THE THEORY BEHIND AUTOMATIC INSPECTION TECHNOLOGIES

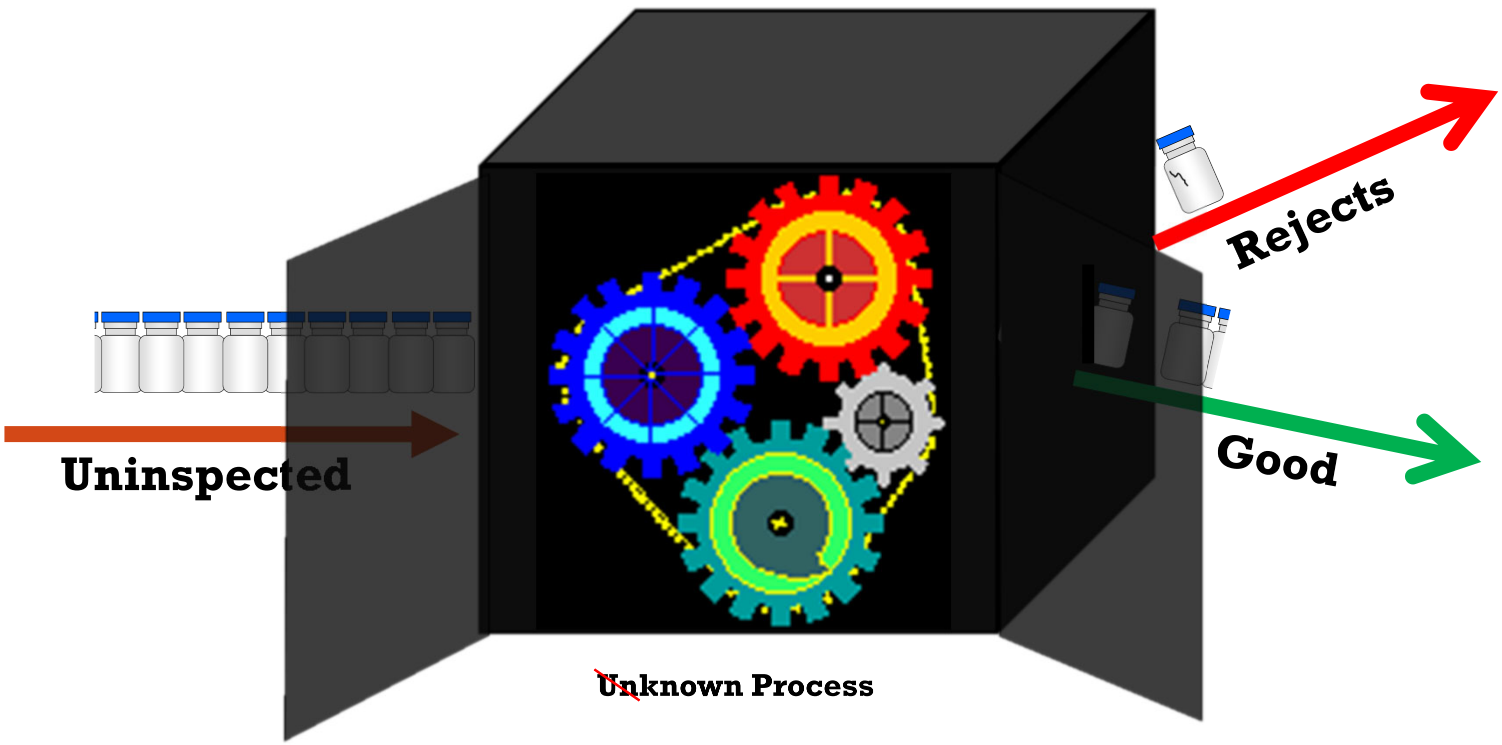
for Subvisible-to-Visible Particle Detection and Container Closure Integrity

Edwin Martinez

Disclaimer

- The views expressed in this presentation come from my 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)

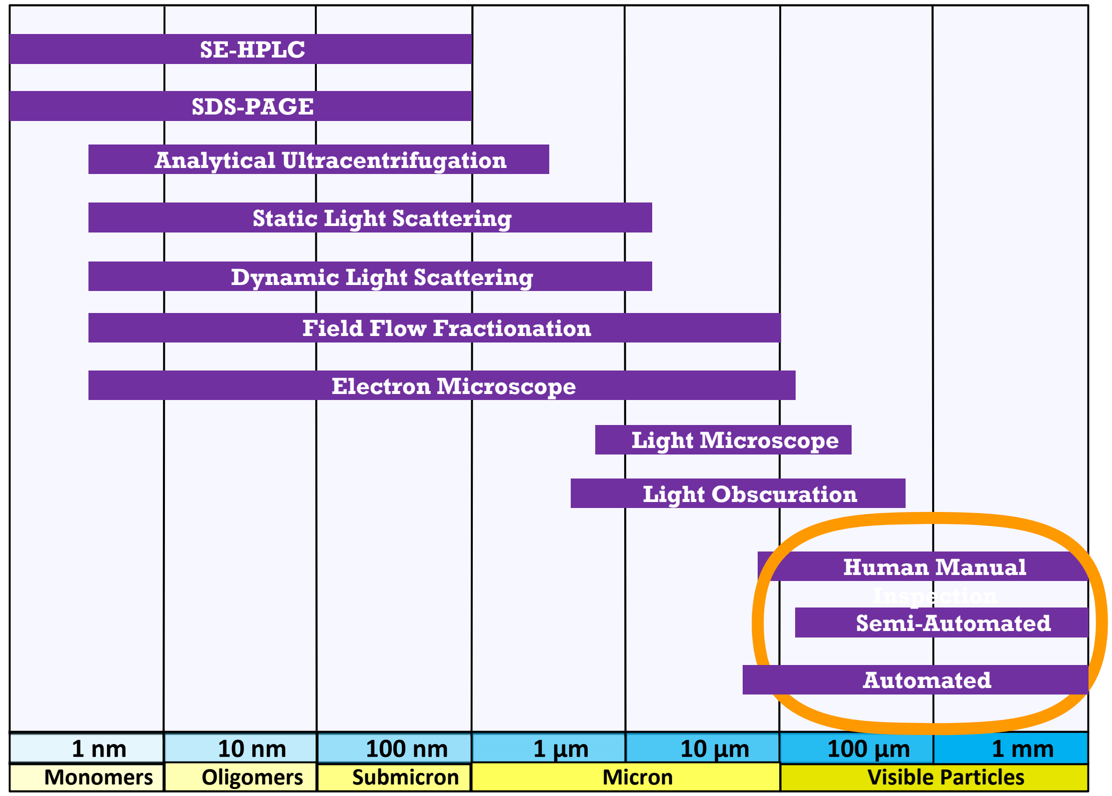
- Summary

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

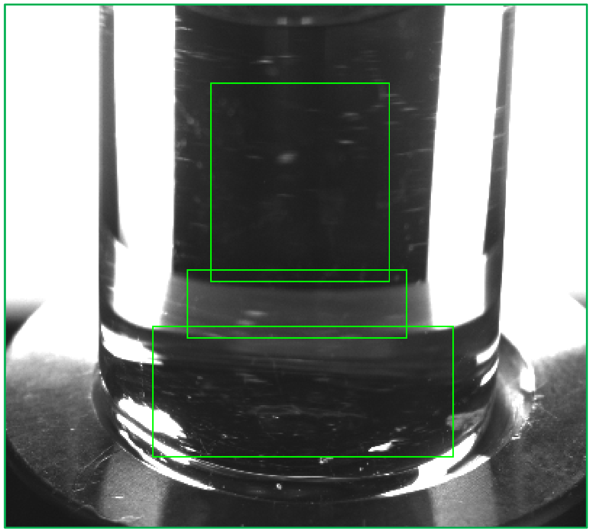


Adapted from Michael Wiggenhorn, Coriolis

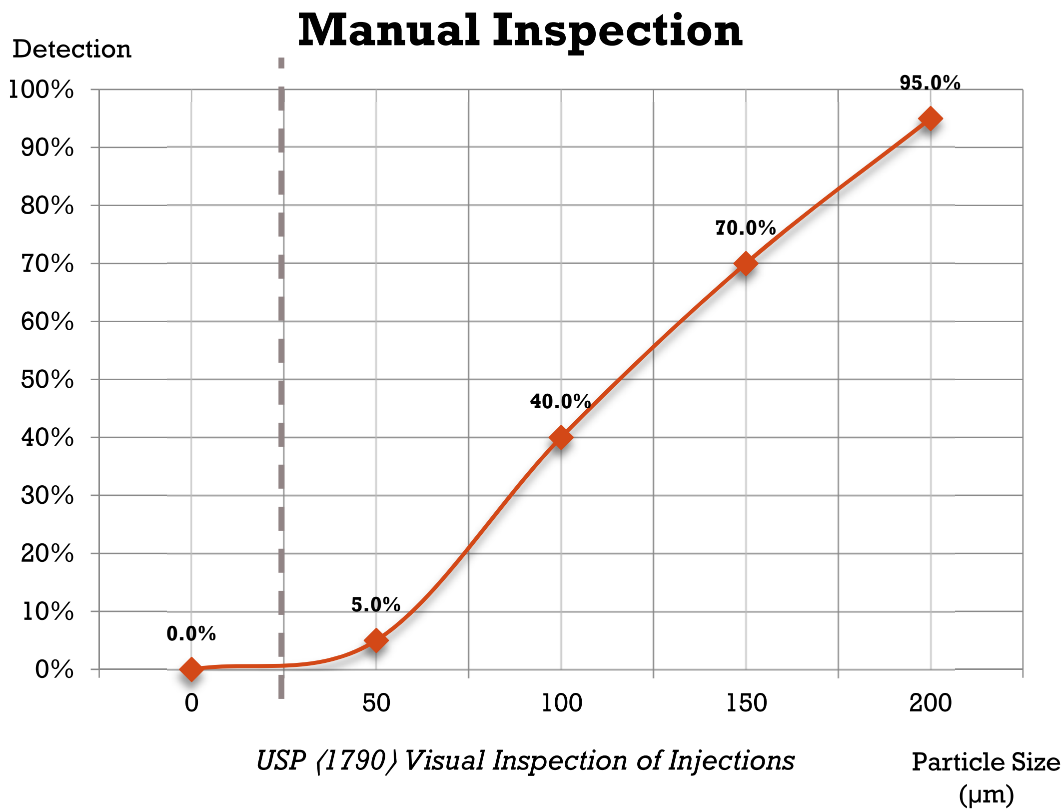
Find additional information on inherent, intrinsic, and extrinsic particulates. Subvisible Particulate Matter in Therapeutic Protein Injections ⟨787⟩

Human Performance

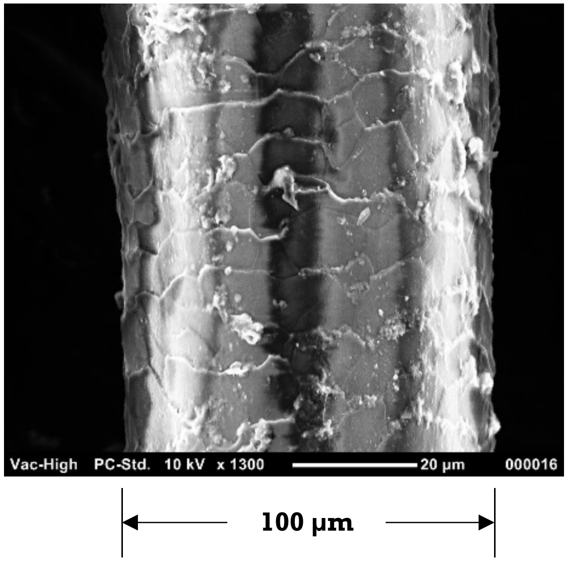
USP ⟨1790⟩ Visual Inspection of Injections The threshold for human 20/20 vision is generally accepted to be ***50 μm***. Individual receptors in the eye have a resolution of ***11 μm***, but typical resolving power is reported as ***85–100 μm***



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***.

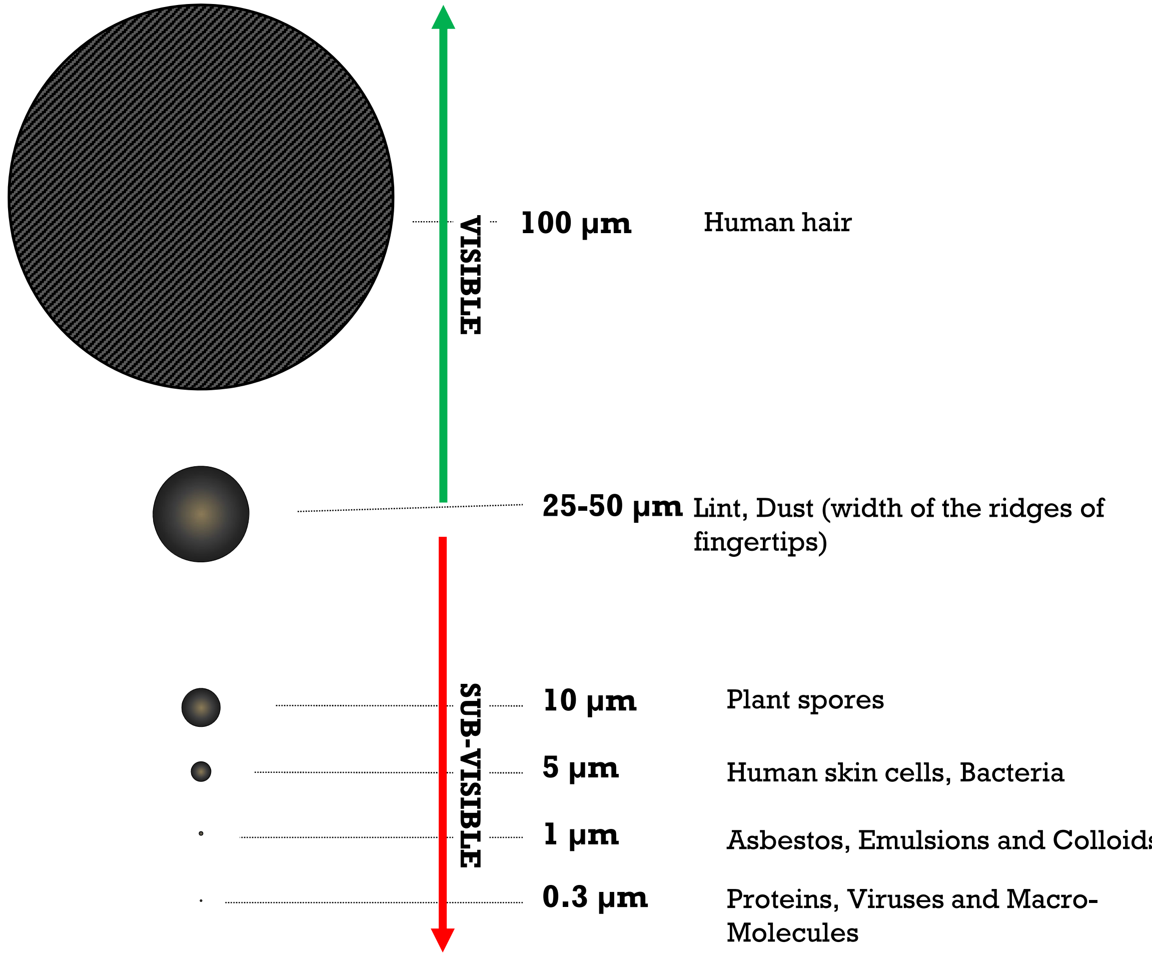


Particle Matter



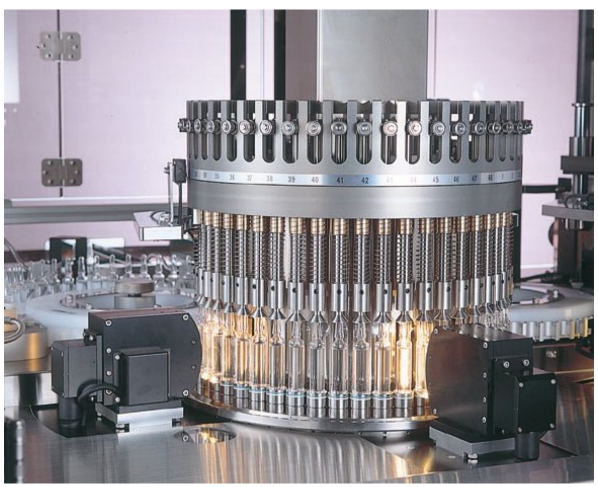
Mert Keçeli, Joanne Wen, Sara Saad, Glenn Elert.
Midwood Science (7 November 2011).

*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

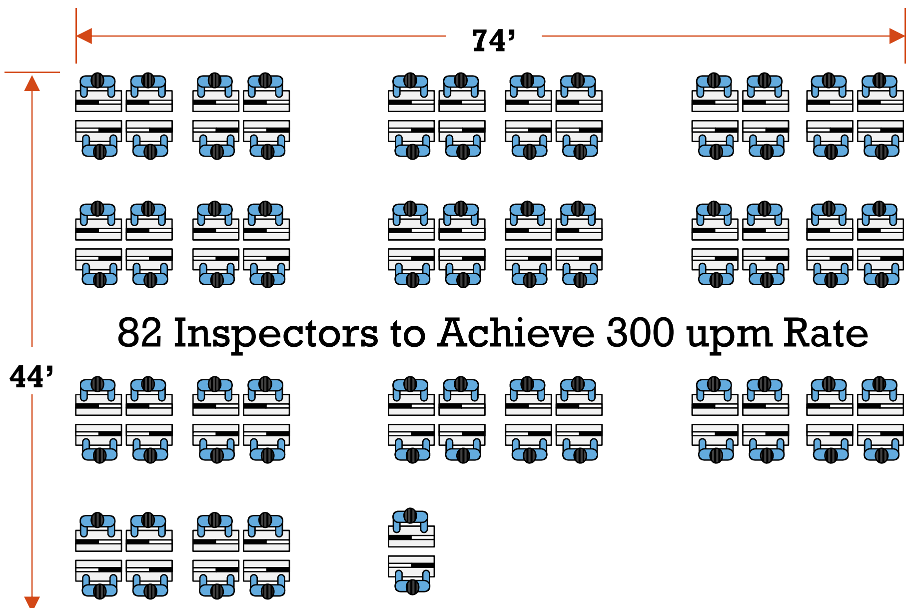
Adapted from John G. Shabushnig, Ph.D, Insigth

Machine vs Humans

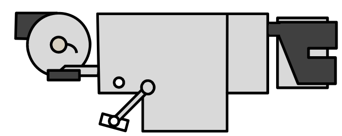
There are workforce and floor space requirements to be considered as a result of the average rate of a manual inspection, example of a **300 parts per minute**.

Average Rate: 3.67 upm

Average Rate: 300 upm



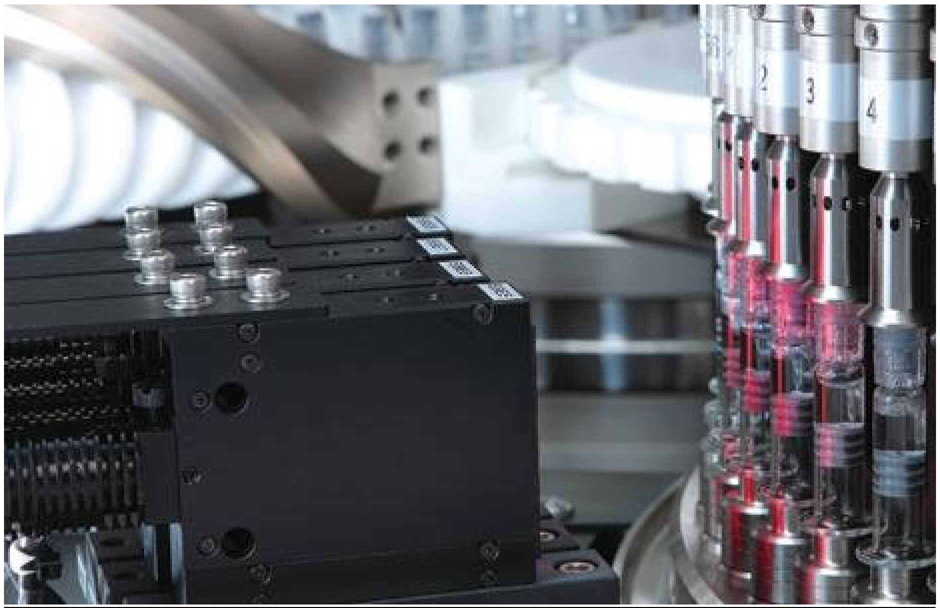
3,256 sq. feet



Average Size: 15’x7’

105 sq. feet

Particle Inspection Methods

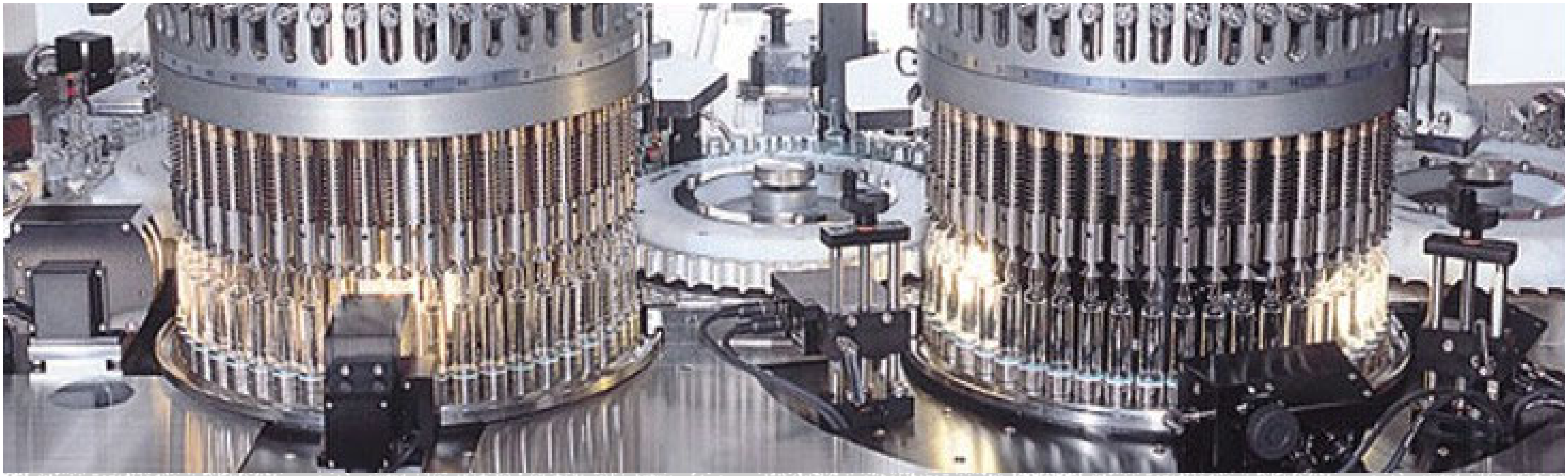


Static Division (SD) Particle Detection

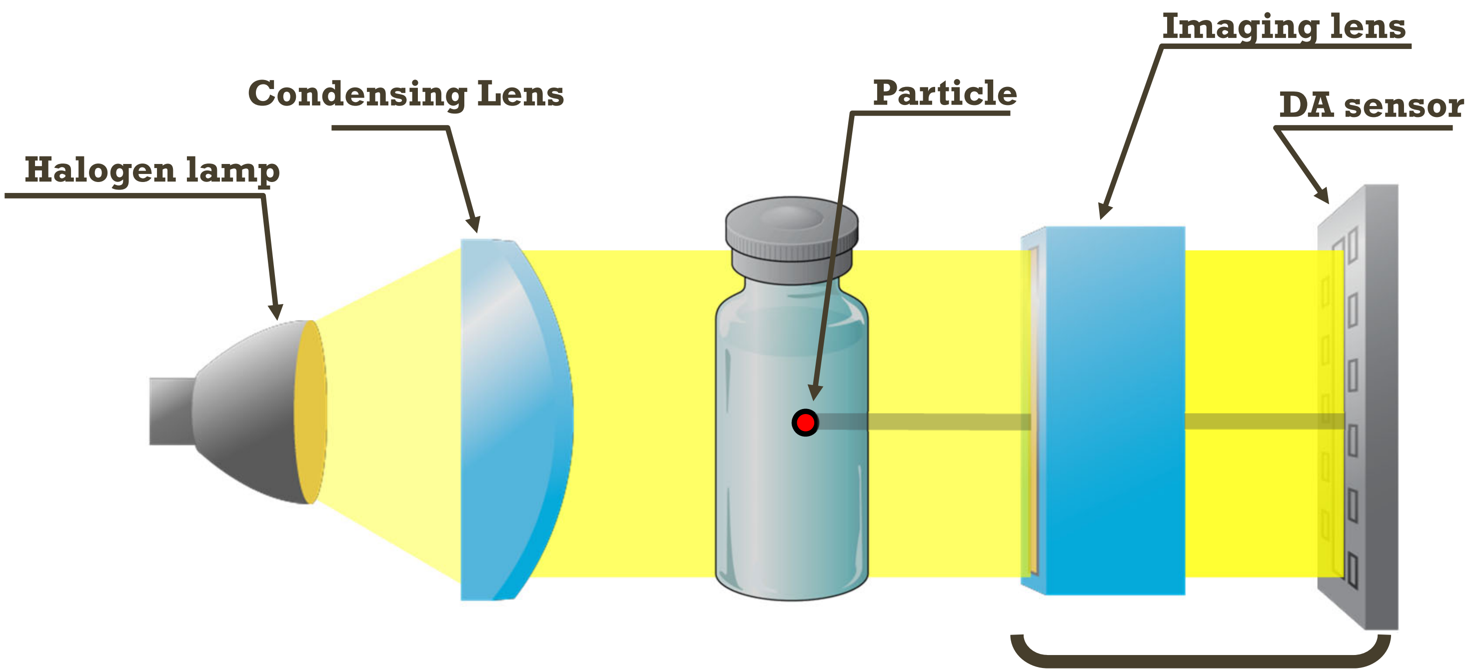
Defect Inspection using Camera

Principles of the Static Division (SD) Detection

PARTICLE INSPECTION METHODS



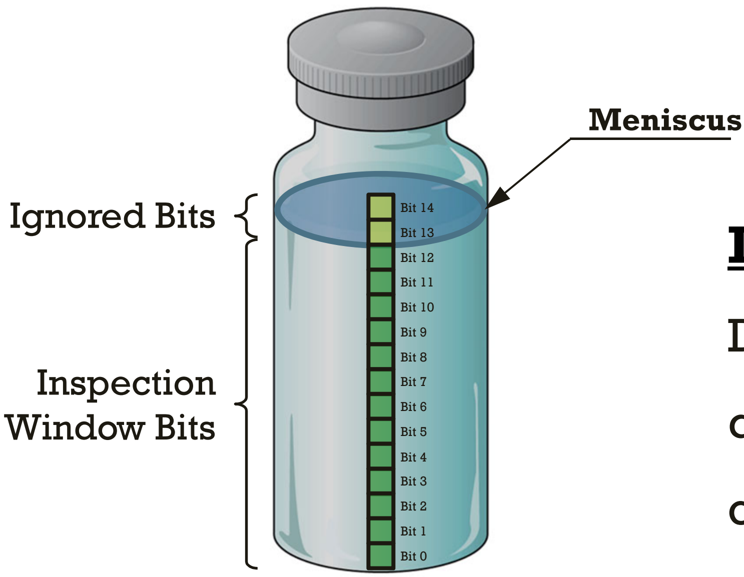
Static Division (SD) Detection Principle



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



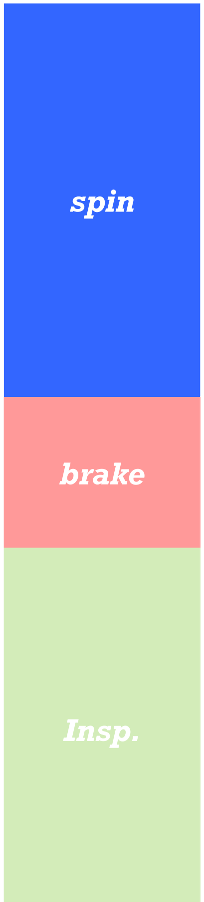
Inspection View Selection

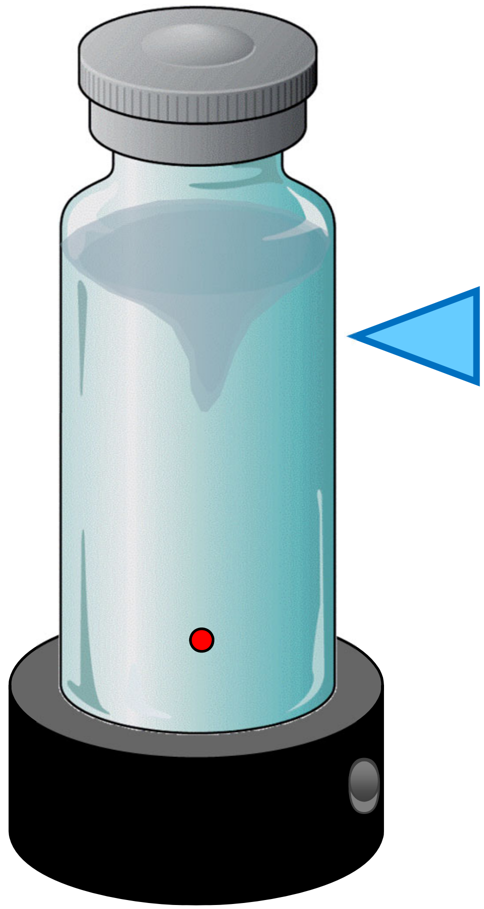
DA sensor is made up an array of small photo diodes that are piled up in vertical direction to cover the required inspection view.

Each photo diode of DA sensor is called "Bit"

Particle Movement

Detection Cycle



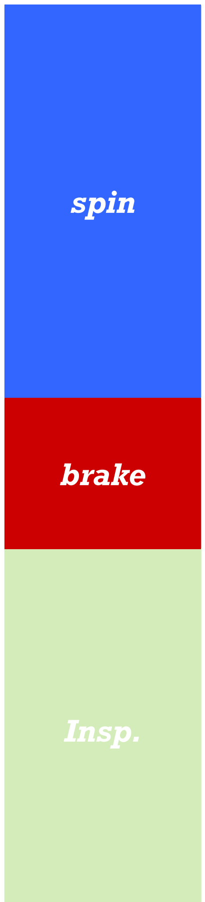


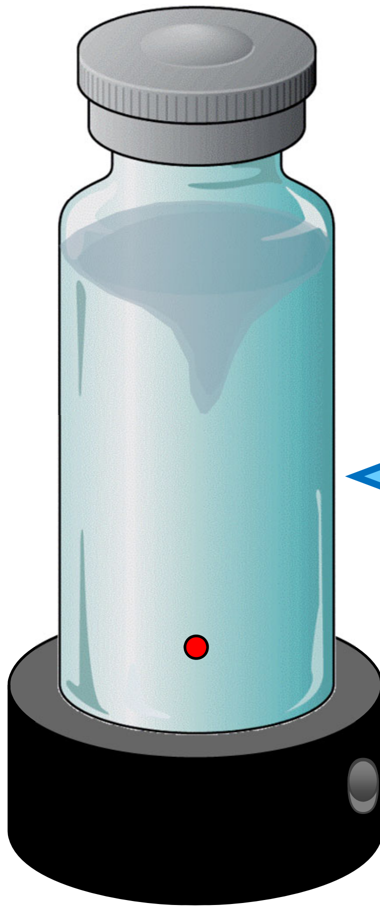
Spin Container

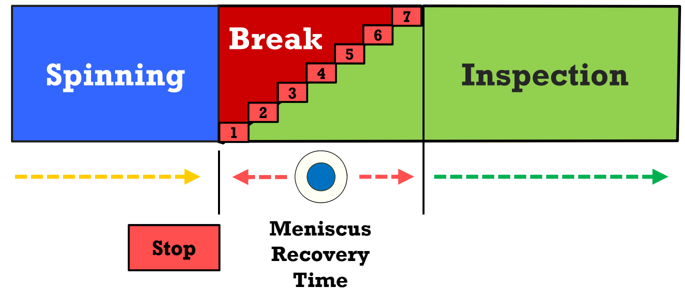
The container is spun, which pushes the contents up the wall of the vial, lowering the level of the meniscus of the solution inside.

Particle Movement

Detection Cycle





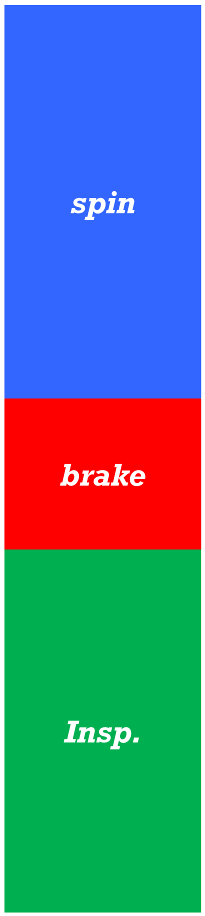


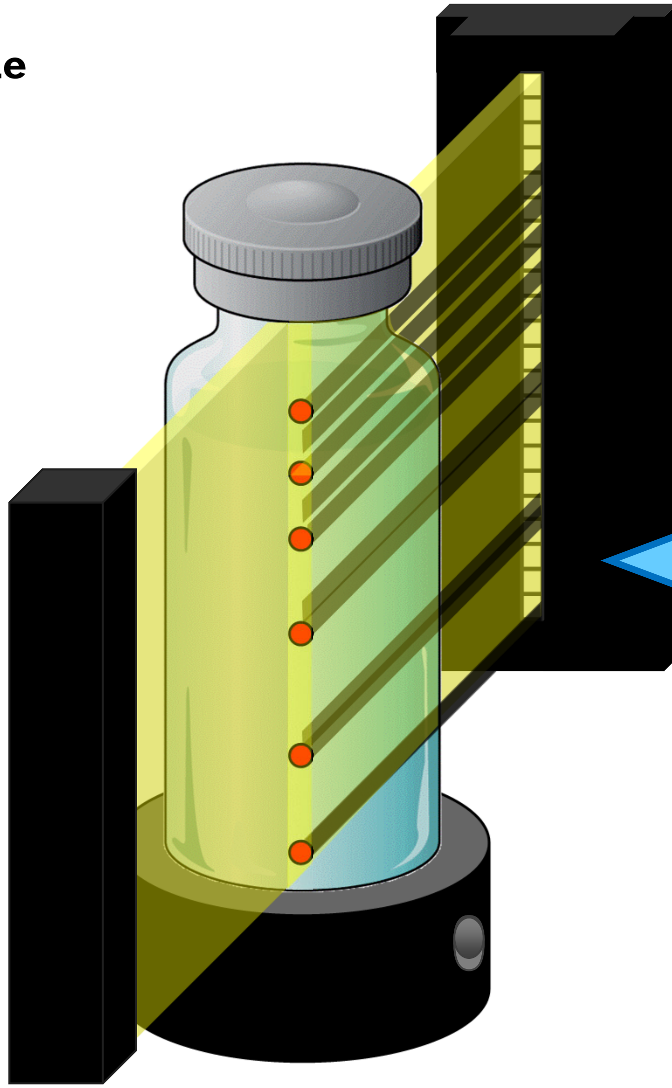
Brake on

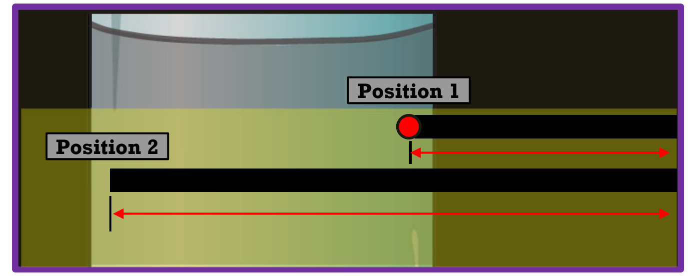
The container is brought to an abrupt halt, forcing the particulate matter into motion.

Particle Movement

Detection Cycle





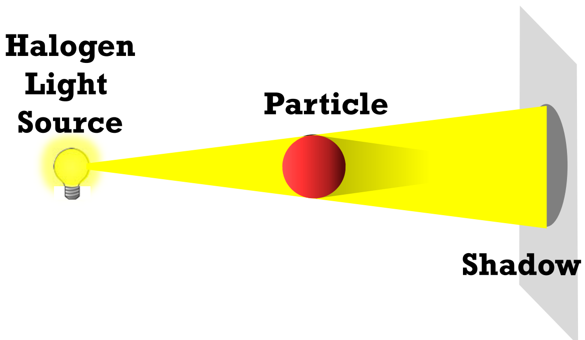


Inspection

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

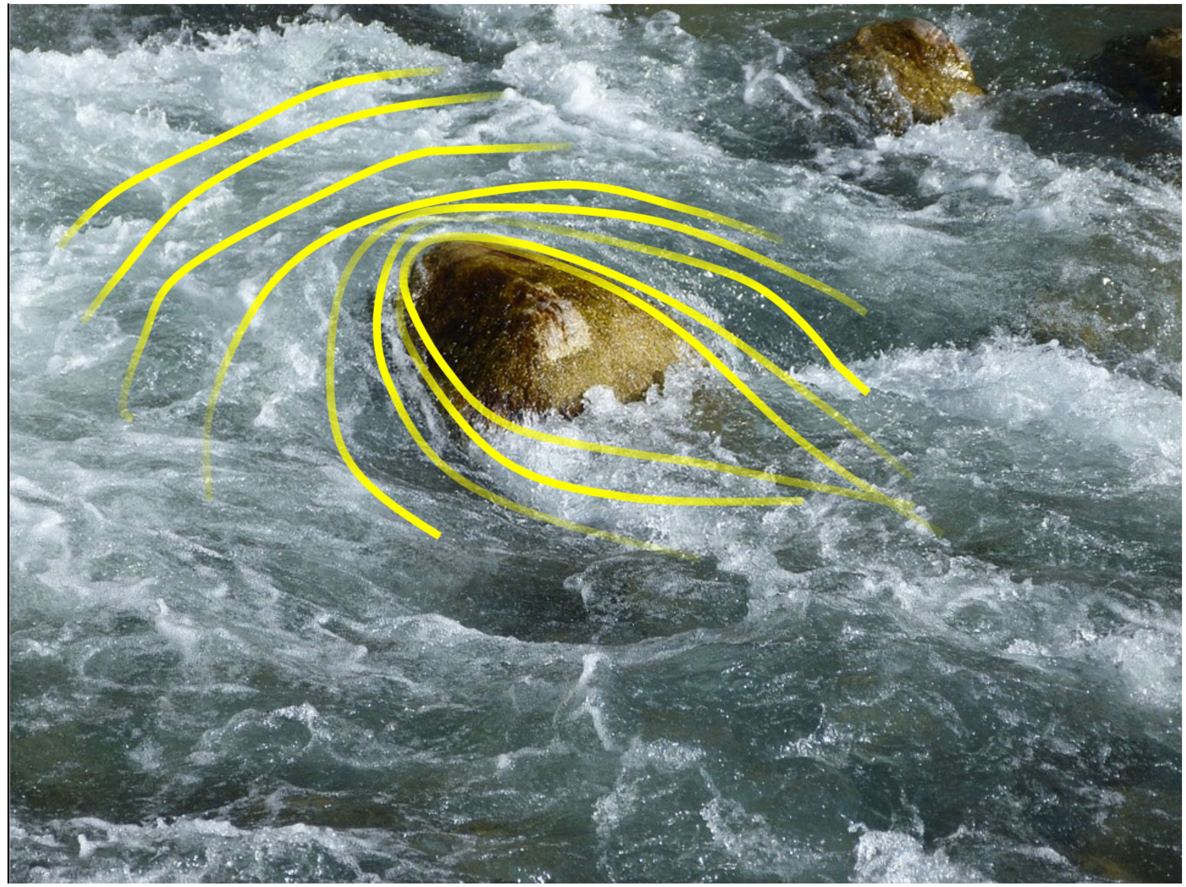
Particle Size Response

Particle Shadow Diffraction



$$U(P_1) \propto \int_0^{2\pi} \int_0^{\infty} g(r,\theta) e^{\frac{i\pi\rho^2}{\lambda}\left(\frac{1}{g}+\frac{1}{b}\right)} \rho d\rho d\theta.$$

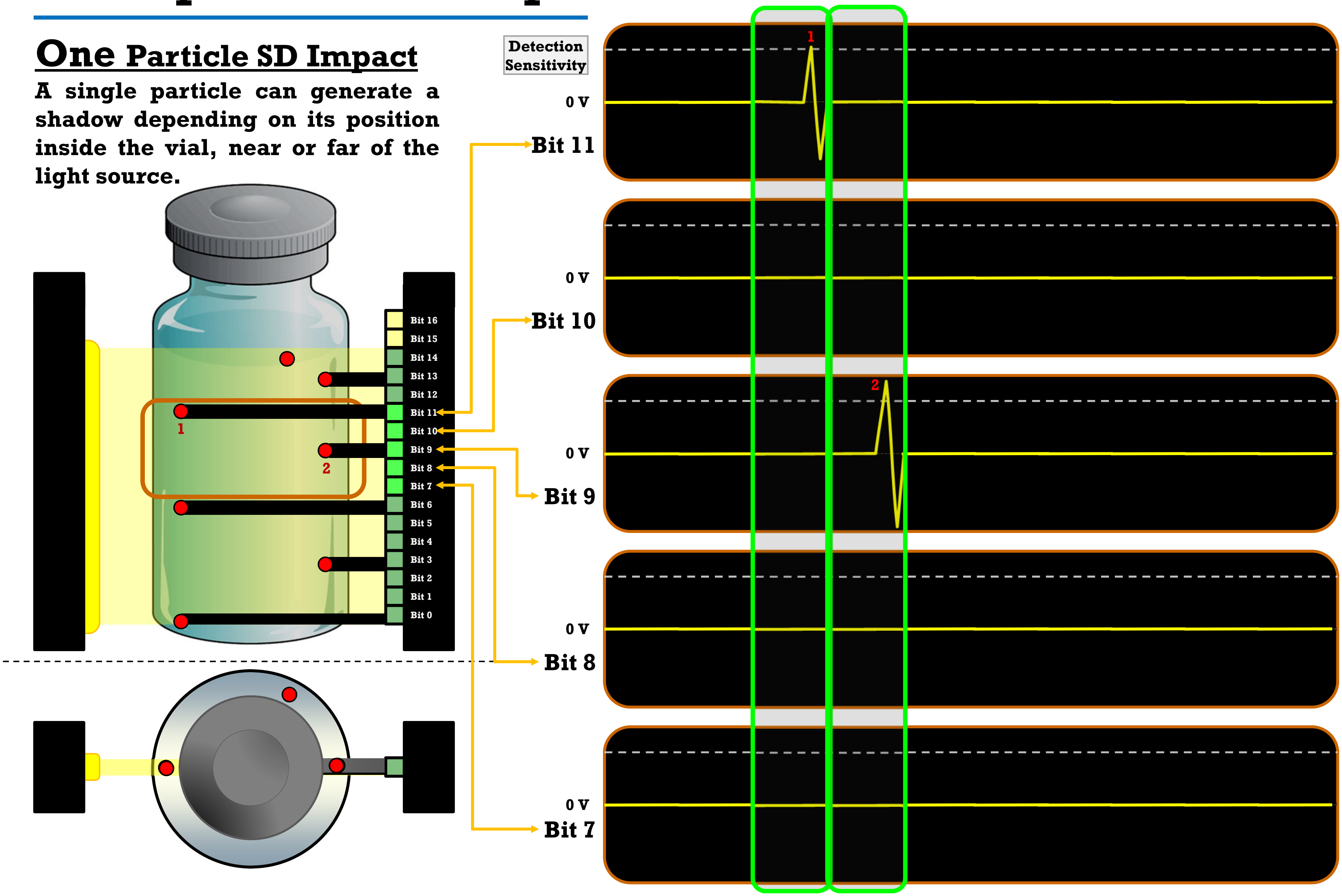
The boundary of a particle geometrical shadow is not sharp. The light is not propagated strictly in straight lines. This phenomena of diffraction, results from the wave nature of light. Banded patterns, are produced near the edges of the shadow.



Multiple Particle Impact

One Particle SD Impact

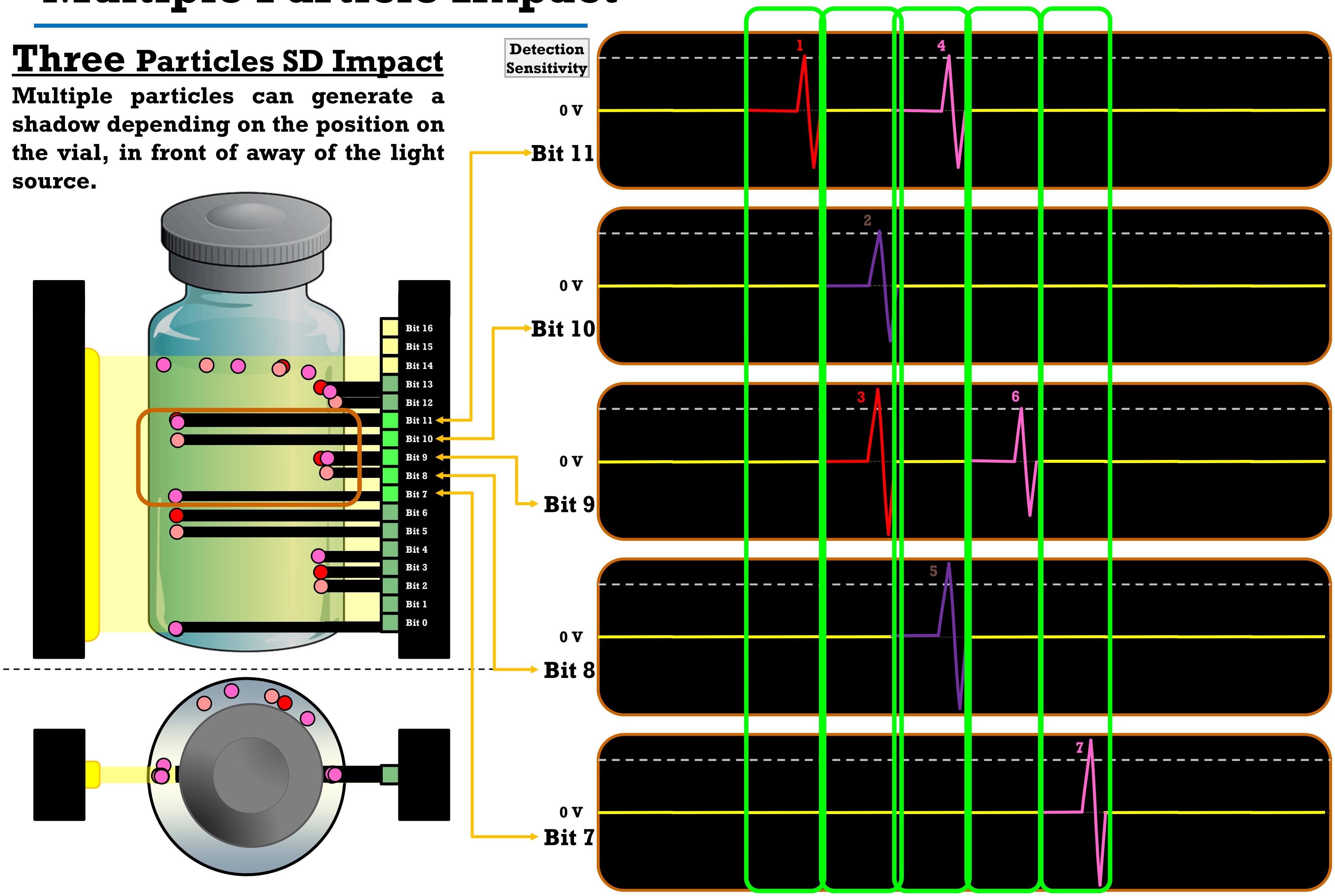
A single particle can generate a shadow depending on its position inside the vial, near or far of the light source.



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.

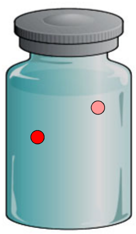
Confidence: 45%

Particles: 1

$Y = 1 - (1 - 0.450)^1$

$Y = 1 - (0.550)^1$

$Y = 1 - 0.550 = 0.450 =$ 45.0%



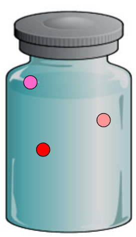
Confidence: 45%

Particles: 2

$Y = 1 - (1 - 0.450)^2$

$Y = 1 - (0.550)^2$

$Y = 1 - 0.303 = 0.698 =$ 69.8%



Confidence: 45%

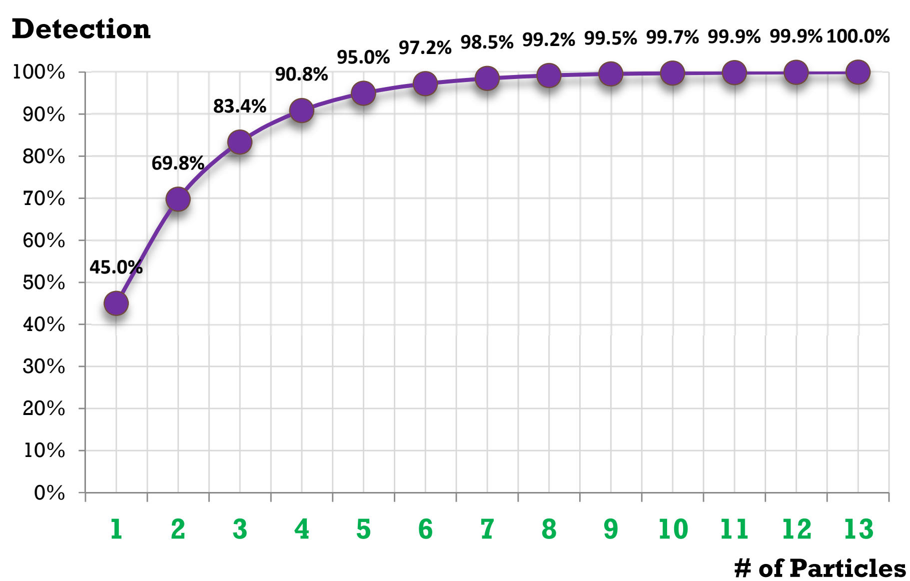
Particles: 3

$Y = 1 - (1 - 0.450)^3$

$Y = 1 - (0.550)^3$

$Y = 1 - 0.166 = 0.834 =$ 83.4%

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



Particle Detection Product Properties Impact

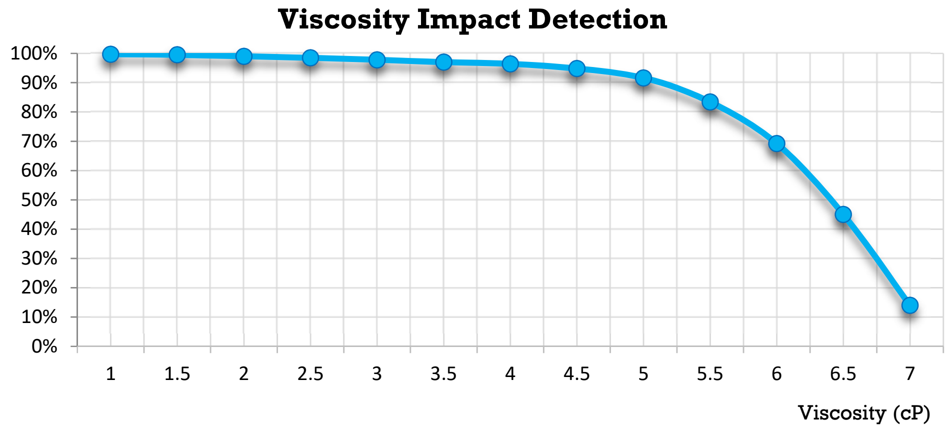
The particle detection its based in the detection of the **particle movement** during a **time lapse**. There are known product properties that directly affect the duration of **particle suspension**, and in consequence the detection performance:

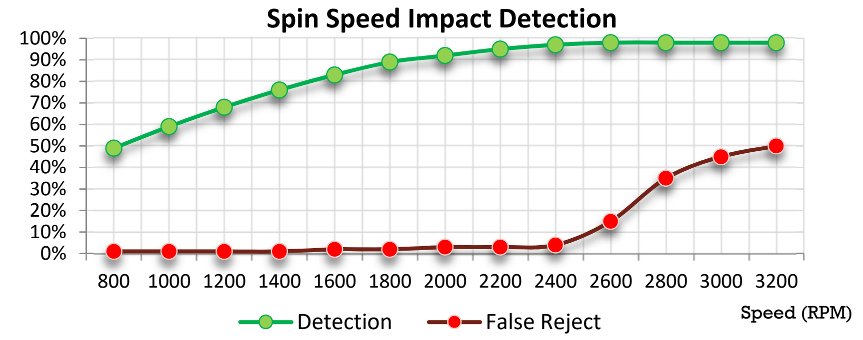
- Viscosity
- Density
- Surface Tension

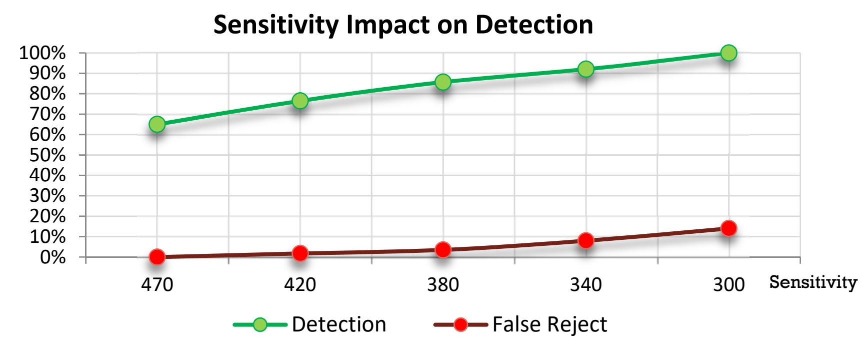
These properties also influence the probabilities of **false rejections** due to the **generation of bubbles**.

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

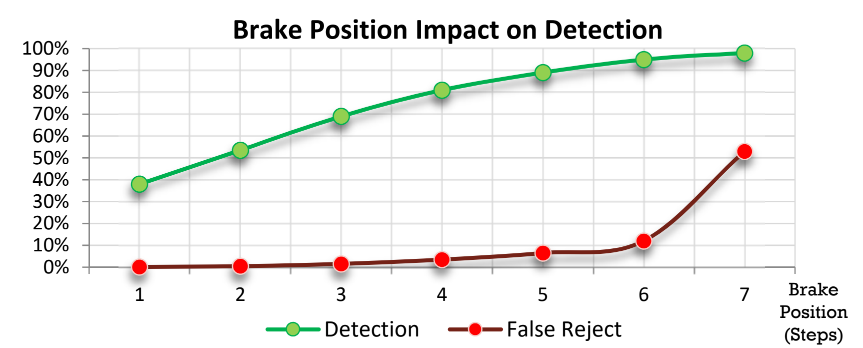
Particle Detection Parameters Impact







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)***



PARTICLE INSPECTION METHODS

Particle Detection using (CCD) Camera

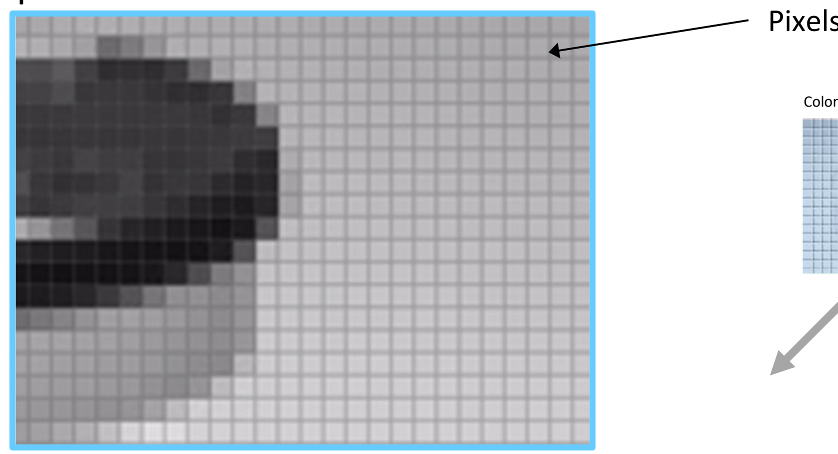
Content

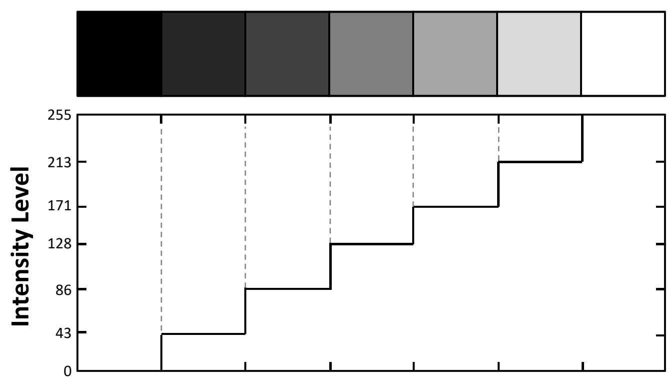
- Particle Detection using Camera (CCD)
  - Raster Image
  - Vision Tools
  - Image Subtraction
  - Cosmetic Inspection using Cameras
  - Fill Level Detection

Camera Inspection

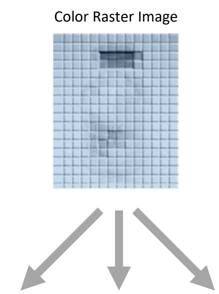
The digital raster images acquired by the digital camera have a finite set of pixels which are the smallest individual element in an image, holding quantized values that represent the brightness of a given color at any specific point. The pixels contain fixed number of rows and columns.

Raster Image
Vial



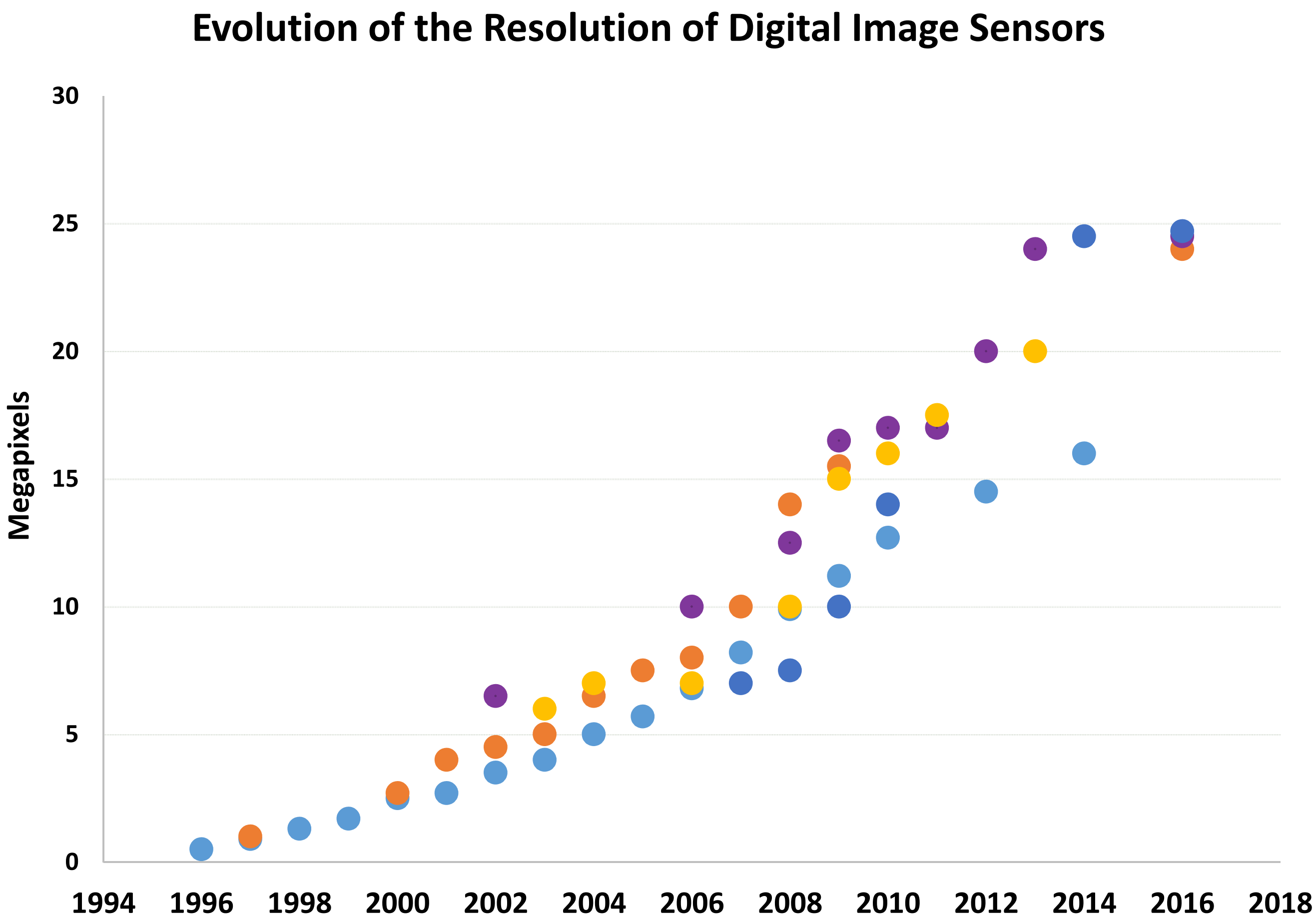


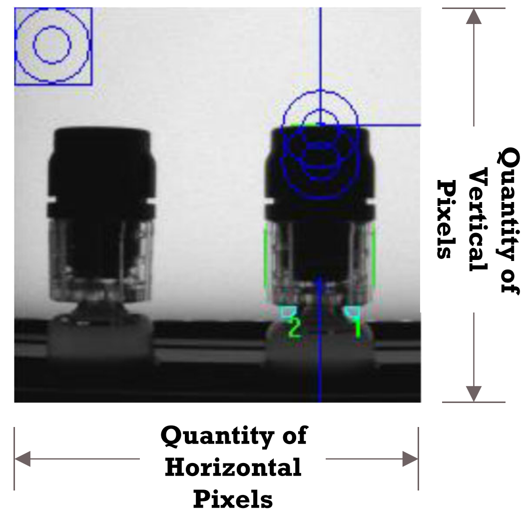
Each **pixel** use **8 bits** which have integer values from 0 to 255 for a total of 256 intensity levels.



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.

Camera Inspection





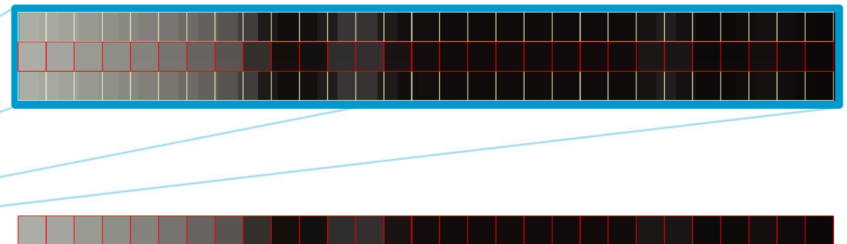
Resolution = **H**pixels **x** **V**pixels

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

7.2 Megapixels

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
- ■ **Eithe**
- ☐ **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

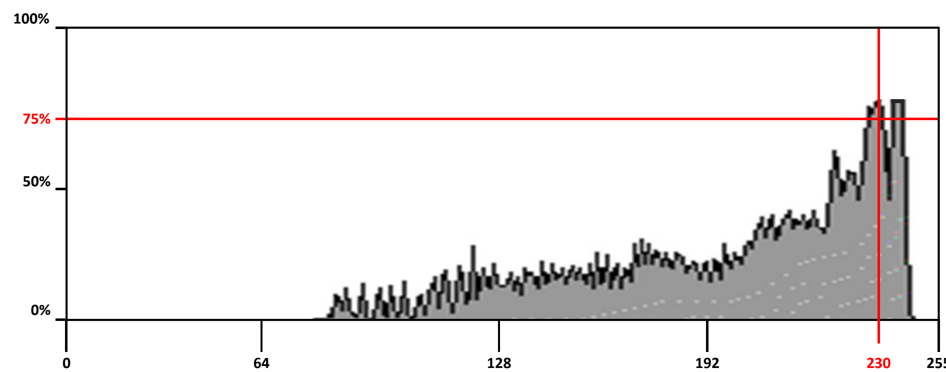
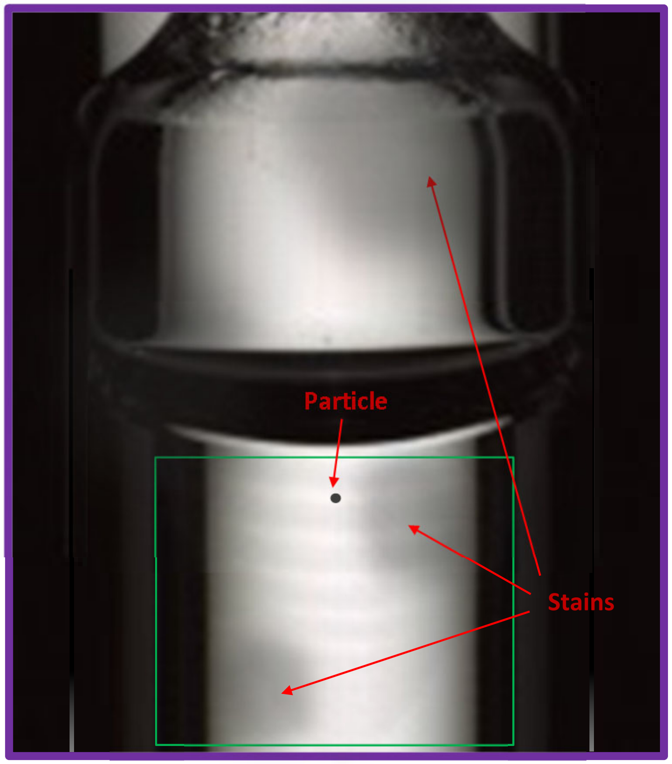
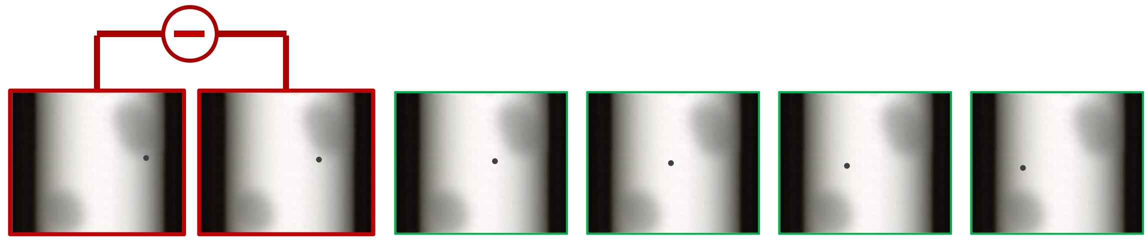


Image Subtraction (Differential Processing)

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).

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





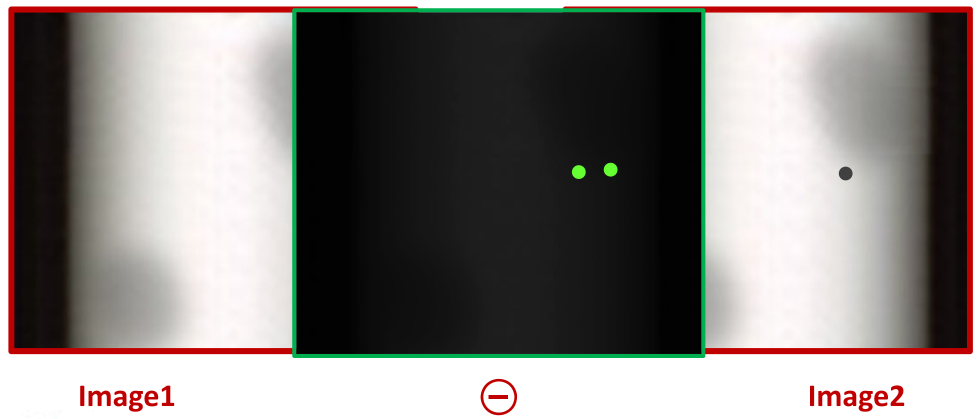
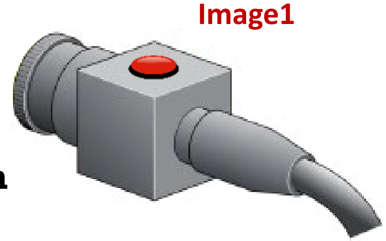


Image Acquisition
Spin Cycle



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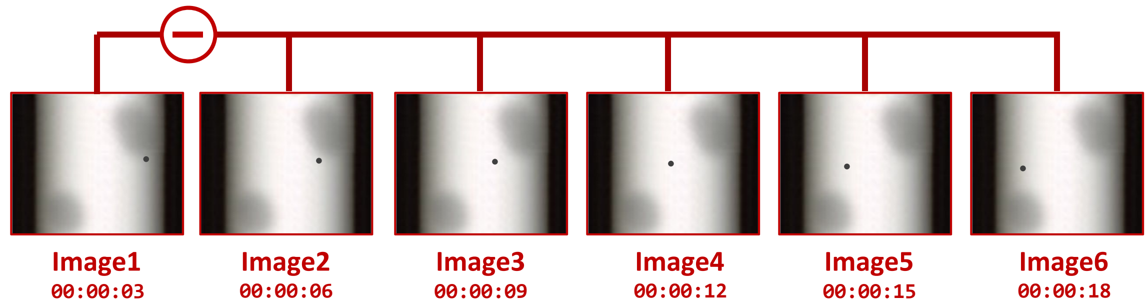
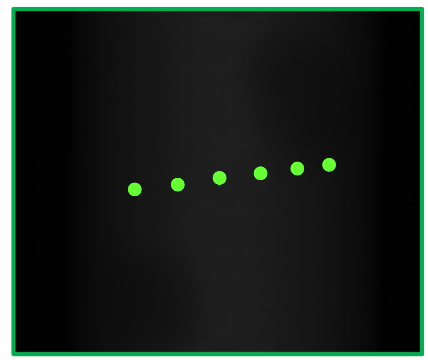
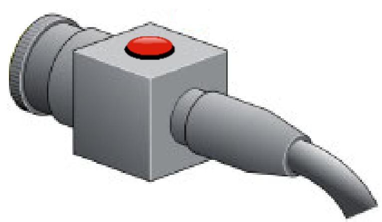




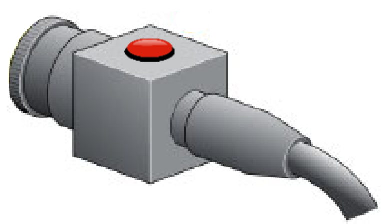


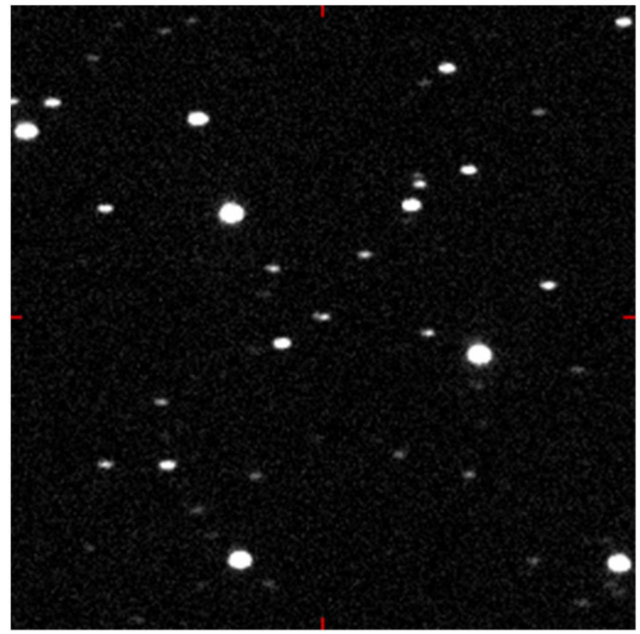
$$Q = \sum_{i=2}^{n} \text{Image1} - \text{Image(i)}$$

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.



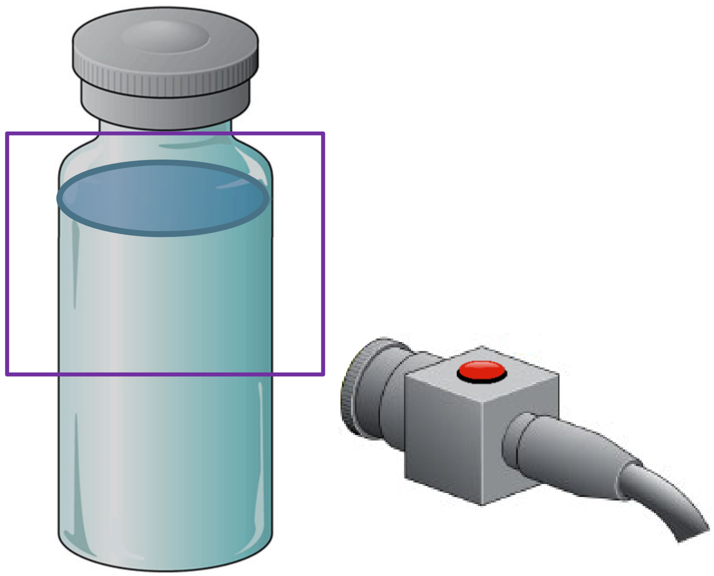


Method often used in Astronomy

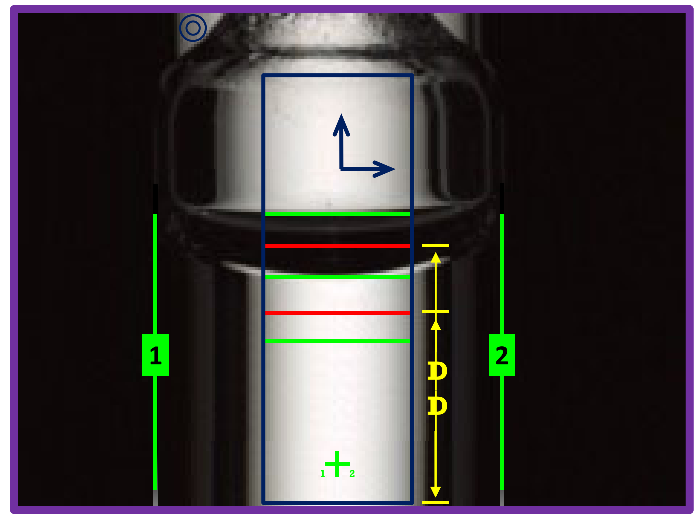
Fill Level Detection

Camera (CCD)

- Vision Tools as Edge Finder
- Higher Resolution than SD



Rejects based on pixel distance measurement.

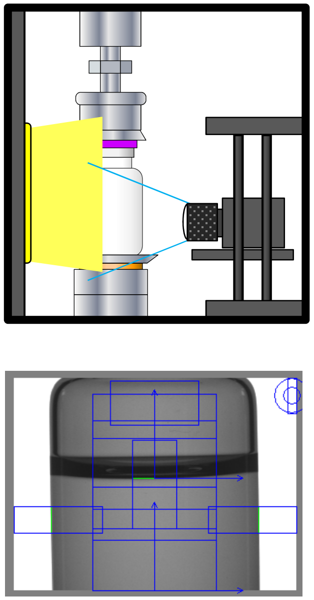


Acceptance Criteria 220< [redacted] < 490

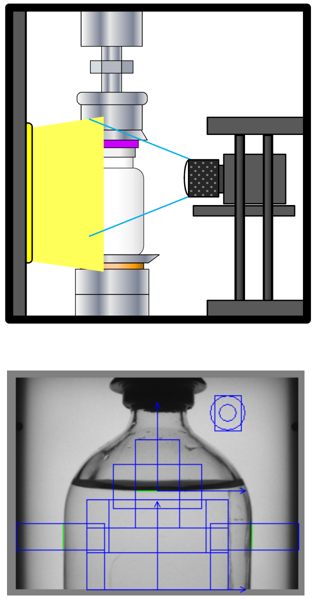
Cosmetic Inspection

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.

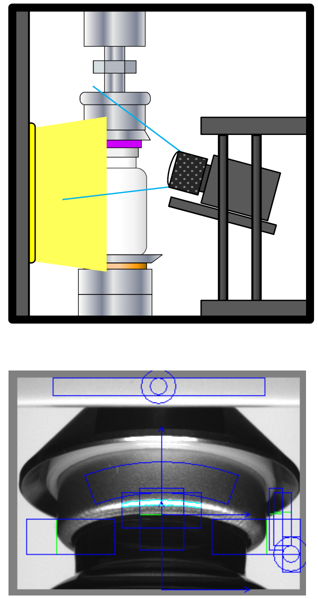
Lower Body



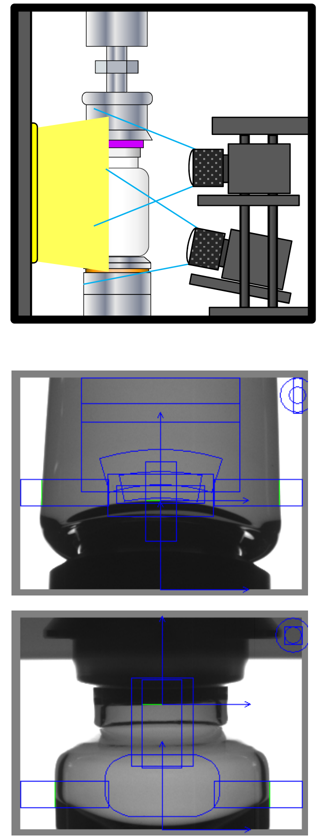
Higher Body



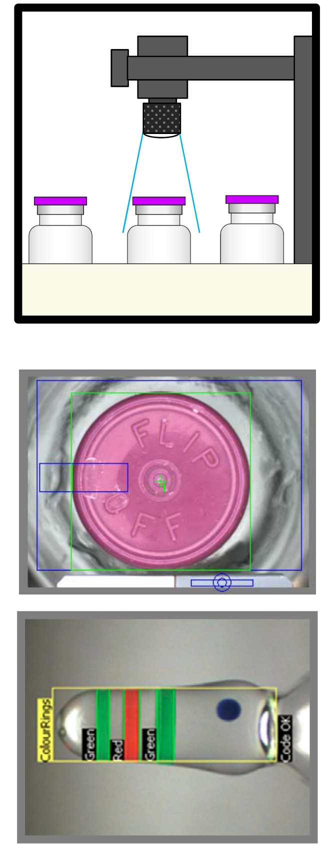
Crimp



Neck & Heel



Cap/Band Color



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

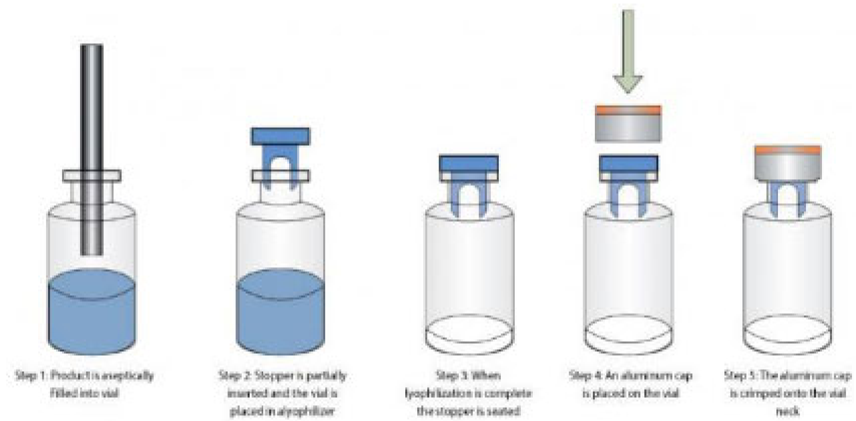
- Metallic Containers
- Opaque Container

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.

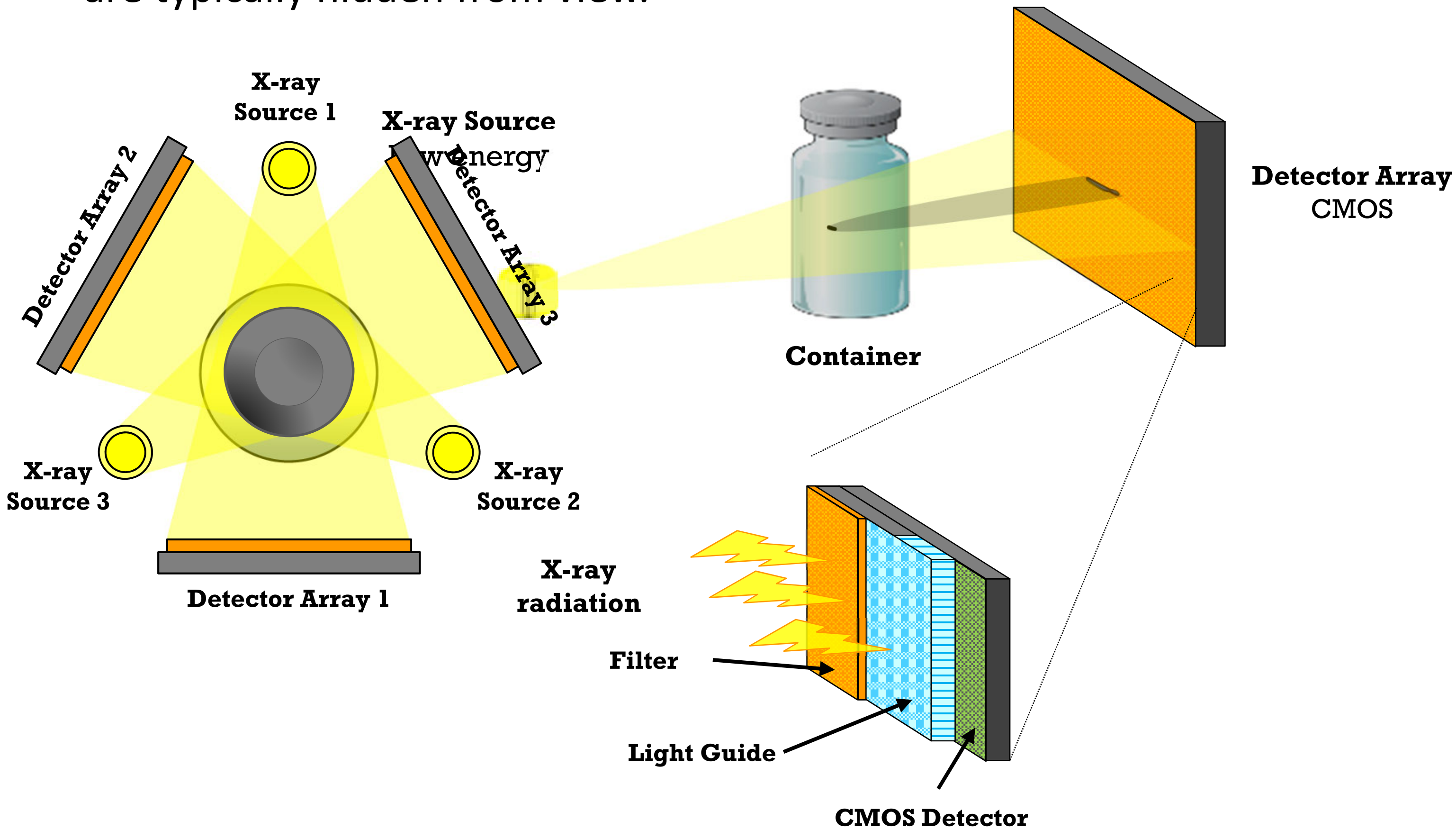
The moving particle detection is not possible in freeze-dried, lyophilized products, because the particulates are steady and hidden inside the solidified Lyo cake, in addition any high spinning cycle could damage the cake.



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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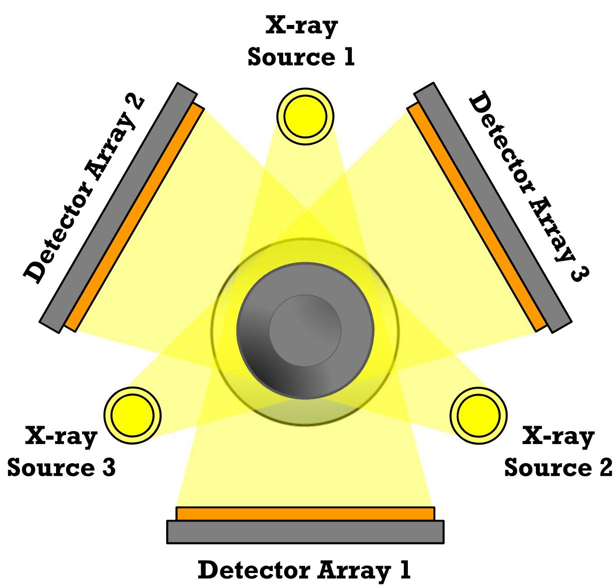
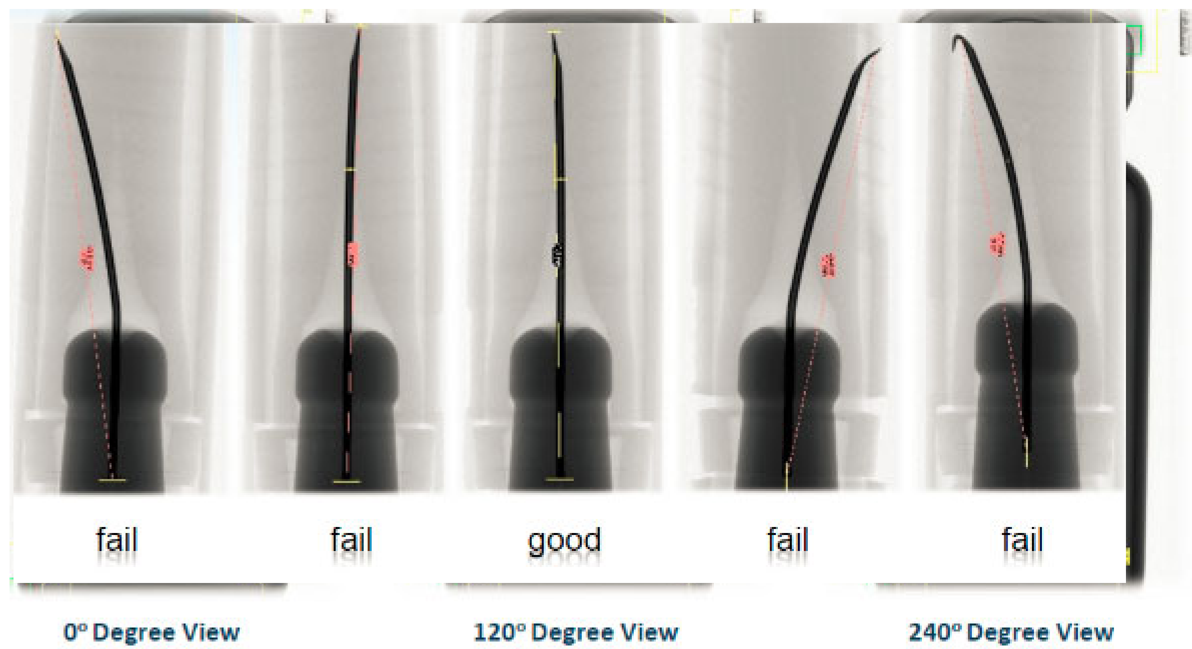


Verification of correct needle alignment

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

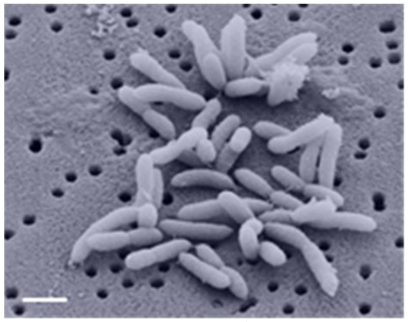
(sometimes called the 'critical leak')

Dana Guazzo, PhD, RxPax, LLC

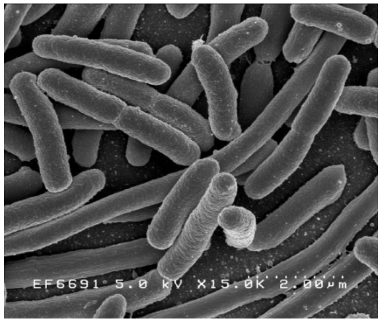
Package Integrity

Smallest leak to allow ingress determination

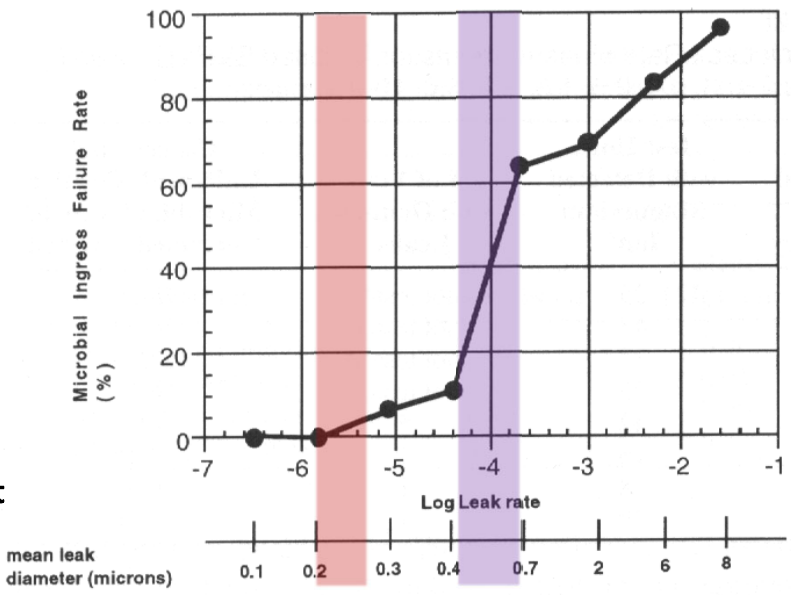
Lee Kirsch, et al, PDA J Pharm Sci & Technol, Vol. 51, No. 5, 1997



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

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

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

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.

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 37°C	**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

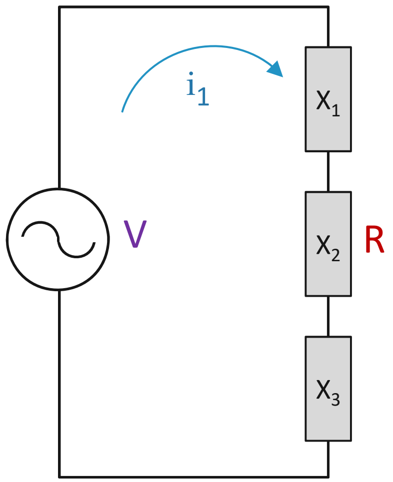
High Voltage Leak Detection (HVLD)

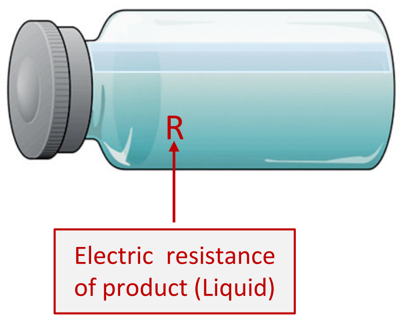
Principles of HVLD

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

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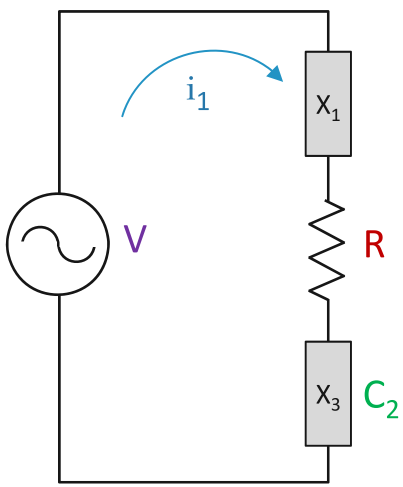
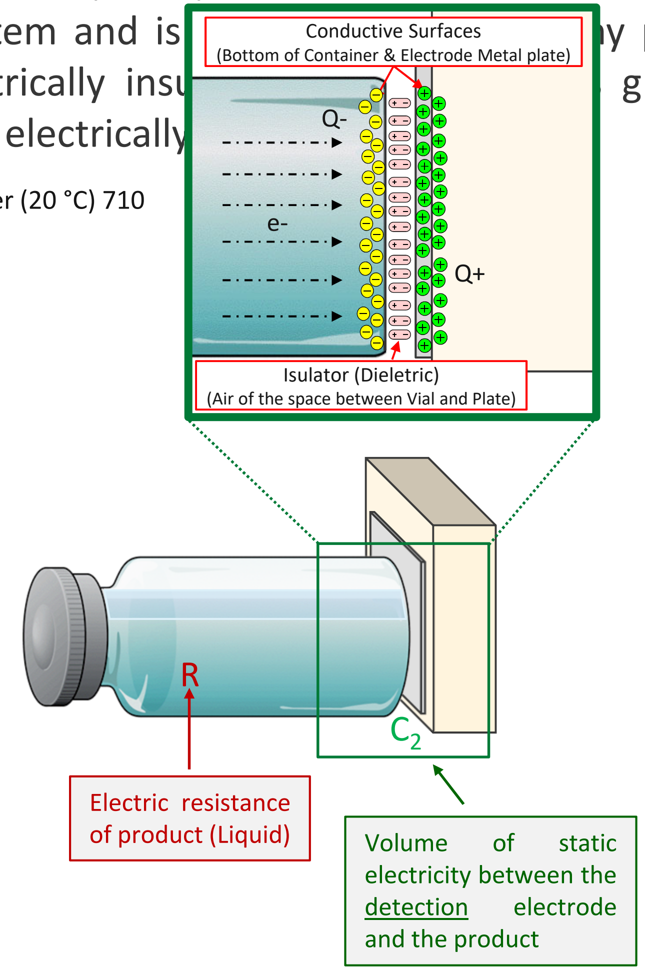
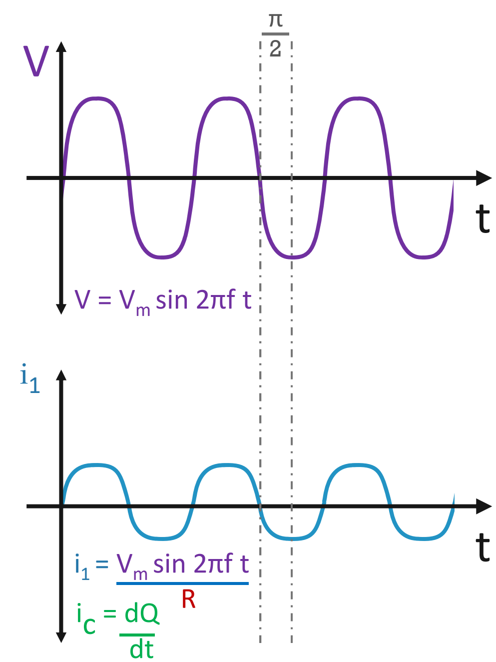
The High Voltage Leak Detection (HVLD) is based on the Ohms Law and the principle of a high voltage spark-test system and is ... y product as long as the container is made of electrically insu... glass, rubber, plastic or plastic film, and contains an electrically ...

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



$$i_m = \frac{V}{X_1 + R + X_3}, \quad X_3 = \frac{1}{2\pi f C_2}$$





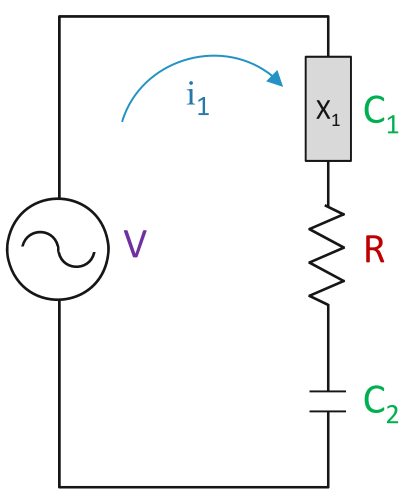
$$i_c = \frac{d}{dt} C V_m \sin 2\pi f t$$

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

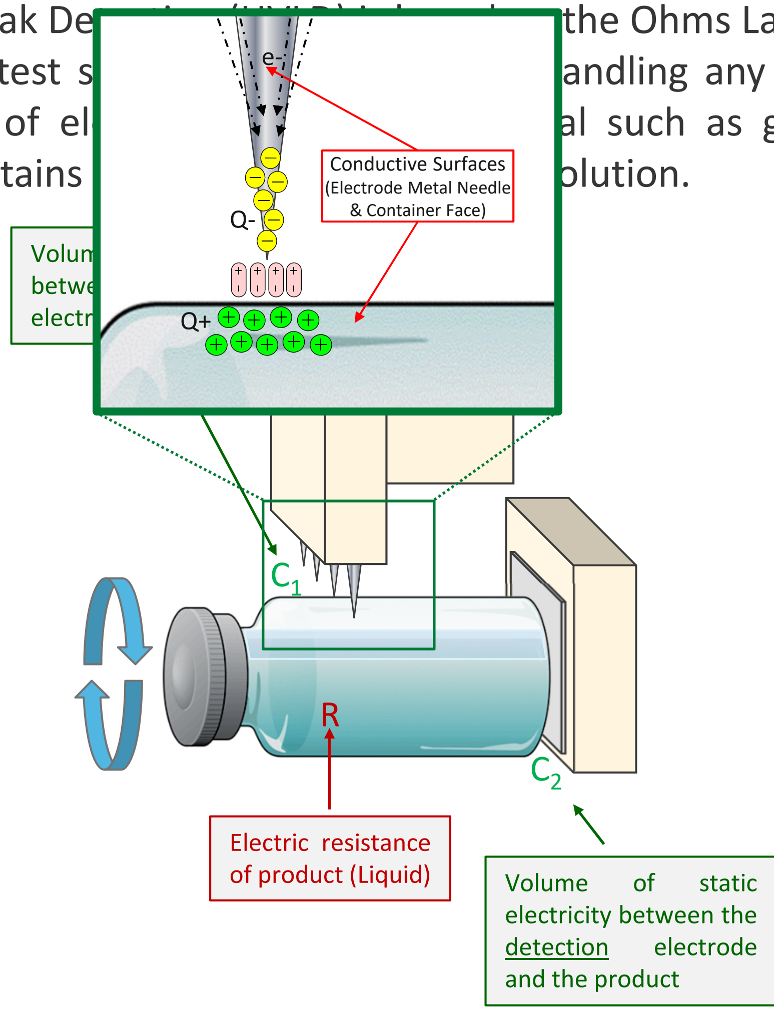
Principles of HVLD

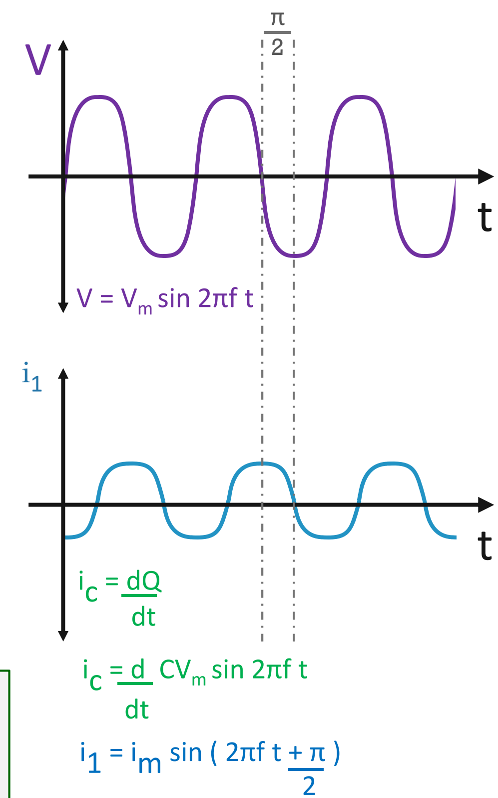
Detection Circuit

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.



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





Principles of HVLD

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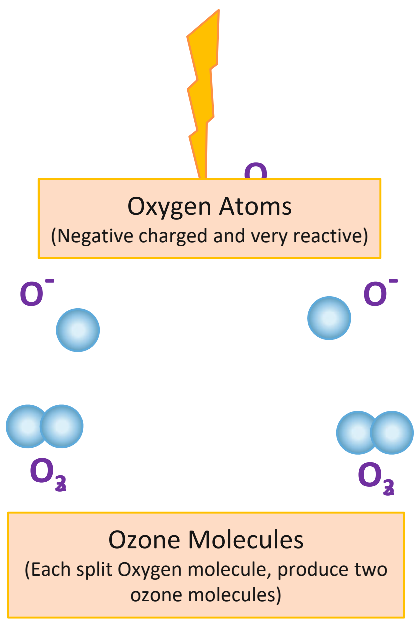
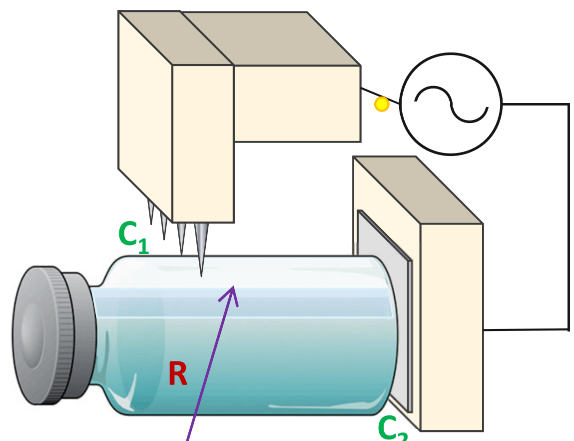




The production of ozone (O_3) by the passage an electric current through oxygen or air could cause the generation of an oxidant inside the vial headspace.

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.

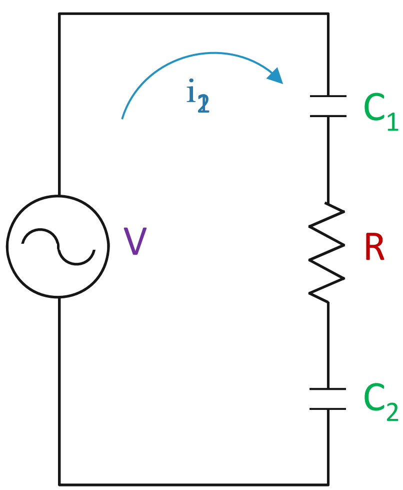
$$C = \frac{K*Eo*A}{d}$$

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

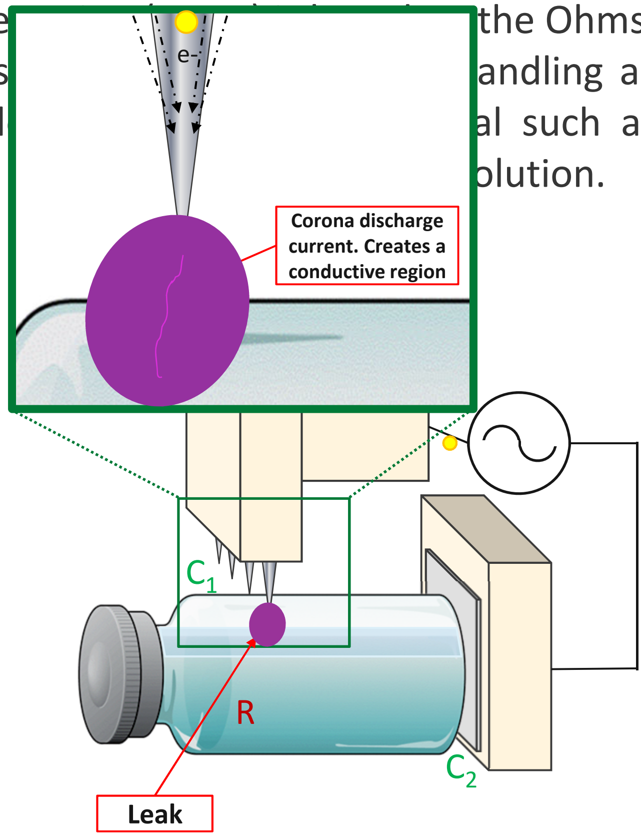
Principles of HVLD

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.



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

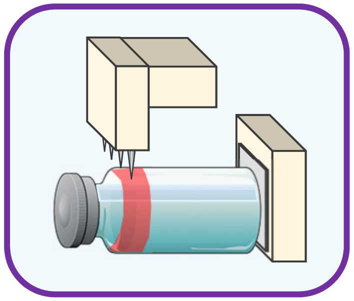


Leaking Containers

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.

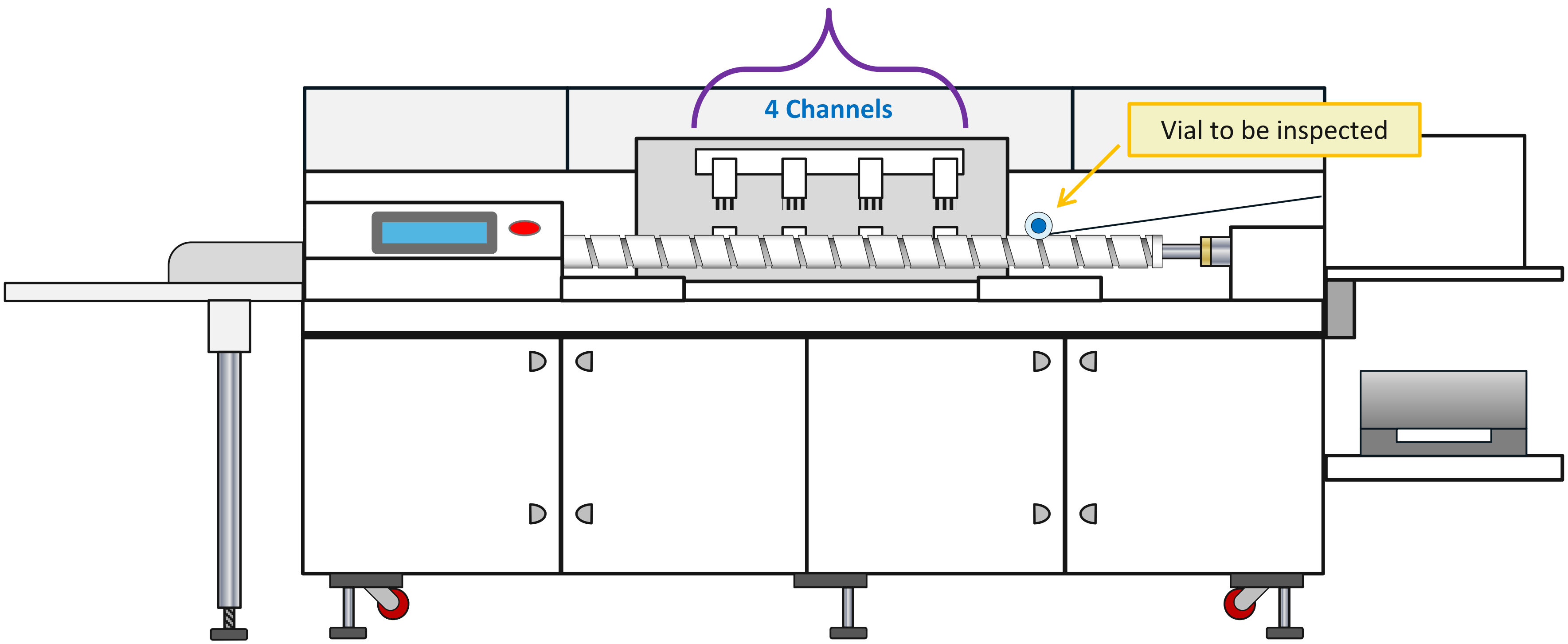
$i_2 > i_1$

Detection Process

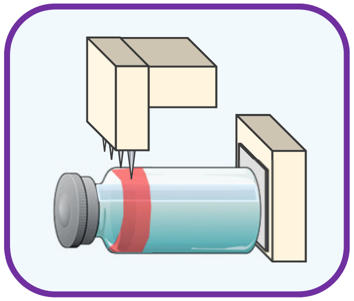


Station 1 (CH 1)
Shoulder of the Vial

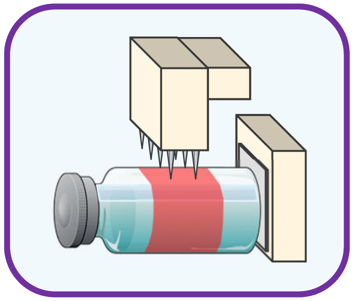
All containers are inspected at specific areas referred to Channels (4). Each one has a different electrode configuration and will produce an individual Inspection Signal Value (data point).



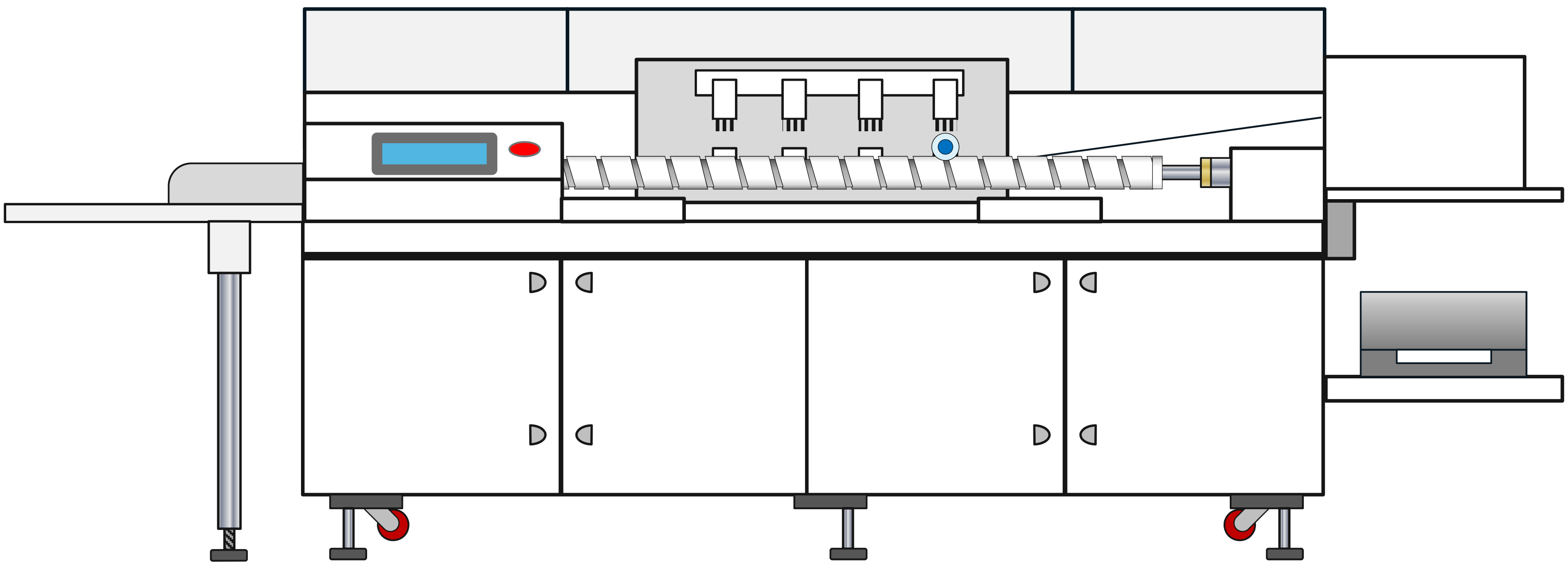
Detection Process



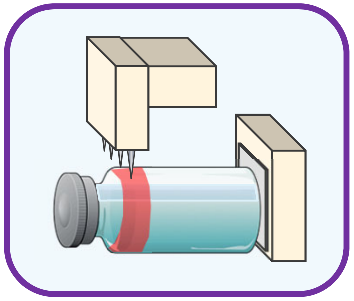
Station 1 (CH 1)
Shoulder of the Vial



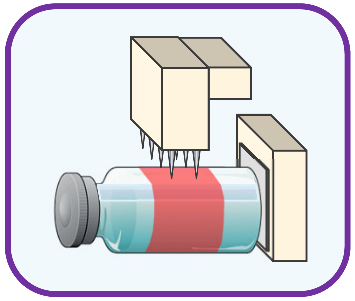
Station 2 (CH 2)
Entire sidewall (body) of the vial



Detection Process



Station 1 (CH 1)
Shoulder of the Vial



Station 2 (CH 2)
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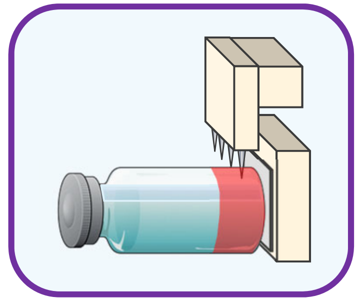
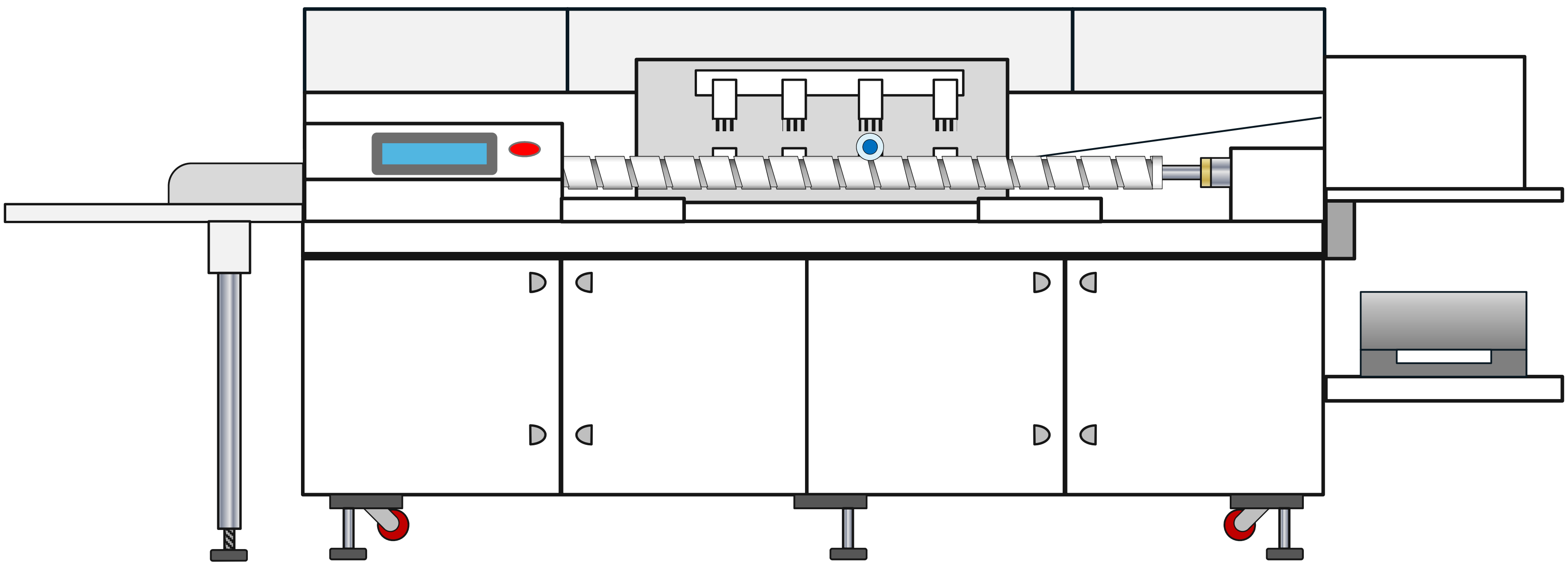
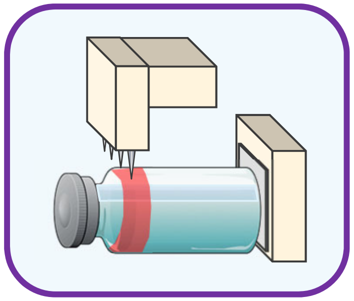


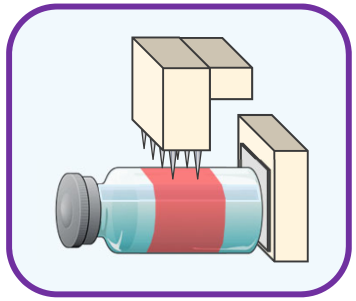
Station 3 (CH 3)
Bottom / Heel of the vial



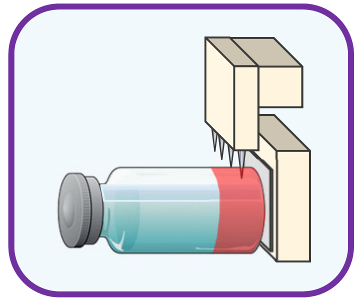
Detection Process



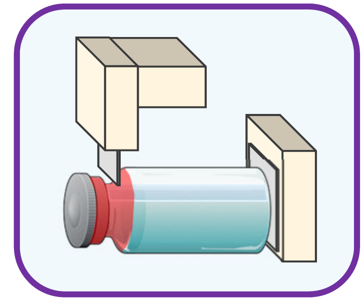
Station 1 (CH 1)
Shoulder of the Vial



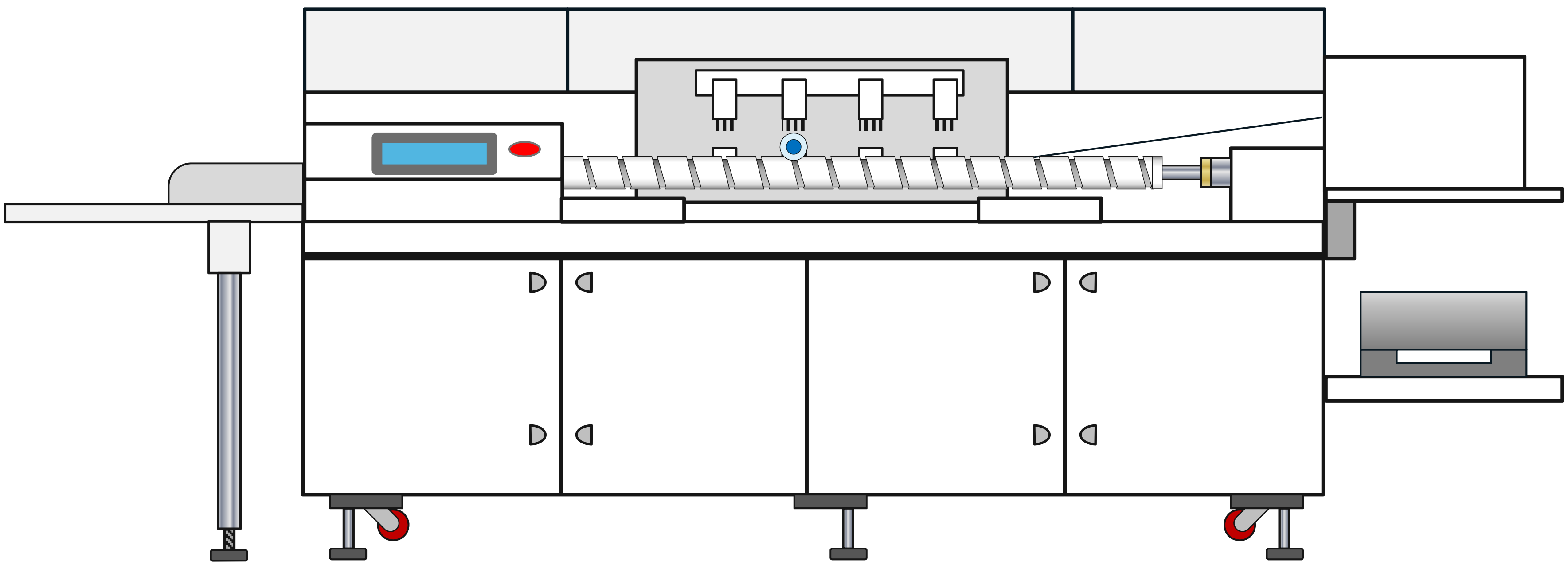
Station 2 (CH 2)
Entire sidewall (body) of the vial



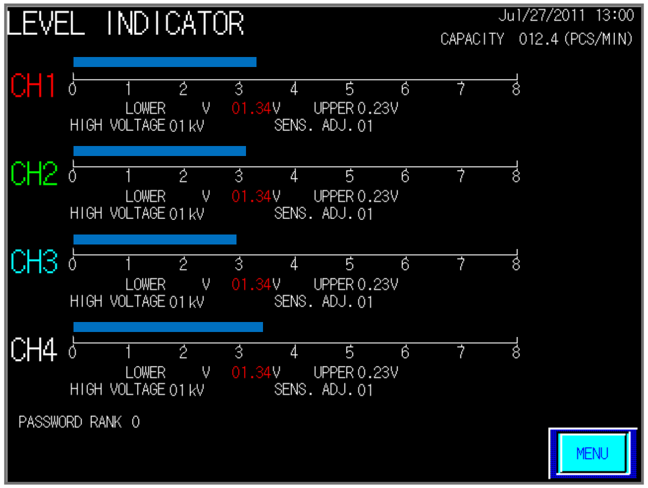
Station 3 (CH 3)
Bottom / Heel of the vial



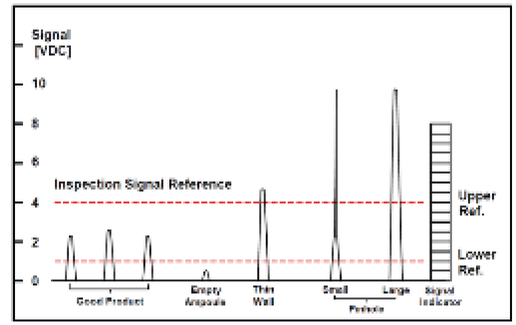
Station 4 (CH 4)
Neck, seal and cap/closure of the vial



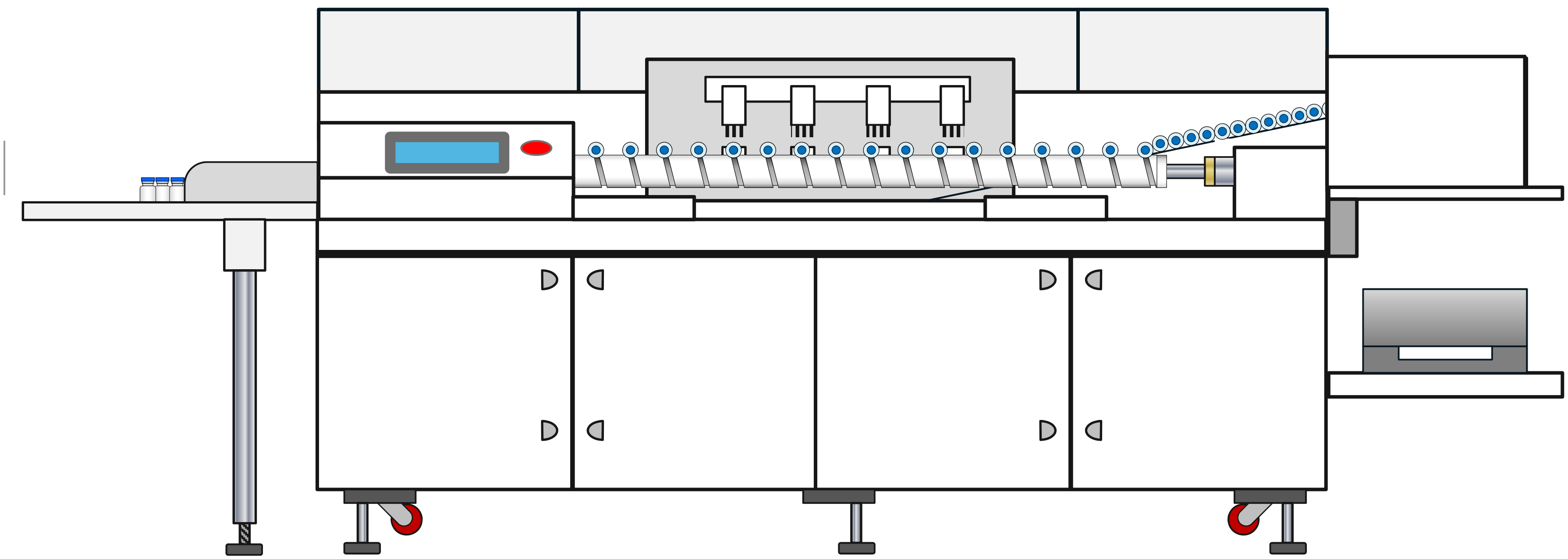
Voltage Reference Adjustment



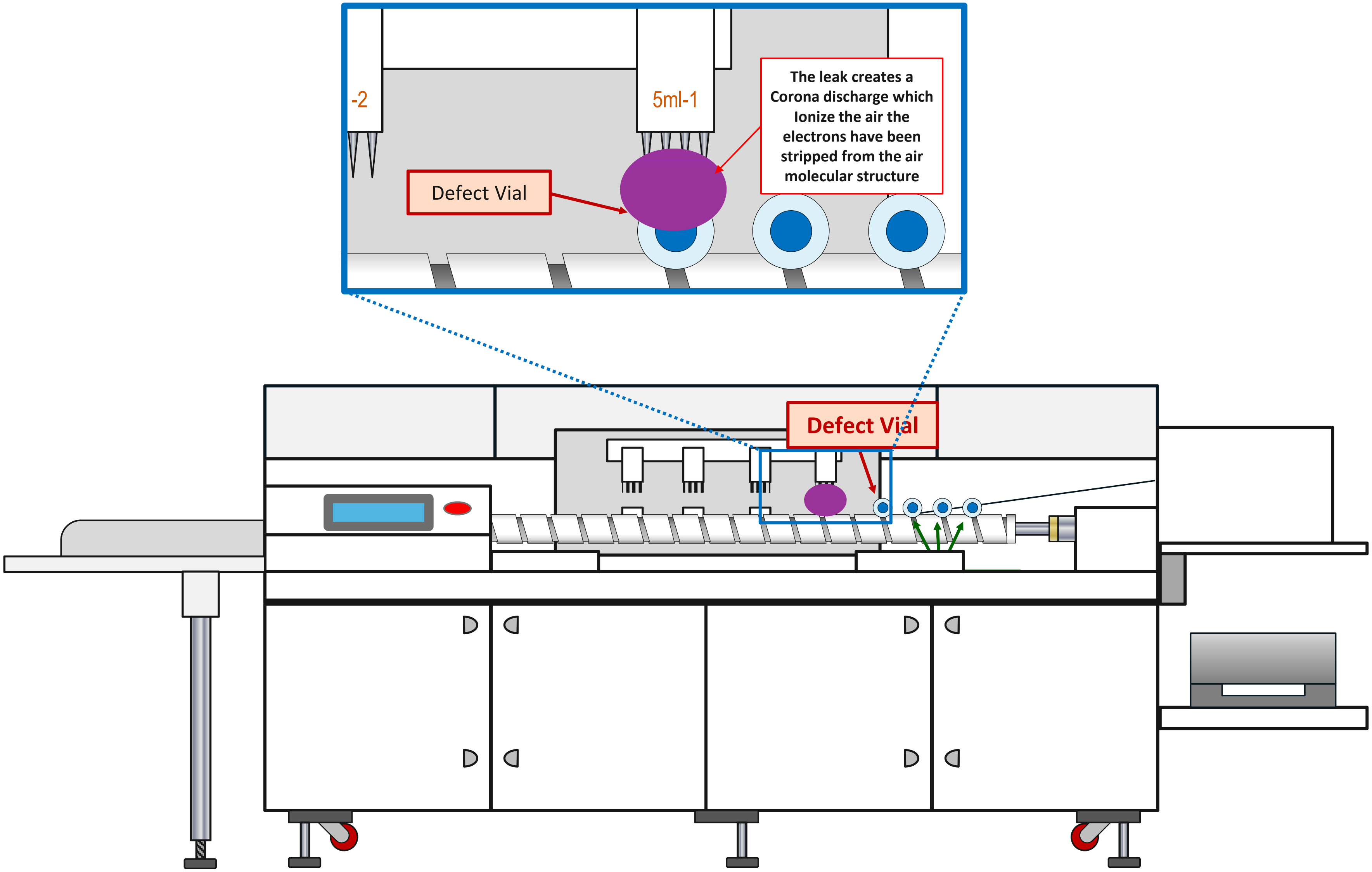
The vial inspection parameters are routinely setup by running sixteen (16) “good” vials through the machine based on the signal generated the machine automatically determines the initial Upper Reference (voltage).



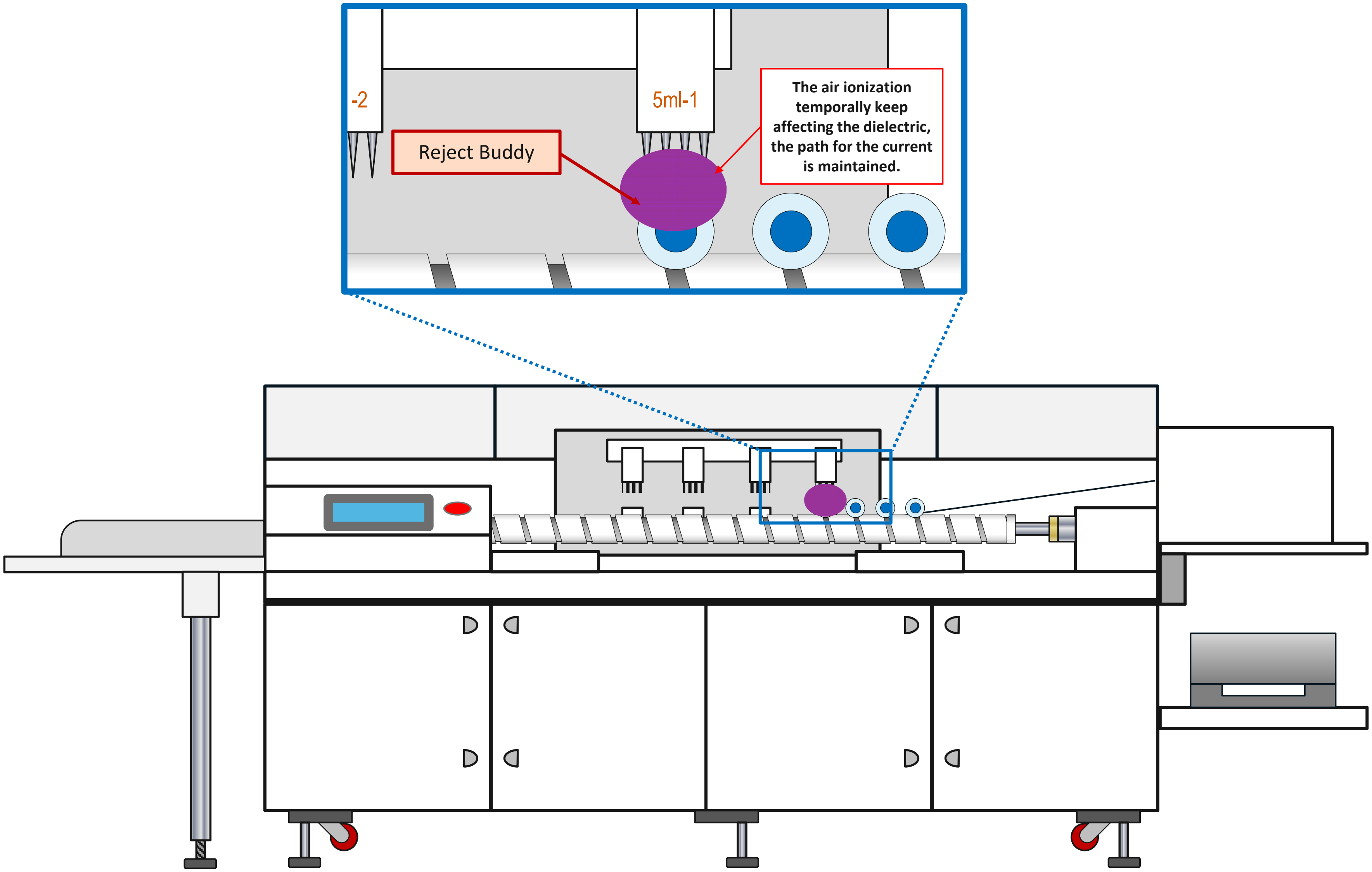
Upper Reference *= Average of 16 good product signals + GAP*
Lower Reference *= 1V (Lower Reference Set key-switch is ON)*
0V (Lower Reference Set key-switch is OFF)



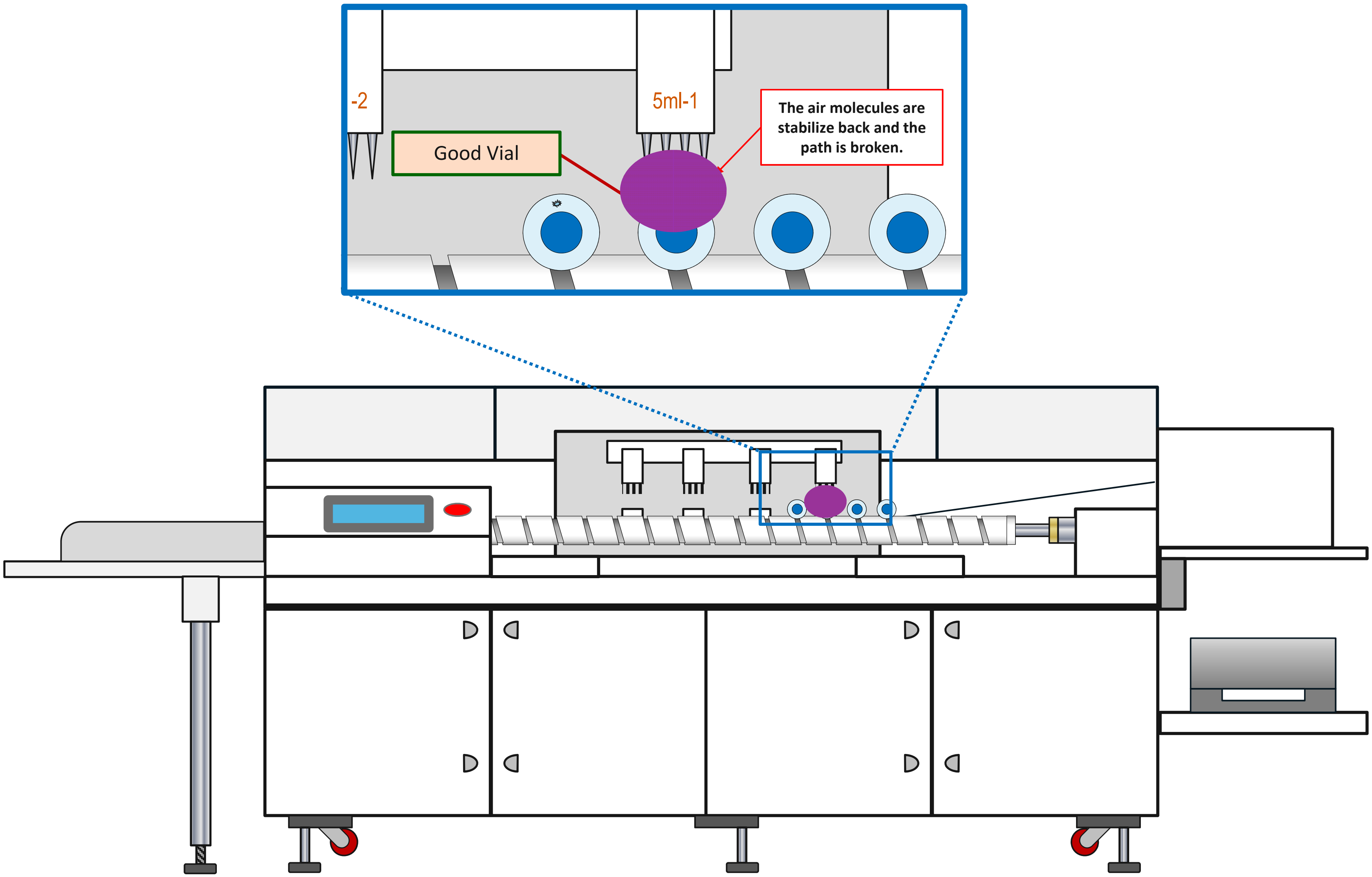
Buddy Reject Effect



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)

WILCOMAT® R MC/P/V Leak tester for vials

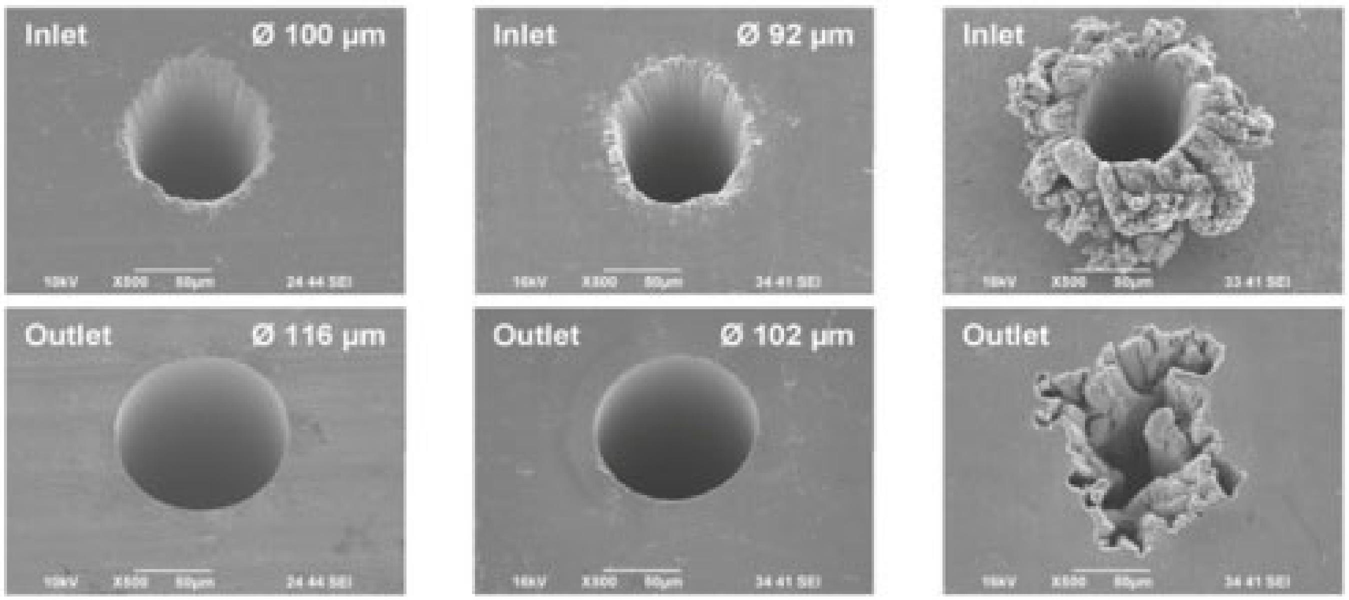
Content

- 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.

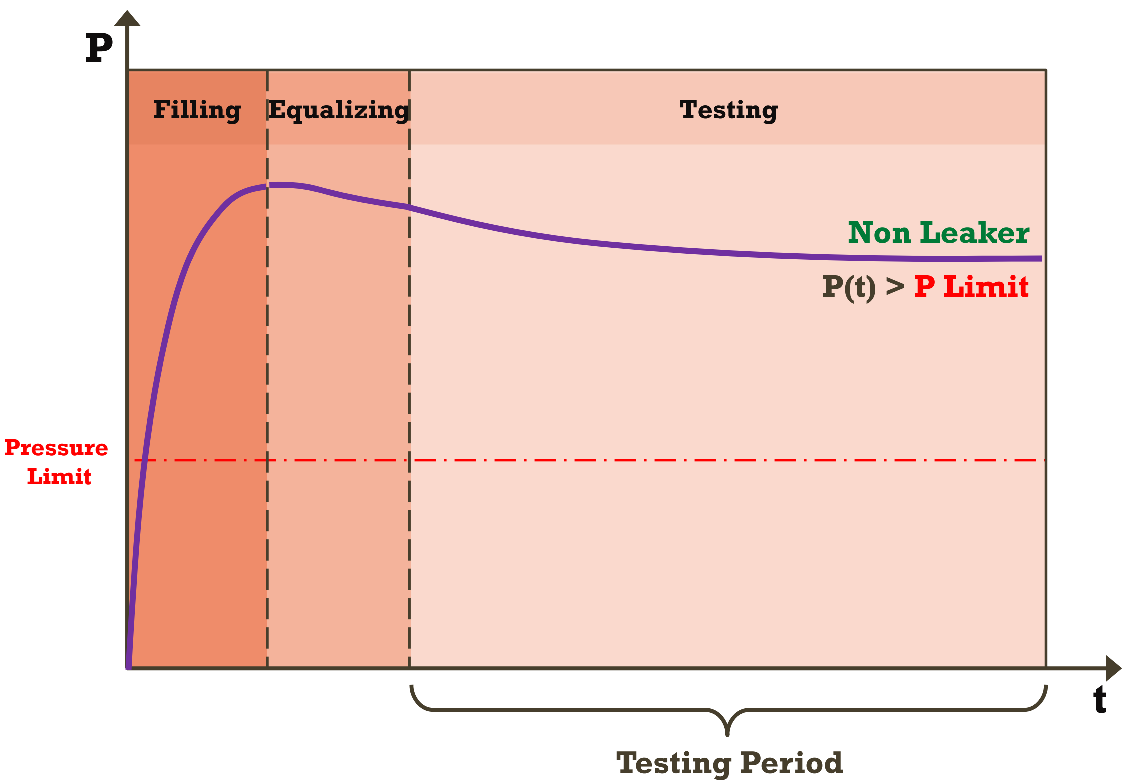


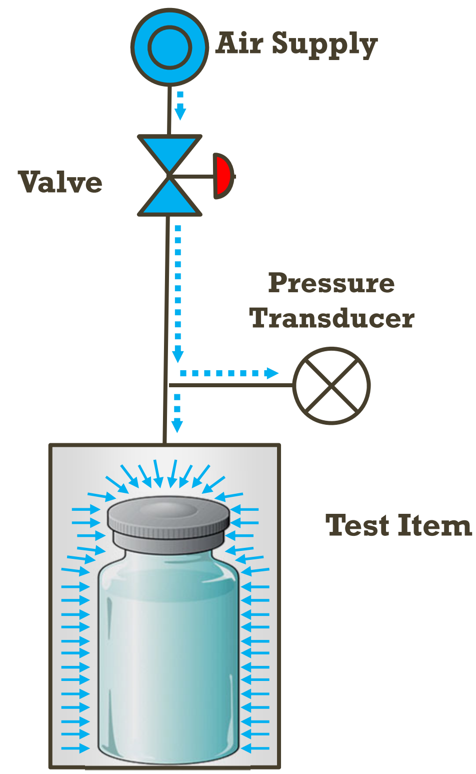
Heat accumulation during pulsed laser materials processing
Rudolf Weber, Thomas Graf, Peter Berger, Volkher Onuseit, Margit Wiedenmann, Christian Freitag, and Anne Feuer

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.





Leak Detection Methods

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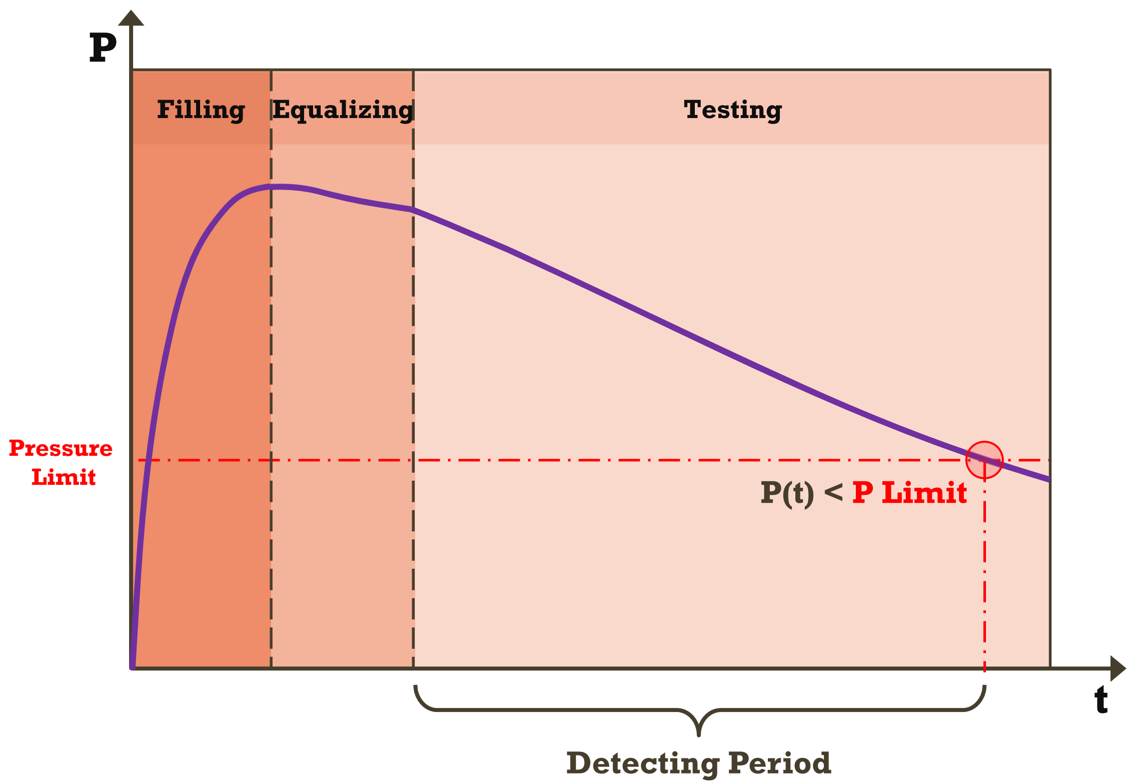
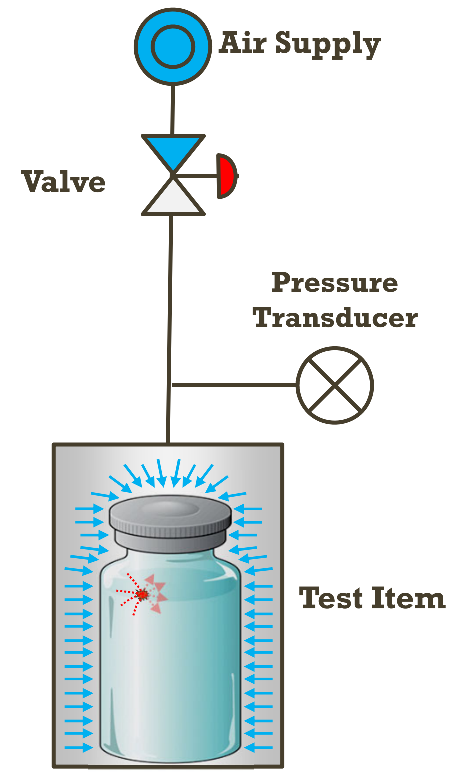
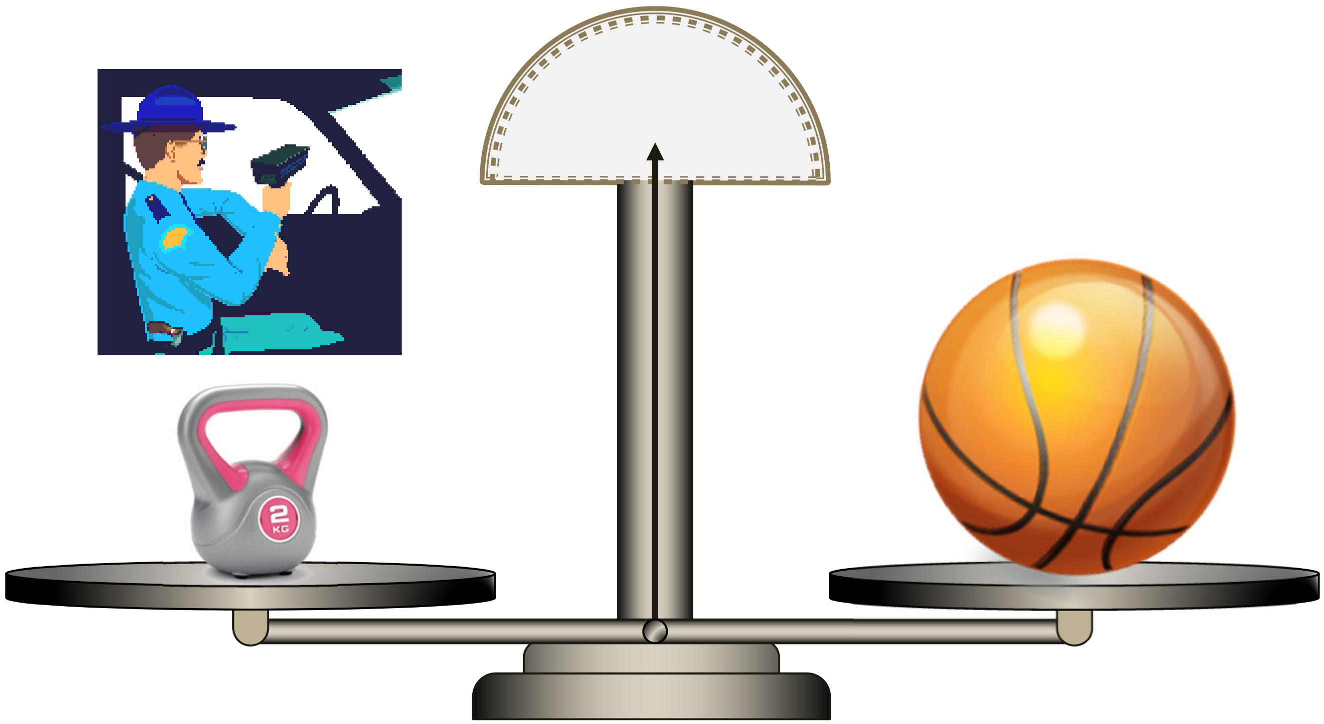




Leak Detection Methods

Differential Measurement

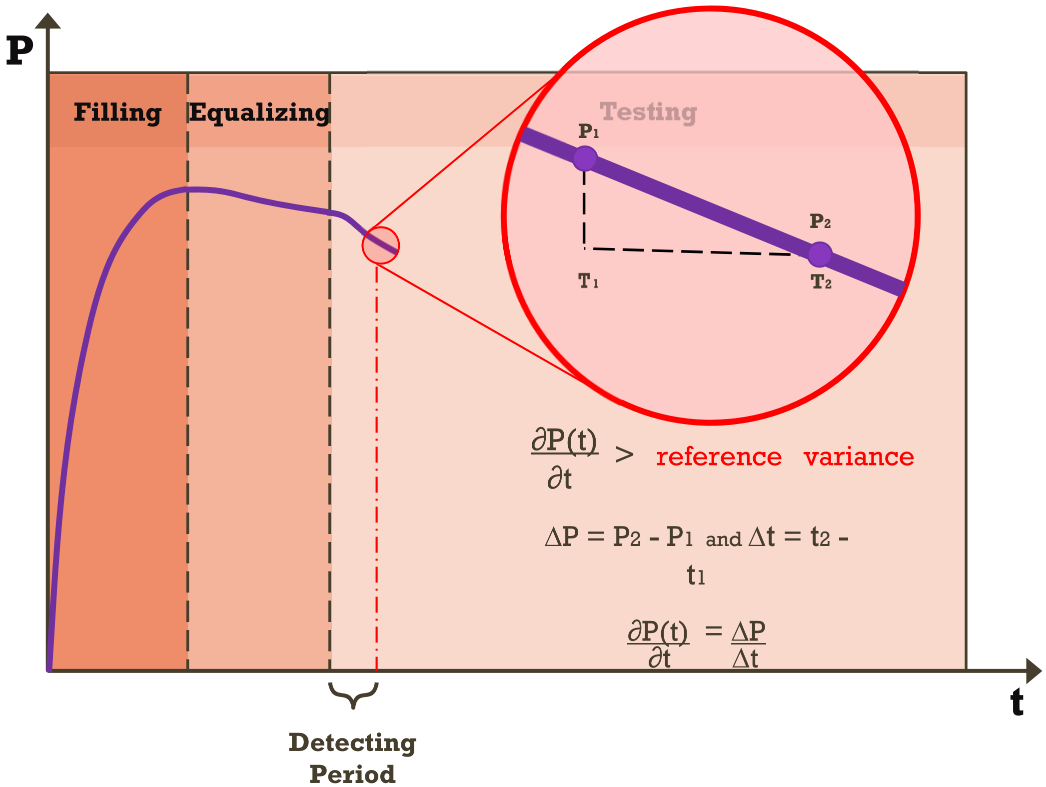
The differential pressure type air leak tester uses the same principle as the balancing scale. The same air pressure is charged to both the test subject and the reference with no leak and the change in pressure balance within a fixed time is checked for the presence of a leak.

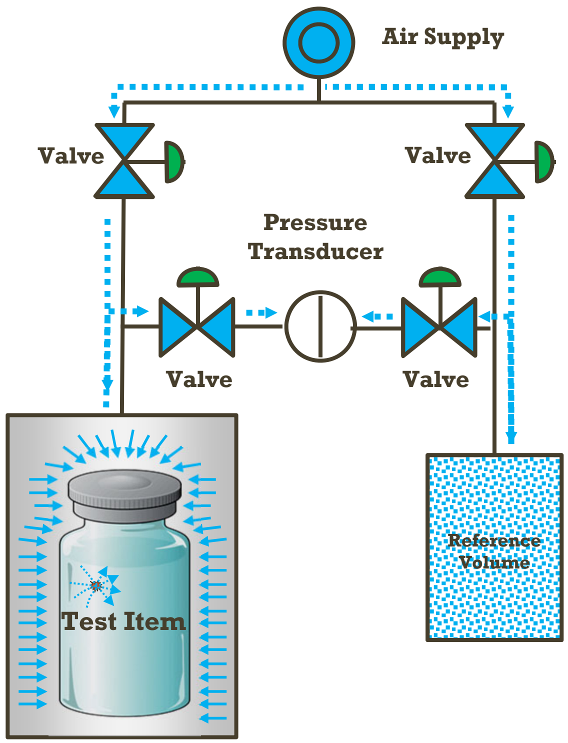


Leak Detection Methods

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**.



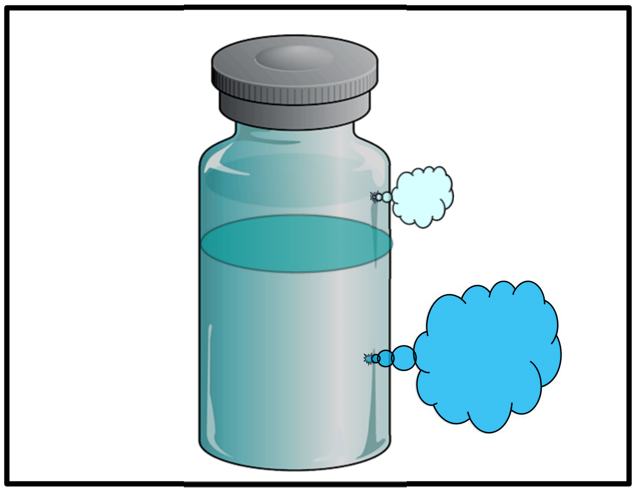


LFC (Liquid Filled Container)

Functional Principle

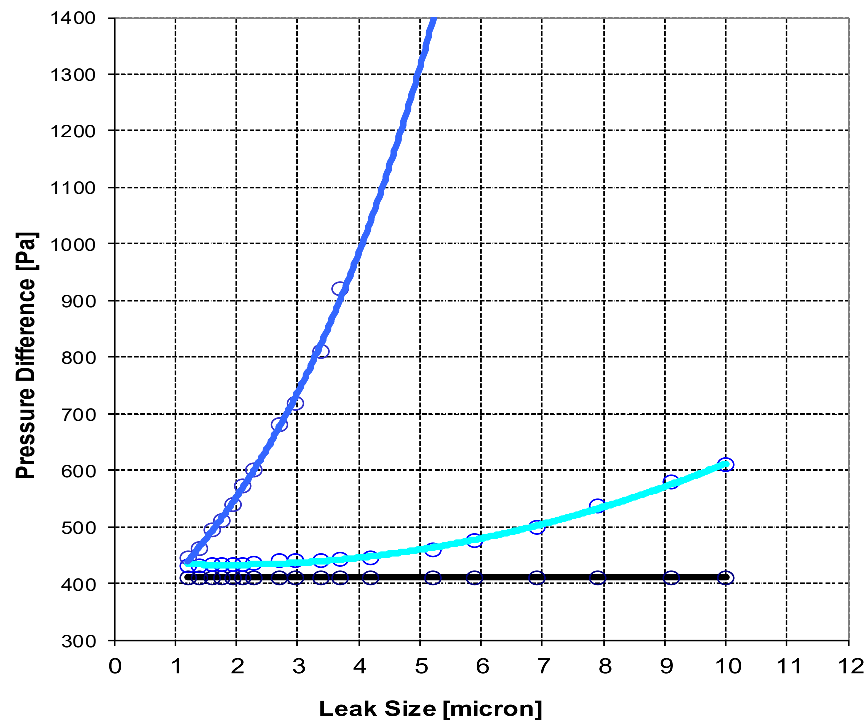
At room temperature 20°C (68°F) water evaporates at 23.4 mbar (17.3 mmhg) absolute pressure. The vapor volume causes a sharp pressure increase inside the test chamber.

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



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

Comparison of the detectable leak sizes with and without evaporation



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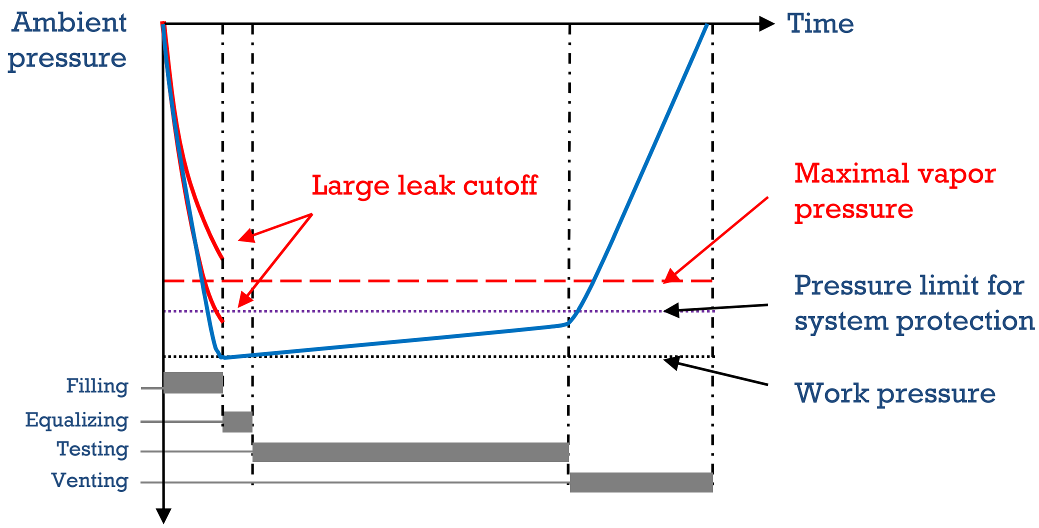
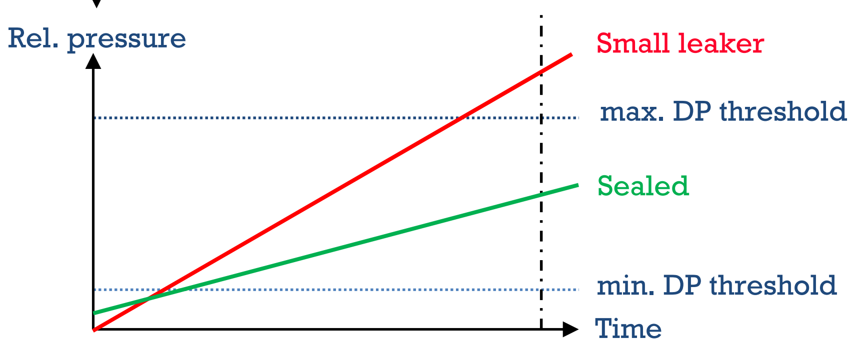
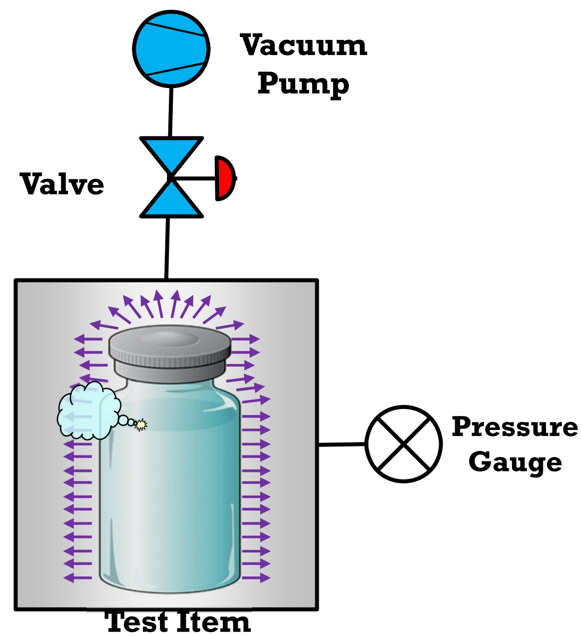


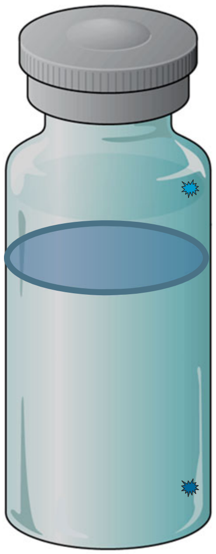


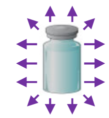


Things to consider using LFC method:

- 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)

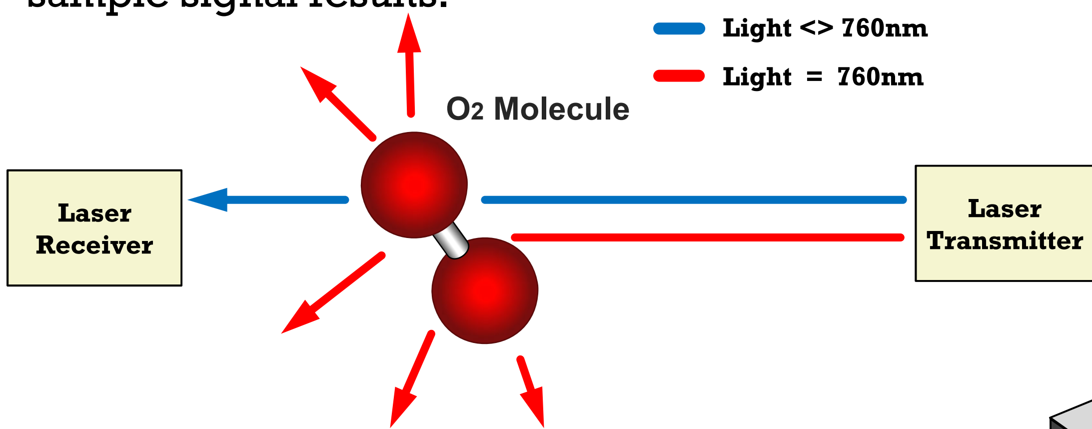
- Product may **clog defects masking their presence**. This is especially a concern with proteinaceous solutions, but has been observed with simple salt solutions as well.
- Because of potential product effects, validation of test methods should employ **product-filled positive controls** (with defect 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.

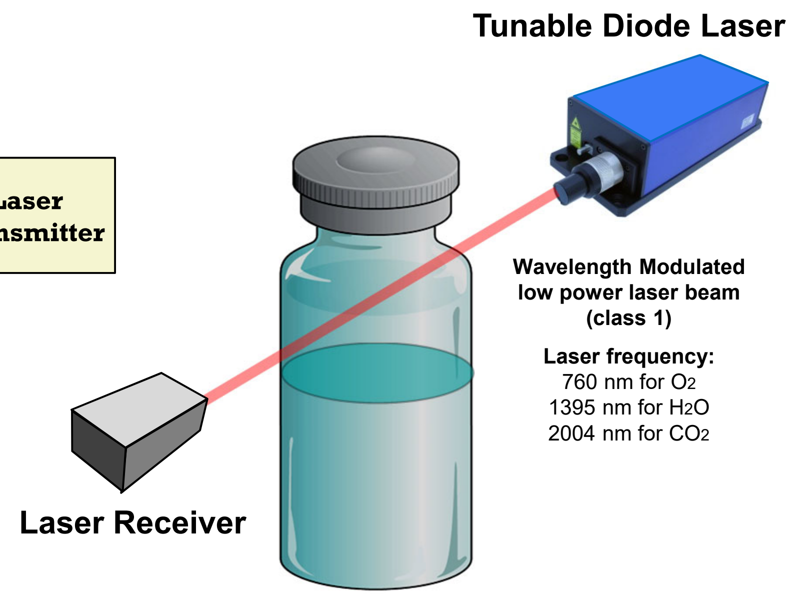
Leak Detection Methods

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.



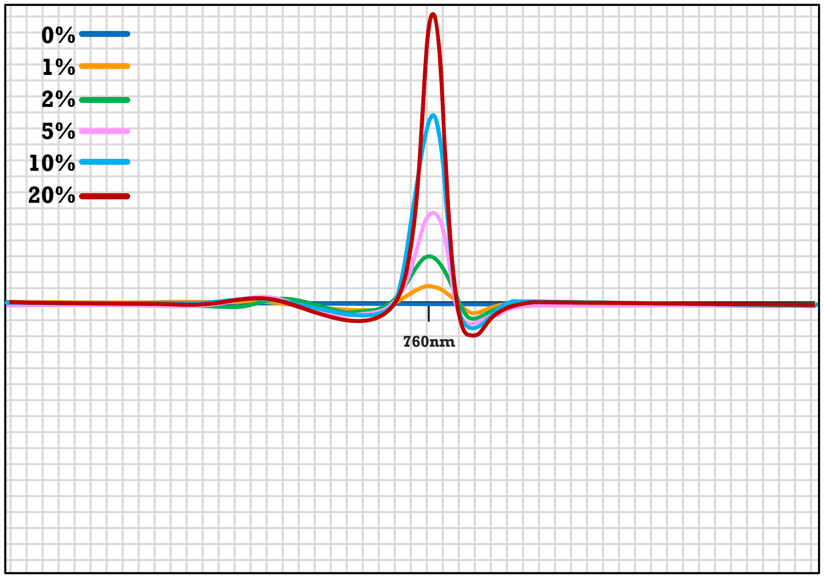
Light absorption is measured by frequency-modulated spectroscopy



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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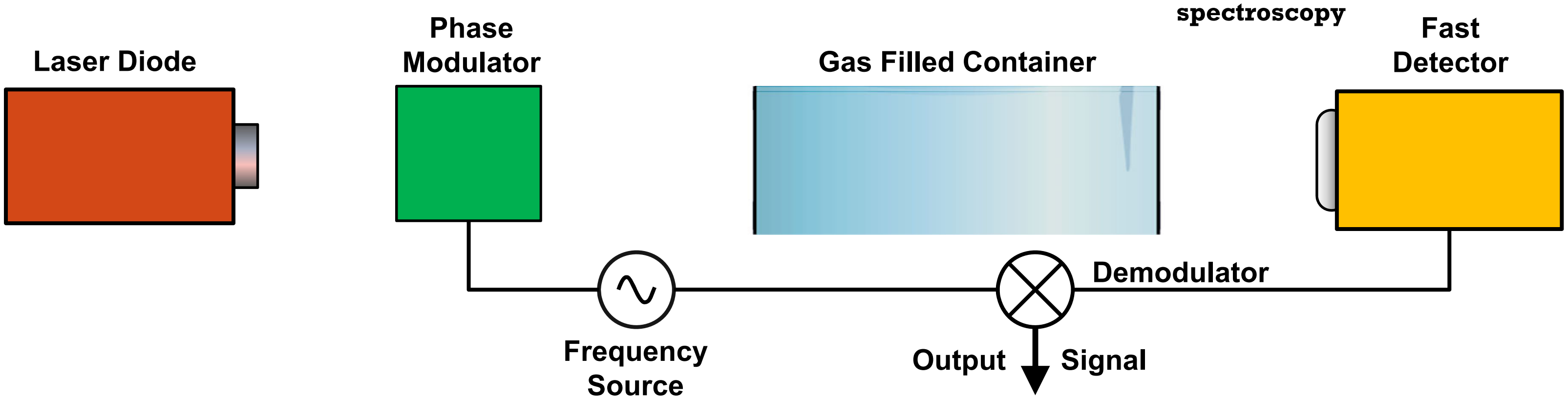


Leak Detection Methods

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.

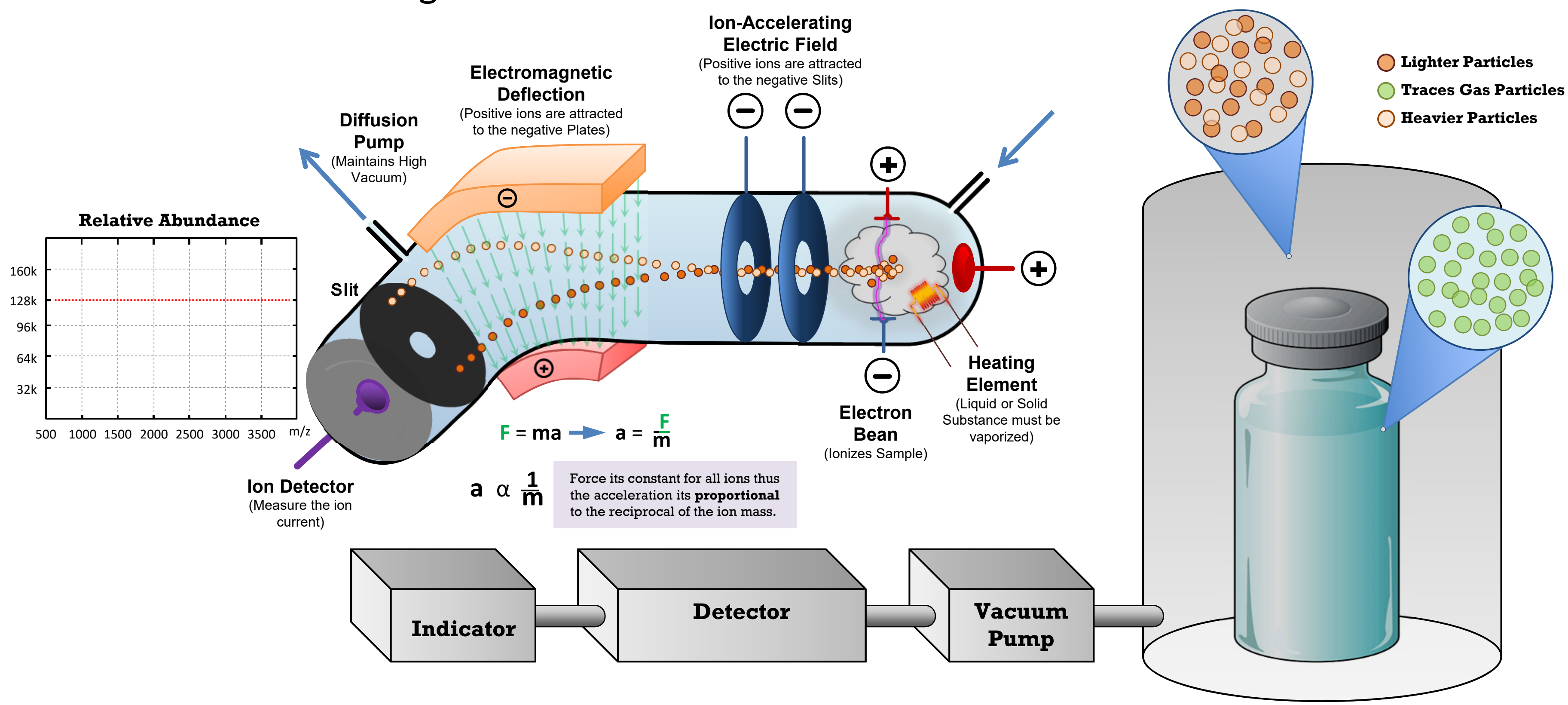
The **headspace pressure** affects the percentage of **gas molecules** inside the head space volume, thus on-line laser based testing isn't a leak test method that is readily linked to a defect size.

WILCOMAT® R HSA Automatic Head Space Gas Analysis

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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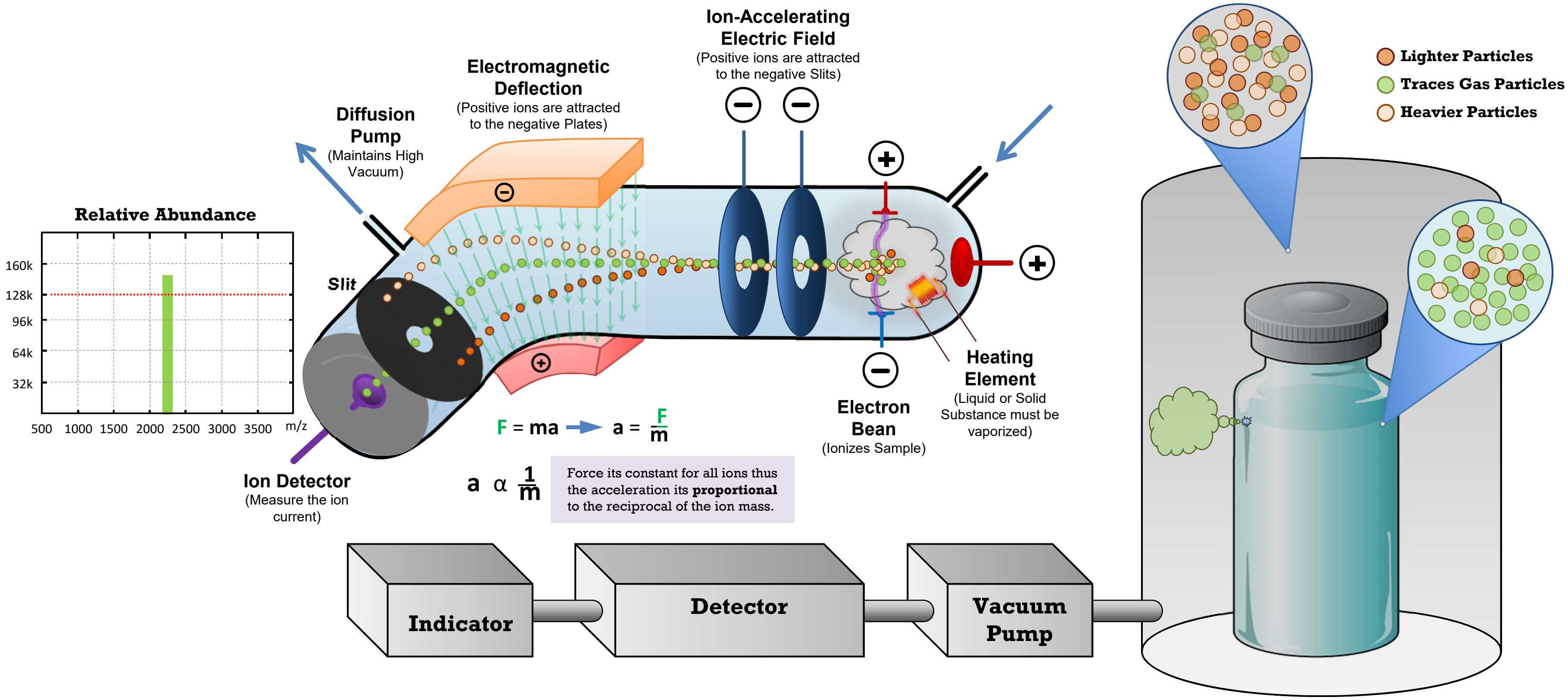
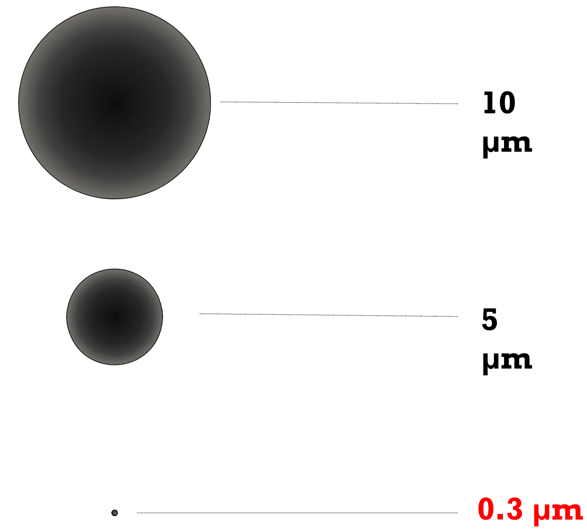


THEORY BEHIND AUTOMATED INSPECTION TECHNOLOGIES.

Summary

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	1 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

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

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THEORY BEHIND AUTOMATED INSPECTION TECHNOLOGIES

Thanks