Contamination Control in a Sterile Manufacturing Facility

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GMP Forum 2017

25 July 2017
A global business

$23.0 billion sales in 2016
Active in more than 100 countries
57,500 employees
Approximately $5.9 billion invested in R&D
Research across 5 countries
Manufacturing in 16 countries

As at 12th January 2017
Globally one of two strategic sourcing locations for BFS products

24 x 7 operation, mix of 8 hour and 12 hour shift patterns

7 x 4010 Respules lines
4 Injectables Lines

30 years of expertise in BFS products

Our Journey

1957
Glass Products

1969
Astra Chemicals, Australia was established

1985
BFS Machines

Tablets Facility

1986
Decision to Consolidate respules manufacture by AZ, leading to site closure Announcement

2009
Reversal of closure due to substantial respules demand from China

2011
$130 million expansion announced for Line 1 to 8

2012 -2013
Additional $100 million Approved for 3 more lines

2015 -2016
Today

Today

2012 -2013
Our Site at a Glance

- 30 Years Of technical leadership in BFS
- Key exporter to 15 global markets*
- 435 million respules**
- A$1075 million in total sales in 2016***
- A$230 million of site Investment from 2011-2019
- Approximately 460 Employees onsite
- 60 years of rich history
- 88 Different manufactured product lines

*2016 Sales **2017 Budget Data ***Export+Domestic
Our Products

435 million
Pulmicort Respules (6 SKUs)
Respules - Supply to Australia, China & Japan

41 million
PE Polyamps (47 SKUs)
Polyamps – Sole suppliers globally

2 million
PP Polybags (30 SKUs)
Polybags - Sole Supplier Globally

1 million
Glass Vials (5 SKUs)
For Australian Markets

*2017 Budget Data Above
Our Capital Expansion Project

Last Year 2016

- 12x Respules Processes
- 2x PE Polyamp Processes
- 1x Polybags Process
- 1x Vials Process

Future State 2021

- 12x Respules Processes
- 2x PE Polyamp Processes
- 1x Polybags Process
- 1x Vials Process
Types of contamination

“Chemical” - Residues from other products as well as cleaning and engineering solutions

“Physical” - Solids/particles such as dust, metal fillings and skin flakes;

“Microbiological” - Viable Microorganisms is a particular threat especially with products that are injected, used in wounds or in the eyes (Sterile products).
Vectors for contamination

We face many potential sources of contamination:

- People
- Raw Materials
- Facility and Construction
- Equipment and Processes
Dispensary

Controls in the dispensing process ensure that only the required materials are available for manufacture.

- Single direction entry and exit for operators.
- Downflow booths providing containment and protection of exposed product.
- Single raw material in each dispensary at any one time.
Cross – Contamination from other products / materials

Manufacturing areas

Segregated manufacturing suites with a clean central corridor.

Each suite is dedicated during manufacture and clean corridor design results in containment within each suite.
Cross – Contamination from other products / materials

- Manufacture of multiple products
- Periodically revalidated with worst case product for each equipment train.
- Validated CIP and manual cleaning processes.
Brownfield construction

Impact on existing manufacturing areas

Adjacent to construction zones.

Large number of contractors.
Brownfield construction

Downgrade and upgrade process
Co-ordination between production, maintenance / engineering, facility support and microbiology. Microbiology are the “gatekeepers”.
People

People are the greatest source of contamination to the manufacture of sterile product.

Three graded areas – CNC, C and B. Different requirements based on risk.
Gowning procedures

Controlled gowning procedures for entry into CNC, Grade C and Grade B.

Following the correct gowning procedure minimises the risk of contamination from personnel.
People

Restricted access

Sterile entry role is controlled and personnel are validated for sterile entry.

C and B grade access are restricted via the security system and require annual training.
New sterile change room

Dedicated change room with micro satellite lab.
## Managing contamination risks

<table>
<thead>
<tr>
<th>Risk Item</th>
<th>Specific Risk</th>
<th>Residual Risk Score</th>
<th>Managed By</th>
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</table>
| Walls     | • Crevices  
           • Sealed  
           • Finishes  | Lack of cleanability leads to potential for cross contamination with product or other substances that affects formulated product | Low | • Enclosed equipment  
               • Wall finishes in process rooms.  
               • Cleaning regime |
| Floors    | • Cleanable  
           • Sealed  
           • Finishes  | As per walls | Low | • Training, procedures and ways of working  
               • Cleaning regime |
| Ceiling   | • Cleanable  
           • Sealed  
           • Finishes  | As per walls | Low | • Cleaning / inspection regime |
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<tr>
<td>Air quality</td>
<td>• Contamination of product leading to failure to meet specifications&lt;br&gt;• Contamination with particles from external air sources&lt;br&gt;• Contamination with particles from internal air sources</td>
<td>Low</td>
<td>• Terminal HEPA filters&lt;br&gt;• Routine filter testing / replacement schedule&lt;br&gt;• Air flow designed to minimise cross contamination&lt;br&gt;• Airlocks to rooms</td>
</tr>
<tr>
<td>Cleaning</td>
<td>• Contamination of product leading to failure to meet specifications</td>
<td>Low</td>
<td>• Validated CIP, manual and facility cleaning processes.</td>
</tr>
<tr>
<td>Process Gases</td>
<td>• Quality at point of use&lt;br&gt;Deterioration of quality between generation and point of use</td>
<td>Low</td>
<td>• Sterile filters at point of use&lt;br&gt;• Flushing of pipework after installation&lt;br&gt;• Regular sampling</td>
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<td>Water for Injection &amp; Steam</td>
<td>• Contamination of product leading to failure to meet specifications</td>
<td>Low</td>
<td>• Routine micro / chemical testing</td>
</tr>
<tr>
<td></td>
<td>• Contamination at generation</td>
<td></td>
<td>• Routine passivation schedule</td>
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<tr>
<td></td>
<td>• Contamination after generation (storage and distribution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel / Dress Code</td>
<td>• Contamination due to failure to follow procedure</td>
<td>Low</td>
<td>• Training and procedures</td>
</tr>
<tr>
<td></td>
<td>Contamination of equipment / product</td>
<td></td>
<td>• Enclosed equipment</td>
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<td></td>
<td></td>
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<td>• Cleaning regime</td>
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