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

Gaetano Baccinelli | Optrel inspection – A Stevanato Group Brand
Stevanato Group Brand Structure

PHARMACEUTICAL SYSTEMS

ENGINEERING SYSTEMS

SERVICES

GLASS PRIMARY PACKAGING

SPECIALTY PLASTICS & DELIVERY DEVICES

GLASS TECHNOLOGY, STERILE PACKAGING & INDUSTRIAL AUTOMATION

PACKAGING, ASSEMBLING & Serialization

PHARMA INSPECTION SYSTEMS

ANALYTICAL SOLUTIONS

SG Ompi

SG Balda

SG Spami

SG SVM

SG Innoscan

SG Optrel

SG Lab
Different options for inspecting

<table>
<thead>
<tr>
<th>Technology</th>
<th>Handling</th>
<th>Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual</td>
<td>Operator</td>
<td>Operator</td>
</tr>
<tr>
<td>Semi-Automatic</td>
<td>Automated</td>
<td>Operator</td>
</tr>
<tr>
<td>Fully Automatic</td>
<td>Automated</td>
<td>Automated</td>
</tr>
</tbody>
</table>
Pro’s Con’s of each Technology

MANUAL

- High Variability due to Human Factor

SEMI-AUTOMATIC

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

FULLY AUTOMATIC

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

**VERY HIGH SPEED**
- Continuous Motion
- Up to 660 pcs/min
- CVT
  - Optical tracking cameras for high accuracy and very high speed

**HIGH SPEED**
- Continuous Motion
- Up to 400 pcs/min
- EXACTA Easy
- EXACTA Plus
- LKD
  - Tracking cameras for high accuracy in detection
  - Fixed cameras for high productivity and low maintenance
  - Leak test machine

**MEDIUM SPEED**
- Intermittent Motion
- Up to 200 pcs/min
- MCA Series
- FD
  - Very flexible machines for inspection of a wide range of products
  - Dedicated machine for Freeze-Dried products

**SEMI-AUTOMATIC**
- Up to 100 pcs/min
- PWL Series
  - Ideal for small volume inspection or critical products
Controls layout for a typical automatic inspection machine

<table>
<thead>
<tr>
<th>Type</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST0 Closure control</td>
<td>Exit</td>
</tr>
<tr>
<td>ST1 Crimping control</td>
<td>Turret</td>
</tr>
<tr>
<td>ST2 Body control lateral</td>
<td>Turret</td>
</tr>
<tr>
<td>ST3 Particle and fill level</td>
<td>Turret</td>
</tr>
<tr>
<td>ST4 Particle inspection</td>
<td>Turret</td>
</tr>
<tr>
<td>ST5 Particle inspection</td>
<td>Turret</td>
</tr>
<tr>
<td>ST6 Floating particles</td>
<td>Turret</td>
</tr>
<tr>
<td>ST7 Bottom inspection</td>
<td>Outfeed</td>
</tr>
</tbody>
</table>
Example of defects

- Particulate Matter
- Closure Integrity
- Cosmetic Defects
Standard transparent solutions: Particles inspection
# Most common foreign matter found in drug production

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

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

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

![Human Inspection Performance Graph](image)

From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995
Different contaminants have different response to light

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

Absorbing
- Carbonization
- Impurities
- Rubber fragments

Reflecting
- Glass fragments
- Crystallization
- Silicone oil
- Delamination

Polarizing
- Fibers
- Impurities
- Product aggregation

Multi-scatter
- Fibers
- Impurities
- Glass fragments
Particle inspection: particle in white background

Possible Source

- Product carbonization for improper flame sealing of ampoules tip
- Impurities from API/WFI
- Rubber particles
Particle Inspection: Particle in Black Background

Reflecting Particles

- Glass fragments, filling needle not centered
- Product crystallization
- Silicone oil from stopper/plunger
- Glass Delamination
Particle Inspection: Fibers in Polarized Light

**Inspection method**
- Polarized light illumination

**Possible Source**
- Fibers from filter/wipper
- Impurities from API/WFI
- Fibers from clothing
How to combine all these setup in a single camera station?

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

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

Compute the sequence of differential images one by one
Background Subtraction

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

The reflexes are removed but sometimes canceling particles.
Optrel: New concept, dynamic analysis

- Particle trajectory reconstruction using the Kalman filter
- Trajectory post analysis filtering
- Analysis of the meniscus
- Analysis of the container bottom
Particle Inspection: Dynamic vs Interframe Analysis
Particle Inspection: Trajectory details

- Diff Threshold = 12
- Area Threshold = 5
- Particle size < 50µm
- Trajectory life = 16 frames
- Field of View = 10 ml
Optrel dynamic analysis, trajectory algorithm

A smart way to reach high efficiency and reduce false rejection in automatic inspection
How to achieve those performances?

New Generation Advanced Vision System Facts

- 64 high resolution images per container per particle station (2000x2000pxls)
- 256 images per container for particle inspection
- 1GB of particle inspection data per container to process in real-time
Trajectory, best solution for floating Particles Inspection
Trajectory, best solution for floating Particles Inspection
Trajectory best performing for bottom Particles Inspection
View of particles inspection on syringes
Particle Inspection: particle white background

To detect absorbing particles
Particle Inspection Video: particle white background
Particle Inspection: particle with frontal light

To detect reflecting particles or fibers
Cosmetic inspection: Heavy particles

Black sphere on the bottom

The particle detected by the inspection of the bottom profile
Suspensions solutions: different approach
Bottom inspection at infeed complement particle inspection
Particle inspection: Suspensions products

Patented light

Sao line 75μ wide
Suspension Products: automatic inspection

Product preparation is fundamental for suspension
High Speed Spinning System

High Speed Spinning System up to 6000rpm
Particle inspection: suspensions

Special light combined with high speed rotation (pat.)
Any questions?
Freeze Dried Inspection
Freeze Dried inspection: Critical Quality Attributes

Color Vision

<table>
<thead>
<tr>
<th>Physical description</th>
<th>Particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collapse</td>
<td>Container</td>
</tr>
<tr>
<td>Meltback</td>
<td>Integrity</td>
</tr>
</tbody>
</table>

A multivariate approach

DCVMN Regional Workshop

08/05/2018
View of some defects
Freeze Dried inspection: Color Camera

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

Color high resolution frame camera allows to better detect the defect inside the cake and it allows to recognize alteration on the product’s color.
Freeze Dried inspection: Color Camera

Result on the inspection of a good sample

Result of the inspection on a defected sample
Top Cake inspection

- Container in rotation for multi-perspective analysis
- Color 2000x2000 area camera at high speed (359 frames/sec)
- Mixed illumination for lighting cake or powder contamination with programmable intensity control
Freeze Dried lateral side inspection: Line scan technology

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

- Flip-off presence
- Alu-Seal Inspection
- Product in Stopper
- Stopper Integrity
- Glass Defects
- Cake Height
- Cake Defects
Lateral Cake Inspection

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

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

High resolution 1400x1000 pixels area color camera
Contamination inside cake?

Some Idea
NIR Imaging: Identification of Contaminants

VIS  Paper fragment  NIR

Plastic trasparent layer
NIR Imaging: Identification of Contaminants

VIS | Blonde Hair | NIR

Glass Fragment
Any questions?
Cosmetic Inspection
Flip Off / Alu Seal inspection: single station
Alu Seal inspection

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

Linear Camera
- Flat illumination
- High contrast
- 360° scan
- No missing defect
- High resolution 2K-4K
Inspection Technology: Linear Scan Camera and/or Matrix camera

Aluseal Inspection
Special Technology Linear Scan Cameras

Possible Source:
• Improper crimping station setup
• Variability on closure components

Resolution:
• Detect crimping defect smaller than 50µm
Linear scan camera for OCR control

• Interactive definition of OCR and CODE READER

• High resolution print verification using linear cameras and special illumination techniques on alu-seal and glass surface
Linear scan camera for glass inspection

Body inspection (scratch on the surface) → Scratch highlighted in red color
Cracks on neck/shoulder area
Special Technology Linear Scan Cameras

Linear Scan Cameras for plunger inspection

Line scan camera sensor

Image construction

‘Unlimited’ horizontal resolution

Fixed vertical resolution
Defects on syringes

- Particulate matter
- Closure integrity
- Cosmetic defects
Cosmetic Inspection : Tip Cap, defect and shape control

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

Cosmetic defect
Good container

Cosmetic defect
Bad container
Finger grip inspection

Inspection Setup

[Diagram of inspection setup]
Any questions?
Leak Detection and Containers Integrity
# Container Closure Integrity: Dye Ingress Leak Detection

<table>
<thead>
<tr>
<th>Dye Method</th>
<th>USP31&lt;381&gt; Ph.Eur. 3.2.9</th>
<th>ISO 8362-5 Annex C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye</td>
<td>0.1% aq. Methylene Blue</td>
<td></td>
</tr>
<tr>
<td>Vacuum</td>
<td>-27KPa</td>
<td>-25KPa</td>
</tr>
<tr>
<td>Time at Vacuum</td>
<td>10 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Time at ambient</td>
<td>30 min</td>
<td>30min</td>
</tr>
<tr>
<td>Detection</td>
<td>Visual inspection</td>
<td></td>
</tr>
</tbody>
</table>

## Risk Of Microbial Ingress if >1um
Container Closure Integrity: Dye Ingress Leak Detection

Dye Test Not Sensitive Enough for Human Operator

Dye Test Sensitive if in conjunction with automatic spectrometer
Container Closure Integrity: HV Leak Detection

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

HV Test Sensitive Enough For Integrity Assurance
# HVLD Exposure Effects on Product P-C Properties

## ImClone Systems Products

<table>
<thead>
<tr>
<th>HVLD Exposure</th>
<th>Product A</th>
<th></th>
<th>Product B</th>
<th></th>
<th>Product C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rel. MW</td>
<td>% Purity</td>
<td>% Purity</td>
<td>% Purity</td>
<td>Rel. MW</td>
<td>% Purity</td>
</tr>
<tr>
<td>None</td>
<td>142</td>
<td>97.6</td>
<td>1.5</td>
<td>1.0</td>
<td>138</td>
<td>98.0</td>
</tr>
<tr>
<td>1 x 25kV</td>
<td>142</td>
<td>97.5</td>
<td>1.5</td>
<td>1.0</td>
<td>138</td>
<td>98.0</td>
</tr>
<tr>
<td>10 x 25kV</td>
<td>142</td>
<td>97.5</td>
<td>1.5</td>
<td>1.0</td>
<td>138</td>
<td>98.0</td>
</tr>
</tbody>
</table>

**Summary:** HVLD exposure demonstrated **no impact**

Source: RxPax, LLC, PDA Metro Chapter, May 2011
Vacuum Decay as alternative solution

For dry or liquid products, most package systems
Detects pressure rise from gas or vapor egress limitations
• Protein clogging often prevents leak detection
• Liquid leaks may contaminate test chamber
Considerations
• Faster tests limit sensitivity
• Instrument design/make can influence test results
  o Transducers and internal system design
  o No-leak baseline stability

Source: RxPax, LLC, PDA Metro Chapter, May 2011
NIR Spectroscopy for Lyophilized products

- Air path layout for easy integration into inspection machine
- H₂O Absorption Band 1400 nm and 1900 nm
Headspace Gas Analysis Measurement Layout
Inspection configuration details

<table>
<thead>
<tr>
<th>Inspection station</th>
<th>Inspection detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0</td>
<td>TIP INSPECTION/ ALU SEAL</td>
</tr>
<tr>
<td>S1</td>
<td>GLASS DEFECT ON LATERAL SIDE STILL PARTICLES VISCOUS PRODUCTS</td>
</tr>
<tr>
<td>S2</td>
<td>PARTICLES / FILL LEVEL</td>
</tr>
<tr>
<td>S3</td>
<td>PARTICLES</td>
</tr>
<tr>
<td>S4</td>
<td>PARTICLES</td>
</tr>
</tbody>
</table>
Any questions?
Thank you for your attention!

For further information please visit www.engineeringstevanatogroup.com