ASEPTIC BLOW-FILL-SEAL FILL/FINISH TECHNOLOGY AND VACCINES

Developing Countries Vaccine Manufacturers’ Network
DCVMN 20th Annual General Meeting
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PRESENTATION OVER VIEW

1. General Introduction to Blow/Fill/Seal
   Advanced Aseptic technology
2. Blow/Fill/Seal, a world wide technology
3. Current status: Vaccines and Blow/Fill/Seal
4. Testing Capabilities
TEMPERATURE SENSITIVITY VACCINES

Vaccines to the left of the line are not damaged by freezing.

Heat sensitivity

Most sensitive

Least sensitive

Freeze sensitivity

Not sensitive

Least sensitive

Most sensitive

Aseptic Fill

Liquid Vaccines

Vaccine formulation

Freeze dried

Liquid, no adjuvant

Liquid, with alum adjuvant

*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.
WHY BLOW/FILL/SEAL

Reduce the cost of the delivered dose

• Current standard is multi-dose glass vials
• Breakage – 10 doses lost
• Wastage - 6 hours to use all 10 doses

Goal → Lower cost for Dose Delivered to GAVI countries

Practical industry considerations:

• Glass quality going down – higher rejection rate in production
• High quality glass cost going up – increased manufacturing cost
WHY BLOW/FILL/SEAL
Reduce the cost of the delivered dose

• BFS is a known technology
  ▪ 50 years in pharmaceutical manufacturing

• Very high aseptic assurance
  ▪ Recognized Advanced Aseptic Technology*

• High capacity, low cost production
  ▪ +4 billion aseptically filled drug products supplied to US market today

• * USP and US FDA
Commitment to Aseptic Fill/Finish Technology

- Innovators Blow/Fill/Seal Technology
  850 People

- Contract Manufacturing utilizing Blow/Fill/Seal
  950 People

Bill and Melinda Gates foundation grant
- Develop New Delivery Systems

Bill and Melinda Gates foundation grant
- Test Vaccines for Compatibility
BLOW/FILL/SEAL BASICS
1962 – GERHARD HANSEN AND BLOW FILL SEAL
REGULATORY ACCEPTANCE FOR ADVANCED ASEPTIC BFS TECHNOLOGY

US FDA 2004 Aseptic Guidance

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container closure processing and reduced human intervention and is often used for filling and packaging ophthalmics, respiratory care products, and, less frequently, injectables. This appendix discusses some of the critical control points of this technology.

Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004
BLOW-FILL-SEAL (BFS) PROCESS: PARISON FORMATION

Blow/Fill/Seal Process: 4-13 seconds

- Medical Grade Polymer fed to an extrusion blow molding system
- Parison formed – empty plastic tube
- Sterile filtered air prevents empty parison from collapsing

Melting polymer & extrusion of parison with sterile air
BLOW-FILL-SEAL (BFS) PROCESS: SHUTTLING

Blow/Fill/Seal Process: 4-13 seconds

• Container is formed

• The container is moved to the point of fill

• The point-of-fill is protected by overpressure sterile filtered air

Sterile Air

Transfer in mould and cutting (overpressure of sterile air)
BLOW-FILL-SEAL (BFS) PROCESS: BLOWING

Blow/Fill/Seal Process: 4-13 seconds

- Sterile filtered air blown into bottle to complete formation

Container blow moulding with sterile air & filling
BLOW-FILL-SEAL (BFS) PROCESS: FILLING AND SEALING

Blow/Fill/Seal Process: 4-13 seconds

• Container is filled
• “head” mould closes and seals the container
PRODUCTS UTILIZING BFS TECHNOLOGY
TRADITIONAL INJECTION METHODS WITH BFS AMPOULE WITH LUER CONNECTION
COMMON APPLICATIONS

Large Volume Parenterals LVP

Injectables - Small Volume Parenterals SVP

Respiratory Care Products, Inhalations

Multi-dose Ampoules
Unit-dose Ampoules

Eye Care, Nose Care, Ear Care, Contact Lens Cleaning

Ointments, Enemas, Gels
COMMON BFS PRODUCTS
COMMERCIAL CONTAINERS FOR INJECTABLE PRODUCTS
LUER CONNECTION FOR SYRINGE

Rommelag CMO

• <1 mL

• Advanced Aseptic

• Other designs being developed

• Glass ampoule replacement
HISTORY OF BLOW/FILL/SEAL WITH VACCINES
DILUENT PRODUCTS

Sterile Water for Injection
VACCINE COMPATIBILITY – NASAL LAV VACCINE

2007-2010

Immunogenicity of a quadrivalent Ann Arbor strain live attenuated influenza vaccine delivered using a blow-fill-seal device in adults: a randomized, active-controlled study*

Eric A. Sheldon,a Robert Jeanfreau,b Joseph A. Sliman,c Supoat Charenkavanich,d Matthew D. Rouscelp, Filip Dubovsky,f Raburn M. Malloryf

*Noninferior Immunologic Response of Quadrivalent, Live Attenuated Influenza Vaccine in a Blow-Fill-Seal Delivery System (Q/LAIV-BFS) Compared with Trivalent LAIV (T/LAIV), IDSA, Annual Meeting 2010, Vancouver BC
VACCINE COMPATIBILITY – NASAL LAV VACCINE

2007-2010

Results: Q/LAIV-BFS was immunologically noninferior to T/LAIV because the upper bounds for all four 95% confidence intervals (CIs) for post-dose strain-specific GMT ratios were less than the predefined margin of ≤ 1.5. Secondary immunogenicity outcomes, solicited symptoms, and AEs were also comparable.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Q/LAIV</th>
<th>T/LAIV</th>
<th>GMT Ratio (T/LAIV / Q/LAIV)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>1176</td>
<td>586</td>
<td>0.95</td>
<td>0.87, 1.03</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>1176</td>
<td>586</td>
<td>0.93</td>
<td>0.85, 1.00</td>
</tr>
<tr>
<td>B Yamagata</td>
<td>1176</td>
<td>294</td>
<td>0.90</td>
<td>0.79, 1.02</td>
</tr>
<tr>
<td>B Victoria</td>
<td>1176</td>
<td>292</td>
<td>0.97</td>
<td>0.87, 1.10</td>
</tr>
</tbody>
</table>

H1N1 & H3N2 data from 2 T/LAIV arms were combined for analysis

Conclusion: The immunogenicity and safety of Q/LAIV-BFS, as defined in this study, were comparable to those of T/LAIV in adults.

This study was sponsored by MedImmune.
VACCINE COMPATIBILITY – ORAL ROTA LAV

2012

• Multiple vaccines tested
• Statistically no difference between BFS and existing packaging
• Existing prefilled plastic tube
• GSK Australia converting to BFS

GlaxoSmithKline Australia VP and General Manager Geoff McDonald in the new vaccine facility. Picture Aaron Francis
BILL AND MELINDA GATES FOUNDATION GRANTS
PATH DEVELOPED PRODUCTION COSTS

Total cost of delivery – Rotavirus vaccine

Updates on Packaging and Delivery for Rotavirus and Oral Vaccines Presentation for the Ninth ARVAC Rotavirus Vaccine Manufacturers’ Meeting Bangkok, Thailand, Jeff Sedita –PATH, June 22, 2017
VACCINES: WHY BLOW FILL SEAL

Container development grant

- Single dose per container:
  - No preservatives
  - Low wastage
  - Low breakage
  - Small cold chain footprint
- Low Cost of Goods
- Vaccine compatibility
CPAD DEVELOPMENT GRANT

- ApiJect Concept container
  - Double needle design
  - Existing BFS container design
GLOBAL GOOD DESIGN – REDUCED CONTAINER SIZE
OPTIMIZED FOR COLD CHAIN
GRANT TO DEVELOP NEW DELIVERY FORMS

Rommelag Engineering

- CPAD – Compact Auto Disable Device
- Replacement for single dose glass vial
- Rommelag Multi-Mono Dose Design
NEXT STEPS – NEW GRANT WORK
CPAD DEVICE – COMPACT AUTO DISABLE DEVICE

ApiJect development
GRANT TO DEVELOP NEW DELIVERY FORMS

Rommelag Engineering

• ApiJect current design
Feasibility Assessment of Novavax RSV F vaccine with Maropack Cold BFS Process in Global Good Design Ampule

- **Objective**
  - Provide feasibility assessment on aluminum phosphate adjuvanted RSV F vaccine in BFS as a potential WHO product presentation, with funding from Bill and Melinda Gates Foundation to Rommelag and Maropack.

- **Scope**
  - Primary: Evaluate aluminum phosphate adjuvanted RSV F vaccine compatibility/stability, potential leachables with BFS containers.
  - Stretch: Evaluate BFS fill system compatibility with recirculation system

- **Outcome:** Recommending further developing BFS as a potential WHO Product Presentation
  - RSV F vaccine stability profile in BFS similar to profiles in glass vials and syringes
  - Minimal concern on potential leachables in simulated leachable study
  - BFS fill process compatible with a recirculation system critical for uniformity control
VACCINE COMPATIBILITY – INJECTABLE

Feasibility Assessment of Novavax RSV F vaccine with Maropack Cold BFS Process in Global Good Design Ampule

- Feasibility study with Global Good BFS ampule design
  - 9 month/2-8 °C stability testing completed; continuing to 24 months
    - Stability profile in BFS, by ELISA, RP-HPLC, SDS-PAGE, similar to profiles in glass vial and PFS

- Further development of BFS container
  - Modify design to fit with WHO pre-qualified auto-disable syringes
  - Design target: similar use experience to glass vial
    - User Requirements Specification based on
      - Lesson learned from current BFS field study
      - WHO Generic Preferred Product Profile for Vaccines
      - Assessing programmatic suitability of vaccine candidates for WHO prequalification
      - WHO Immunization in Practice
      - WHO Cold chain preference & vaccine vial monitor implementation
INVENTPRISE VACCINE TESTING

Rommelag CMO

- Successful stability trial
- Injectable vaccine
- Containing adjuvant

- Supported by Global Good
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