MassBioLogics

Welcomes

The New England Chapter

Parenteral Drug Association

March 12, 2008
MassBioLogics & NEPDA
Welcome and thank sponsors:

<table>
<thead>
<tr>
<th>Sponsor</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Althea Technologies</td>
<td>Genesis Machinery Co.</td>
</tr>
<tr>
<td>Aramark Cleanroom Services</td>
<td>Hyaluron</td>
</tr>
<tr>
<td>B&amp;V Testing, Inc</td>
<td>Masy Systems</td>
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<td>BioVigilant Systems, Inc</td>
<td>Microtest</td>
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<tr>
<td>Eisai Machinery</td>
<td>Rapid Micro Biosystems</td>
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<td>Formatech</td>
<td>Sartorius-Stedim</td>
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MBL – MassBioLogics

MBL -  Medicine for Better Lives
Agenda

- Facility Description
- Equipment Description
- Validation Approach
- Product Characteristics
- Aseptic Simulation Approach
- Lessons Learned
Facility Layout

- Shipping, Receiving, Warehousing
- Fill and Finish Area
- Monoclonal Antibody Production
- Administration & Common Areas
- Laboratories
Facility Layout
Filling & Visual Inspection Equipment

• Support Equipment
  – Parts Washer – Lancer
  – Autoclave – Primus
  – PMS non-viable sampler
  – SMA viable sampler
  – HVAC / Room Environment
  – Process Control System; Superior Controls
  – Cold / Warm Rooms

• Utilities
  – WFI – MECO vapor compression
  – Clean Steam – MECO
  – Clean Air

• Filling Line
  – Vial Washer – Penntech
  – Depyrogenation Tunnel – Bosch
  – Filler / Stopper – Bosch
  – Capper – Bosch
  – Encoder – Bosch

• Visual Inspection
  – Eisai VIS-1000 Dual Semi-Automatic Machine
Warehouse Storage
Depyrogenation Tunnel

Vial Washer
Product Line Pass-thru from Filler
Aseptic Filling
Capper
KIV – 2D Matrix Imprinter on Seal
Vial Tray Loader
Eisai Visual Semi-Automated Visual Inspection
WIP Coldroom 2-5 C
# Filling Line Commissioning & Qualification

<table>
<thead>
<tr>
<th>Unit</th>
<th>FAT</th>
<th>SAT</th>
<th>IQ</th>
<th>OQ</th>
<th>PQ</th>
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<tbody>
<tr>
<td>Vial Washer</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Depyro Tunnel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>•Depyro</td>
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<td></td>
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<td>•Sterilization</td>
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<tr>
<td>Filler / Stopper</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Cleaning Validation SIP Filler</td>
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<tr>
<td>Capper</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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## Project Timeline

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<td>2 Site Acceptance Testing</td>
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<tr>
<td>3 Filling Equipment IQs, OQs, SIP, CIP</td>
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<tr>
<td>4 Water Runs</td>
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<tr>
<td>5 HVAC / Room Environment Qualifications</td>
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<tr>
<td>6 Alum Suspension Runs (six runs)</td>
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<td>7 Media Fills</td>
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<td>8 Consistency Lots</td>
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PRODUCT CHARACTERISTICS
PREVIOUS PRESENTATION:

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE

10 mL molded vial, 9 mL fill volume

1888 gray natural rubber stopper

Preservative containing multi-dose vial
NEW AND CURRENT PRESENTATION:

PRESERVATIVE FREE TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE

3 mL tubular vial, 0.72 mL fill volume

4588/40 rubber stopper

Preservative free, single dose vial
Product Characteristics

- Aluminum Phosphate Adjuvant
  - Cannot be sterile filtered
  - Requires continuous mixing or recirculation
  - Challenge to clean
  - Requires cold storage

- Batch volume 200 L or 280,000 vials / batch
  - 16 hours of run time at maximum efficiency (IF everything goes smoothly)

PLANNED FOR 2 TEN HOUR FILLING EVENTS AND A BACK UP
Line Characteristics

• No Barrier or Isolator
• No RABs
• Conventional !!

However…..

• Rigid Workspace to Ceiling Barriers
• High Speed Automated Line
• Automated check weighing
• Air Changes exceed 400 per hour
Facility Characteristics

• Zone concept and cascade
  - areas of different class > 0.05 inches of water
  - areas of the same class > 0.02 inches of water
• Continuous monitoring of room conditions and pressures.
• Air changes per hour are very high – room 1061 > 400 ACH
• Nearly 100% HEPA ceiling in the filling room
• Cleanable surfaces
• Daily, thorough cleaning with a dedicated crew
• Large viewing corridor
EM Monitoring Strategy

- We did not grid map; risk analysis prevailed.
- Continuously monitor NVPs and VPs; including 5 um particles.
- In process monitoring once per shift of class 10000.
- Full monitoring and contact plates end of fill.
- Personnel monitored at each exit.

Routine Monitoring all areas on a weekly basis – viables and non-viables
## EM Data

### Fill Area

<table>
<thead>
<tr>
<th>Fill Area</th>
<th>Alert</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine Monitoring</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>InProcess Monitoring</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

### Totals By Area

<table>
<thead>
<tr>
<th>Totals By Area</th>
<th>Grand Total</th>
<th>%Alert</th>
<th>%Action</th>
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<tbody>
<tr>
<td>Routine Monitoring</td>
<td>11,588</td>
<td>0.19%</td>
<td>0.09%</td>
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<tr>
<td>InProcess Monitoring</td>
<td>1,192</td>
<td>0.17%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
Nearly Fully Automatic
Simulation Approach

TR-22 Process Simulation Testing for Aseptically Filled Products
Aseptic Simulation

GOAL – Complete 3 fills, each one representing at least 20% of the filled lot size or at least 30,000 vials, with no evidence of microbial contamination.
Aseptic Simulation Challenges

Easy

- Vial Size
- Vial configuration
- Fill volume
- Product flow / mixing characteristics
Aseptic Simulation Challenges

Not So Easy

• Worst case filling speeds
• Duration of each fill or 12.5 hrs estimated
• Shift changes and staffing levels
• Routine and non routine interventions
• Atypical circumstances (manual check weigh)
• Holding times post sterilization
• Delivery from tank to filling line via a manifold
Filling Manifold
Aseptic Simulation Challenges

Interventions

• Remove stabilization bar at outfeed of tunnel
• Remove downed vials at infeed table, conveyor, and outfeed conveyor
• Replenish stoppers
• Reference the Filler
• Clear jam at reject station, stopper hopper, and stopper chute
• Clean the balances, starwheel, and grippers
• Send vials to the reject station
# Aseptic Simulation Outcome

<table>
<thead>
<tr>
<th>Qualification #</th>
<th>Media Lot #</th>
<th># Vials Filled</th>
<th>Date</th>
<th># pos</th>
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<tbody>
<tr>
<td>PQ-06309-1</td>
<td>TSB-180A</td>
<td>32,333</td>
<td>8-06</td>
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<tr>
<td></td>
<td>TSB-182</td>
<td>31,390</td>
<td>8-06</td>
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<td></td>
<td>TSB-183A</td>
<td>31,997</td>
<td>9-06</td>
<td>0</td>
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<tr>
<td></td>
<td>TSB-183B</td>
<td>37,704</td>
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<tr>
<td>PQ-06309-2</td>
<td>TSB-189</td>
<td>36,083</td>
<td>5-07</td>
<td>0</td>
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<tr>
<td>PQ-06309-3</td>
<td>TSB-191</td>
<td>38,283</td>
<td>1-08</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>207,790</strong></td>
<td></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>
Aseptic Simulation Issues

• Reconciliation
• Personnel Monitoring Results
• Equipment issues

483 Observation: Stopper charging in class 10000 area
483 Response: Vestibule installation
Lessons Learned
(hard and agonizing)

• FAT & SAT should include full-shift testing
  – Shorter runs may not sufficiently challenge the line mechanically
  – Overall run productivity must be met at FAT and SAT

• Gain more run time experience before MF protocol

• Develop a bullet-proof method of reconciliation

• Investigate component charging during a run

• Pre-determine a checklist of all inserts and attachments to the protocol
Lessons Confirmed

• Keep intervention list updated for next media fill

• Document all rationales for media fill test procedures in protocol; document and mimic “worst case” fill scenarios
  – Number and duration of runs
  – Number of vials filled per run
  – Staffing
  – Interventions
  – Equipment configuration
CONCLUSION

PEOPLE ARE OUR GREATEST
AND
OUR STRONGEST LINK
BUT....
TECHNOLOGY AND DESIGN DO HELP!!!

(Non-microbiologically speaking!)