

MassBioLogics

Welcomes

The New England Chapter  
Parenteral Drug Association

March 12, 2008

# MassBioLogics & NEPDA

Welcome and thank sponsors:

Althea Technologies

Aramark Cleanroom Services

B&V Testing, Inc

BioVigilant Systems, Inc

Eisai Machinery

Formatech

Genesis Machinery Co.

Hyaluron

Masy Systems

Microtest

Rapid Micro Biosystems

Sartorius-Stedim

# MBL – MassBioLogics

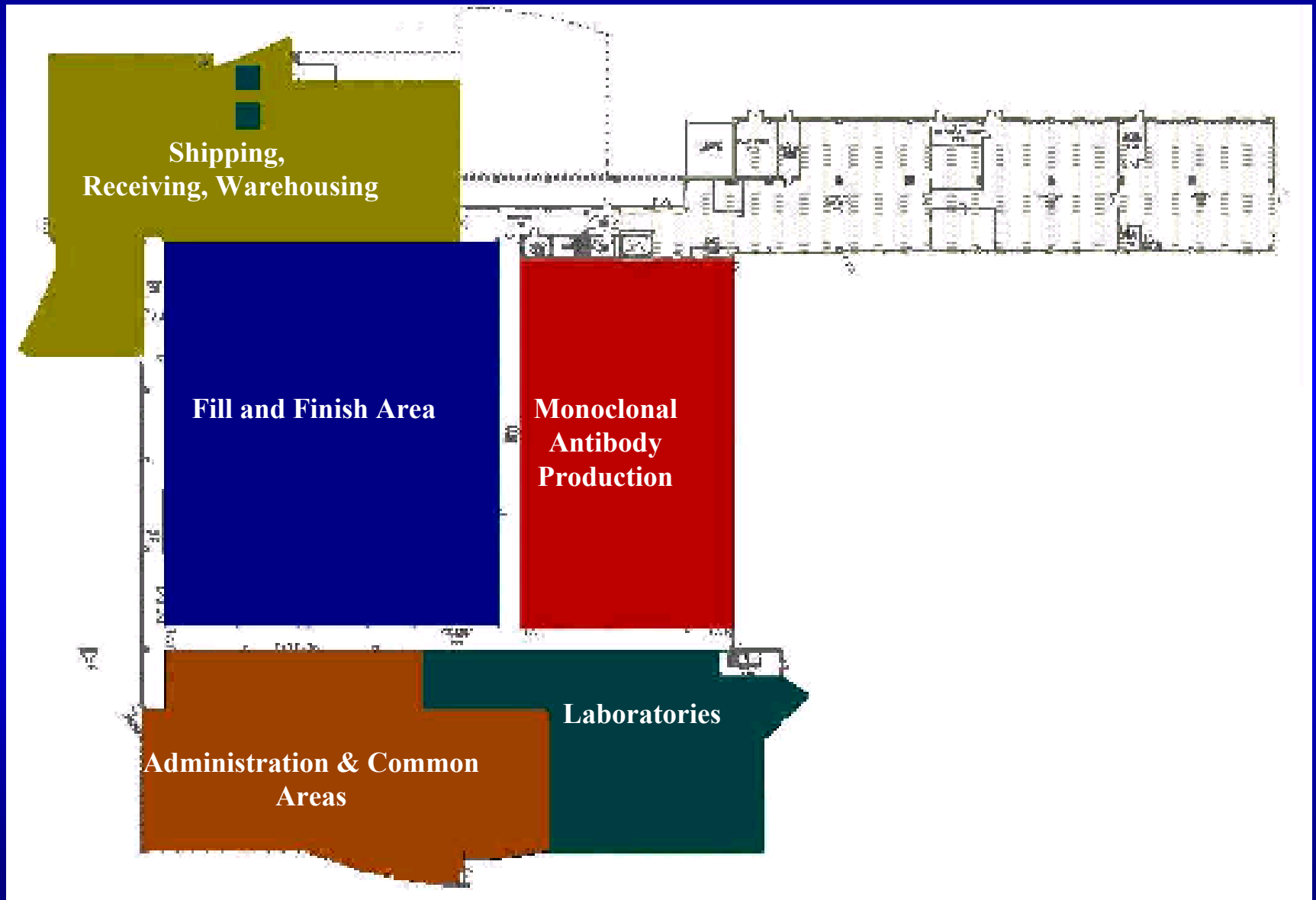


MBL - Medicine for Better Lives

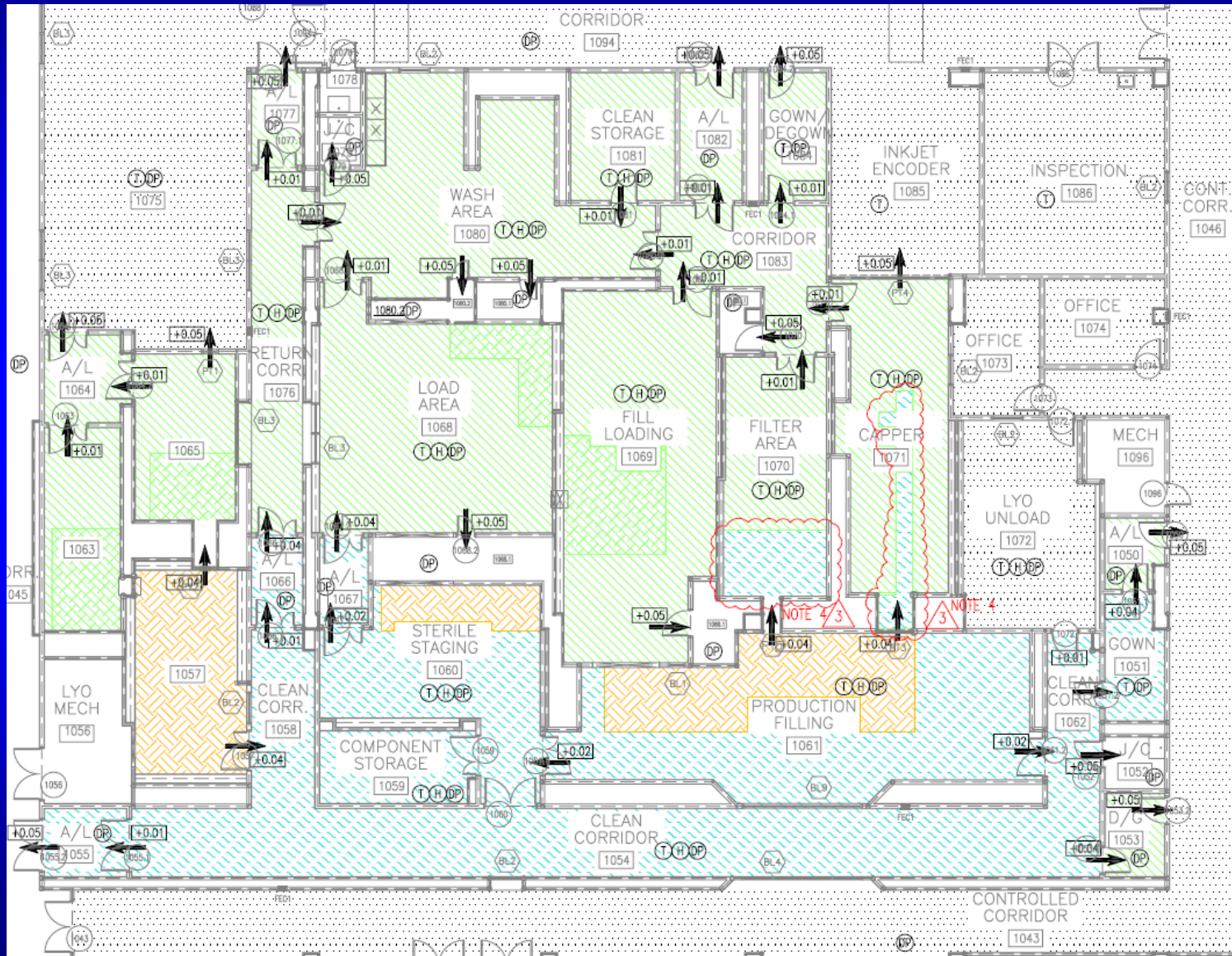
# Agenda

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

# Facility Layout



# 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







Vial Washer

Depyrogenation  
Tunnel



# Product Line Pass-thru from Filler



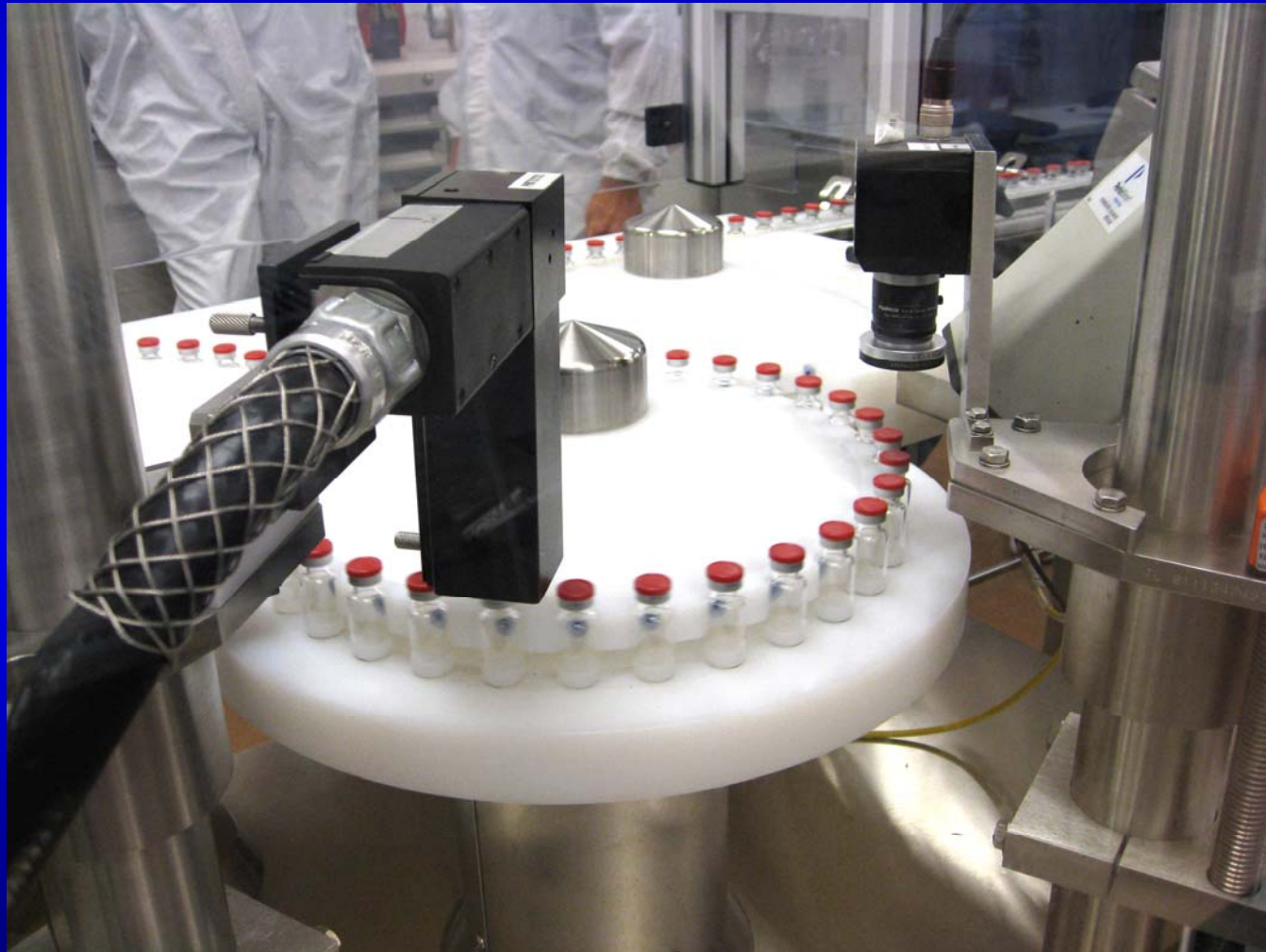
# Aseptic Filling



# 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

Unit	FAT	SAT	IQ	OQ	PQ
Vial Washer	√	√	√	√	--
Depyro Tunnel	√	√	√	√	<ul style="list-style-type: none"> <li>•Depyro</li> <li>•Sterilization</li> </ul>
Filler / Stopper	√	√	√	√	Cleaning Validation SIP Filler
Capper	√	√	√	√	--

# Project Timeline

	Task Name	2005				2006				2007			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	Line Installation		■										
2	Site Acceptance Testing			■									
3	Filling Equipment IQs, OQs, SIP, CIP			■	■								
4	Water Runs					■	■	■	■				
5	HVAC / Room Environment Qualifications					■							
6	Alum Suspension Runs (six runs)						■	■	■	■			
7	Media Fills							■					
8	Consistency Lots									■	■		

PAS July, 2007 > PAI October, 2007 > Nov. 2007

# 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)

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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	Total	
	Alert	Action
Routine Monitoring	22	10
InProcess Monitoring	2	0

Totals By Area	Grand Total	
	%Alert	%Action
Routine Monitoring	11,588	
	0.19%	0.09%
InProcess Monitoring	1,192	
	0.17%	0.00%

# 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

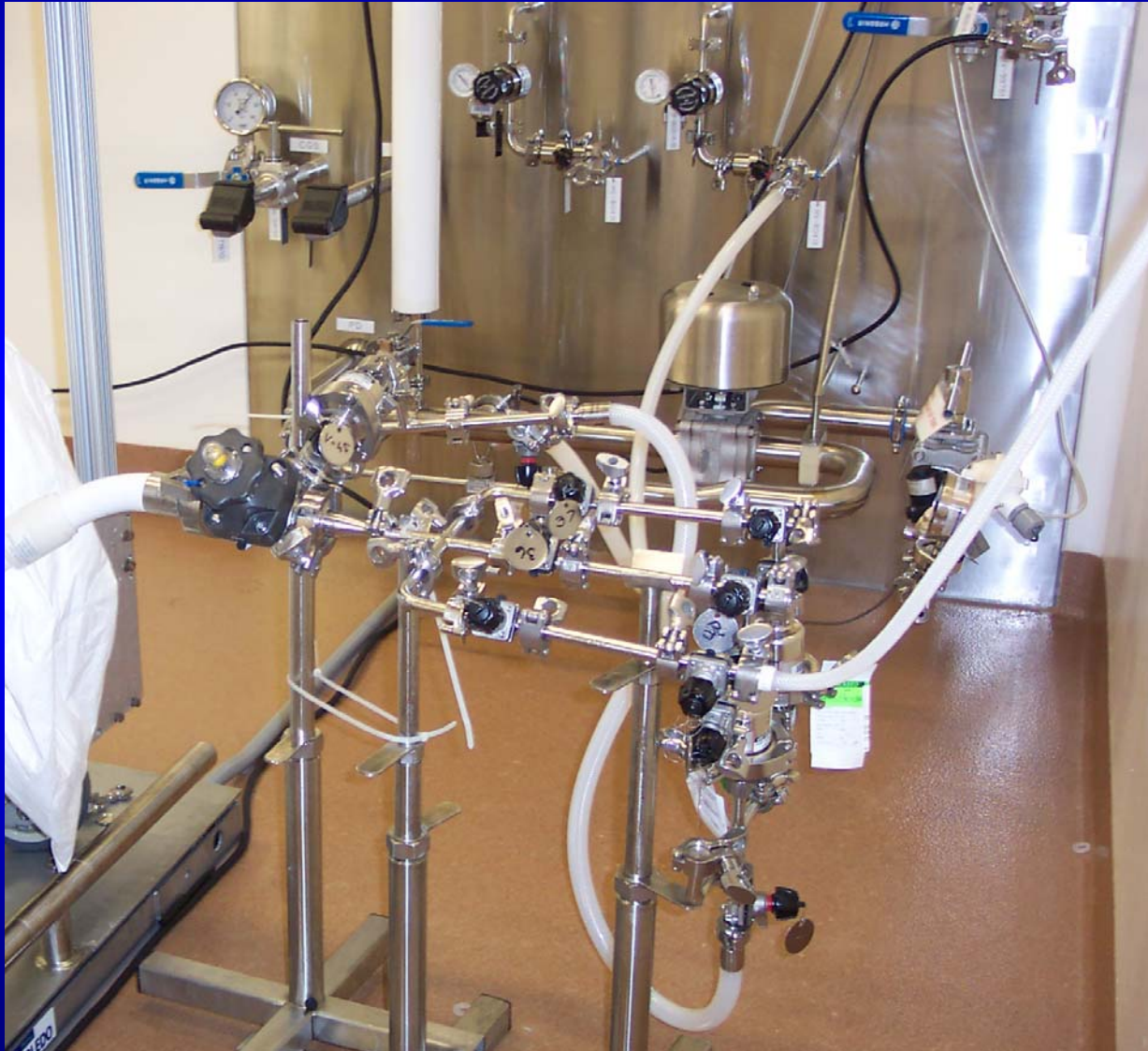
- Vial Size
- Vial configuration
- Fill volume
- Product flow / mixing characteristics

# 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

Qualification #	Media Lot #	# Vials Filled	Date	# pos
PQ-06309-1	TSB-180A	32,333	8-06	0
	TSB-182	31,390	8-06	0
	TSB-183A	31,997	9-06	0
	TSB-183B	37,704	9-06	0
PQ-06309-2	TSB-189	36,083	5-07	0
PQ-06309-3	TSB-191	38,283	1-08	0
Total		207,790		0

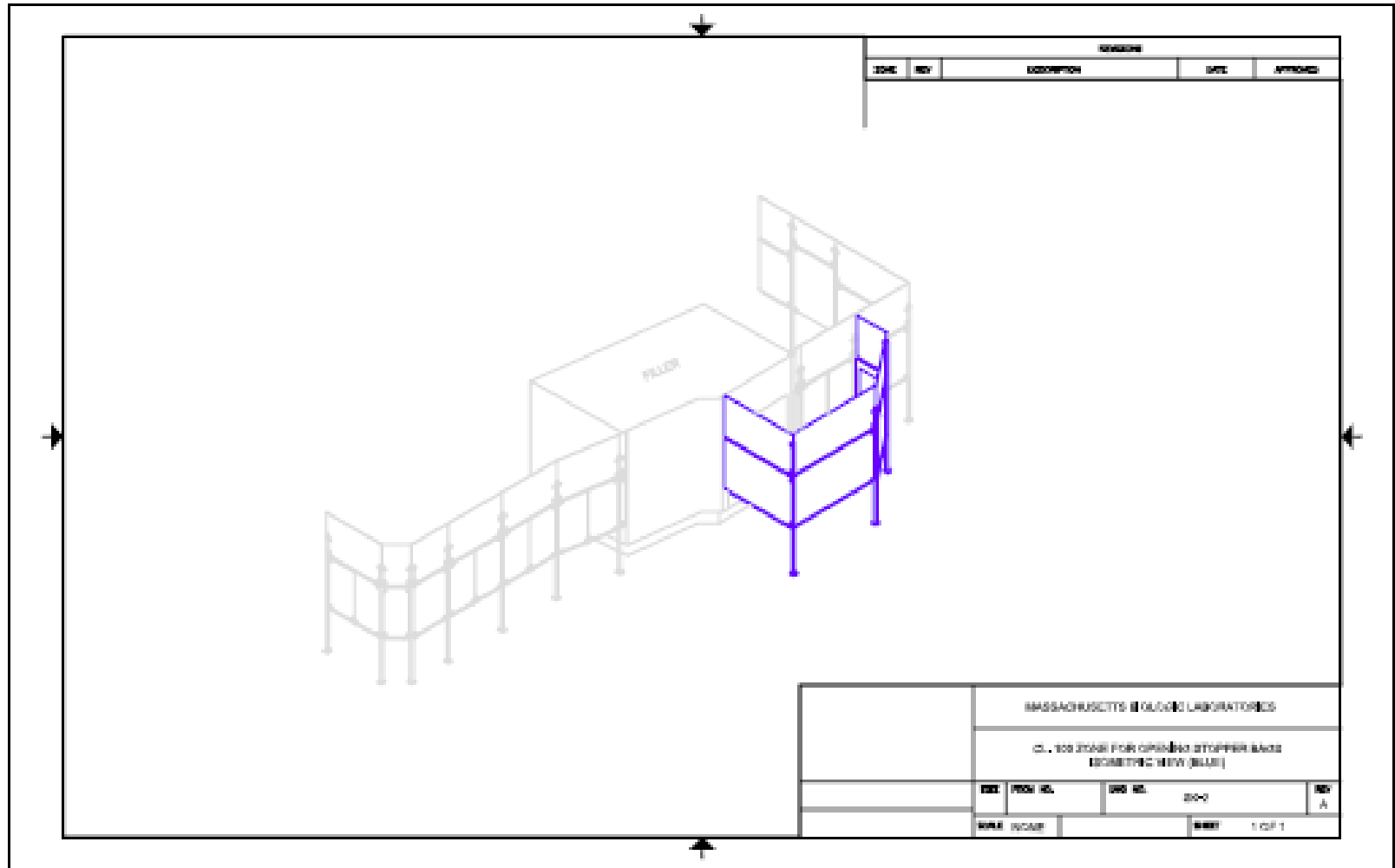
# Aseptic Simulation Issues

- Reconciliation
- Personnel Monitoring Results
- Equipment issues

483 Observation: Stopper charging in class 10000 area

483 Response: Vestibule installation

# Stopper Charging Issue



# 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!!!