A CMO’s Journey to Higher Containment

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Outline of the Presentation

1. About Cambridge Major Laboratories, Inc.
2. Starting out on the Journey
3. Improved Engineering Controls for a current commercial process
4. What’s next?

NOTE: The following is based on a summary of quality control principles. It is not to be interpreted as engineering, operational or legal advice. Circumstances vary, and any action based on this presentation is taken at the reader's sole risk. Readers should consult with experts of their own choosing before applying any aspect of this summary to their own situation.
WHO WE ARE

CML is a leading provider of global, integrated drug development and manufacturing services. Our commitment to Quality, performance culture, and project-focused organizational alignment ensure a superior track record of exceeding client expectations for outsourced Chemistry, Manufacturing, and Controls (CMC) services.

WHY WE ARE HERE

We are proud to help thousands of people overcome some of life’s biggest challenges. Using our chemistry expertise we help our clients develop new, lifesaving treatments for patients, so they can sustain a high quality of life. Our passion for chemistry is what makes us so successful. Our passion for life is why CML exists.

WHAT WE STAND FOR

At CML, we understand that market growth is a natural outcome of listening to our customers, adopting a compliance focus, and making a commitment to invest in technology and innovation. These anchors focus our efforts every day, and help reinforce a culture of accountability and mutual respect.

In 2012, over one million patients were touched by Active Pharmaceutical Ingredients developed and supplied by CML.
Facilities Overview

Three production sites with over 400,000 square-feet, equipped with state-of-the-art technology and infrastructure

- Nearly $70 million invested over the last four years, to build and improve CML’s state-of-the-art facilities
- Strategically located in the U.S and Europe to serve the Company’s global customer base
- US facility promotes "under one roof" capability
- Strong track record of environmental and regulatory compliance

US Development Facility
- 75,000 sq ft
- Wide range of technologies
- 4 separate analytical/QC labs
- 6 R&D labs; 5 GMP kilo lab suites
- Pilot plant to 2000 L scale reactors

US Large-scale API Production Facility
- 200,000 sq ft
- Footprint allows for significant additional capacity
- Invested >$40MM
- Reactors up to 8000 L scale

European Development Facility
- 135,000 sq ft
- Acquired in 2007 (Chemshop)
- Minimal investment required to expand capacity
- Solid state chemistry labs
- Efficient access to European clients
Handling Higher Potency Compounds:

Starting out on the Journey

• Devise a Robust On-boarding Process for New Projects
  – Determine what level of potent compounds can CML handle
  – Develop Health Hazard Category (HHC) bands
  – Adopt a Risk-based Exposure Assessment Process
  – Use DEREK Nexus Software to obtain SAR data for new chemical entities
  – Environmental and Occupational Toxicologist on retainer as needed

• Undertake a Multi-faceted System-wide Approach
  – From raw material handling through API testing and shipment
  – Address issues in R&D, Process Development, Manufacturing, Analytical Sciences and Logistics
  – Leverage Industry experts in containment strategies

• Provide adequate Worker Training Program to ensure Compliance
CML Health Hazard Category bands were generated:

<table>
<thead>
<tr>
<th>Category</th>
<th>SafeBridge OEL</th>
<th>CML HHC OEL</th>
<th>General Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 500 µg/m3</td>
<td>OEL &gt; 100 µg/m3</td>
<td>Use good work practices and general ventilation</td>
</tr>
<tr>
<td>2</td>
<td>10 µg/m3 &lt; OEL &lt; 500 µg/m3</td>
<td>10 µg/m3 &lt; OEL &lt; 100 µg/m3</td>
<td>Use local exhaust ventilation and PPE</td>
</tr>
<tr>
<td>3</td>
<td>0.03 µg/m3 &lt; OEL &lt; 10 µg/m3</td>
<td>1 µg/m3 &lt; OEL &lt; 10 µg/m3</td>
<td>Enclose the process with containment</td>
</tr>
<tr>
<td>4</td>
<td>OEL &lt; 0.03 µg/m3</td>
<td>OEL &lt; 1 µg/m3</td>
<td>Seek expert advice</td>
</tr>
</tbody>
</table>
Overall Implementation Strategy

• Upgraded Engineering controls for:
  – R&D, Kilo Lab and QC personnel
  – Reactor design, including solution transfer of HPAPI during workups
  – Weighing and dispensing of Raw Materials and Intermediates during manufacture
  – Discharging, weighing, analyzing and transporting API’s after manufacture

• Worker training to understand HPAPI’s and current EHS projects to improve containment
Engineering Controls for R&D

- Incorporation of Ductless Laminar flow technology from AirClean Systems
- Meets ISO 5 and FS209E Class 100 clean bench standards
Engineering Controls for Quality Control

- Powdersafe B Enclosure from AirClean Systems
- Allows for effective weighing to 5 decimal places
- Continuous HEPA filter monitoring with HEPASafe™ filter change technology
Dispensing Isolator from Powder Systems Limited
Reactor Charging System

Installation of the EZI-Dock system for charging Raw Materials and Intermediates into the reactor
Contained reactor charging using the ILC Dover DoverPacSF & FCG Valve.

NOTE: ILC Dover slide used with Permission
Continuous Liner System

The continuous liner system provides a simple means to protect both the chemical and operator from exposure.
2 new Agitated Filter Dryers have been installed

- Steri Technologies 0.4 m² Hastelloy C-22 unit at Grant Drive facility
- PSL 0.15 m² Hastelloy C-22 unit at Washington Drive facility
- Both units have Gloveboxes for containment during discharge
Handling Higher Potency Compounds:  
... and the Journey continues

• CML has been producing multi-tonne quantities of a commercial API since 2009
• The current process has been changed and improved.
• This is an example of CML commitment to Sustainability.
The Current Process

Reactor Charging is completed using a De Dietrich Powder Transfer System.
The Current Process

The product is isolated by using a Horizontal peeler centrifuge
The product is dried using a Conical Dryer.
The New Process

- The process has been revisited, improved and is currently going through revalidation.
- Reactor Charging will occur through Chargepoint valves, using ILC Dover’s DoverPacs
The New Process

Solids isolation and drying will occur in 2 AFD’s with Isolators for improved Engineering controls.
## Comparison of the 2 Processes

### Sustainable Development

<table>
<thead>
<tr>
<th>People Issues</th>
<th>Current Process</th>
<th>New Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hazardous Solvents</td>
<td>Uses Chlorinated Solvents</td>
<td>No Chlorinated Solvents</td>
</tr>
<tr>
<td>2. Containment Strategy</td>
<td>Uses Engineering Controls and PPE for the Containment strategy</td>
<td>The process is contained. Engineering Controls are improved; PPE is secondary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Planet Issues</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Waste Generated</td>
<td>200 L / kg API</td>
<td>110 L / kg API</td>
</tr>
<tr>
<td>2. Water Use</td>
<td>73 L / kg API</td>
<td>27 L / kg API</td>
</tr>
<tr>
<td>3. Catalyst recovery</td>
<td>Too dilute for recovery</td>
<td>Recovery Project being studied</td>
</tr>
<tr>
<td>4. Manufacturing Footprint</td>
<td>6 kg / unit vol</td>
<td>36 kg / unit vol</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Prosperity Issues</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Labor</td>
<td>3.6 h / kg API</td>
<td>1.5 h / kg API</td>
</tr>
<tr>
<td>2. Cycle Time</td>
<td>2.8 h / kg API</td>
<td>1.2 h / kg API</td>
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</table>
What’s Next on our Journey?

• CML is engaged in a feasibility study to build a High Containment API Manufacturing Facility.

• More on this later…
Thank you!
Questions?

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