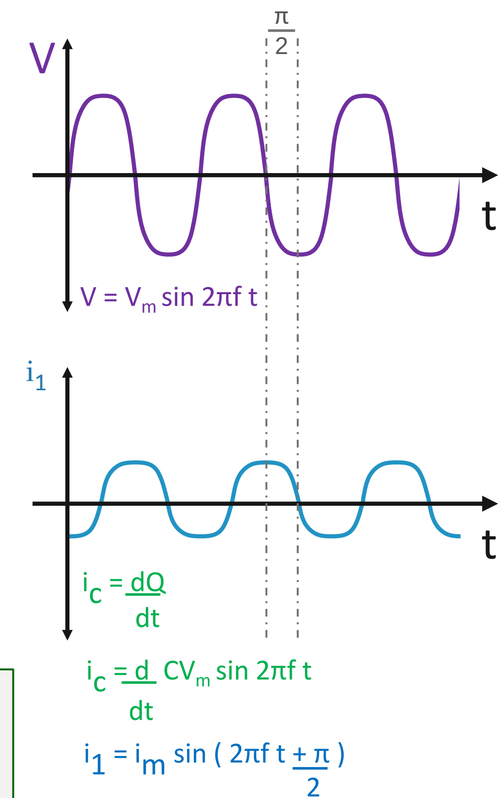
Detection Circuit

The High Voltage Leak De … the Ohms Law and the principle of a high voltage spark-test s … andling any product as long as the container is made of el … al such as glass, rubber, plastic or plastic film, and contains … olution.



$$i_m = \frac{V}{X_1 + R + \frac{1}{2\pi f C_2}}, \quad X_1 = \frac{1}{2\pi f C_1}$$

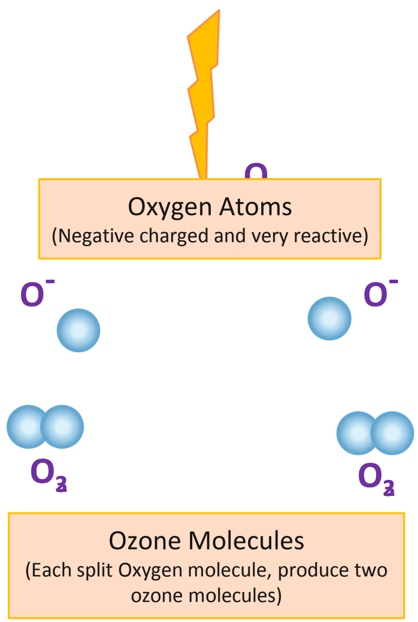


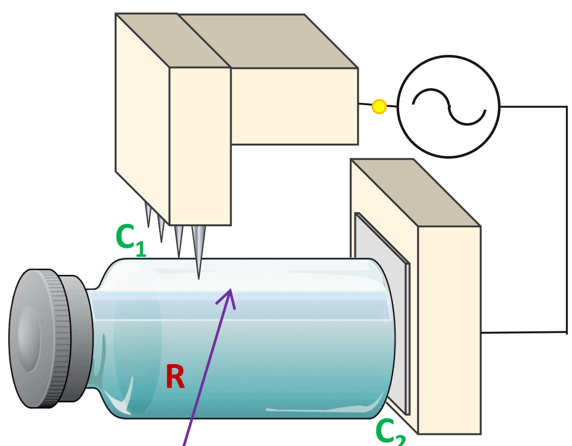


Principles of HVLD

Detection Circuit

The High Voltage Leak Detection (HVLD) is based on the Ohms Law and the principle of a high voltage spark-test system and is capable of handling any product as long as the container is made of electrically insulated material such as glass, rubber, plastic or plastic film, and contains an electrically conductive solution.





The production of ozone (O_3) by the passage an electric current through oxygen or air could cause the generation of an oxidant inside the vial headspace.

Good Containers

The value of the current i_1 will have similar levels in a population of N good sealed containers.

The variables are maintained, thus the only source of a possible fluctuation is the distance of the gap between the electrodes and the containers body.

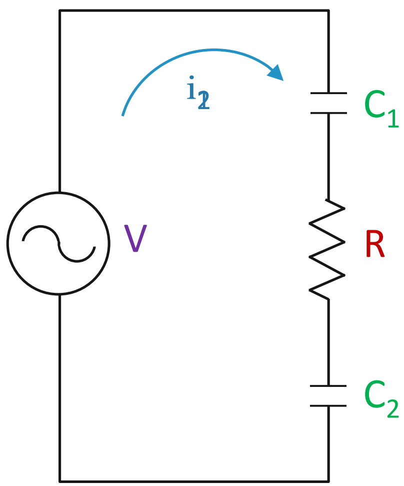
$$C = \frac{K * Eo * A}{d}$$

Eo = 8.854×10^{-12} $C^2/N.m^2$ (Electric Constant)
K is the material dielectric constant.
A is the surface area of the points.
d is the distance between the electrode and the container.

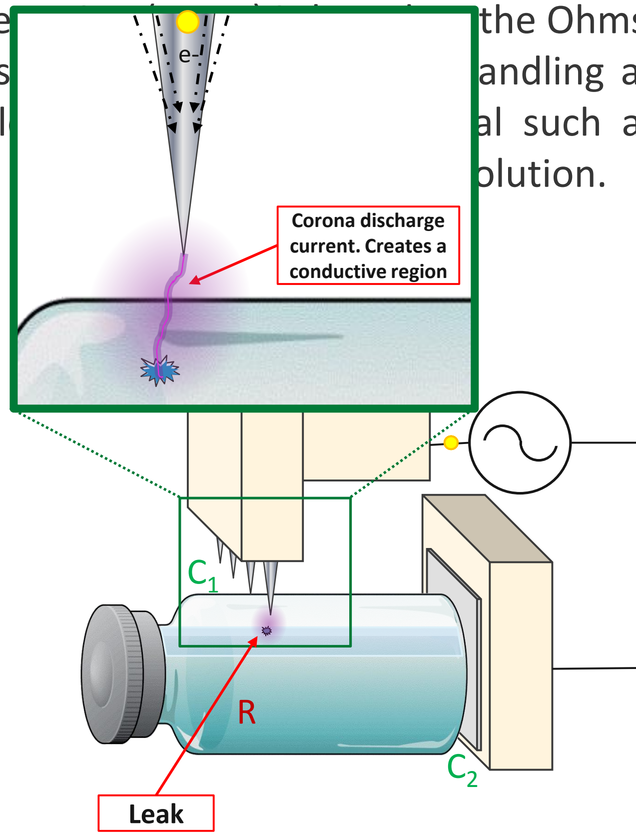
Principles of HVLD

Detection Circuit

The High Voltage Leak De … the Ohms Law and the principle of a high voltage spark-test s … andling any product as long as the container is made of el … al such as glass, rubber, plastic or plastic film, and contains … olution.



$$i_2 = \frac{V}{\frac{1}{2\pi f C_1} + R + \frac{1}{2\pi f C_2}}$$



Leaking Containers

With a constant voltage being applied to the container, a defective container will have a larger electric current volume i_2 than a container with no leak present i_1. The difference of the electric current volume determines whether the seal is defective.

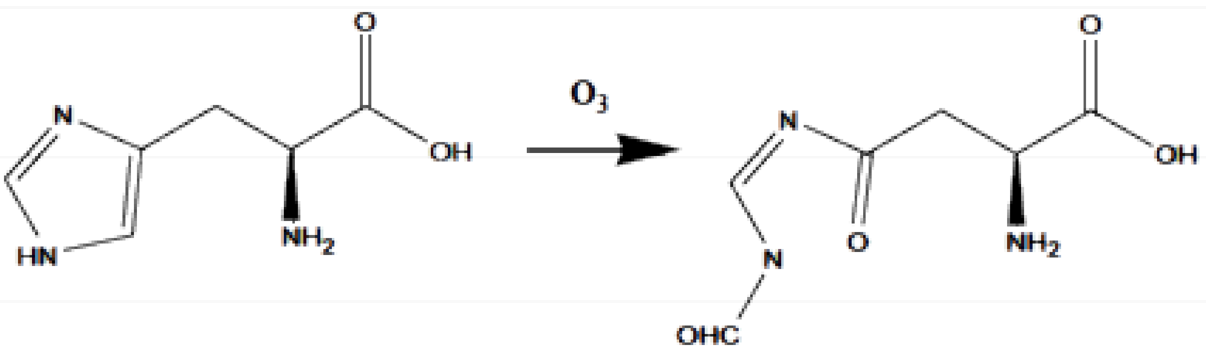
$i_2 > i_1$

Principles of HVLD

Concern exists surrounding the use of HVLD for biopharmaceuticals due to the possible degradation caused by the ozone attacking the proteins.

- Ozone attack is generally directed towards **aromatic rings**
- Histidine displays reactivity to ozone, due to the presence of an imidazole ring, which is in agreement with the Hospira study when oxidation of the imidazole ring in the drug product occurred

The effect of ozone on histidine:



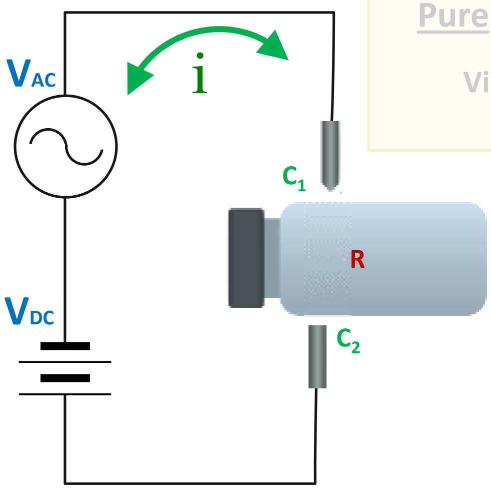
Histidine

Histidine oxidation product

McGinley, C. M., et al. Poster: Degradation of Drug Product Caused by a Leak Detection Instrument: Mechanistic Studies of Degradation. Hospira, Inc., Lake Forest, IL 60045.

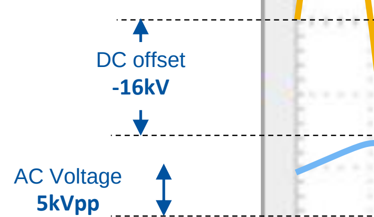
MicroCurrent HVLD

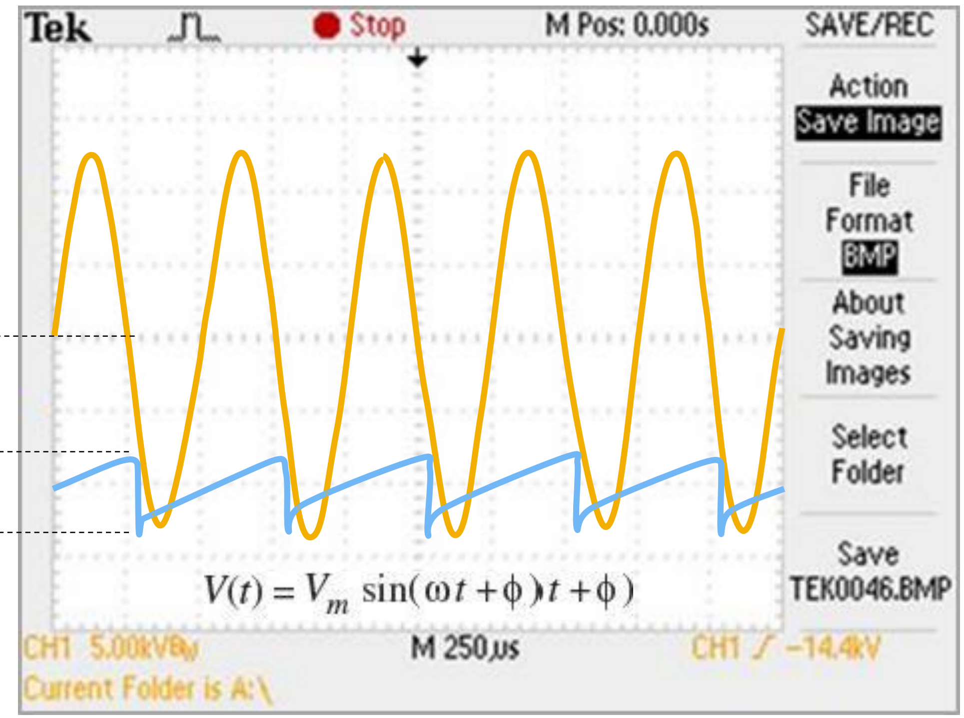
This new technology applies less than ***50% of the voltage*** used with conventional high voltage technologies and the product its exposed to less than a ***5% of the voltage exposure*** experienced when testing with comparable HVLD solutions.



Regular HVLD
Pure AC voltage:

Vi: 18.5kVpk
F: 2khz



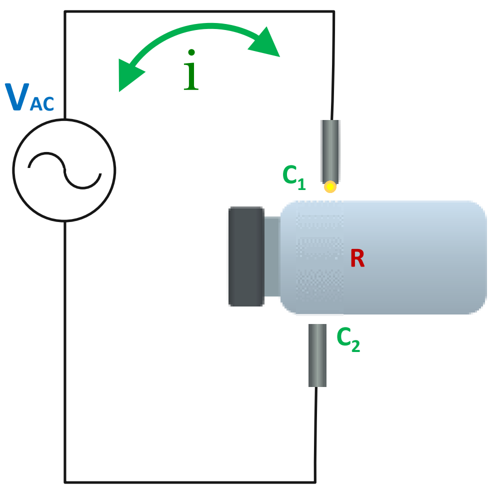


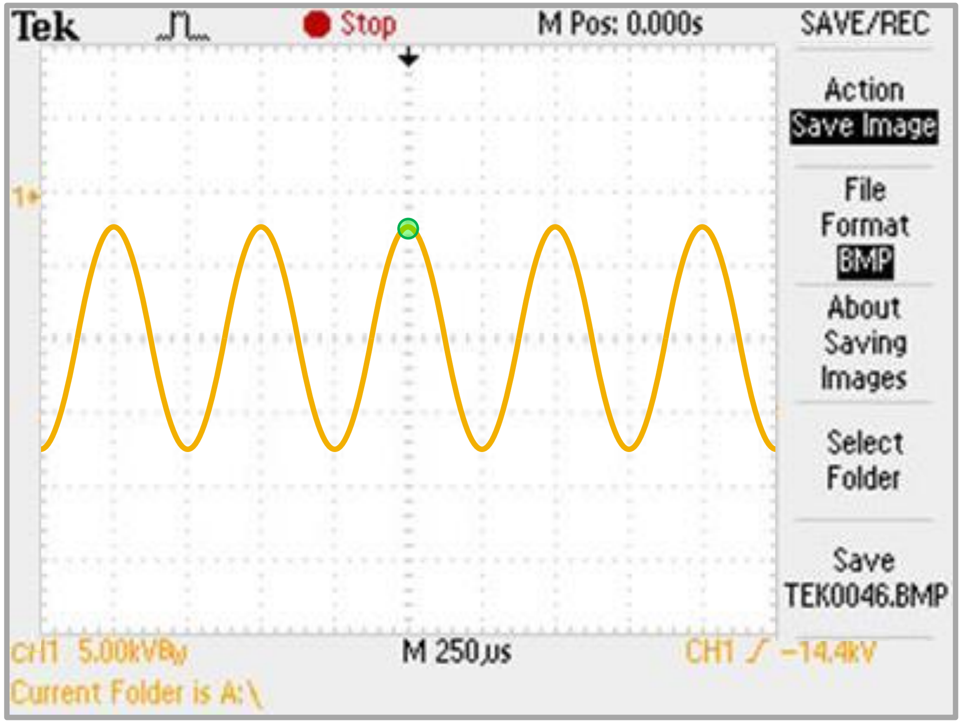
MicroCurrent HVLD
AC + DC voltage:

Vi: -18.5kVpk
F: 2khz

Standard HVLD (AC Voltage)

The regular High Voltage Leak Detection System, can only inspect aqueous solutions with a conductivity value of over 1.2µS cm².

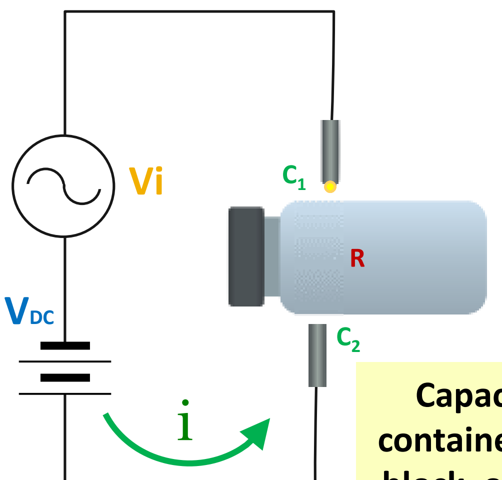




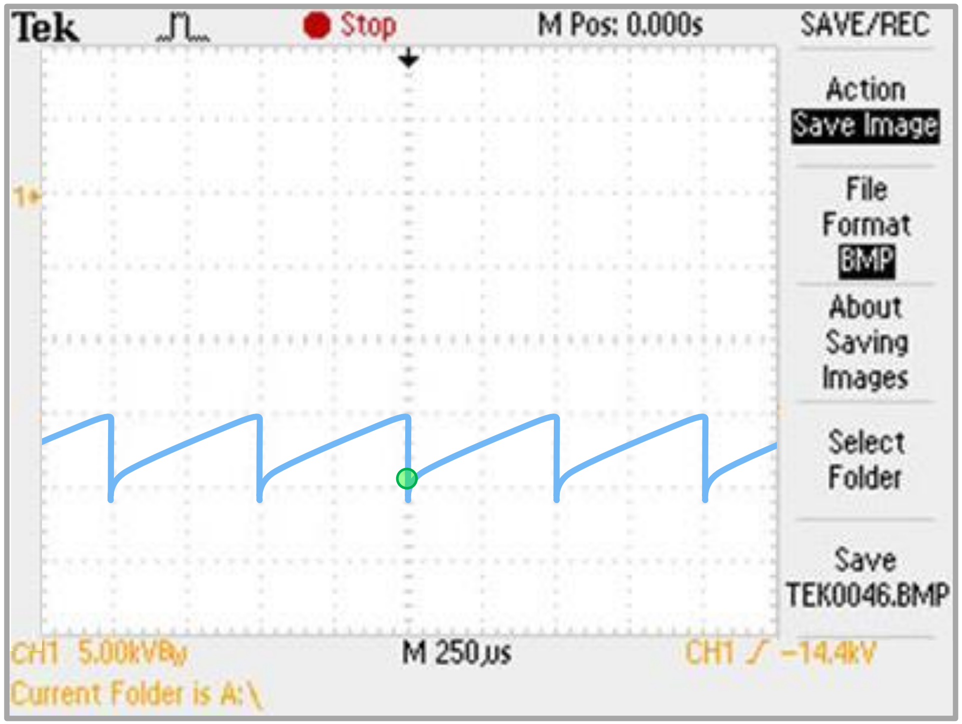
In a regular HVLD system the polarity of its electric field **alternates** with frequency of the AC high voltage, during an inspection.

MicroCurrent HVLD (DC Voltage Offset)

The nature of this solution allows the testing of packages with extremely low conductivity liquids such as sterile water (WFI).



Capacitance of the container material fully block, or attenuate the DC high-voltage

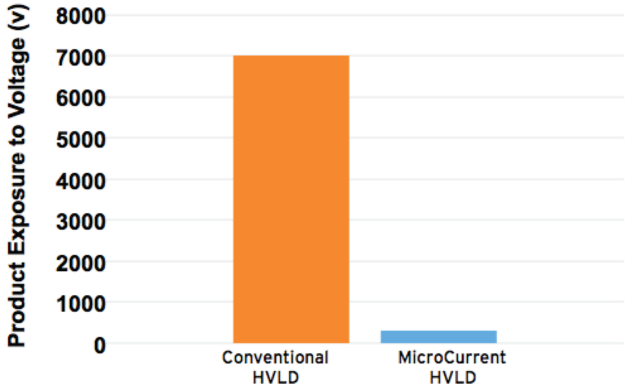


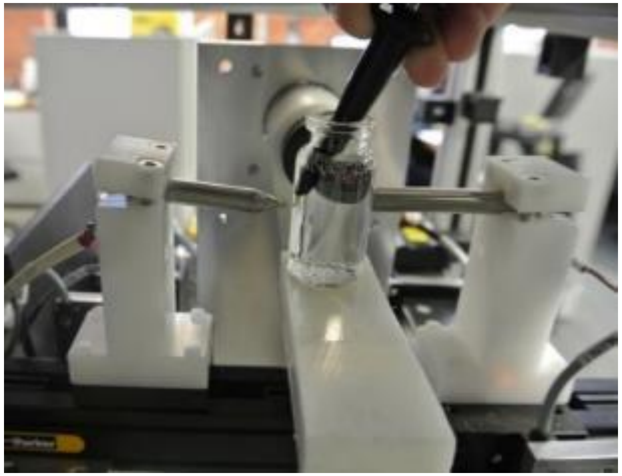
In a MicroCurrent HVLD system the polarity of its electric field **does not alternate**.

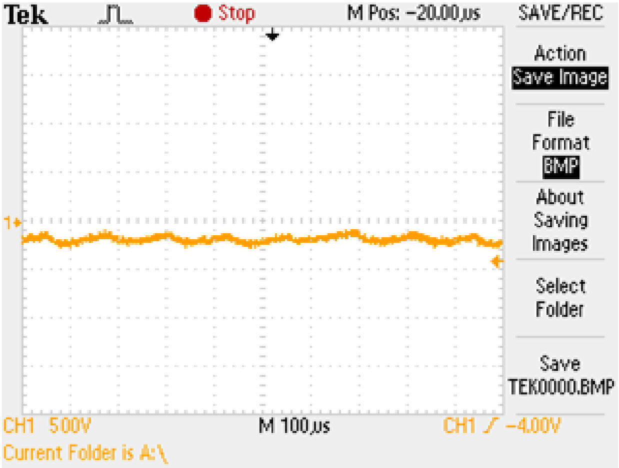
MicroCurrent HVLD

The MicroCurrent applied to the product during the test greatly reduces the voltage exposed to the product and environment.

Exposure Voltage	
Conventional HVLD	MicroCurrent HVLD
7,000 V	300 V
4.3%	





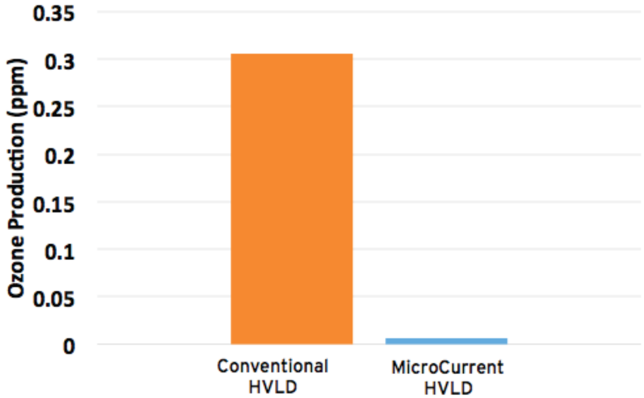


Source: PTI / Packaging Technologies and Inspection

MicroCurrent HVLD

The MicroCurrent applied to the product during the test greatly reduces the voltage exposed to the product and environment.

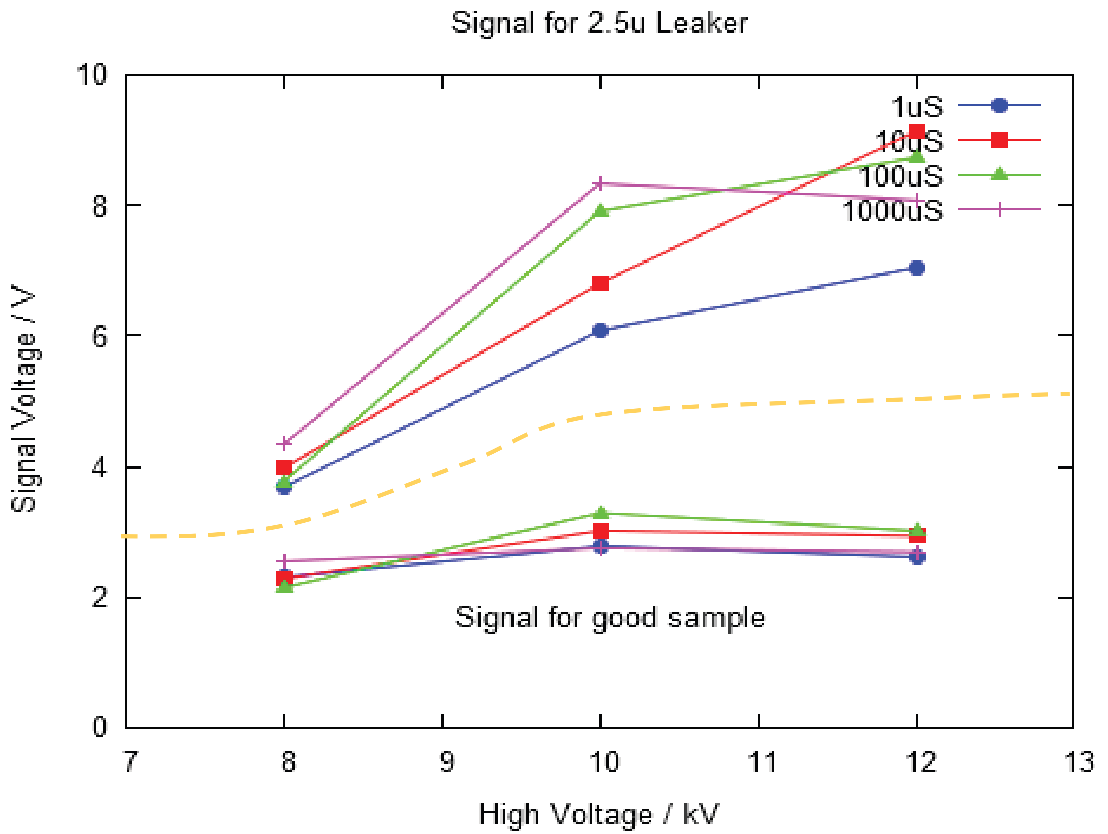
Ozone Production	
Conventional HVLD	MicroCurrent HVLD
0.305 ppm	0.006 ppm
2.0%	



Source: PTI / Packaging Technologies and Inspection

MicroCurrent HVLD

The nature of this solution allows the testing of packages with extremely low conductivity liquids such as sterile water (WFI).



Source: PTI / Packaging Technologies and Inspection

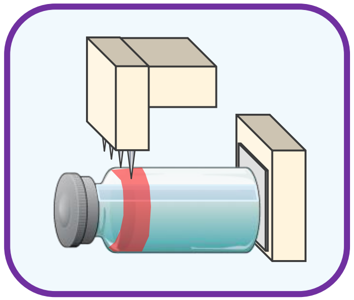
MicroCurrent HVLD

Method Comparison using a leak detector with Standard HVLD and a MicroCurrent HVLD

	HVLD	MicroCurrent HVLD
Product safety	**7,000 Volts** was exposed to product inside the vial directly when 18.5kV high voltage was used for inspection.	Only **300 Volts** was measured inside the vial filled with product when -18.5kV voltage was used for inspection.
Ozone production	**0.305ppm** ozone was produced during **1min** @ 18.5kV high voltage	**0.004pp**m ozone was produced during **10min** @ -18.5kV voltage
Sensitivity	The ratio of the signal levels for syringes with and without defect was 5.3V/3.5V=**1.5** @ 12kV high voltage	The ratio of signal levels for syringes with and without defect was 7.7V/2.2V=**3.5** @ -10kV high voltage

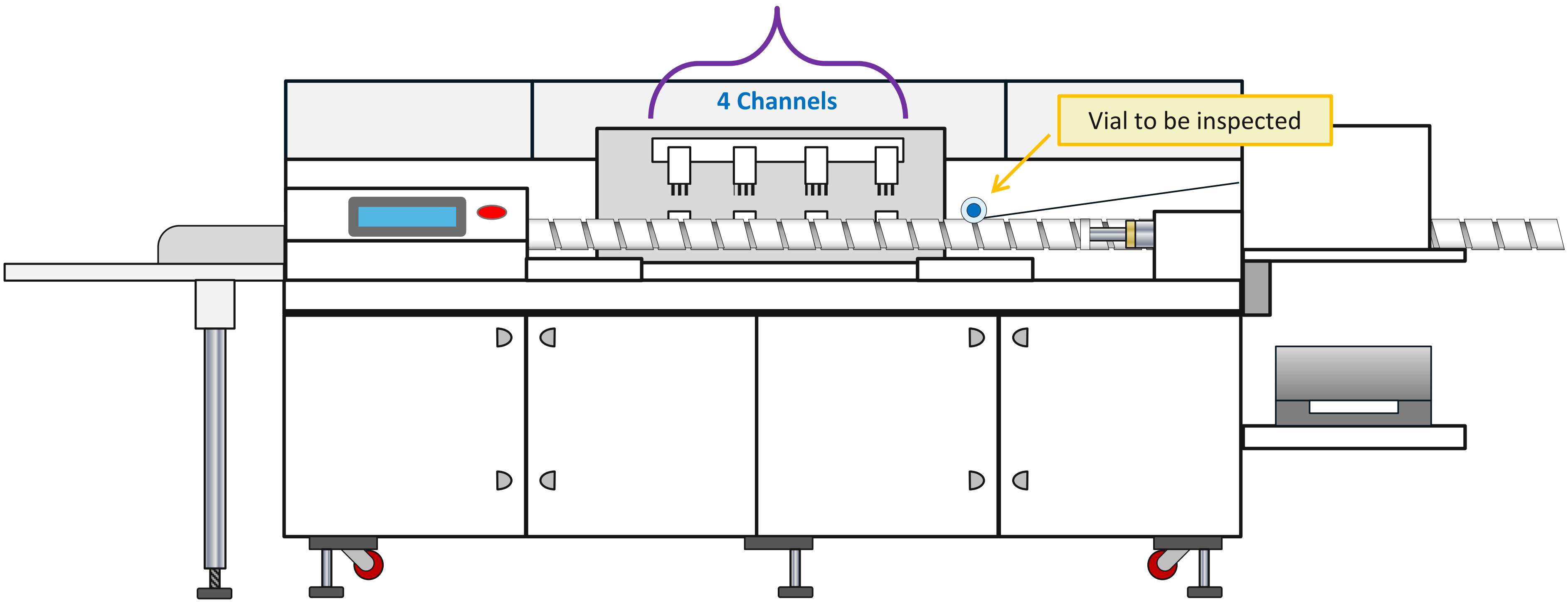
Source: PTI / Packaging Technologies and Inspection

Detection Process

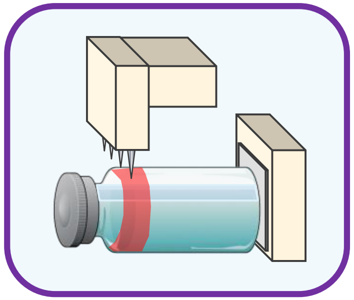


Station 1 (CH 1)
Shoulder of the Vial

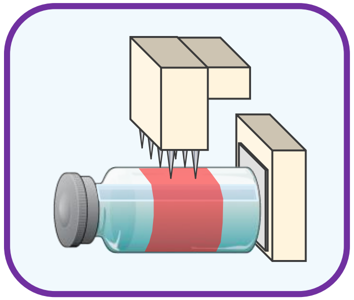
All containers are inspected at specific areas referred to Channels (4). Each one has a different electrode configuration and will produce an individual Inspection Signal Value (data point).



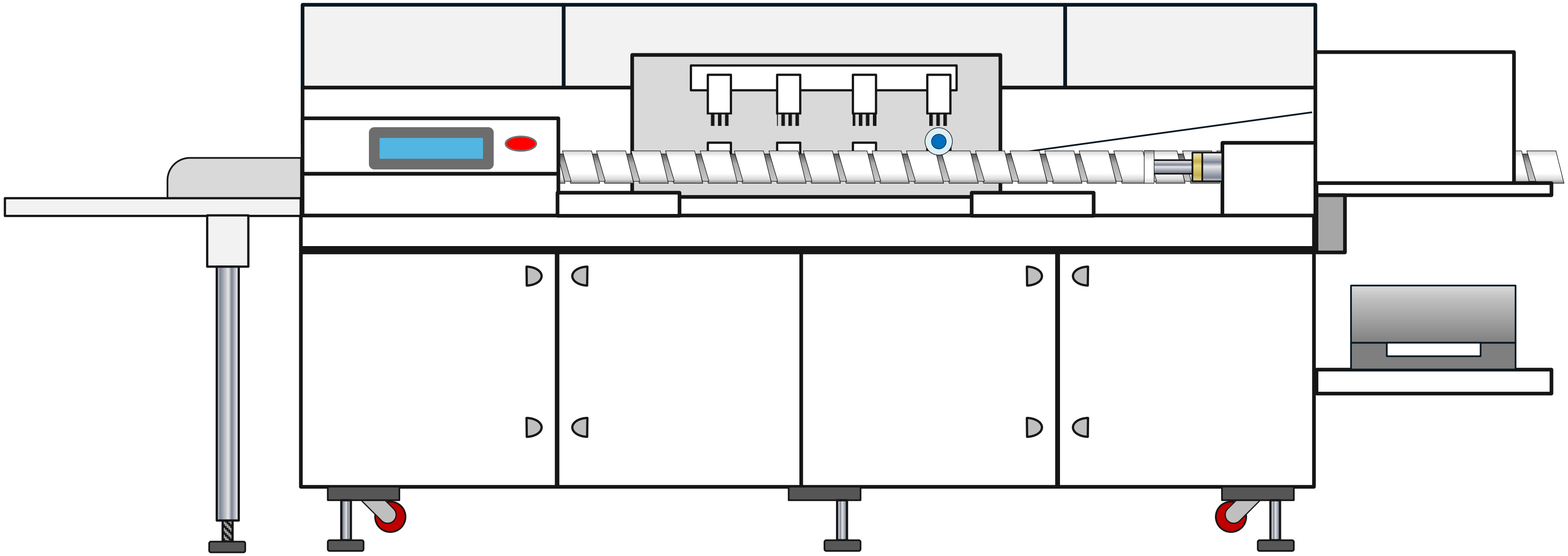
Detection Process



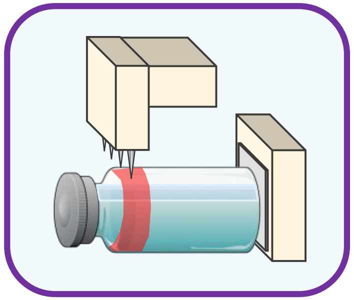
Station 1 (CH 1)
Shoulder of the Vial



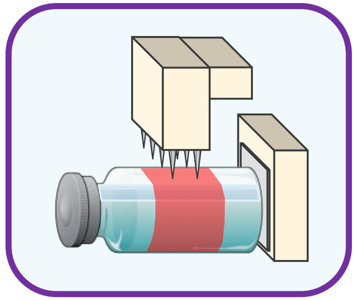
Station 2 (CH 2)
Entire sidewall (body) of the vial



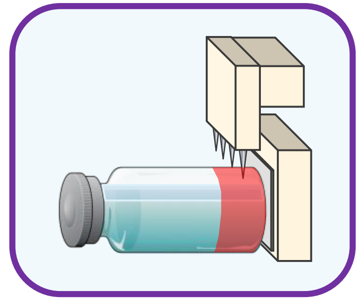
Detection Process



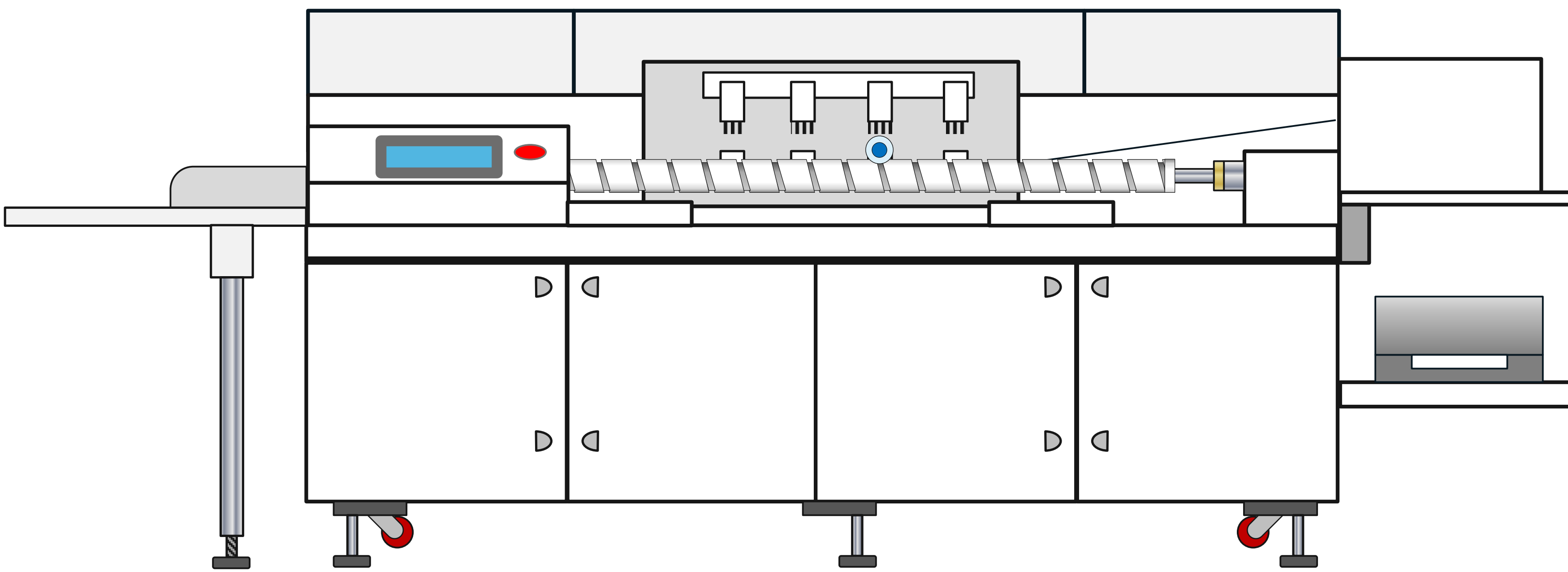
Station 1 (CH 1)
Shoulder of the Vial



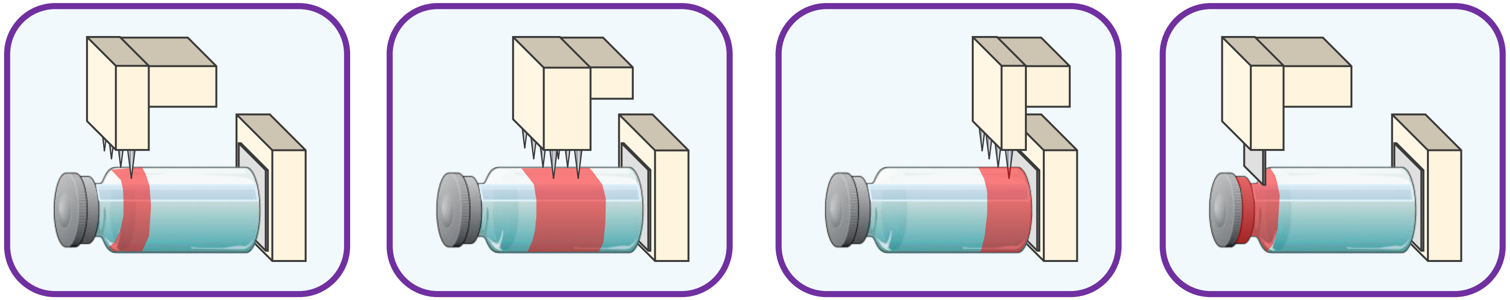
Station 2 (CH 2)
Entire sidewall (body) of the vial



Station 3 (CH 3)
Bottom / Heel of the vial



Detection Process

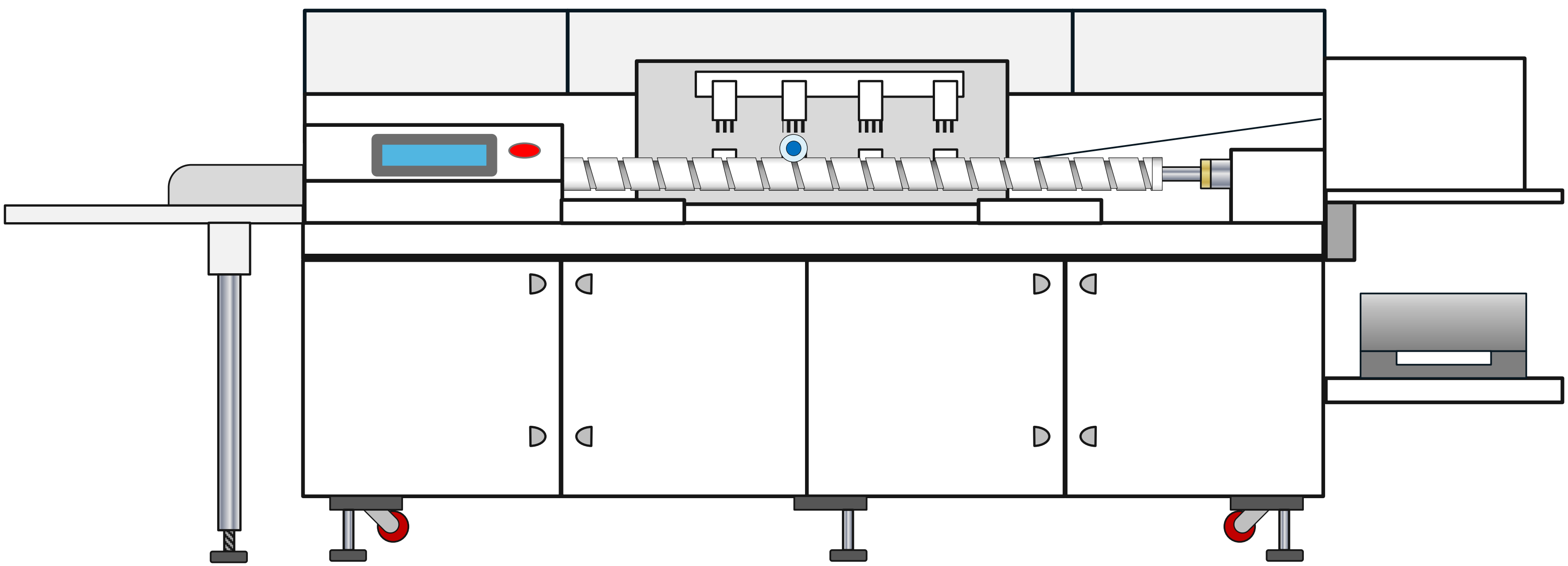


Station 1 (CH 1)
Shoulder of the Vial

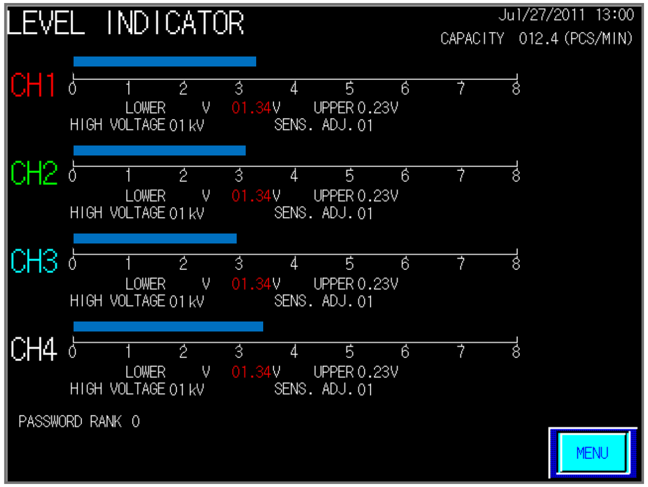
Station 2 (CH 2)
Entire sidewall (body) of the vial

Station 3 (CH 3)
Bottom / Heel of the vial

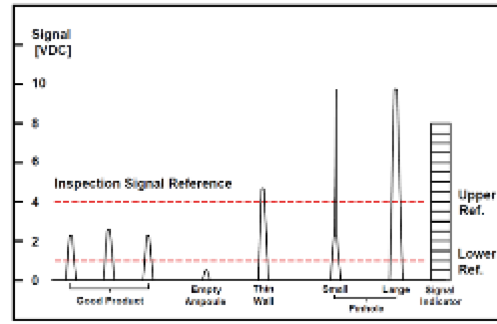
Station 4 (CH 4)
Neck, seal and cap/closure of the vial



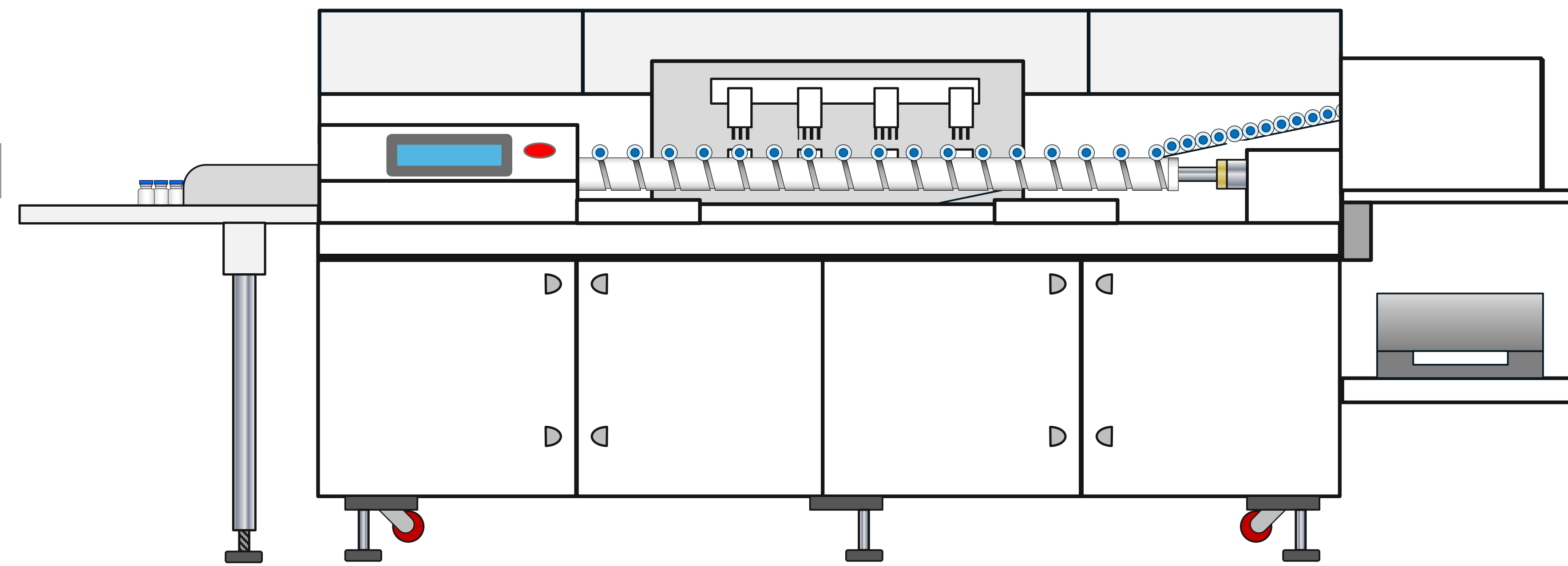
Voltage Reference Adjustment



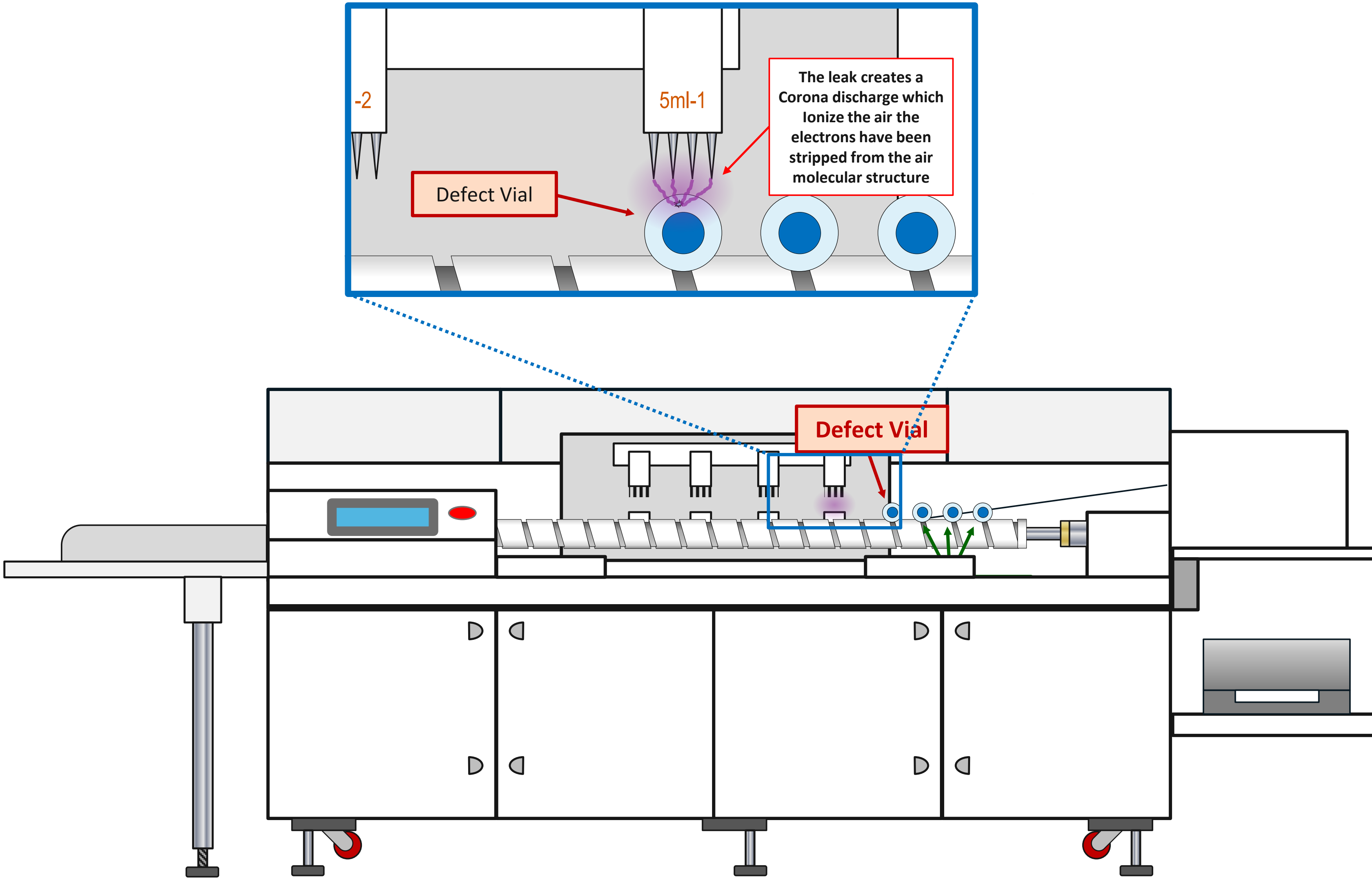
The vial inspection parameters are routinely setup by running sixteen (16) “good” vials through the machine based on the signal generated the machine automatically determines the initial Upper Reference (voltage).



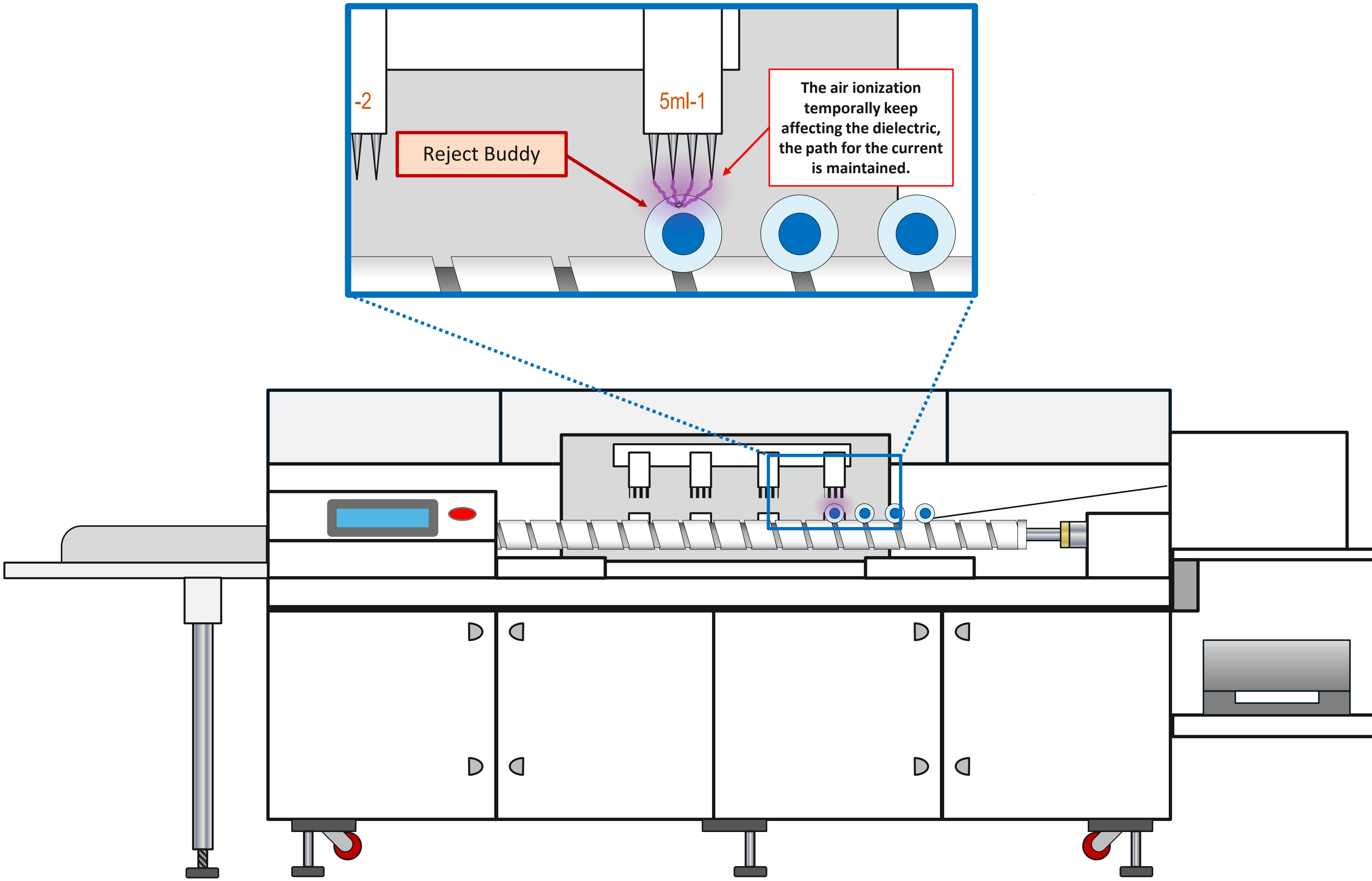
Upper Reference *= Average of 16 good product signals + GAP*
Lower Reference *= 1V (Lower Reference Set key-switch is ON)*
0V (Lower Reference Set key-switch is OFF)



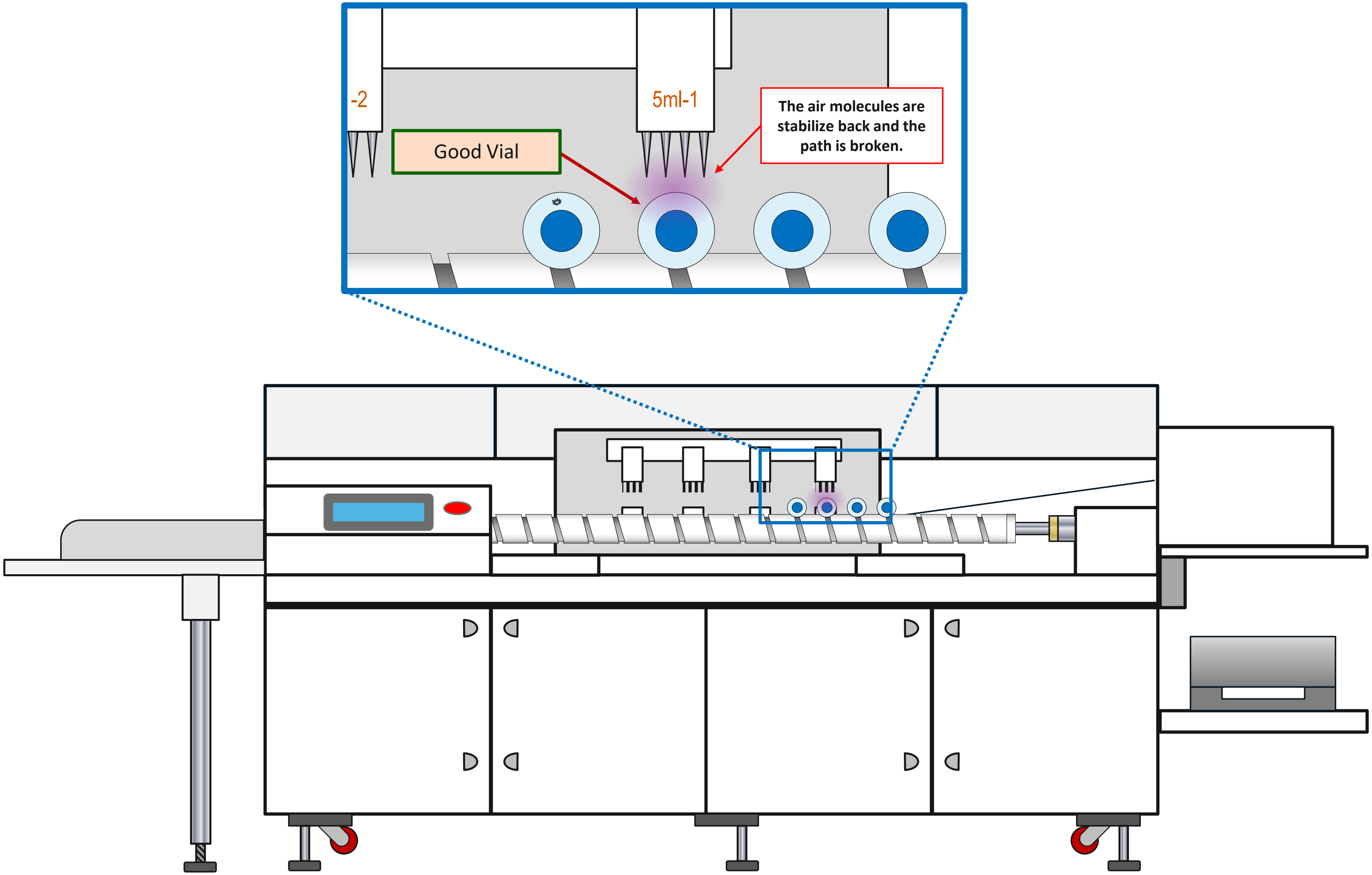
Buddy Reject Effect



Buddy Reject Effect



Buddy Reject Effect



Summary: HVLD Contraints

Types of Products that CANNOT be Inspected

Products

- × Aqueous solutions with a conductivity value of less than 1.2µS cm^2
- × Oil Based Products
- × Flammable Products
- × Products with > 25% Alcohol Content
- × Many Gel Products
- × Oxidant Sensitive Solutions

Containers

- × Metallic Containers
- × Aluminum Induction Sealed Bottles
- × Metalized Film Material

When testing oxygen sensitive products, It is important that method development tests verify that the equipment setup and exposure to electricity will not cause ozone build-up that can result in oxidation.

LEAK INSPECTION METHODS

PRESSURE & VACUUM LEAK DETECTION (P/V)

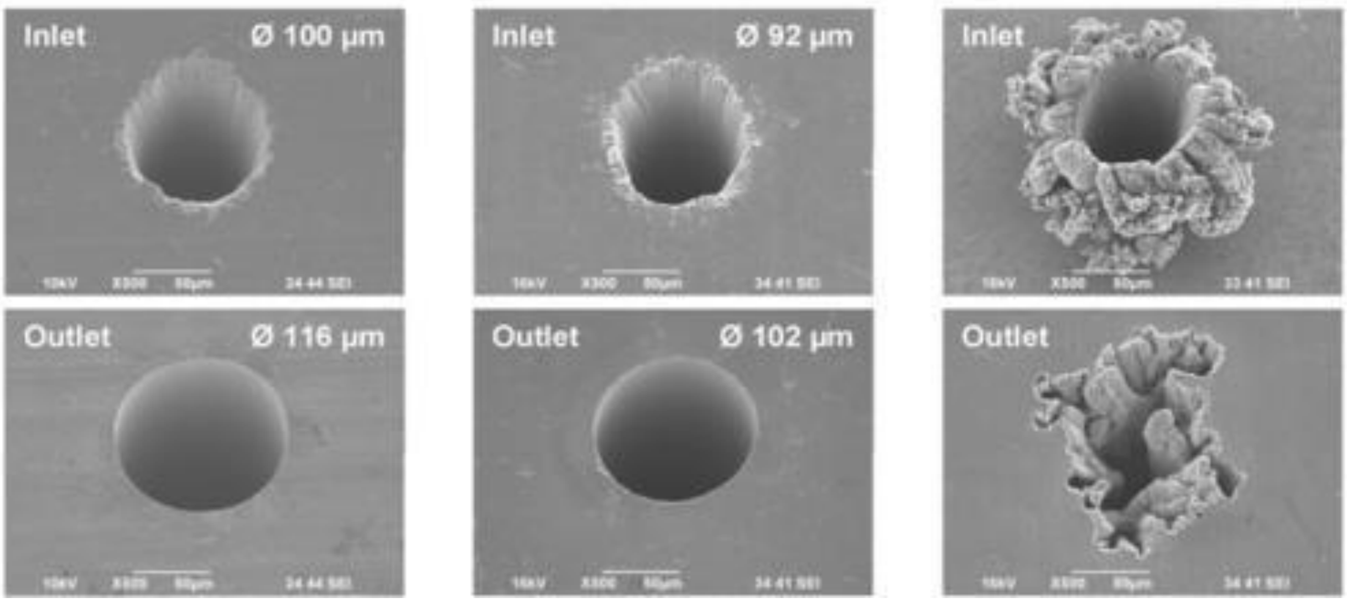
Content

- Pressure Leak Detection Methods
  - Pressure Decay
  - Differential Pressure
  - Vacuum Decay
  - LFC (Liquid Filled Container) Method
- Laser Head Space Analysis (HSA)
- Tracer gas (vacuum mode)

Certification of a Leak

The drilling process produces **variability to the topography of the orifice**. Sometimes a Certificate of Conformance of the orifice dimension may not be enough to support a qualification process.

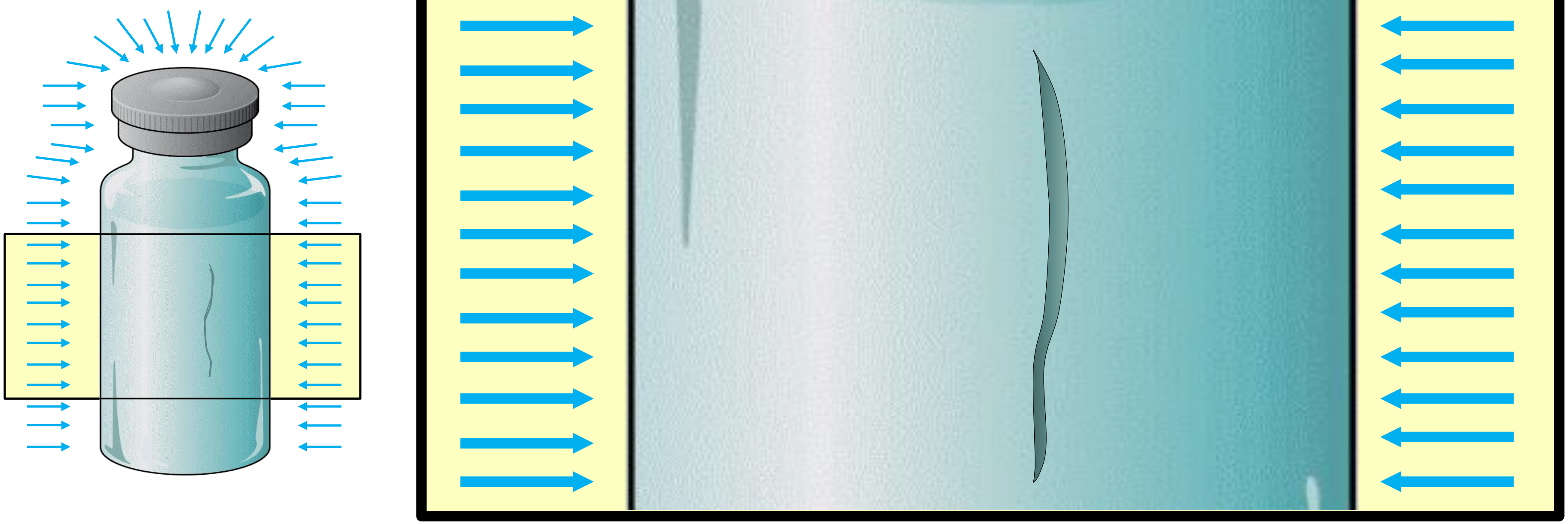
The theoretical diameter of a circular hole, that allows a corresponding gas flow, can be calculated.



Heat accumulation during pulsed laser materials processing
Rudolf Weber, Thomas Graf, Peter Berger, Volkher Onuseit, Margit Wiedenmann, Christian Freitag, and Anne Feuer

Certification of a Leak

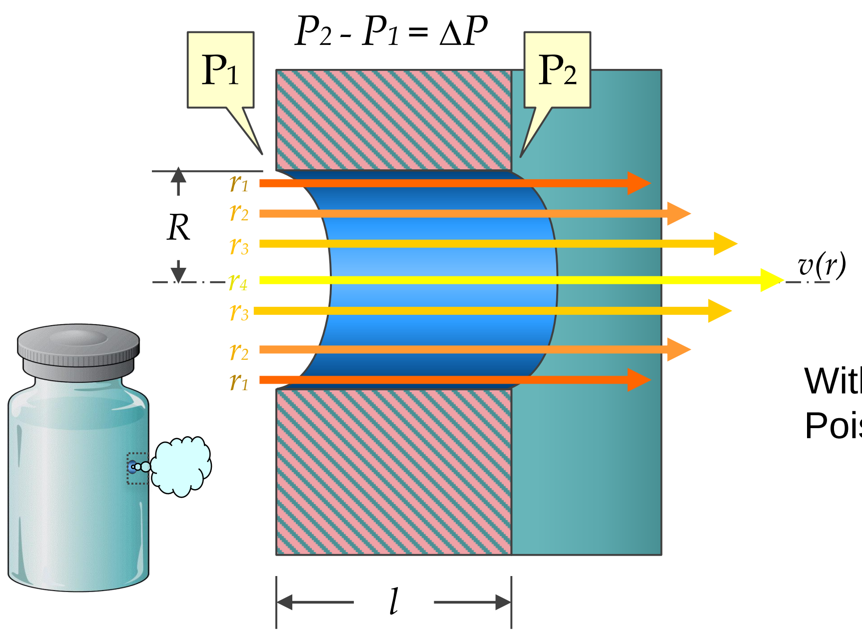
The use of pressure during the leak testing cycle could close or reduce the dimensions of the crack, preventing the detection.



Certification of a Leak

Considering a system under an adiabatic condition and not providing any energy/work to the environment, the gas flow through an opening is calculated as follows:

Due to the viscosity of the flowing media (air) the volume flow through a orifice depends on the length, shape, and the smoothness of the leak conduit. The sketch below shows the volume flow through a circular hole according to Hagen-Poiseuille.



$$v(r) = \frac{\Delta P}{4.\eta.l}(R^2 - r^2)$$

With η = dynamic viscosity of air at a known temperature

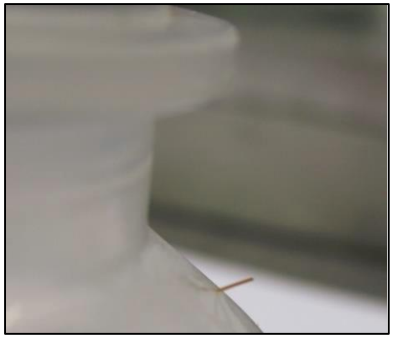
The lower the r value the faster the air flow

$$v(r_4) > v(r_1)$$

With a airflow considered laminar, the Hagen-Poiseuille relation can be used.

$$Qpv = \frac{\pi}{128\,\eta} \times \frac{d^4}{l} \times \frac{(pi^2 - pa^2)}{2}$$

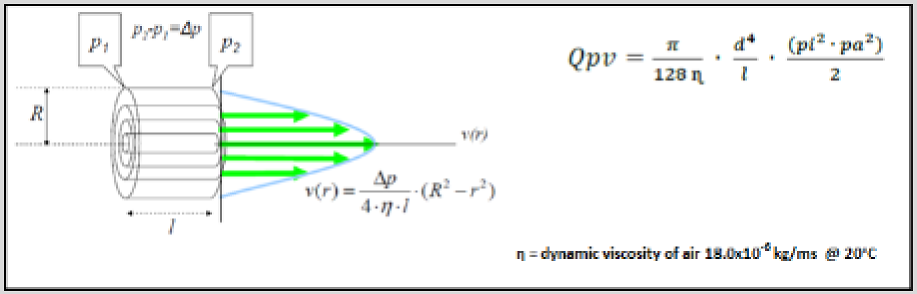
Certification of a Leak



Capillary or micropipettes are cut according to a calculated length and then glued into the container, it always has to be verified that the airflow passing through the conduit is in accordance with the target hole diameter. This method requires an experience user for avoiding any blockage of the capillary as well as a good closure around the capillary.

Capilaries Calculator

Hagen-Poiseuille Model



Capilary Diameter	50.0	µm	0.0485	Actual Inner Diameter
Capilary Length	14.9	mm	Qpv = 3.1019	cc/min
Test Pressure (P₁)	750.0	mbar	15	µm

Capilary Diameter	30.0	µm	0.03	Actual Inner Diameter		
Target Diameter	10.0	cc/min	1.414	flow cc/min	Length = 4.8	mm
Test Pressure (P₁)	750.0	mbar				

Edwin Martinez

d micr	d mm	p mb	p psi	w m/s	cc/s	leakrates (V) cc/10s	leakrates (V) cc/min
1	0.001	750	10.875	280	0.0002	0.0022	0.0132
5	0.005	750	10.875	290	0.0057	0.0569	0.342
10	0.010	750	10.875	300	0.0236	0.236	1.414
15	0.015	750	10.875	300	0.0530	0.530	3.18
20	0.020	750	10.875	300	0.094	0.942	5.65
25	0.025	750	10.875	300	0.147	1.473	8.84
30	0.030	750	10.875	300	0.212	2.121	12.72
40	0.040	750	10.875	300	0.377	3.770	22.62
50	0.05	750	10.875	300	0.589	5.890	35.3
75	0.08	750	10.875	300	1.325	13.3	80
100	0.10	750	10.875	300	2.356	23.6	141
150	0.15	750	10.875	300	5.30	53.0	318
200	0.20	750	10.875	300	9.42	94	565
250	0.25	750	10.875	300	14.73	147	884
300	0.30	750	10.875	300	21.21	212	1'272
500	0.50	750	10.875	300	58.90	589	3'534

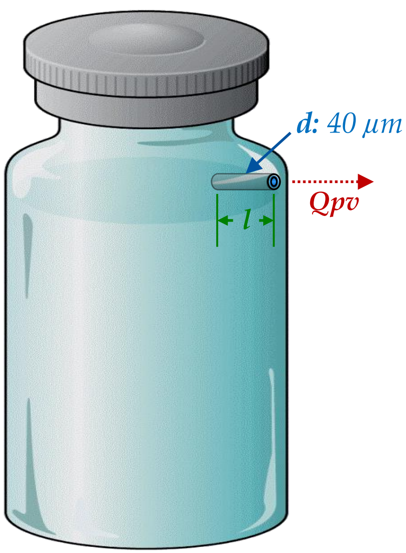
d micr	d mm	p mb	p psi	w m/s	cc/s	leakrates (V) cc/10s	leakrates (V) cc/min
1	0.001	850	12.325	280	0.0002	0.0023	0.0138
5	0.005	850	12.325	290	0.0058	0.0577	0.346
10	0.010	850	12.325	300	0.0231	0.231	1.384
15	0.015	850	12.325	300	0.0519	0.519	3.11
20	0.020	850	12.325	300	0.092	0.922	5.53
25	0.025	850	12.325	300	0.144	1.441	8.65
30	0.030	850	12.325	300	0.208	2.076	12.45
40	0.040	850	12.325	300	0.369	3.690	22.14
50	0.05	850	12.325	300	0.577	5.765	34.6
75	0.08	850	12.325	300	1.297	13.0	78
100	0.10	850	12.325	300	2.306	23.1	138
150	0.15	850	12.325	300	5.19	51.9	311
200	0.20	850	12.325	300	9.22	92	553
250	0.25	850	12.325	300	14.41	144	865
300	0.30	850	12.325	300	20.76	208	1'245
500	0.50	850	12.325	300	57.65	577	3'459

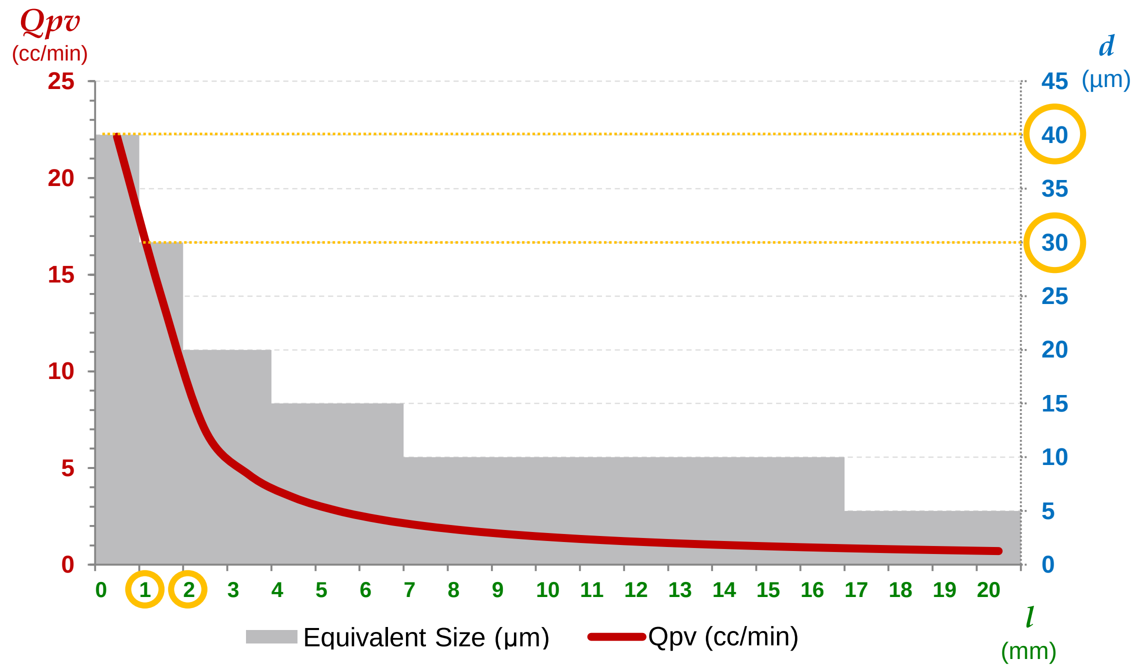
Length calculator developed for a validation process using micropipettes

Certification of a Leak

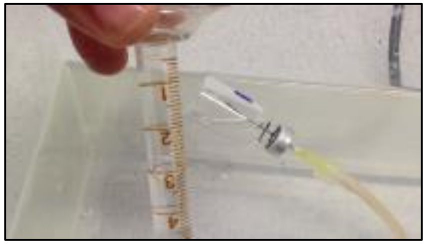
Capillary or micropipettes are cut according to a calculated length and then glued into the container, it always has to be verified that the airflow passing through the conduit is in accordance with the target hole diameter

$$l = \frac{\pi}{128\,\eta} \times \frac{d^4}{Qpv} \times \frac{(pi^2 - pa^2)}{2}$$

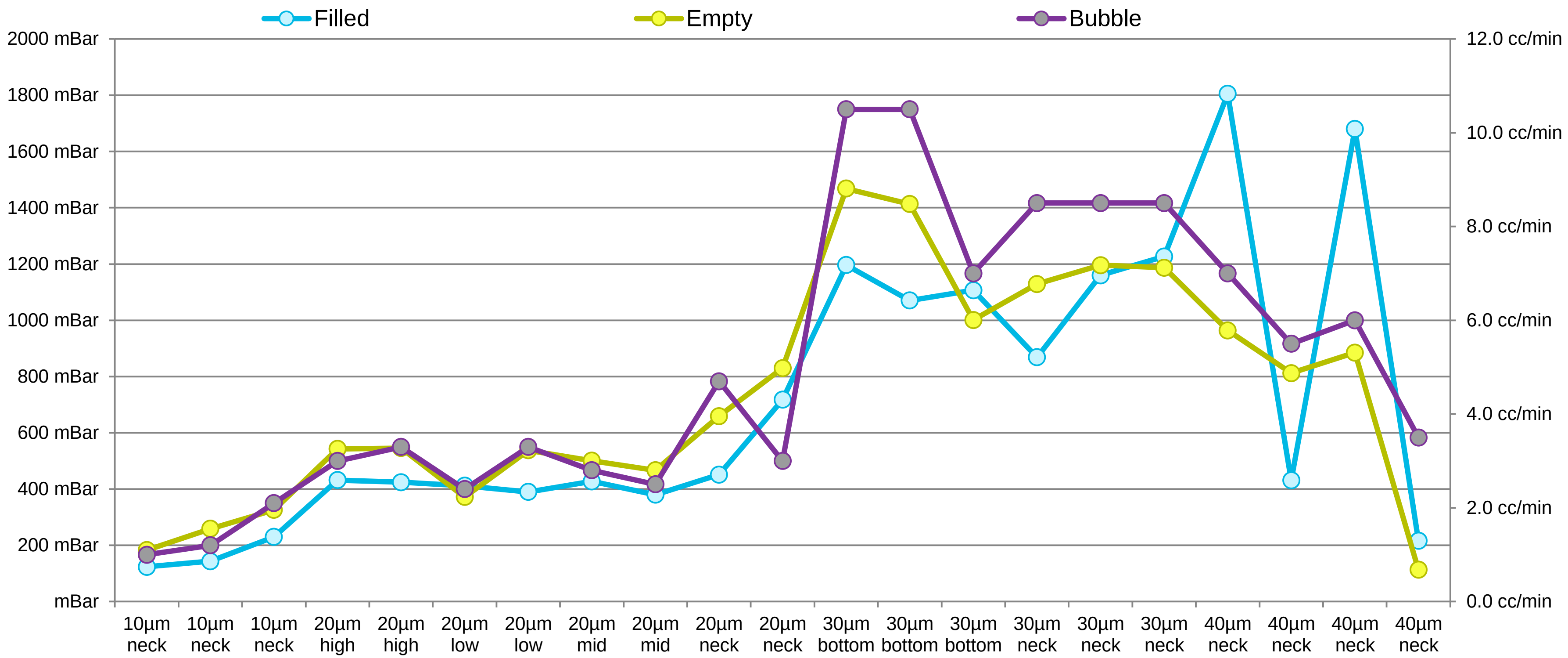




Leak Detection Methods



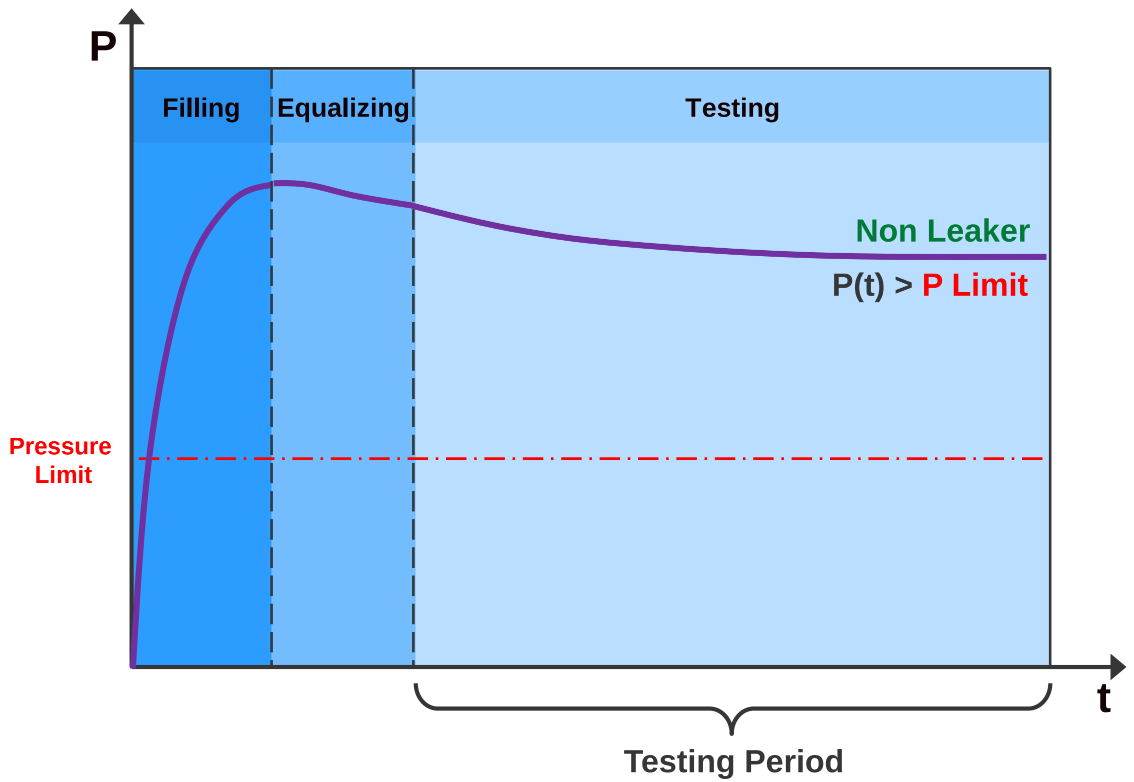
A visual comparison between the curves representing the results of the (3) different measuring approaches, a similar response can be observe on the domain of these tree (3) waves.

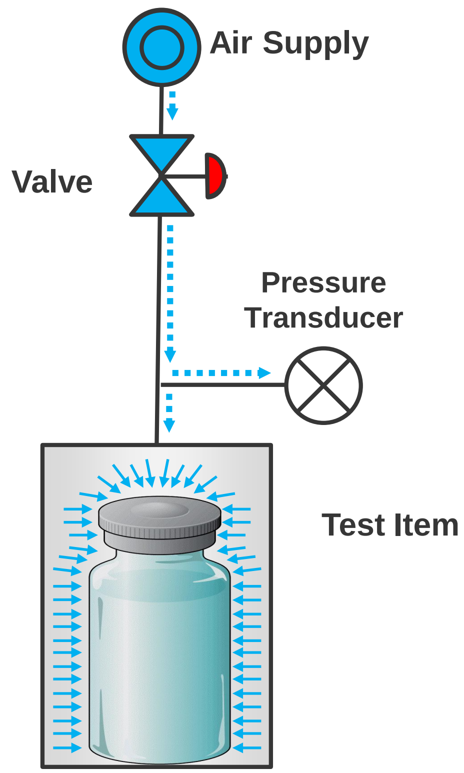


Leak Detection Methods

Test Chamber Pressure Decay Method

In the pressure-decay method for leak testing, a item is pressurized, the test circuit is isolated. A transducer reads the pressure change, and the pressure drop associated with a minimum accepted pressure limit.





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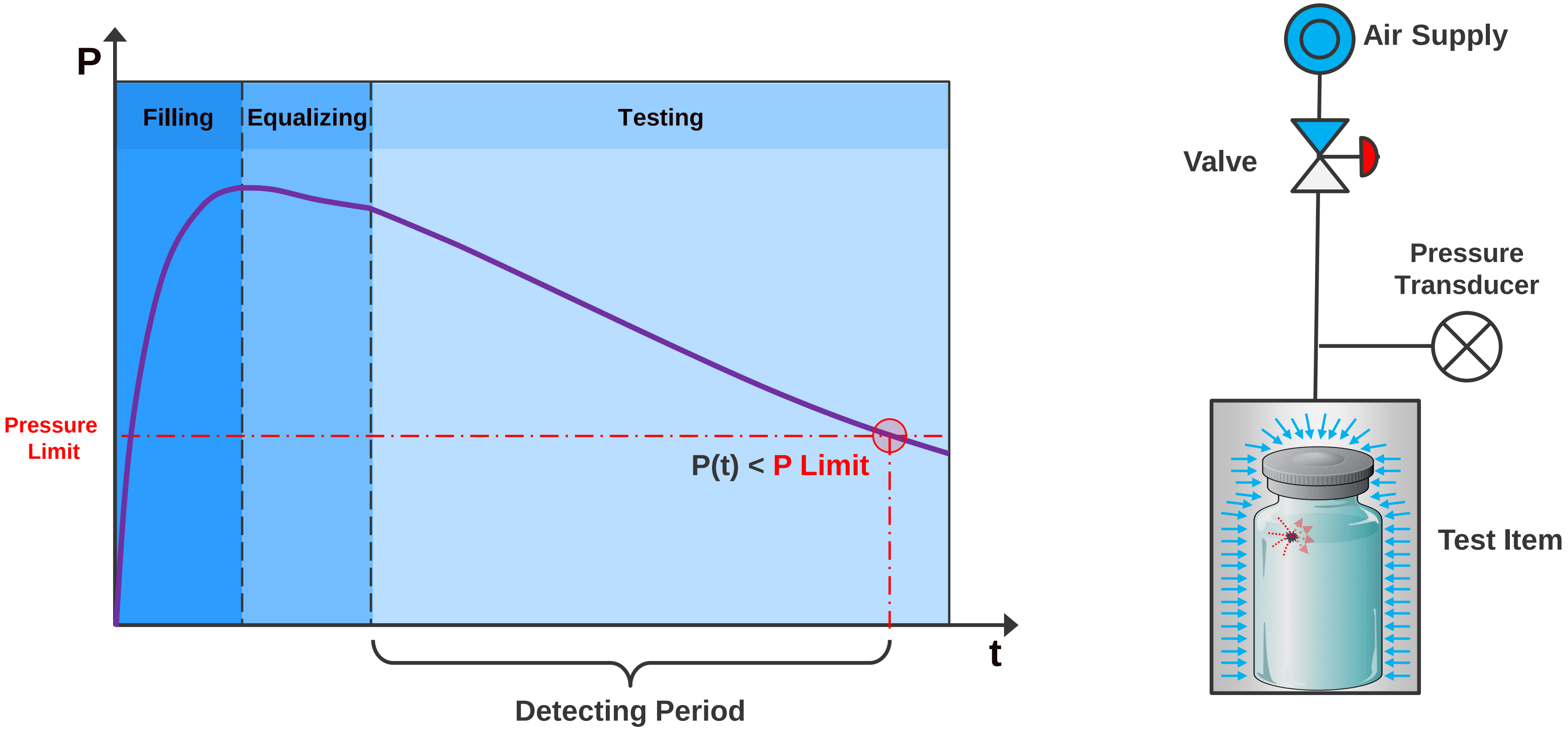
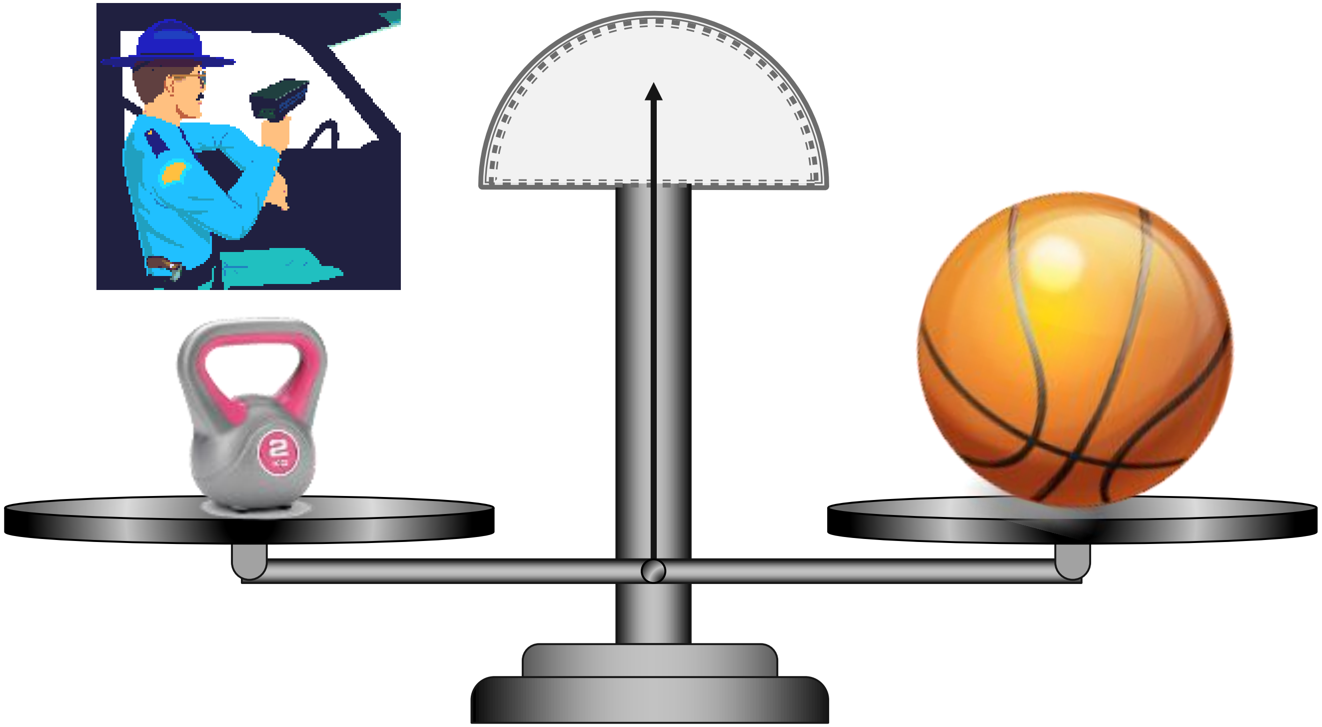


Leak Detection Methods

Differential Measurement

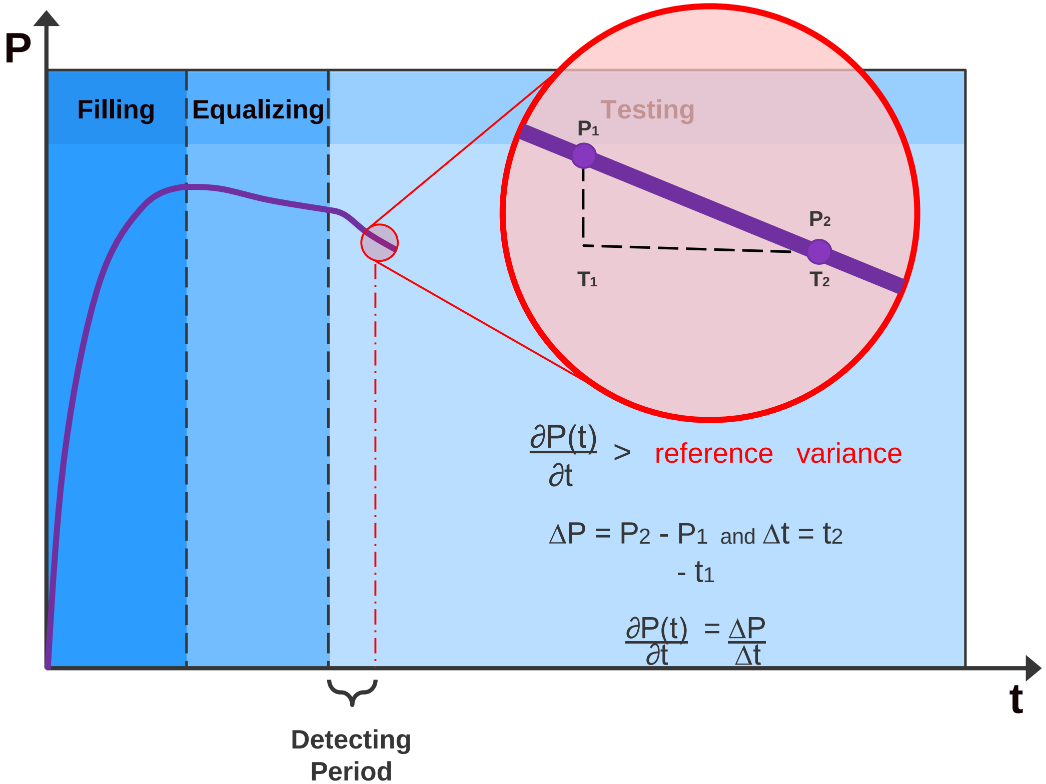
The differential pressure type air leak tester uses the same principle as the balancing scale. The same air pressure is charged to both the test subject and the reference with no leak and the change in pressure balance within a fixed time is checked for the presence of a leak.



Leak Detection Methods

Differential Pressure

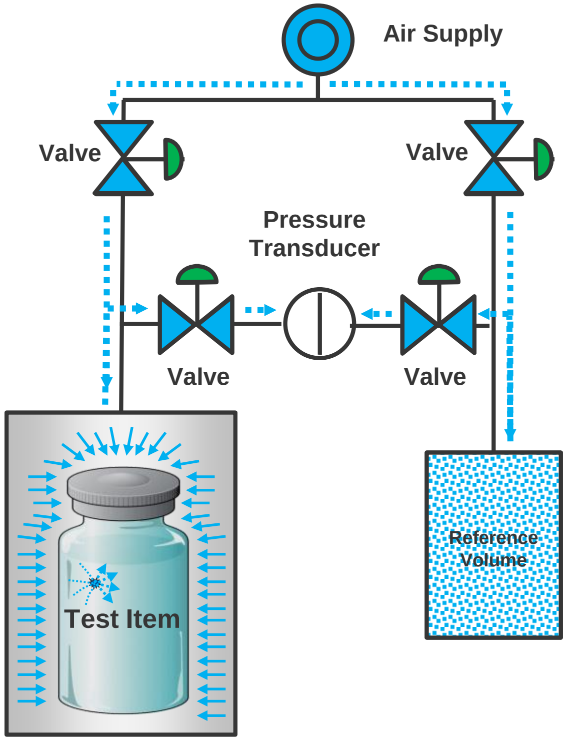
Testing involves pressurizing a reference volume along with a test part. The pressure differential between the non-leaking reference volume and the test item is then measured by a transducer over time. This method requires measuring pressure at **two points in time** to obtain a **pressure change** reading. It is an indirect method of measuring leakage rate because the time and pressure data must be converted into **leakage rate**.



$$\frac{\partial P(t)}{\partial t} > \text{reference variance}$$

$$\Delta P = P_2 - P_1 \text{ and } \Delta t = t_2 - t_1$$

$$\frac{\partial P(t)}{\partial t} = \frac{\Delta P}{\Delta t}$$



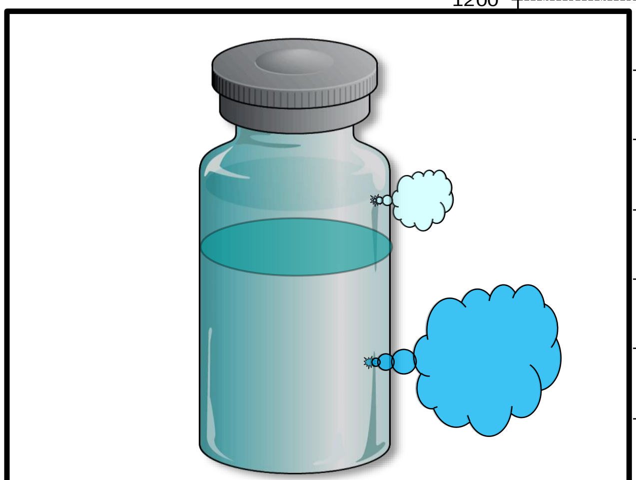
LFC (Liquid Filled Container)

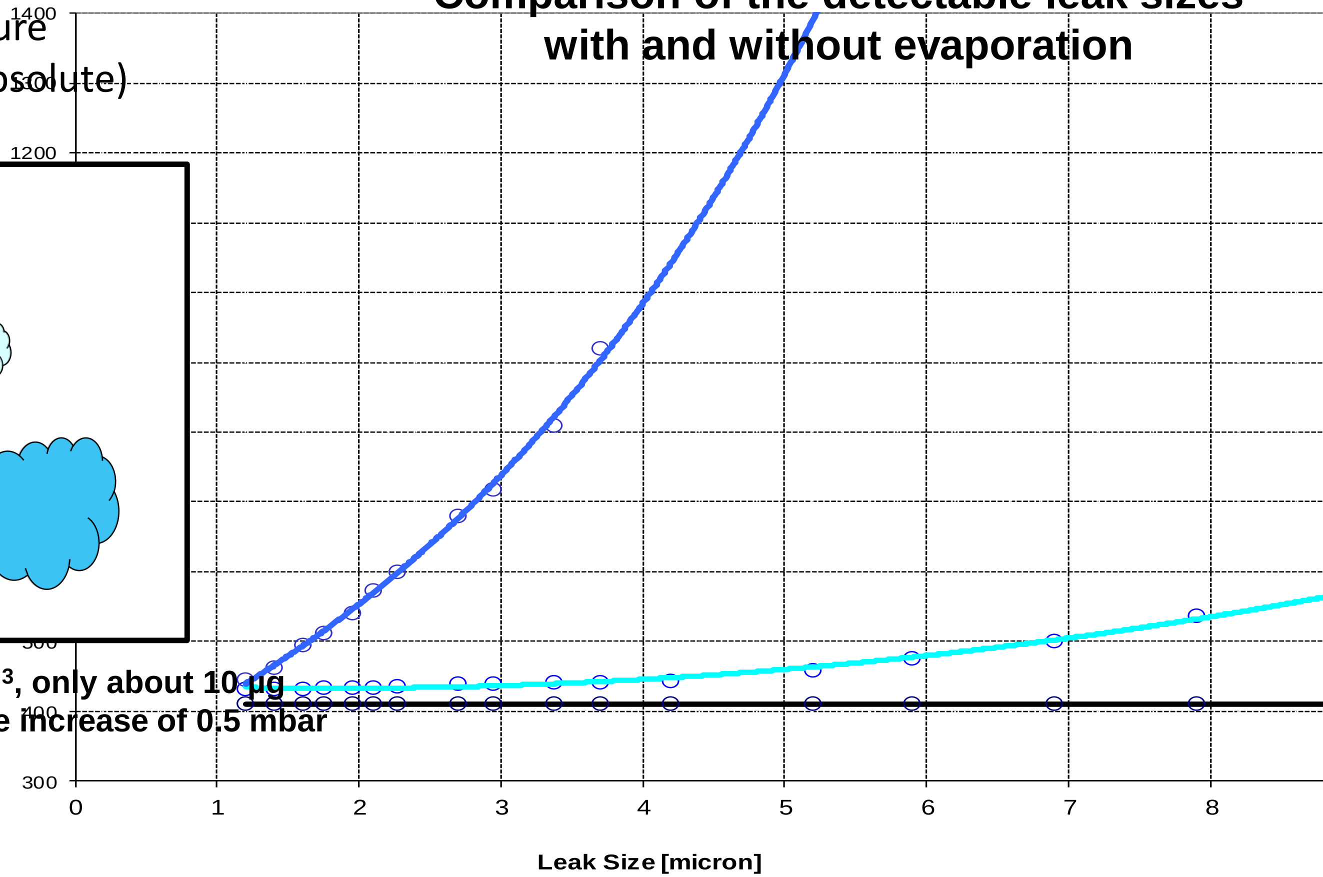
Functional Principle

At room temperature 20°C (68°F) water evaporates at 23.4 mbar (17.3 mmhg) absolute pressure. The vapor volume causes a sharp pressure increase inside the test chamber.

Test chamber evaporated below maximal H_2O vapor pressure (20°C at 23.4 mbar absolute)

Comparison of the detectable leak sizes with and without evaporation





At a constant test volume of 25 cm³, only about 10 µg water vapor are needed for a pressure increase of 0.5 mbar

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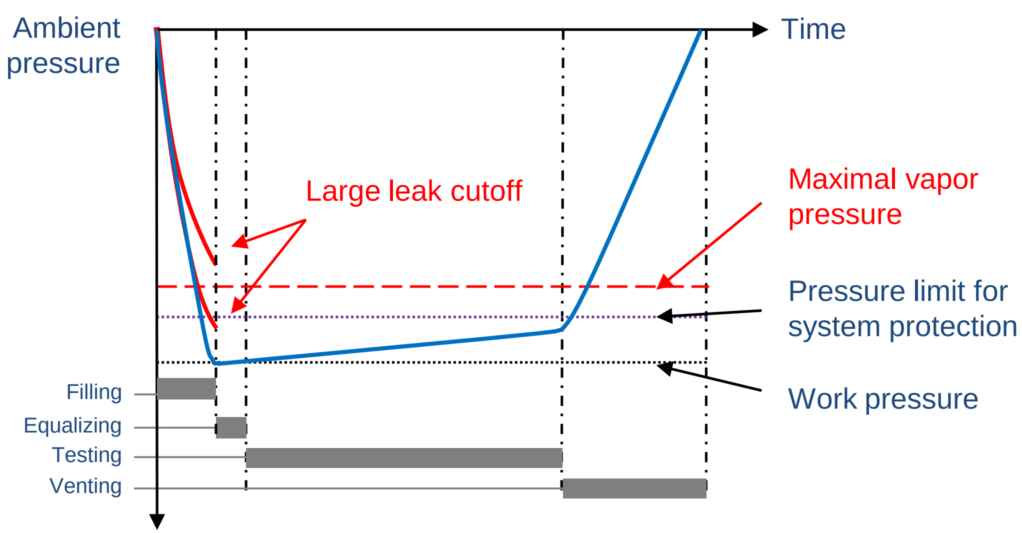
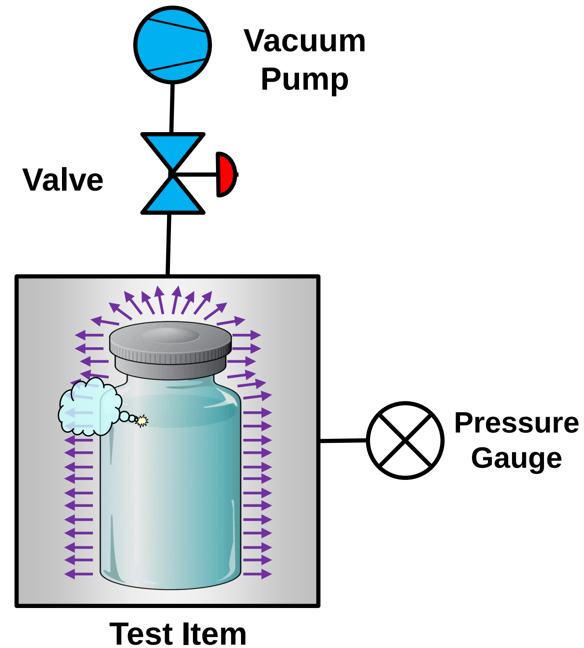
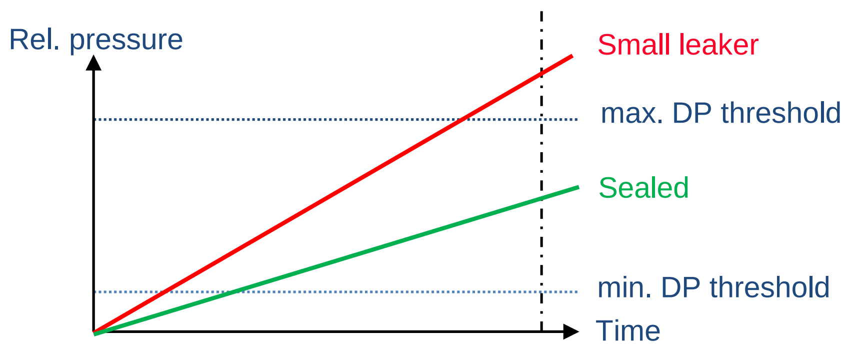


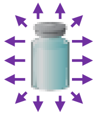




Things to consider using LFC method:

- The product has to be dry on the outside
- If the liquid becomes high in viscosity (oil-based) it may not vaporize anymore

Summary: P/V Inspection Constraints



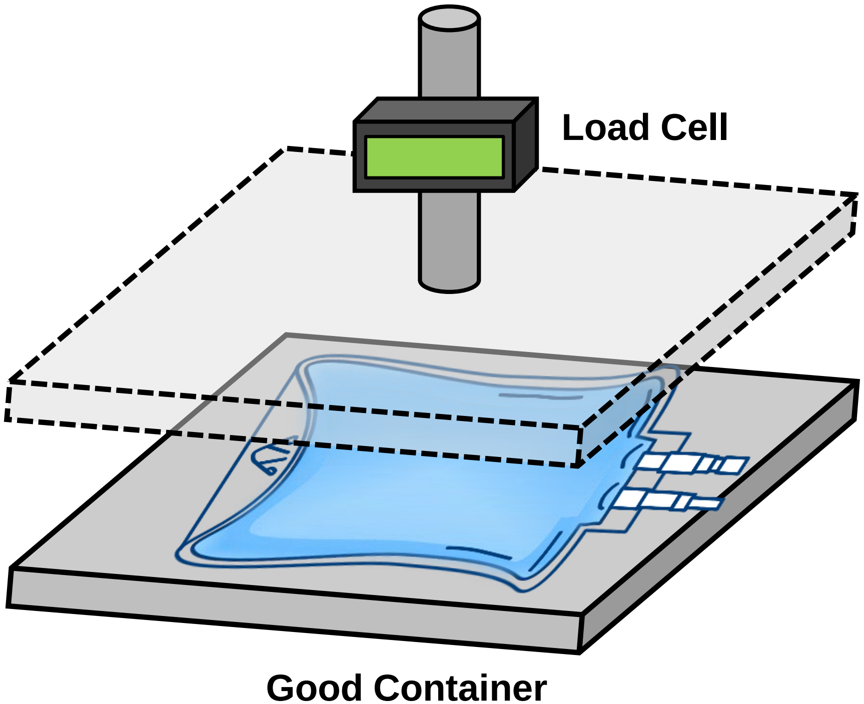
Pressure[2]	Vacuum[2]
10 µm[1] (Risk of closing a leak by pressing the stopper against it. Depending on Vial/Stopper combination.)	**10 µm[1]**
10 µm[1]	**10 µm[1]**
The headspace volume is impacting the detectability of gross leaks. The smaller the head space the more difficult it is to detect gross leaks by using the P/V method.	
10 µm[1] (needs to mitigate the force generated by the weight and viscosity of the solution volume)	**10 µm[1]** (suction force could crystalize the solution at the leak and block the flow)

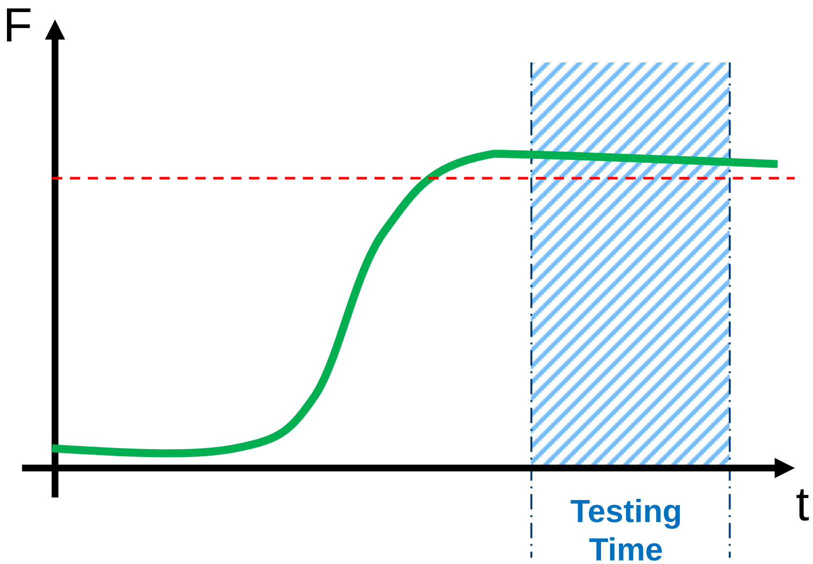
- Product may **clog defects masking their presence**. This is especially a concern with proteinaceous solutions, but has been observed with simple salt solutions as well.
- During the qualification the detection is normally tested using **laser drilled** holes due to the challenge to detect some type of **cracks**.
- Because of potential product effects, validation of test methods should employ **product-filled positive controls** (with defect packages).
- Exposure of defective packages to vacuum **can draw product into the test chamber** and test system. A plan to address such contamination must be developed (beyond simply 'drying out' the chamber with vacuum).

1 – Based on manufacturer information and preliminary studies.
2 – By increasing the testing time, the limit of detection can be improved to leak sizes smaller 10 microns. If for any reasons pressure or vacuum closes a leak (e.g. a crack with different layers), this cannot be detected.

Leak Detection Methods

A force sensor measures the expansion force of the flexible container.
The force of the bag is measured with a force measuring system and by analyzing the curve shape of the force a fine leak can be identified.





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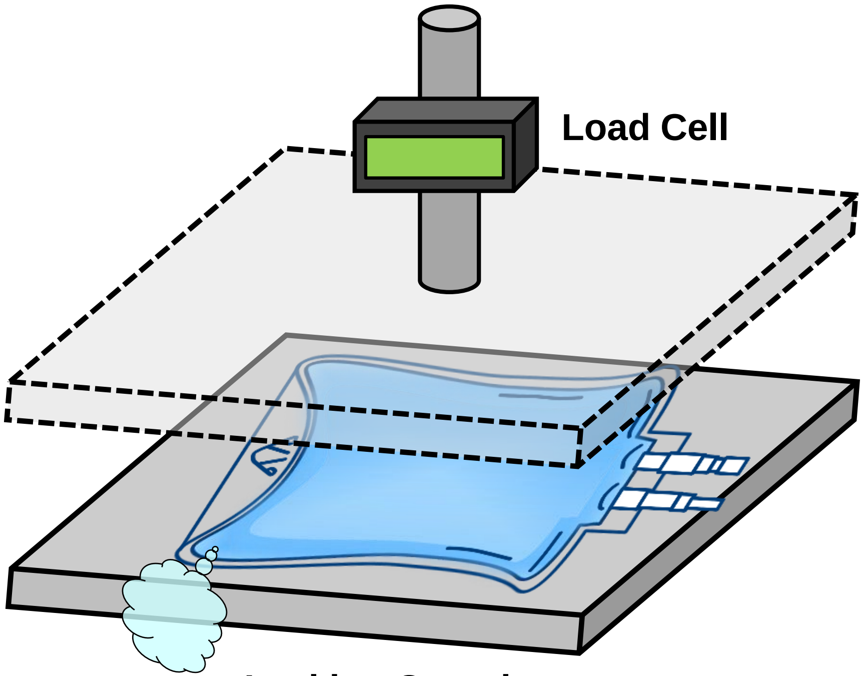
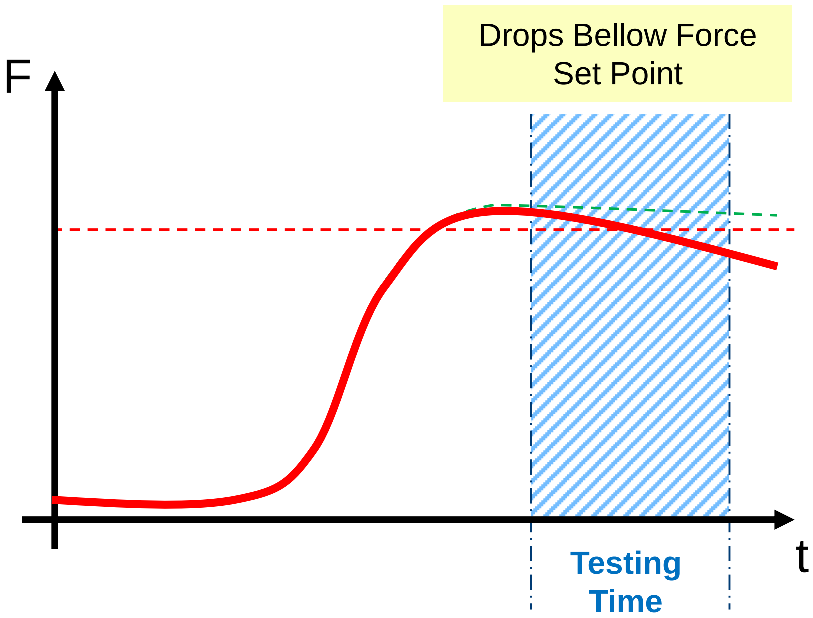
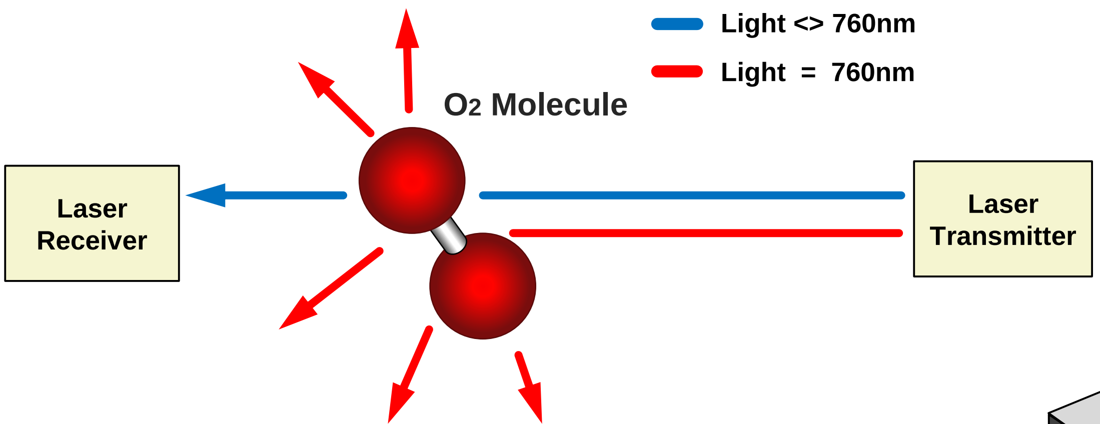




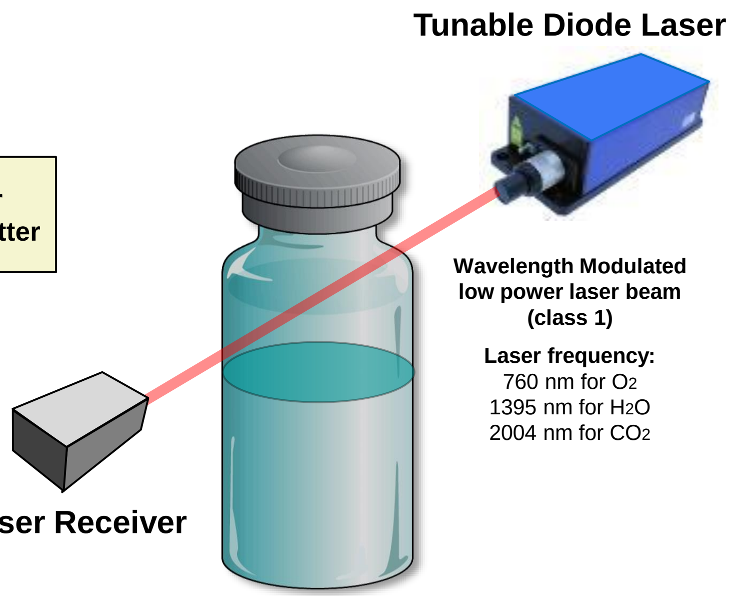
Leak Detection Methods

Head Space Analysis (HSA)

Upon test start, frequency-modulated spectroscopy is used to cause a near-infrared (IR) diode laser light to pass through the gas headspace region of the sealed test sample. Light is absorbed as a function of **gas concentration** and **pressure**. The absorption information is processed using phase-sensitive detection techniques; a mixer demodulates the signal. The output voltage, which is proportional to the absorption line shape, is digitally converted and further analyzed by a microprocessor, yielding test sample signal results.



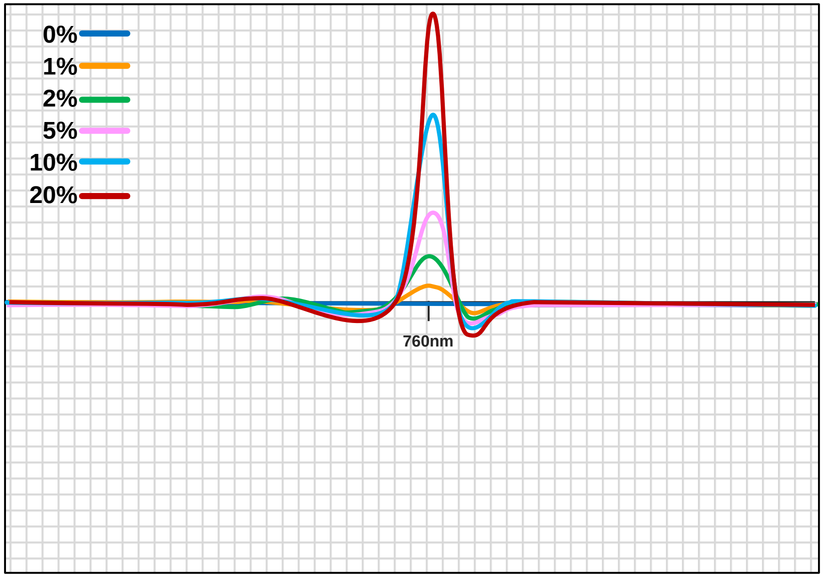
Light absorption is measured by frequency-modulated spectroscopy



Leak Detection Methods

Head Space Analysis (HSA)

- Measuring of oxygen concentration or gas total pressure in sealed containers.
- The technology used is the Laser absorption spectroscopy (TDLAS)
- Used for verification of nitrogen gassing efficiency, vacuum efficiency and Container Closure Integrity testing



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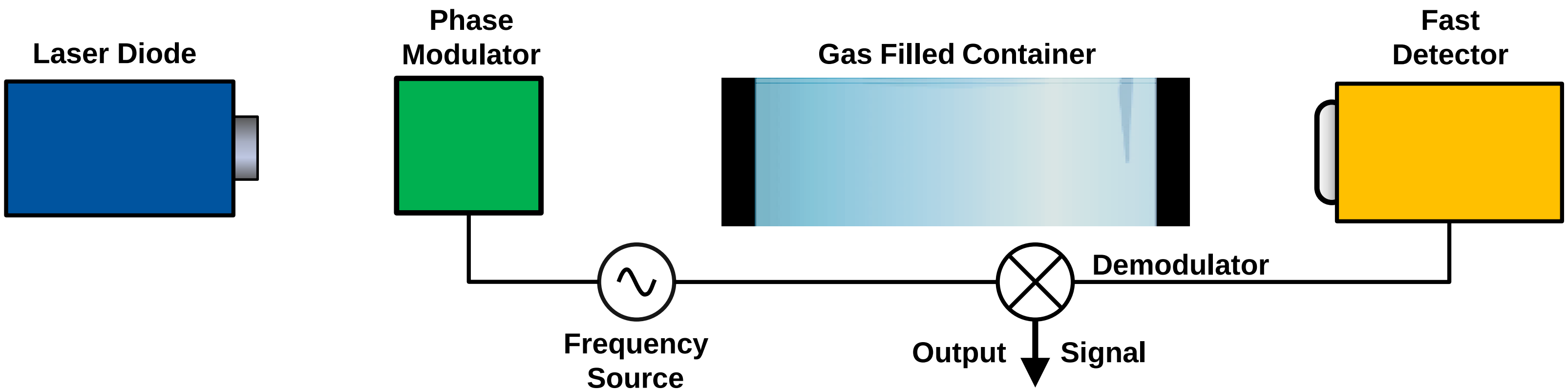

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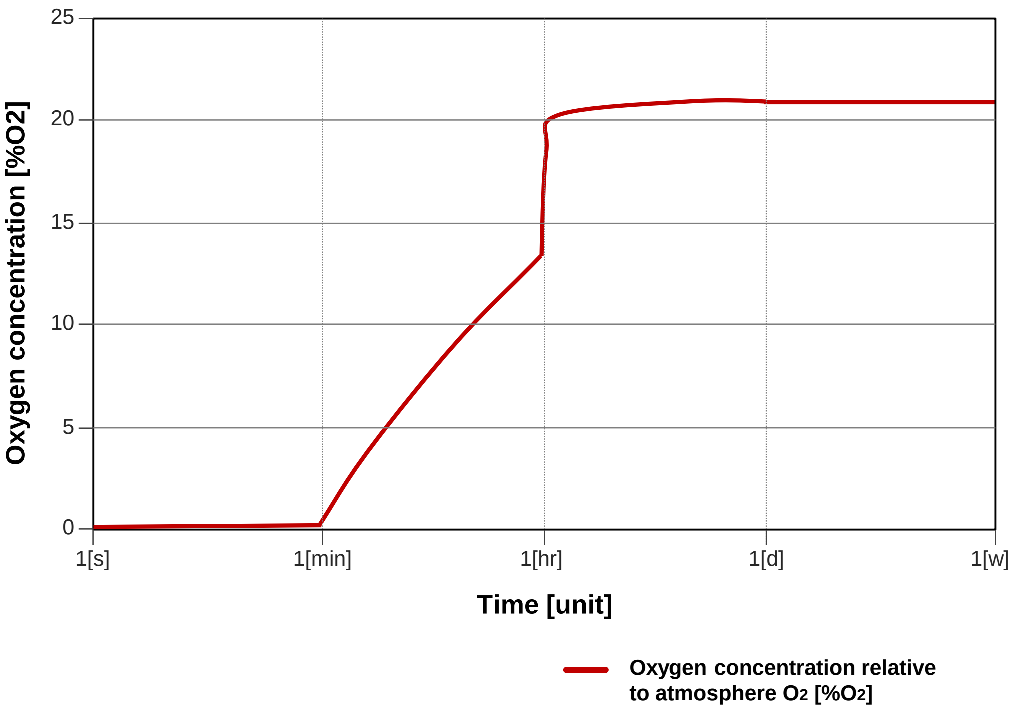


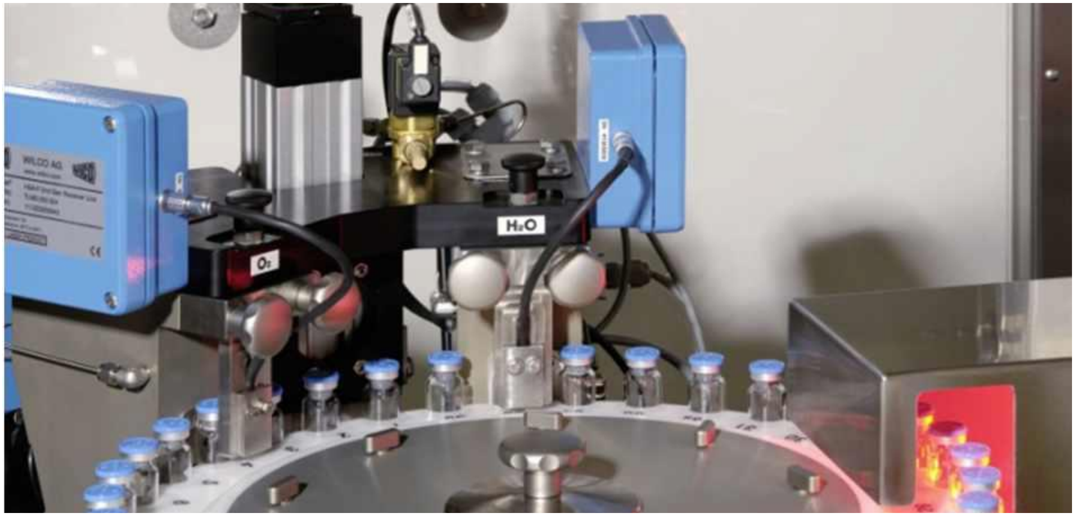
Sample:
- 10ml Vial
- 10 micron leak
- 300 mbar N_2

Leak Detection Methods

Summary: Head Space Analysis (HSA) Constraints

With laser-based methods, **single test point** on-line test results may or may not be related to leakage. Loss of headspace may be the result of **improper headspace flushing/vacuum**, or due to **poor stopper insertion** prior to final aluminum seal application, for example.

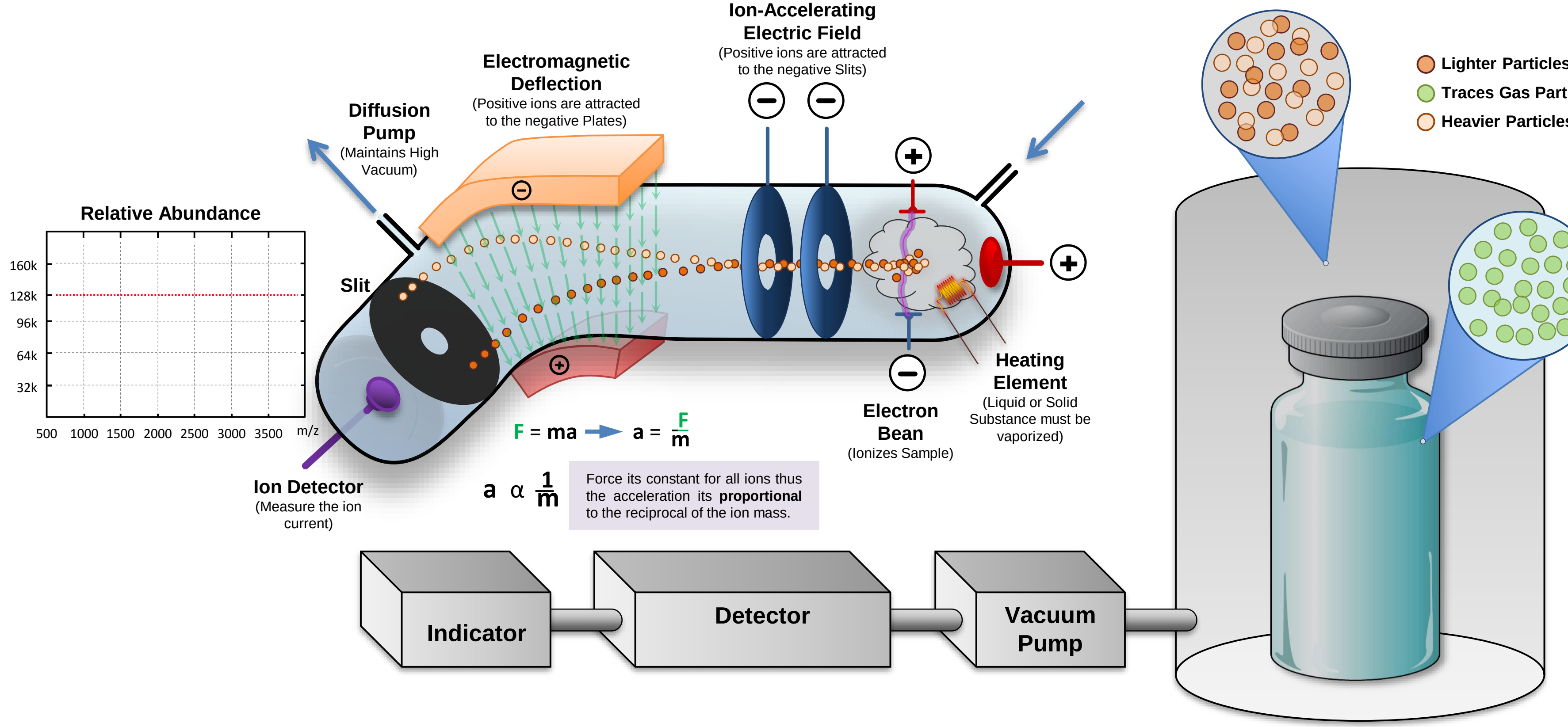
The **headspace pressure** affects the percentage of **gas molecules** inside the head space volume, thus on-line laser based testing isn't a leak test method that is readily linked to a defect size.



Tracer gas (vacuum mode)

Functional Principle

The container headspace its filled with a tracer gas (ex: Helium) and placed in a chamber connected to spectroscopic analyzer. A vacuum pump drawn the gas into the analyzer which measures the gas mass flow rate.



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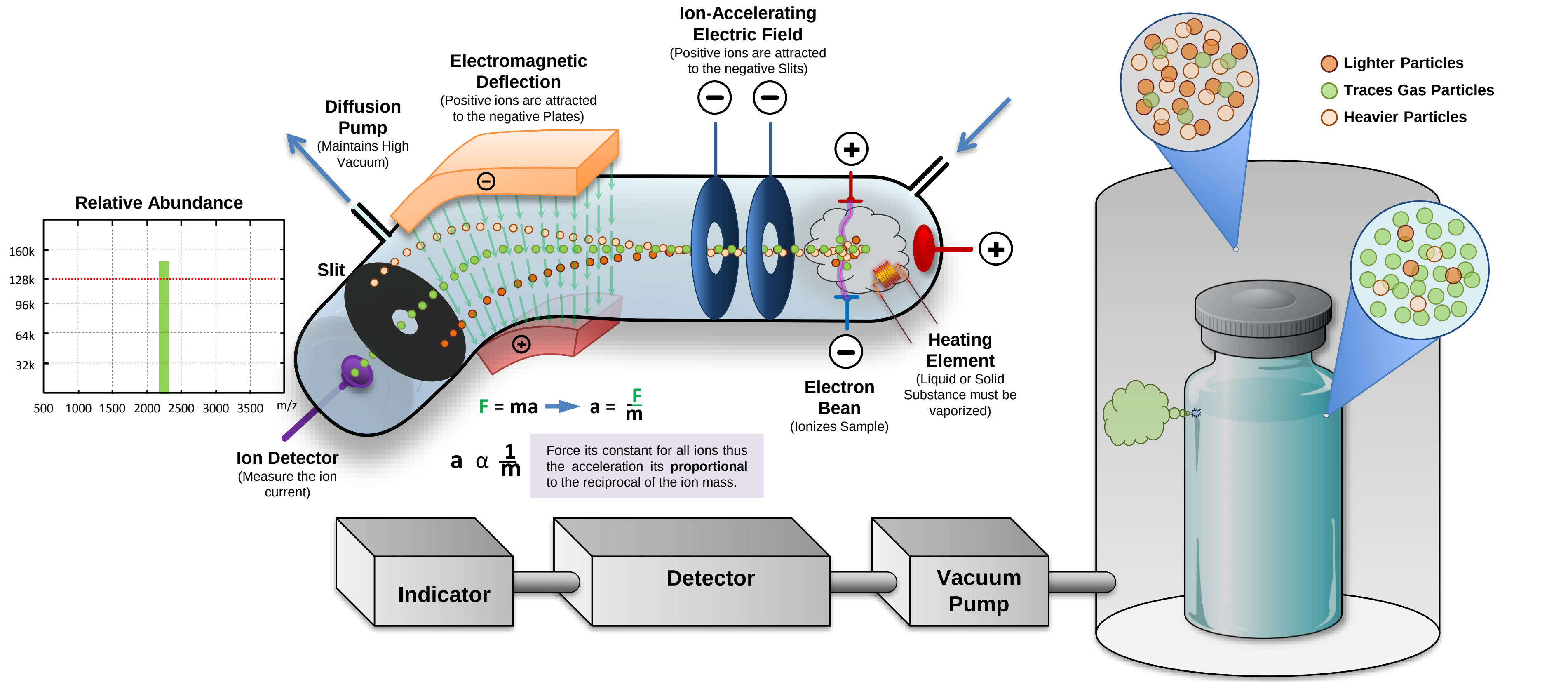


QUALIFICATION STRATEGIES.

Content

- Seeded Defect Test Sets
- Manual Inspection Qualification
- Knapp Studies
- Pre-Determined Acceptance Level

Seeded Defect Test Sets

- Seeded Defect Test Sets are critical to the qualification of a visual inspection program; manual and automated
- Comprehensive range of units for defects the process is designed to detect; including possible types and sizes of that particular defect category and are typical of the process/container configuration
- Defect Test Sets should include both good units and defect units
- Defect units can be collected from the Production process (i.e. rejected units) or can be prepared in a controlled environment

Seeded Defect Test Sets

- Below are examples of Defect units

Particulate Defects		
Material	**Shape**	**Size (microns)**
Stainless Steel	Amorphous	100 through 1000
Glass Sphere	Spherical	100 through 1000
Glass Shard	Amorphous	100 through 1000
Elastomer Material	Amorphous	100 through 1000
Light Colored Fiber	Fiber/String	500 through 2000
Dark Colored Fiber	Fiber/String	500 through 2000
Integrity Defects		
Defect Types	**Location**	**Size**
Small Cracks	Bottom, Heel, Sidewall, Barrel, Shoulder, Neck	1/16" to 1/8"
Medium Cracks	Bottom, Heel, Sidewall, Barrel, Shoulder, Neck	1/8" to 1/4"
Large Cracks	Bottom, Heel, Sidewall, Barrel, Shoulder, Neck	> ¼"
Laser Drilled Pin Holes	Bottom, Heel, Sidewall, Barrel, Shoulder, Neck	5 µ through 40 µ
Closure Defects	Neck/Tip Opening	Missing stopper, overseal, or tip

Manual Inspection

- The Qualification of an Automated Visual Inspection Process usually starts with a Manual Visual Inspection Program
- Manual Visual Inspection is generally considered the baseline to compare the performance of the Automated Process
- A Manual Visual Inspection Program should include a phase approach that may include Defect Recognition Training, Defect Qualification, and On the Job Training
- A Manual Visual Inspection Program should utilize a white background; black background; illumination between 2000 and 3750 lux; and specific procedures to manipulate and view the container

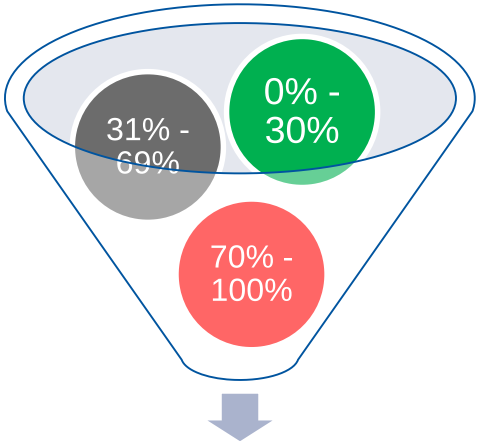
Knapp Studies

- A method to establish a baseline for the performance of manual inspection (for comparison to automated inspection) is the Knapp Studies
- There are different views of Knapp Studies, but generally they include:
  - A Seeded Defect Test Set (normally just for Particulates)
  - Qualified Inspectors
  - Multiple Inspection per Inspectors
  - Simulated Production Environment
- Probability of Detection (POD)
  - Per original Knapp – Reject Zone Defects (i.e. 70% to 100%) should be utilized for comparisons
  - Other approaches may utilize Gray Zone Defects (i.e. 31% to 69%) and Accept Zone (i.e. 0% to 30%)

Knapp Studies

SEEDED DEFECT TEST SET

QUALIFIED INSPECTORS



PROBABILITY OF DETECTION (POD)

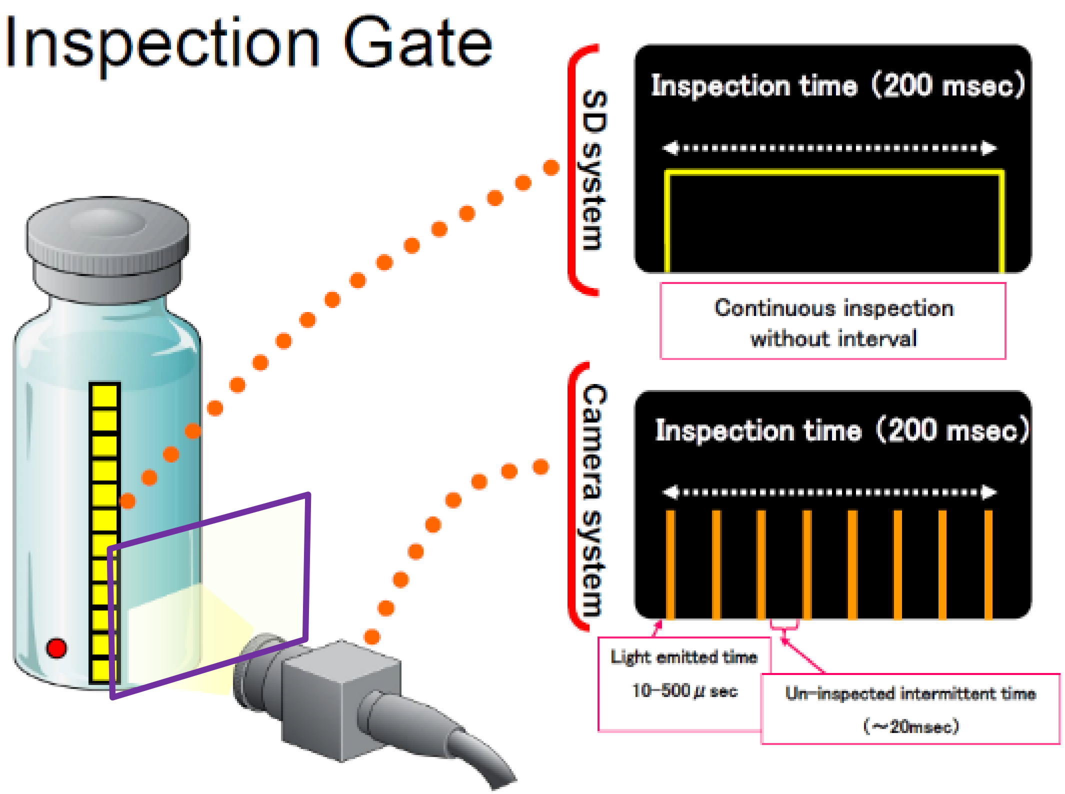
Pre-Determined Acceptance Level

- Another approach for Qualification is to utilize a pre-determined acceptance level (i.e. 100%, 90%, 80%, etc.)
- This approach maybe better suited for integrity defects. Many of the aforementioned technology can accurately and repeatedly detect integrity defects.
- For particulate defects, a pre-determined acceptance level could be utilized but may be more challenging for the qualification process.

THEORY BEHIND AUTOMATED INSPECTION TECHNOLOGIES.

SUMMARY

Summary: Particle Inspection Methods Comparison

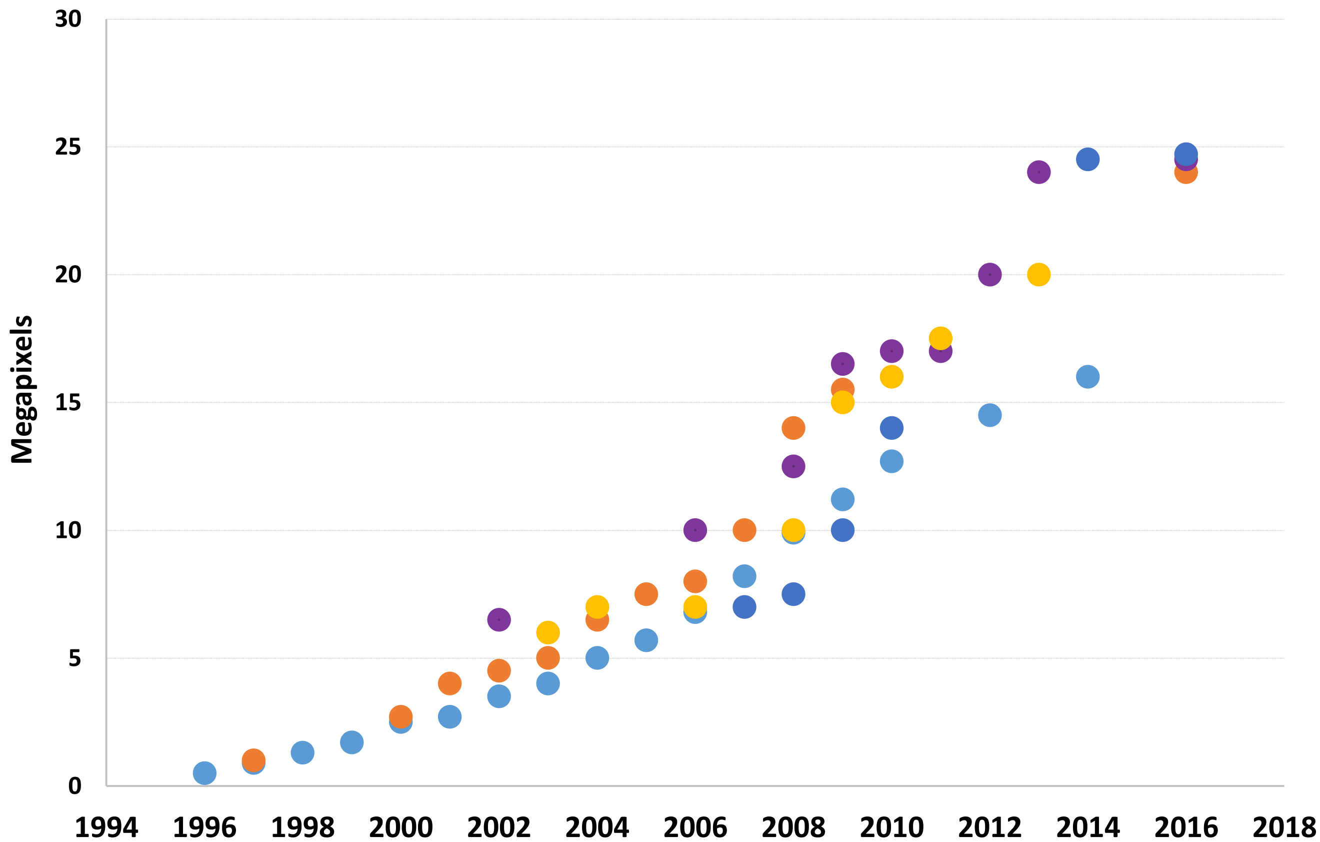


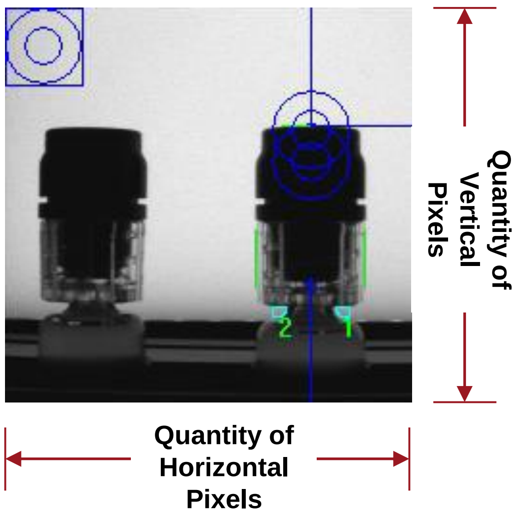
- ✓ Continuous Inspection
- ✓ Faster Response
- ✓ Self contain
- × Narrow Inspection View
- × Color Blind

- ✓ Larger Inspection Area
- ✓ Highly Customizable
- ✓ Color Detection
- × Sampling Time
- × Complex Configuration
- × Limited Particle Size*

Summary: Camera Inspection

Evolution of the Resolution of Digital Image Sensors



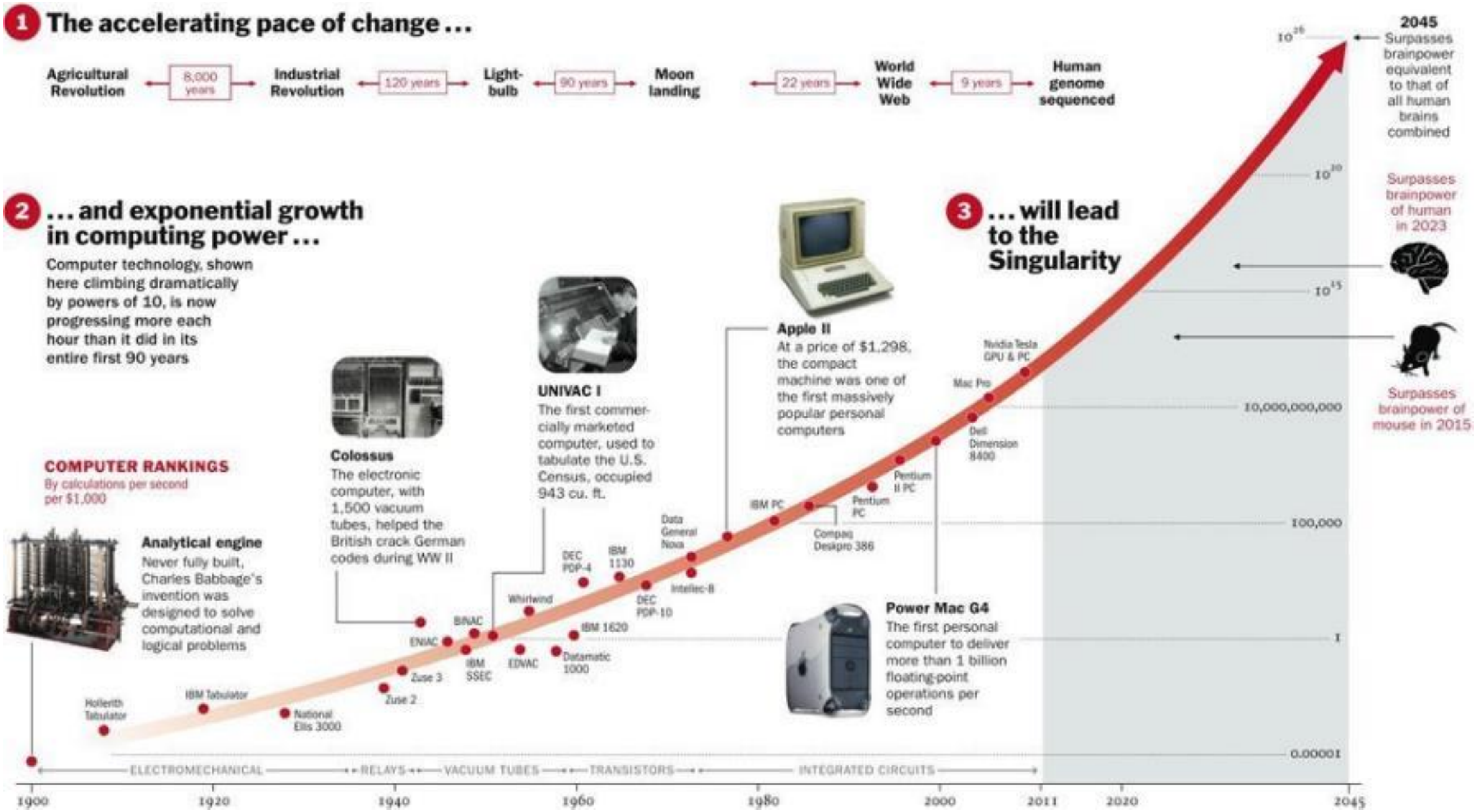


Resolution = **H**pixels X **V**pixels

Example:
2,400px x 3,000px = 7,200,000

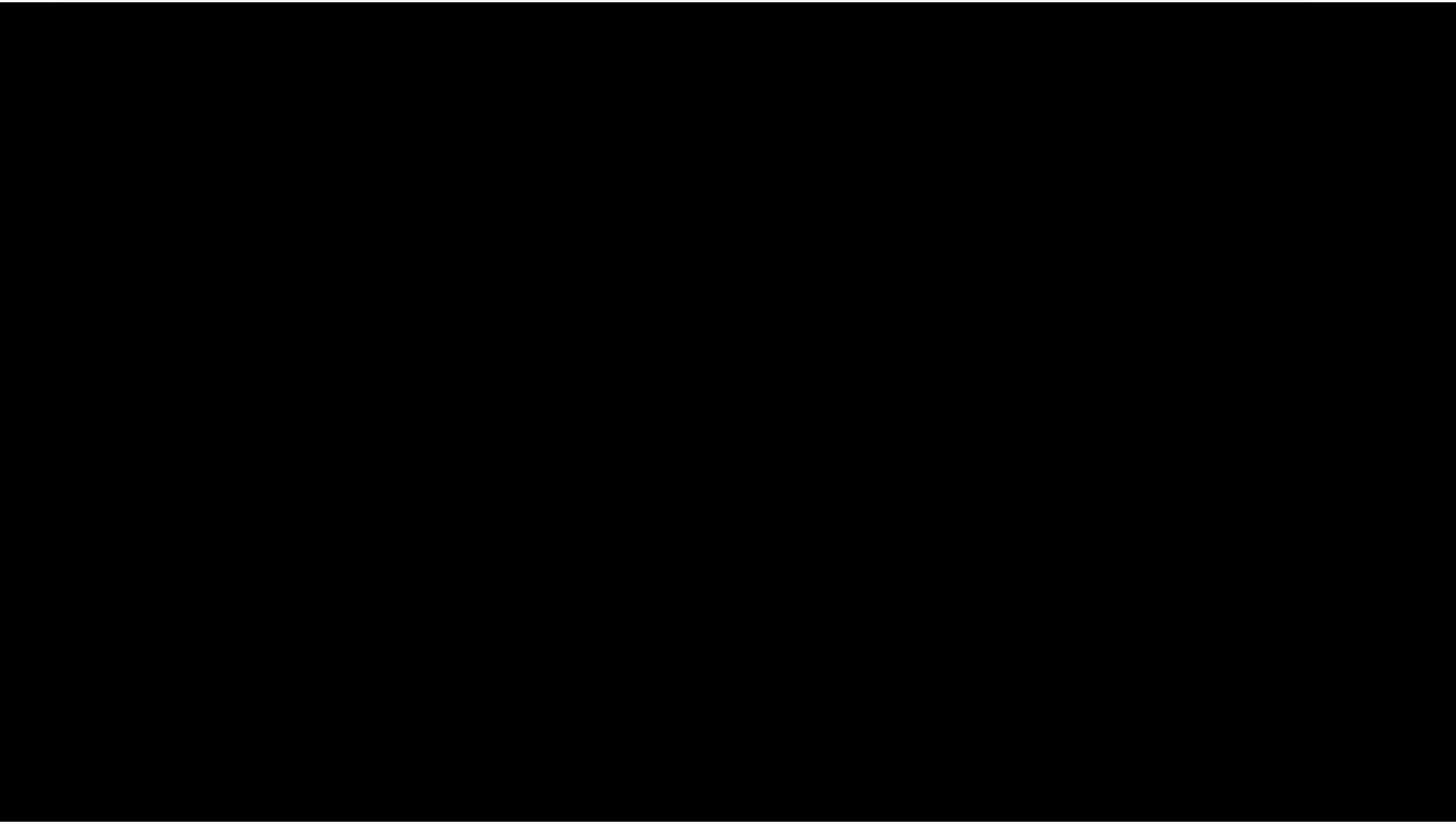
7.2 Megapixels

Summary: Camera Inspection



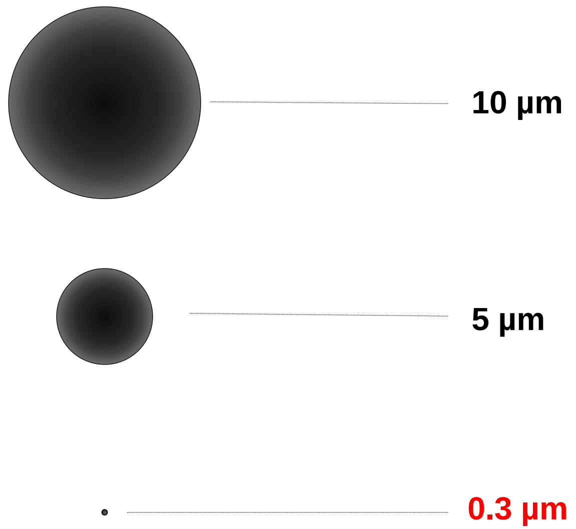
Accelerating Peace of Change
Ray Kurzweil, Singularity Institute

Summary: Camera Inspection



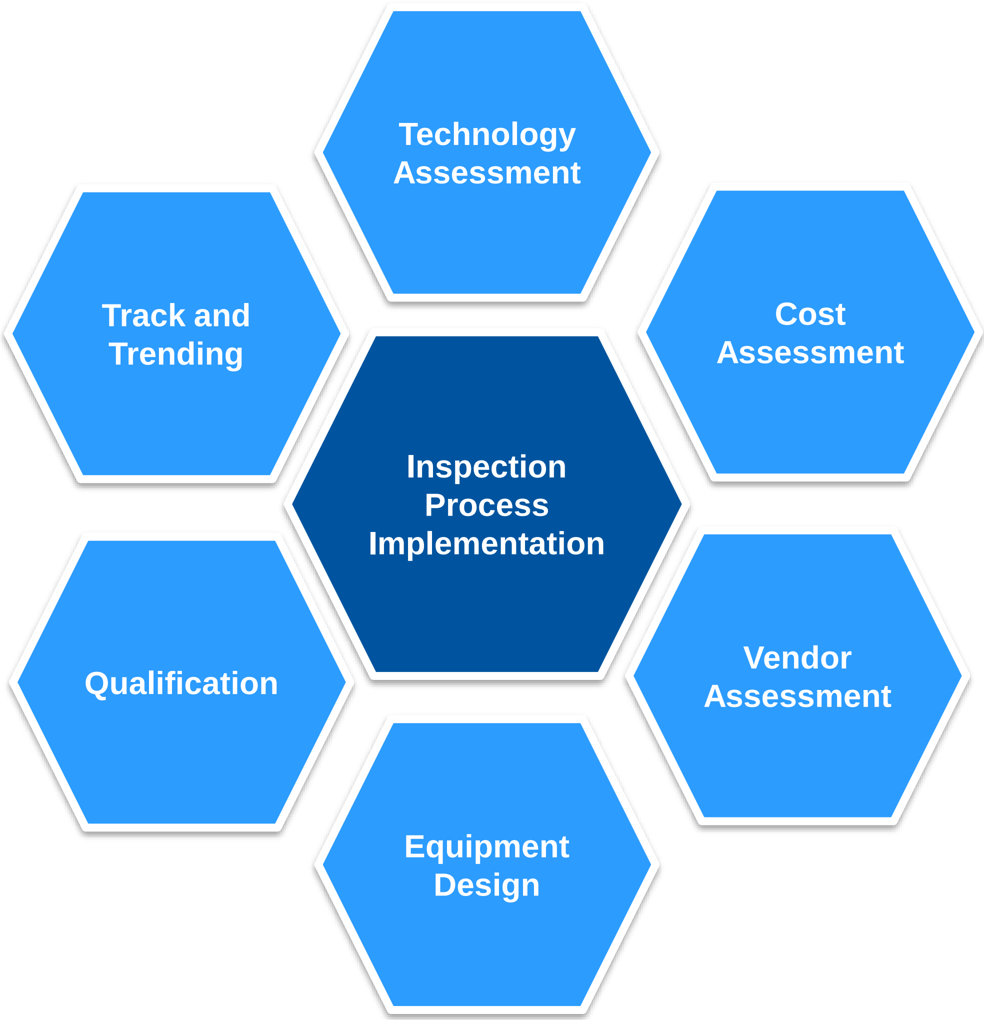
Summary: Leak Inspection Capabilities

Method	Off-Line	In-Line
Electrical Conductivity and Capacitance	2-5 µm	5-10 µm
Pressure Decay	2-5 µm	8-10 µm
Vacuum Decay	2-5 µm	8-10 µm
LFC (Liquid Filled Container)	2-5 µm	5-10 µm
Laser-Based Gas Headspace Analysis	0.1 µm	2-5 µm
Tracer Gas Detection, Vacuum Mode	<0.01 µm	--
Mass Extraction	2-5 µm	--



- **None of the in-line methods** presented, **can detect** a leakage from a orifice of **0.3 µm in size**.
- The packaging development; the testing and qualification activities **should use appropriated test methods** to challenge the detection of leakages on the **0.3 µm range**.
- The In-line testing methods offer means to monitor your process and detect leaks on the range of **8 µm and up**, commodity defects or that could be produced during the transport or the process.

Summary: Implementation



Track and Trending

Monitor the infeed and outfeed process.

- Adjust detection parameters to respond to the latest process defect trends.
- Reduce scrap rates by adjusting tools based on historical data analysis.

Acknowledgements

John G. Shabushnig, Ph.D. Insight Pharma Consulting, LLC

"Particulate Matter Definitions "

Michael Wiggenhorn, PhD. Coriolis PharmaService GmbH

"Complementary analytics needed to cover the size range"

Thomas Reisinger, et al. "Poisson's spot with molecules."

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BOSCH | Nikka | pti Packaging Technologies and Inspection, LLC | SEIDENADER | WILCO

THEORY BEHIND AUTOMATED INSPECTION TECHNOLOGIES

THANKS