Design Aspects for a Bio Fill and Finish Facility

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Technology Manager, M+W Group
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AGENDA

• Project Idea, Definition and Scope
• Project Design
  – “BFS” – Blow Fill Seal Technology
  – Bio Fill & Finish Process and Critical Steps
  – Biosafety versus GMP
  – Facility Concept and Utilization of the Building
• Project Realization and “Hand Over”
• Conclusion and “Q&A”
Project Idea

- Novel filling of biological products up to a BSL 2 level based on BFS (Blow Fill Seal) technology.

Function, Operation & Shape of the Facility are driven by the Process!
Project Definition („BIGH“*)

• New Fill and Finish (F&F) multi-use facility
  – Modular design with possibilities for future expansion
  – Using BFS technology
  – Filling and packaging of sterile and bio- products (up to BSL 2)
    • Active substances and biological drugs, Immunologic drugs, Drugs including genetic modified organism, Gene therapeutics, monoclonal antibodies etc.
  – Advanced facility and HVAC design
  – Following local and international standards, guidelines and regulations during the design and execution
    • Special requirements for personal and product protection (cGMP, Biosafety regulations, EU GMP Guideline Annex 1 and Annex 2, FDA Aseptic Guidance, ISPE Guidelines

*BIGH = Biologisches Gebäude (Biological Building)
Project Scope

- Design Build (General Contractor)

- Technical Information Building/Clean Room
  - Building volume $15,000\ m^3$
  - Clean room volume $2,500\ m^3$
  - Total Area $3,665\ m^2$
  - Clean room $785\ m^2$
  - Numbers of rooms 56
    (7 E zone, 16 in D zone, 9 in C-zone)
Project Scope

• Technical Information
  – UPS System with 180 kW
    • After power failure the product can be regardless maintained for further 7 minutes
  – Integration of “Bottelpack 3012”  10.1 cycle/minute

– HVAC System
  • Outside Air Supply  22.000 m³/h
  • Recirculation air  58.000 m³/h
  • Exhaust Air  21.000 m³/h
“BFS” – Blow Fill Seal Technology

- BFS Technology – an alternative for filling biologic drug products
  - Adapted BFS machine with a "cool BFS filling System™"
  - Full container sealing functionality
  - Additional temperature sensors at critical points
“BFS” – Blow Fill Seal Technology

- Factors related to temperature controlled BFS packaging
  - **Product**
    - Characteristic
    - Temperature from holding tank to point of fill
    - Product filling volume
  - **Container**
    - Container design
    - Container wall thickness
    - Resin characteristics
  - **Machine**
    - Mold cycle time
    - Machine operating parameters
  - **Environment of the Product (Room)**
    - Humidity
    - Temperature
# Types of “BFS” Machines

<table>
<thead>
<tr>
<th>Traditional BFS machines (shuttle type) is installed</th>
<th>Rotary type BFS Machine (test started on machines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation of plastic tube (&quot;parison&quot;) from extruded plastic polymer granules</td>
<td>The parison is not cut</td>
</tr>
<tr>
<td>Molding of the container by blowing air and/or vacuum through the parison while it is in the mold</td>
<td>Instead multiple molds fill and seal plastic ampoules in a serial manner</td>
</tr>
<tr>
<td>Product filling – The filling needles are not surrounded by the sterile parison for the entire process.</td>
<td>Filling - There is very little opportunity for contamination of product with viable microbes or particulates</td>
</tr>
<tr>
<td>Extrusion with longer cycle time</td>
<td>Continuous extrusion and reduced cycle time</td>
</tr>
<tr>
<td>Lower output than Rotary type (depending on wall thickness)</td>
<td>High output and lowest cost per bottle with high initial capital investment</td>
</tr>
<tr>
<td>High production efficiency</td>
<td>Very high production efficiency</td>
</tr>
</tbody>
</table>
Advantages of „BFS“ Technology

– Advanced aseptic process technology with precise dosing
– High production rates with low operating costs
– High automated level (reduced human intervention)
– Customized container design to meet product delivery requirements
– Container are individual tested for leaks
– Can withstand liquid nitrogen freezing
– Very low product loss due to transport damages
– Anti counterfeiting – custom designs, containers are destroyed when colors are removed and the container cannot be refilled
– Waste can be recycled or easily destroyed
Bio Fill and Finish Process

• Preparation - Filtration - BFS Process

Possible Options:
- Final formulated product for filling delivered in stainless steel vessels
- Final formulated product for filling delivered in disposables
- All formulation and process steps by the manufacturer
• **GMP critical Process steps and parameters**
  
  – Incoming bulk tank (visual clean, tightness)
  
  – Transfer bulk tank to docking room (clean room conditions, cleaning, sampling)
  
  – Docking of the sterile bulk vessel to filling system (tightness of the joints – filling, CIP, SIP, DIP)
  
  – Filling of the product with the „bottelpack machine“ (product temperature, clean room conditions, tightness of ampoules, filling volume etc.)
  
  – Packaging – right labeling
  
  – Storage → temperature and humidity
Biosafety versus GMP

- Environmental requirements for the clean rooms and BFS aligned with FDA and EU guidance.
- Room classification reflects ISO 14664 (international standard organization)

<table>
<thead>
<tr>
<th>BIOSAFETY</th>
<th>GMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protect the employees</td>
<td>Protect the product</td>
</tr>
<tr>
<td>Prevent escape of materials</td>
<td>Minimize cross contamination</td>
</tr>
<tr>
<td>Production flow: Clean to dirty!</td>
<td>Production flow: Dirty to Clean!</td>
</tr>
</tbody>
</table>

Bio safety

GMP
Biosafety Regulations

- “BIGE” Facility complies with EU/Swiss and international regulations
Biosafety / containment is about maintaining control and safe handling:

- Which biologic agents (micro-organism) are processed?
- Which kind of activities are carried out (Process)?
- What are the safety measures?

**Risk Assessment**

How to classify biosafety and containment?

- Non-pathogenic
- Pathogenic

1. Canine hepatitis etc.
2. Influenza A etc.
3. M. Tuberculosis etc.
4. Ebola Virus
Biosafety Level 1
“P1 Measures”

• Precautions against the bio hazard (standard microbiological practice)
• Personnel protection in critical areas
• Biosafety manual and procedures e.g. decontamination procedure
• Laboratory personnel have specific training
• No barriers normally required - work conducted at “BIGH” in biosafety cabinets

BFS under BSL1 Conditions
Biosafety Level 2
“P2/P3 Measures”

• Extreme precautions with contamination
• Access to the production area and laboratory is limited when work is being conducted
• Certain procedures for operations in the facility e.g. decontamination of waste and rooms
• Autoclave and waste water treatment
• Primary barriers BSCs for manipulations of agents and samples
## Closed versus Open System

<table>
<thead>
<tr>
<th></th>
<th>Closed</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expose product to</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control/classified</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Equipment</td>
<td>Layout &amp; HVAC</td>
</tr>
<tr>
<td>Validation</td>
<td>Equipment</td>
<td>Room</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comfort</td>
<td>Personnel &amp;</td>
<td>Equipment</td>
</tr>
<tr>
<td></td>
<td>Material Flows</td>
<td>Operation</td>
</tr>
<tr>
<td>System flexibility</td>
<td>lower</td>
<td>high</td>
</tr>
<tr>
<td>Scale</td>
<td>large</td>
<td>small</td>
</tr>
<tr>
<td>&quot;GMP perception&quot;</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td><strong>Area</strong></td>
<td>Vessel CIP/SIP</td>
<td>Filling</td>
</tr>
</tbody>
</table>
Realization Biosafety versus GMP

- Equipment and room arrangement

AHU = Air Handling Unit

H13 Filter

Machine with in-line sterile room

LF Curtain

BFS Machine

-15 Pa
## Risk Assessment

- Modified FMEA approach for Safety classification
- Project Examples

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cleaning of product transfer line</td>
<td>Pipe work un-tight</td>
<td>Defect material, corrosion</td>
<td>Released product and cleaning agent</td>
<td>Maintenance</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Filling of product</td>
<td>Product blurred</td>
<td>Filling not stable - system is not closed</td>
<td>Release of product aerosol (open ampoules)</td>
<td>None</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>Valve not airtight in case of the fumigation</td>
<td>Valve works not proper</td>
<td>Defect drive, installation failure, no electricity connection</td>
<td>Fumigation can not be started</td>
<td>Control via monitoring program</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Filter NSC casing (H13 Recirculation filter)</td>
<td>Entrance of air cause contamination to the environment</td>
<td>Handlings mistake or material problem – filter changing</td>
<td>Contamination of personnel and environment</td>
<td>None</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>75</td>
</tr>
</tbody>
</table>
## Risk Assessment

- Safety Classification and derived primary and secondary actions

<table>
<thead>
<tr>
<th>No.</th>
<th>Functional element /step</th>
<th>Primary Action</th>
<th>Factor A</th>
<th>Factor B</th>
<th>Factor C</th>
<th>RPZ</th>
<th>Secondary Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cleaning of product transfer line</td>
<td>Pressure test of the transfer line</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>Protection cloth, change gloves, in case of appearance the air change rate increases, leave the room via emergency exit, room decontamination, employee training</td>
</tr>
<tr>
<td>2</td>
<td>Filling of product</td>
<td>Change design of filling machine</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>Clothes, fluids to be decontaminated any time, fumigation after appearance, filtration of the air, increase air exchange rate, all operator have to leave the room</td>
</tr>
<tr>
<td>3</td>
<td>Valve not airtight in case of the fumigation</td>
<td>Test during OQ and during yearly maintenance (monitoring)</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>15</td>
<td>Steady control of the valve position and alarm function via monitoring - the valve position will be monitored during all operations incl. Fumigation</td>
</tr>
<tr>
<td>4</td>
<td>Filter NSC casing (H13 Recirculation filter)</td>
<td>OQ Filter tightness certificate, re-qualification - yearly maintenance and check of filter</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>Check of filter sealing before and after installation</td>
</tr>
</tbody>
</table>
Biosafety Risk and Measures

- From Organism to safety measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Safety level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Biohazard sign</td>
<td></td>
</tr>
<tr>
<td>Access restricted</td>
<td></td>
</tr>
<tr>
<td>Lock room</td>
<td></td>
</tr>
</tbody>
</table>

- Special Cases e.g. microbiological safety cabinet
Access – Biosafety and GMP

• Door access to BSL area
Facility Concept – Modular Design

- Module 0 – Admin, social rooms, central gowning, logistic
- Module 1 is an independent fully functional module for bio F&F with BFS technology (high standardization)
- Module 1 is the base pattern for further modules
- Filling room designed for several BFS machine types
- Easy connection to future Module 2
- Connected without interruption of the production process
Facility Concept – Utilization

• Building Utilization and functional areas

- HVAC, Utility System, Offices
- Piping, HVAC components, ducts and supply systems
- PAL, MAL, Production, Packaging, Supporting Areas, Laboratory, Logistic
Facility Concept – Production Area

- Modular design and segregation of layout (BSL)
- Technology – BFS
- Personal flow
- Material flow
- Hygienic zones and Clean room Classification
# Classified and Controlled Space

<table>
<thead>
<tr>
<th>Grade</th>
<th>0.5 μm/ft³</th>
<th>CFU/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>&lt;1</td>
</tr>
<tr>
<td>C</td>
<td>100.000</td>
<td>100</td>
</tr>
<tr>
<td>D</td>
<td>ND</td>
<td>200</td>
</tr>
<tr>
<td>CNC</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

- **Point of Fill**
- **Blow Fill Seal Machine**
- **Vessel docking**
- **Packaging, Laboratory area**

**In Operation**
Airlock Function

An airlock is a dynamic transition zones between two different areas/environments.
Pressure and Air Lock Concept
PAL/MAL and Gowning Concept

- Select clothing (furniture, storage etc.)
- Leasing, buying, single use
- Select vendor
- Training of the personal
Facility Concept – HVAC System

- Ground floor – Production, Packaging, Lab and logistic areas
- Intermediate walkable ceiling – HVAC components, supply systems
- First floor - Technical area for HVAC and utility systems, Offices

Supply air, Recirculation air and exhaust air for the whole building

Air supply from all clean rooms zone C-E via the intermediate ceiling H14 filter (supply air) / H13 filter (exhaust air) (GMP)

External air intake via facade

Production rooms zone C, D with LF outlet and supply of E area
HVAC and Clean room

- Principle consideration for the design of the air handling:
  - Heating and Cooling
  - De- and humidification
  - Air Filtration of intake air
  - Keep room pressure (positive / negative)

- HEPA-Filter to be foreseen for Clean room class A, C in the “BIGE” building
- HEPA-Filter keeps back particles and aerosols
Principle HVAC and Filter Concept Grade D

Inlet air → TECHNICAL AREA

F7 F9

Supply air

PRODUCTION AREA

H14 HEPA filter

Clean rooms

H14

H13

Exhaust air (via roof) → TECHNICAL AREA

Exercise air

Ceiling-, wall-extraction with H13 HEPA filters or others depending on the application

Filter F7...F9 central

Weather protection

Exhaust opening

Ventilator

Filter entrance

Filter outlet
Principle HVAC and Filter Concept Grade C (Aseptic and bio-active filling)
HVAC Components for Grade C (BSL)

- CG Distribution – fine micro fabrics

Perforated Plate vs. CG Distribution
(Filling Room – Grade C)

- Bag in Bag system for safe filter replacement
Clean Room Monitoring

• **GMP-Principle**: All room parameters which has impact on the product have to be controlled and monitored!

• **Monitoring-System**: Continuous system for routine monitoring, recording and alerting of the following parameters:
  – Particle concentration (0.5 µm and 5 µm)
  – Flow velocity (LF, SWB)
  – Room differential pressure
  – Air-temperature and relative air humidity
Clean Room Monitoring

- „Measuring Point Diagram“ – Product transfer and MAL

- Test / Measuring point air germ
- Swap test floor („Abklatschtest“)
- Swap test door handle
- Test / Measuring point temperature and humidity
Fumigation of the Clean Rooms

- Defined areas for decontamination:
  - Filling room
  - Docking area product vessel
  - PAL/Emergency exit

- Fumigation options considered during design and execution:
  - Direct addition of H2O2 (evaporation) via nozzles at the HVAC system
  - With H2O2 generator e.g. Steris, Bioquell – max. 200 m³
  - MinCare System (Disinfection time 2-4 h, room size up to 1000 m³)
Fumigation of the Clean Rooms

• Biological and chemical Indicators used for testing

• Design considerations
  – Materials in use have to be resistant against H2O2
  – Surfaces must be clean and dry
Fumigation of the Clean Rooms

- Sterilization Cycle (development) and requirements

- Process parameters – humidity, temperature, air flow rate, pressure and time to be controlled
- Reach H2O2 concentration e.g. 1-2 mg/l by 22 °C and keep it stable
- Release room by reaching H2O2 concentration < 1 ppm
Facility Concept – Summary BSL

• **BSL enhanced:**
  - Hazard identification and areas of contamination (filling room, docking of bulk vessel)
  - Risk assessment (GMP and Biosafety)

• **Purpose of Biosafety - to protect:**
  - The worker, co-worker and those who interface with the production area/lab
  - The “product”
  - The environment

• **Facility requirements and safety equipment:**
  - Negative pressure rooms and biosafety cabinets for laboratory
  - Decontamination of manufacturing and quality control areas
  - Decontamination of all waste (thermal inactivation, autoclave)
  - HVAC design - extract and supply HEPAs for BSL2 areas
  - Equipment design and connection (e.g. closed system)
  - Fire water retention
Facility Concept – Energy Program

- High efficient heat recovery system for the HVAC system
- No cross-contamination risk (common circulation system water/air)
- Night time and weekend temperature reduction (60% of the air volume and less humidification)
- On- and off function for humidification (adsorption dryers) by non-critical products
- Cooling machine with free cooling system
Project Realization

- Project Responsibility and interface management:
  - Process driven by new technology of filling biologics
  - Building and clean room driven – new design with uncertainties?

### Technical Disciplines – PM and Quality Management

- Building Services/HVAC
- Building Automation
- Clean Rooms
- Clean Room Monitoring
- Qualification HVAC and Clean Room
- Qualification Process
- Filling Machine (BFS)
- Process Equipment
- Process Automation

### Clients Responsibility
- M+W Responsibility
- Architecture Responsibility
Project Realization – Time Line

- **March 2010**
  - Project Assignment

- **Apr. 2010**
  - Project Start – Kick off
  - Detail Engineering, Tendering and Construction

- **Dec. 2010**
  - Completion of Construction

- **May 2011**
  - Commissioning, Qualification (HVAC / Clean room systems)

- **Q3/Q4 2012**
  - GMP Production

- **Project Start of “M+W Group” “Execution Packages” after ground breaking in Dec. 2009**

- **Continuous Project Coordination**
  - Monthly report and cost controlling
  - Change Management

- **First technical trials (non GMP conform started)**

- **Final “M+W Group” Project Report/Debriefing Summary with “maropack AG”**
Project Realization – Air Handling

• Quality Assurance duct work during CC

- “Transportation and storage” of packed ducts and HVAC components
- Additional “cover foil” on both ends of the parts (ducts)
- “Cover plate” remains by interruption of the installation work
- “Approval of the cleaning” by the CM (Construction management)

- “Piping network is protected” after installation and commissioning by air filters and over-pressure
- “Flushing procedure” before start of clean room classification
- “Classification of clean rooms” according the defined clean room classes during the qualification
Project “Hand Over”

• Acceptance was carried out in 3 basic steps:
  • Step 1 - „Provisional Acceptance“ (Supplier)
    – Equipment commissioned and operational
    – Training for operators and maintenance personnel
      » e.g. bag filter for safety replacement
    – Issue IQ/OQ protocols and generate punch list for IQ/OQ
    – Resolve critical items in the punch list (class A items)
    – „Legal start-up“ to be granted by the safety representative
Project “Hand Over”

• **Step 2 - „Provisional Hand Over“ with the client**
  - The IQ/OQ certificates has been issued
  - The equipment ownership is handed over for routine operations.

• **Step 3 - „Final Hand Over“ with the client**
  - All punch lists have been closed
  - The documentation handed over to the users and maintenance personnel
  - Final signatures are given by package owner (discipline engineer)
Project “Hand Over”

- Project Close Out
  - Report type and standard defined in the beginning
    - Short form type applied for the “BIGE” project
    - Last project report e.g. key figures Planning and Building
    - Cost report with cost Structure, KPIs/benchmarks
    - Lessons Learned
    - Project pictures
  - Financial Close Out
    - Financial Audit and reporting
  - Human Resource Close Out
    - Staffing decision
    - Service agreements for TFM
Project “Hand Over”
Technical Facility Management

- Service conducted for clean rooms/HVAC:
  - Commissioning
  - Qualification (IQ/OQ)
  - Flow visualization
  - Training in operational safety

- After sales service provided for:
  - Maintenance
  - Trouble shouting
  - Re-qualification
Official Opening of „BIGE“

• Film prepared for the official opening ceremony and celebration of the new Bio Fill and Finish facility with international business guests.

• Involved project managers and engineers were assisting “maropack ag” by introducing the guests the new technical achievements and the facility in operation.
Conclusion

- BFS technology has great potential in the field of biopharmaceuticals because of reduced human intervention during the production process and ease of use in form of plastic ampules.
- The unique aspects of BFS operation call for a balanced empirical and systematic approach during process development and process validation.
- New fill and finish technologies such as “Blow-Fill-Seal” (BFS) for biologics can reduce costs, reduce overall manufacturing time, increase flexibility, and facilitate tracking/distribution.
- Modular facility design leads to faster project realization and to more cost effective future expansions.
- Advanced facility and clean room execution prevents for contamination and cross-contamination. Multi use facility can meet aseptic and bio-containment operation.
Questions & Answers
Thank you for your attention!

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