Astellas Ireland Company Ltd. (Kerry Plant)
Ampoule Inspection Machine

Eoin O’Sullivan
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Facility History
Location

- AICL-Kerry Plant
- AICL-Dublin Plant
ASTELLAS IRELAND CO., LTD

• April 1, 2005: Astellas Pharma Inc. was established following the merger of the former Fujisawa Pharmaceutical Co., Ltd and the former Yamanouchi Pharmaceutical Co., Ltd.

• October 1, 2005: Establishment of Astellas Ireland Co., Ltd (AICL) comprising of
  • Astellas Ireland Kerry Plant
  • Astellas Ireland Dublin Plant (API)
  • Corporate Affairs, Dublin (Finance, IT, HR and ILB)
Ampoule Filling Lines

OLD     NEW
Ampoule Visual Inspection

OLD     NEW

OLD    NEW
Overview of Activities
# Summary of Processing and Packaging Lines

<table>
<thead>
<tr>
<th>Processing/Packaging Line</th>
<th>Product(s) Processed/Packaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampoule Production</td>
<td>Component preparation, Aseptic Filtration &amp; Filling, Inspection</td>
</tr>
<tr>
<td>Component Preparation and Filling</td>
<td>and Packaging of Prograf Ampoules</td>
</tr>
<tr>
<td>Two Capsule Blending Lines</td>
<td>Formulation and Filling of Prograf and Advagraf Capsules</td>
</tr>
<tr>
<td>Three Filling Lines</td>
<td></td>
</tr>
<tr>
<td>Two Blister Packaging Lines</td>
<td>Packaging of Prograf and Advagraf Capsules</td>
</tr>
<tr>
<td>One Ointment Packaging Line</td>
<td>Secondary Packaging of Protopic Tubes</td>
</tr>
<tr>
<td>One Vial Packaging Line</td>
<td>Secondary Packaging of Mycamine Vials</td>
</tr>
</tbody>
</table>
Prograf Ampoules

Sterile Prograf solution is aseptically filled and sealed into sterilised glass ampoules.

Each ampoule is visually inspected.

Each ampoule is labelled and packaged.

Packaged ampoules are sold worldwide.
Validation Approach
Justification for the introduction of the AIM

- More consistent results – no person to person variation

- Speed of Visual Inspection process
  - 150 amp / min vs. 4 amp / min (5mg) and 1.1 amp/ min (2mg)

- More real-time feedback on batch filling performance

- Improved defect detection – particularly with smaller sized defects

<table>
<thead>
<tr>
<th>Item</th>
<th>PRG 5mg</th>
<th>PRG 2mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Manual VI time per batch</td>
<td>8 days</td>
<td>43 days</td>
</tr>
<tr>
<td></td>
<td>Approx. 2 weeks</td>
<td>Approx. 9 weeks</td>
</tr>
<tr>
<td>Total AIM VI time per batch</td>
<td>1 Day</td>
<td>2 Days</td>
</tr>
</tbody>
</table>
System description

- The AIM - “Ampoule Inspection Machine” is used in AICL for visual inspection of Prograf ampoules.

- Machine throughput is 150 Ampoules per minute.
Collection of Sample Rejects

- Prior to implementing the project, live sample rejects from manual visual inspection were collected over a two year period.

- Samples were categorised into sample type, size and category.

- Identification of sample rejects was complete using a letter and numbering sequence while maintaining a full record on a data system.

- Sample rejects were identified by applying their unique letter and number to the tip of the ampoule using a thin black marker or by means of U.V. pen.
Theory of Operation

• The AIM has 22 separate cameras - each designed to detect specific types of defects
  • Particles
  • Colour ring
  • Scratches / cracks
  • Tip defects
  • Blue Dye
  • Fill Volume

• Colour ring, scratches, cracks, tip, fill volume and blue dye defects are all detected by absolute methods – i.e. measurement against set points

• Particles are detected by dynamic comparison under both transmission and reflected light.
Oscillating drive

• The oscillating drive allows camera to move with ampoule when taking pictures
  – Patented technology by Eisai
  – Allows taking pictures in static mode – no differential speed between the ampoule and the camera
  – Maximises inspection time without throughput impact
  – No stop / start action required with the machine for inspection – smooth ampoule flow path
The purpose of the pre-spin was an Astellas driven requirement to
1. Eliminate the Schlering effect (shown in the picture)
2. Eliminate any bubbles in the solution pre-inspection – presence of bubbles would lead to false rejects
Particle Inspection Methodology

- The particle inspection methodology is based on the principle of
  
  1) Spinning the container and liquid
  2) Stopping the container suddenly
  3) Taking a sequence of pictures while the liquid inside the container is still spinning.
  4) Comparing each picture in this sequence of pictures - a difference will show up between pictures if there is a moving defect present in the liquid.

See explanation videos below

Particle Motion  Detected fibre  Spin Cycle Video
Inspection Criteria

• **Detection probability**
  – Characterisation of the particle detection process was driven by trying to maximise detection probability.
  – For particles this drove the design of the system with multiple cameras to increase detection probability.

• **False Reject Rate**
  – A key focus in the AIM development was to minimise the false reject rate in order to eliminate unnecessary yield loss.

• **Improvement on Manual VI performance**
  – The AIM underwent a Knapp test as part of the validation process to prove it’s superior detection performance to Manual VI.
Overall detection – Manual VI vs. AIM

- A Knapp test was completed to compare Manual VI performance vs. AIM performance.

- The efficiency value obtained from manual inspection is considered the comparison parameter. The automated system must at least replicate this value if not improve upon it, if it is to be considered a superior form of inspection.

- As the ratio of FQA (manual visual inspection) verses FQB (Automatic inspection) was 102.9%, AIM performance was proven to be greater than manual visual inspection.
Strategy for balancing reject rate vs. detection capability

- The ideal solution would be 100% detection of all defects with no false rejects thereby minimising the reject rate.
- However no vision process (manual or automatic) can give 100% detection performance.
- Therefore in the interest of quality and safety we erred on the side of higher defect detection performance and compromised with increased reject rate.
Reject Rate vs. FRR

<table>
<thead>
<tr>
<th></th>
<th>5mg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT FRR</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>2nd FAT FRR</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>SAT FRR</td>
<td>0.5%</td>
<td></td>
</tr>
</tbody>
</table>

This data was based on a small sample set and captured in a non production environment.

- Since the FAT / SAT the AIM sensitivity has been adjusted to minimise FRR.
- However getting real data on the FRR is difficult because
  - 1) The AIM can see more defects than a human – so classifying what is real and what is not is difficult.
  - 2) The FRR has a random element to it – e.g. dust caused by environmental conditions – the AIM sees the dust and captures this image but when checking the ampoule later the dust is gone.
  - 3) Some FRR is possibly still caused by variation in ampoule shape (e.g. base) Most this has been tuned out now
Visual Inspection Approach
Functional & Challenge Testing

- Upon completion of machine reassembly after cleaning, a functional test is performed to ensure machine is mechanically put together correctly.

- After the functional test, a Challenge test is run through the machine ensure all cameras are functioning correctly.

- The Challenge test is made up of at least one type of each of the critical rejects the AIM is capable of detecting. These rejects are from commercial batches.

- The AIM must reject all ampoules in the challenge set before proceeding to inspection of the batch.
Visual inspection of a batch

- Ampoules are loaded onto infeed belt and pass through all inspection stations of the AIM.
- Accept ampoules are discharged into one of two accept trays.
- Reject particle ampoules are discharged to reject tray no. 1, reject cosmetic / tip ampoules are discharged into tray no. 2
- Forced rejects (if the machine is powered down during the inspection or if an alarm occurs) are discharged into tray no. 3 for re-inspection on completion of the main batch.
• An AQL is from every batch processed through the AIM is manually visually inspected.

- **Critical** is any particle >200 μm & any fibre > 2000 μm, Tips, height, blue dye, chip, liquid volume & cross contamination
- **Major** is any particle <200 μm & any fibre < 2000 μm
Specific Challenges
## Specific Challenges for AIM

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Viscosity - Schlering effect &amp; bubbles</strong></td>
<td>Pre-spin table</td>
</tr>
<tr>
<td><strong>Product temperature requirements</strong></td>
<td>LED lighting – low heat</td>
</tr>
<tr>
<td><strong>Not having a clear requirement of what the AIM needed to reject &amp; no measurement of particle sizes</strong></td>
<td>List of defects put together &amp; some ampoules sent off site for sizing.</td>
</tr>
<tr>
<td><strong>Difficulty in detecting all defects types - cracks, particles, shape, colour</strong></td>
<td>Combination of backlight and reflective light as well as colour and greyscale camera systems</td>
</tr>
<tr>
<td><strong>Two fill volumes – 2mg &amp; 5mg</strong></td>
<td>Upper and lower camera sets with minimum changeover required</td>
</tr>
<tr>
<td><strong>Transition from Manual VI to automatic</strong></td>
<td>Knapp testing to prove the increased performance of the AIM</td>
</tr>
<tr>
<td><strong>False Reject Rate</strong></td>
<td>Sensitivity, designed blind spots, Environment.</td>
</tr>
<tr>
<td><strong>Blind spots</strong></td>
<td>Minimise un-inspected areas. Lower sensitivity inspection windows in close proximity to blind spots – to maximise the overall inspection area</td>
</tr>
</tbody>
</table>
AIM Limitations

- The known limitation of the AIM, from a particle detection perspective, is that it is designed to detect defects in the product solution.

- If a defect falls out of solution (e.g. sticks to the upper wall of the ampoule) then there is a likelihood of no detection.

- A risk assessment was completed to focus on preventing possible defects falling out of solution and preventative actions have been implemented to mitigate against the risk, however it cannot be 100% guaranteed that all particles will remain in solution.
Changes made since the introduction of the AIM

- High tip reject rate – recipe developed further to allow acceptance of correctly shaped tips.
- Incoming ampoules had a raised base causing false rejects, changes made to window on base camera to accept these ampoules.
- False rejects were occurring during 2mg ampoule visual inspection due to a reflection on the meniscus of the liquid - The two upper inspection window positions were changed to “tilt” them in order to follow the meniscus slope.

As “Prevention is better than Cure” ongoing improvements are being completed at the filling stage to prevent generation of unacceptable ampoules.
The Regulators

Two issues have been highlighted during regulatory inspections since the introduction of the AIM in 2010.

• **No expiry on the ampoules contained within the Challenge Set.**

  - Where possible an explanation was given as to why an expiry was not required, i.e.: tip reject, studies were performed to assess the expiry for other categories i.e.: blue dye ampoules from integrity testing & for the remaining ampoules they are manually visually inspected every quarter by trained & assessed operators ensuring that the defect may still be seen.

• **No visibility as to the correct version number in use for a particular recipe.**

  - A document was created detailing the breakdown of each recipe and its corresponding current version number. There is a requirement in the MBR to check the recipe on the AIM screen versus the document ensuring both recipes match.
THANK YOU