Establishing a Facility for GMP Manufacture of High Potency Biologics

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June 22, 2016
One Global Company

3 SITES
Billingham, UK
College Station, TX
RTP, North Carolina

1,100 EMPLOYEES
World Wide

6 LICENSES
For commercial manufacturing.

300+ MOLECULES
In process development and/or manufacturing.

35+ YEARS
Of Biologics CDMO experience.
With you all along the road
to clinical success
High Potency Biologics

Orally dosed proteins

Transgenic Expression

Precision Medicines

Breadth and Depth in our experience

60+ mAb, mAb-like and Ig-fusion molecules

175+ non-mAb recombinant proteins

30+ Vaccine programs
Full development / GMP manufacturing
High Potency Biologics Manufacturing

Opportunity and Challenges

• High Potency Biologics - an increasingly important class of therapeutics

• Cytotoxic proteins
  - Apoptosis signals (TNFα and variants)
  - Some cytokines (Interleukins)

• Significant business opportunity

• Significant challenge to establish a multi-product facility
  - Facility design
  - Operating strategy
Banding Scheme at Fujifilm Diosynth*

<table>
<thead>
<tr>
<th>ADE Category</th>
<th>ADE Range</th>
<th>Approach</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Band A</td>
<td>&lt;1ng/day</td>
<td>Not manufactured in FDB multiproduct facility</td>
<td>Lethal toxins e.g. botulinum toxin, diphtheria toxin</td>
</tr>
<tr>
<td>Band B</td>
<td>1ng-100ng/day</td>
<td>Risk assessment - additional controls necessary</td>
<td>Toxins, apoptosis signals, some cytokines e.g. TNFα, Interleukins</td>
</tr>
<tr>
<td>Band C</td>
<td>100ng-10ug/day</td>
<td>Risk assessment – some additional controls likely</td>
<td>Cytokines, growth factors e.g. interferons, human growth hormone</td>
</tr>
<tr>
<td>Band D</td>
<td>&gt;10ug/day</td>
<td>Existing controls appropriate</td>
<td>Monoclonal antibodies, antibody fragments, scaffold proteins, enzymes, insulin</td>
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High Potency Biologics Manufacturing Facility

Project Goals

- Establish a GMP Facility for manufacturing (microbial derived) High Potency Biologics

- GMP production from vial thaw to drug substance bulk fill

- Multi-product capability/versatility was critical

- Suitable for manufacture of early/late phase clinical and commercial products
High Potency Biologics Manufacturing Facility

**Project Strategy**

- Re-purpose and upgrade an existing microbial GMP facility to provide self-contained cleanrooms with separate HVAC system(s)

- Design facility in consultation with the UK regulatory agency (MHRA) to expedite regulatory approval

- Completion of expertly detailed Failure Mode Effects Analysis (FMEA) assessment on existing procedures. Outputs of FMEA embedded in facility design, equipment URS’, procedures and training
Design and Construction Timelines

**Design Phase**
- March 2014 - July 2014

**Consultation**
- MHRA
- August 2014

**Construction Begins**
- July 2015

**Construction Ends**
- February 2016

**Commissioning**
- Qualification Complete
- April 2016

**First GMP Batch Begins**
- April 2016

**Seven (7) Months**

**Three (3) Months**

Two Years from concept to fully operational
High Potency Facility Floorplan

Total floor area: ~3000 sqft
Upstream processing: ~1000 sqft
Downstream processing: ~1250 sqft
Suite Layout: USP
Suite Layout: USP/DSP Transfer Port
Suite Layout: DSP
Operations

Guiding Principles

- FACILITY OPERATING STRATEGY
- HIGH POTENCY BIOLOGICS GMP PRODUCTION
- PROCESS CONTAINMENT STRATEGY
Operating Principles

- Segregated “once through” HVAC system with HEPA extraction
- Dedicated personnel and material access routes
- **Dedicated direct product contact equipment**
- Non-product contact equipment with disposable flow-path remains multi-product use where risk assessment allows:
  - Surface Removal and Product Degradation Methods Established
  - Execution Of Qualified Surface Cleaning Protocols
Personnel and Process Controls

**Personnel**
- Single Use Disposable Gowning
- Control Of Personnel Movement Between Facilities

**Engineering solutions eliminate all risk of contamination to utilities**
- Closed processing unit ops...as far as possible - minimizing exposure of operators and facility to product
- If closed processing operations are not achievable for certain unit ops they are operated within a secondary containment envelope
Risk assessments (FMEA) performed to ensure appropriate mitigation to minimize loss of process containment

Additional risk mitigation:

- Closed sampling and analysis
- Testing of connections and joints, prior to use
- Use of single use disposable consumables including columns
- Deactivation / flushing of product flow-path prior to breaking of connections
- Tube welding used for process connections
- Use of tube sealing at point of disconnection
- Aerosol generation studies for higher risk areas
- All process waste collected for off-site disposal
- Segregated vent lines
Enhanced Control Procedures: Loss of containment

- Enhanced procedures followed in the event of a leak, drip or spill
- Rapid response to loss of containment events following procedure specified above
- Procedure to utilize clean-up agent and contact time that has been demonstrated to achieve effective product removal and degradation
- Frequent in-glove changing following high risk activities
- Sample transport mechanism to provide secondary containment
- Spill equipment / materials availability utilizing low aerosol generation clean-up technology
- Waste containment and disposal
Conclusions

- Establishment of facility from concept to commissioning took 2 years

- Operational and Procedural control strategies are in place

- Facility is up and running - Late Phase Clinical Manufacturing project underway

- GMP Facility is now available for High Potency Biologics Production (‘clinical and commercial ready’)
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CDMO Partner of Choice