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

Gaetano Baccinelli, Sales Manager
Stevanato Group Engineering Systems
Stevanato Group Brand Structure

PHARMACEUTICAL SYSTEMS
- Ompi
- Balda
- Spami
- SVM
- Innoscan
- Optrel

ENGINEERING SYSTEMS
- Glass Primary Packaging
- Specialty Plastics & Delivery Devices
- Glass Technology, Sterile Packaging & Industrial Automation
- Packaging, Assembling & Serialization
- Pharma Inspection Systems

SERVICES
- Analytical Solutions
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

<table>
<thead>
<tr>
<th>Speed Level</th>
<th>Speed Range</th>
<th>Series</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VERY HIGH SPEED</strong></td>
<td>Up to 600 pcs/min</td>
<td>CVT Series</td>
<td>• To inspect challenging, high value drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Optical tracking cameras for high accuracy and very high speed</td>
</tr>
<tr>
<td><strong>MEDIUM - HIGH SPEED</strong></td>
<td>Up to 400 pcs/min</td>
<td>Plus Series</td>
<td>• To inspect complex products</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• High resolution images</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Leak test machine</td>
</tr>
<tr>
<td><strong>MEDIUM - HIGH SPEED</strong></td>
<td>Up to 400 pcs/min</td>
<td>Easy Series</td>
<td>• To inspect water-like products</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Value-for-cost choice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Easy to maintain</td>
</tr>
<tr>
<td><strong>SEMI-AUTOMATIC</strong></td>
<td>Up to 100 pcs/min</td>
<td>PWL Series</td>
<td>• Ideal for small volume inspection or critical products</td>
</tr>
</tbody>
</table>
### Controls layout for a typical automatic inspection machine

<table>
<thead>
<tr>
<th>Type</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST0</td>
<td>Closure control</td>
</tr>
<tr>
<td>ST1</td>
<td>Crimping control</td>
</tr>
<tr>
<td>ST2</td>
<td>Body control lateral</td>
</tr>
<tr>
<td>ST3</td>
<td>Particle and fill level</td>
</tr>
<tr>
<td>ST4</td>
<td>Particle inspection</td>
</tr>
<tr>
<td>ST5</td>
<td>Particle inspection</td>
</tr>
<tr>
<td>ST6</td>
<td>Floating particles</td>
</tr>
<tr>
<td>ST7</td>
<td>Bottom inspection</td>
</tr>
</tbody>
</table>
Example of 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.
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
Particles inspection: particle in white background

Possible Source

• Product carbonization for improper flame sealing of ampoules tip
• Impurities from API/WFI
• Rubber particles
Particles 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
Particles inspection: dynamic vs interframe analysis
Particles inspection: trajectory details

- Diff Threshold = 12
- Area Threshold = 5
- Particle size < 50µm
- Trajectory life = 60 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 performing for bottom particles inspection
View of particles inspection on syringes
Particles inspection: particle white background

To detect absorbing particles
Particles inspection: particle white background
Particles inspection: particle white background
Particles 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

Bottom inspection at infeed complement particle inspection
Particles inspection: suspensions products

Patented light

Scanline 75µ wide
Suspension Products: automatic inspection

Product preparation is fundamental for suspension
High speed spinning system

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

Special light combined with high speed rotation (pat.)
More examples of particles inspection
More examples of particles inspection

Figure 4 Sample #09, small black particle

Figure 6 Sample #29, white fibre
Freeze Dried Inspection
Freeze dried inspection: critical quality attributes

<table>
<thead>
<tr>
<th>Color Vision</th>
<th>Vision X-ray Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense</td>
<td></td>
</tr>
<tr>
<td>Porous</td>
<td></td>
</tr>
</tbody>
</table>

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

- **Physical description**
- **Particles**
- **Collapse**
- **Container**
- **Meltback**
- **Integrity**

A multivariate approach
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
More from bottom
Contamination inside cake?

Some Idea
NIR Imaging: identification of contaminants

VIS

Paper fragment

NIR

Plastic transparent layer
NIR Imaging: identification of contaminants

VIS  Blonde Hair  NIR

Glass Fragment
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

Fixed vertical resolution

‘Unlimited’ horizontal resolution

Image construction
Defects on syringes
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
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

USP/PhEur Dye Ingress Test Samples


RoPax, LLC, PDA Metro Chapter, May 2011
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

<table>
<thead>
<tr>
<th>Vial hole size (µ)</th>
<th>Packages tested (#)</th>
<th># Packages ID'd as LEAKING DAY 1</th>
<th># Packages ID'd as LEAKING DAY 29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vacuum decay</td>
<td>HVLD</td>
</tr>
<tr>
<td>PRODUCT-FILLED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PLACEBO-FILLED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

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></th>
<th>Product B</th>
<th></th>
<th></th>
<th>Product C</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monomeric Peak</td>
<td>High MW Species</td>
<td>Low MW Species</td>
<td>Monomeric Peak</td>
<td>High MW Species</td>
<td>Low MW Species</td>
<td>Monomeric Peak</td>
<td>High MW Species</td>
<td>Low MW Species</td>
</tr>
<tr>
<td></td>
<td>Rel. MW</td>
<td>% Purity</td>
<td>% Purity</td>
<td>Rel. MW</td>
<td>% Purity</td>
<td>% Purity</td>
<td>Rel. MW</td>
<td>% Purity</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>
<td>0.5</td>
<td>1.1</td>
<td>170</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>
<td>0.5</td>
<td>1.1</td>
<td>170</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>
<td>0.5</td>
<td>1.1</td>
<td>170</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
- H$_2$O Absorption Band 1400 nm and 1900 nm
Headspace gas analysis measurement layout
Fully integrated solution

<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>
Thank you for your attention!

For further information please visit
www.engineeringstevanatogroup.com