Vaccines for the World - Insights into Design and Execution of a BSL2 Fill-Finish Facility

Rutger Vandiest - Sr. Director, Head of Sales, CDMO
Bavarian Nordic A/S
Presentation overview

- Bavarian Nordic
  - Introduction to Bavarian Nordic
  - Viral vaccines
  - Challenges in working with live viral vaccines

- IPS
  - Facility design - process architecture
  - Project team
  - Planning and Timelines
  - Challenges on project execution

- Syntegon
  - Technological high-lights of the isolator line
  - Filling equipment

- Bavarian Nordic
  - Summary

Presenters:

Bavarian Nordic
- Rutger Vandiest
  - Sr. Director - Head of Sales, CDMO

IPS
- Mark Miller
  - Director of Engineering, EMEA

Syntegon
- Matthias Angelmaier
  - Global Product Manager
  - Isolator and Processing Technology
Bavarian Nordic - Company overview

**Life-saving vaccines**

Bavarian Nordic is a fully integrated biotechnology company developing, manufacturing and commercializing vaccines for the prevention and treatment of life-threatening diseases.

**FACTS**

- Founded 1994, IPO 1998
- HQ: Hellerup - Denmark
- +700 Employees
- First product approved in 2013 (MVA-BN as smallpox vaccine)
- Commercial products, Long-term R&D and delivery contracts with the US government and Development partnerships with industry partners

By 2025, we aspire to be one of the largest pure play vaccine companies improving and saving lives by excelling in R&D innovation, manufacturing and commercialization

**A company driven by commercial excellence**

Establish a full-scale commercial operation to expand the business and drive profitable growth

**Develop innovative life-saving vaccines**

Expand and advance portfolio of pipeline projects

**Best in class vaccine manufacturer**

Expand manufacturing expertise and capacity
Advancing COVID-19 vaccine program with AdaptVac
BN has entered a headsof agreement with AdaptVac, a joint venture between ExpreS2ion Biotechnologies and NextGen Vaccines (spin-out from University of Copenhagen), to license their capsid virus like particle (VLP) based SARS-CoV-2 subunit vaccine.
• Traditional activities for live viral vaccines manufacturing

- MVB (Master Virus Bank)
- MSV (Master Seed Virus)
- WSV (Working seed virus)
- BDS (Bulk Drug Substance)
- FDP (Final Drug Product)

- Embryonated eggs
  - Pre-incubation
  - CEF preparation

- Cell Culture System
  - Cell Line
  - Virus inoculation
  - Bioreactor
  - Purification
  - Freezing

- Roller Bottles
  - Virus inoculation
  - Growth & harvest
  - Purification & freezing

- Wave Bioreactors
  - Virus inoculation
  - Growth & harvest
  - Purification & freezing

- Millipore Bioreactors
  - Virus inoculation
  - Bioreactor
  - Purification
  - Freezing
Bavarian Nordic: Full CDMO Services

- EXPERTISE AND KNOWLEDGE – PASSION – SHARING – COLLABORATION

**Process Development**
- Process characterization
- BSL2/GMO2 pilot facility - Up to 50L
- Scale up capabilities upstream/downstream 1L up to 250L
- Formulation development
- Analytical method development
- Virus banking

**Drug substance**
- Tech transfer management
- Preclinical / Clinical / Commercial Mfg
- Cell culture based on adherent and suspension cell platforms
- Process technology
  - Bioreactors
  - Roller bottles
- Recovery & purification
  - Harvest vessel
  - Clearance
  - Purification

**Drug Product**
- Tech transfer management
- Excipient preparation and formulation
- Aseptic liquid vial filling and lyophilization
- Inspection and packaging

**Manufacturing support**
- Manufacturing support
  - Environmental monitoring - IPC
  - Assay qualification and validation
  - DS/DP batch full release testing
- Regulatory support
  - IND preparation
  - CMC filing assistance
- Lab testing & Storage
  - Stability study
  - QC release testing
  - Different storage T: 5°C, -20°C, -50°C, -80°C
- Project management

Experts in vaccines
Experience with transfer from and to external sites
Extensive experience working with external partners
EMA and FDA complaint site
BSL2/GMO2 classified facility
Large scale lyo capabilities
Live, attenuated viral Vaccines

Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacterium in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. They have been available since the 1950’s.

- They elicit strong cellular and antibody responses with lifelong immunity with only one to two doses
- The immune response is virtually identical to natural infection
- Must replicate to produce an immune response
- A live attenuated vaccine virus could theoretically revert to its original pathogenic (disease-causing) form
- They are fragile and must be stored and handled carefully. They usually require refrigeration, which can make availability to remote areas/countries challenging
- They are generally contra-indicated in persons with weakened immune systems

**General Rule:**
The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.

**Currently available live attenuated vaccines**
- Measles
- Mumps
- Rubella
- Vaccinia
- Varicella
- Zoster (which contains the same virus as varicella vaccine but in much higher amount)
- Yellow fever
- Rotavirus
- Influenza (intranasal)
- Oral polio vaccine
- Live attenuated bacterial vaccines are bacille Calmette-Guérin (BCG) and oral typhoid vaccine.

The first vaccine used by Jenner is of this type: vaccinia virus (cowpox) inoculation of humans confers immunity to smallpox but does not cause smallpox.
Complexity in Fill&Finish of Live viral Vaccines

• Complexity driven by

**Nature of the Product**
- Live attenuated virus
- Complex, fragile molecules
- Expensive products

**Required Environment**
- Aseptic manufacturing
- Biosafety level
- Multi-product facility

Resulting in complex manufacturing and supply chain

A high level of expertise is required!
Basic Design concept for Fill&Finish

• Product considerations

<table>
<thead>
<tr>
<th>Nature of the product</th>
<th>Design concept</th>
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<tbody>
<tr>
<td>Live attenuated virus</td>
<td>• Adequate Bio Safety Level</td>
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<tr>
<td></td>
<td>• Adequate cleaning and decontamination</td>
</tr>
<tr>
<td></td>
<td>• Full Single-use technology</td>
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<td></td>
<td>• Full isolator technology</td>
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<tr>
<td>Complex, fragile molecules</td>
<td>• High speed filling line</td>
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<tr>
<td></td>
<td>• Low pressure peristaltic pumps</td>
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<tr>
<td></td>
<td>• Lyophilization capabilities</td>
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<td></td>
<td>• Minimized transport between activities</td>
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<td>• Cold storage capabilities for different T.</td>
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<td>• Reduced TOR</td>
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<tr>
<td>Expensive products</td>
<td>• Minimize product losses</td>
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<td></td>
<td>• Enable small bulk volumes</td>
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</tbody>
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Summary - take home messages

• Complex project
  • Very tight timeframe
  • Minimized facility space

• Goal achieved by:
  • Very clear design specifications
  • FDA Type C meeting very early in the design phase
  • Choice for proven technology
  • Strong project management
  • Aligned teamwork

Thank you to IPS, Syntegon and all involved and committed stakeholders!
Thank you for your attention!

- Rutger.Vandiest@Bavarian-Nordic.com
Part II – Vaccines for the World – Insights into the Design & Execution of a BSL2 Fill-Finish Facility

March 23rd, 2021
Facility Design – Process Architecture

Design Objectives
- Commercial & Clinical
- Multi-product
- FDA / EU GMP compliance
- GMO2 / BSL2 compliance

Containment & GMP – EHS v’s Quality
- Isolator technology
- Pressure regimes
- Uni directional flows

Challenges
- Footprint constraints
- Refurbishment

Functionality
- Cold Storage
- Formulation
- Filling
- Lyophilization
- Terminal Sterilisation
- Wash & Sterilisation
- Decontamination
- Inspection
- Packaging + Serialisation
Project Team

Client
Bavarian Nordic

Key Equipment Suppliers

Local Installation Subcontractors

EPCMV Services
IPS

Sisk
Orbicon

Syntegon
IMA
Getinge
Seidenader
Merck Millipore
BWT
Stilmes
Envirodts

"If you want to go fast and far, work together."

Planning & Timelines

- Oct 17: Filling Line Order
- Jul 19: Filling Line Delivery
- Oct 19
- Mar 20
- Dec 21

- 24 mths - Start of Detailed Design to Construction Complete
- 6 mths - Construction Complete to OQ Complete
- TARGET: 21 mths - OQ Complete to Regulatory Approval
Project Execution Challenges

- Basic Design changes
- Site noise constraints
- Local construction supply chain design capability
- Package Coordination – language, geography, culture
Thank you!

Mark Miller
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mamiller@ipsdb.com
Technological Highlights
Isolator Line
DCVMN Webinar, March 23rd, 2021
Technological Highlights Isolator Line

Line overview

- BSL application
- Liquid and lyo products
- Vial filler with 100% IPC and Isolator
- Lyo loading/unloading Isolator
- Capper in Closed RABS
- Outside Cleaning in Containment
- Wireless Glove Testing
- Stand-alone Transfer Chamber ISS
Line overview

- BSL products
- Pressure concept for both **operator** as well as **product** protection

**Infeed Turntable Isolator**
+35 Pa

**Lyo loading/unloading Isolator**
+25 Pa / -10 Pa

**Outside Washer Containment**
-15 Pa

**Filling Machine Isolator**
+25 Pa

**Capper Closed RABS**
+15 Pa / -10 Pa

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Fill-Finish Equipment

- Usage of proven technology
- High-speed filling machine up to 400pcs./min
- 100% IPC
- Focus on highest product yield
- Dose-In/Dose-Out function
- Optimized stoppering
Fill-Finish Equipment

- 8-head peristaltic pumps
- Filling needle movement
- Environmental monitoring
- 100% IPC
Focus on product and operator protection

- Dedicated pressure concept
- 2 dedicated VHP cycles
  - **Decontamination** as part of line changeover
  - **Inactivation cycle** for BSL 2 products
- Additional filter systems (SafeChange) for incoming and outgoing air
Capping Machine

- Separated Closed RABS Segment
- VHP inactivation cycle
- Integrated Camera Systems
  - Crimping Quality
  - Stopper position check
Outside decontamination of vials

- Outside cleaning machine
- Containment execution
- 2 separated areas for cleaning and drying
- High-pressure cleaning of outer vial surfaces
- Vial neck area gets protected by active airflow
Sampling and Material Transfer

- Usage of VHP transfer chamber
- Double functionality:
  - Material transfer via RTP port
  - Inactivation of outer surfaces of samples
- Customer specific racks and containers
- Rapid biodecontamination cycle time
- Simplified air handling with catalytic converter
THANK YOU!
ANY QUESTIONS?
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