VACCINE PACKAGING WITH BLOW/FILL/SEAL TECHNOLOGY: DEVICES, VACCINE COMPATIBILITY AND ECONOMIC CONSIDERATIONS

Developing Countries Vaccine Manufacturers’ Network
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Kunming, China

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Rommelag CMO
ROMMELAG BLOW/FILL/SEAL ASEPTIC TECHNOLOGY

Welcome to DCVMN 19th AGM 2018. Kunming
PRESENTATION OVER VIEW

1. General Introduction to Blow/Fill/Seal Advanced Aseptic technology
2. Blow/Fill/Seal, a world wide technology
3. Vaccines and Blow/Fill/Seal
4. Next steps
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 system locations
BLOW/FILL/SEAL BASICS
BLOW-FILL-SEAL (BFS) PROCESS
Blow/Fill/Seal Process: 4-13 seconds

Melting polymer & extrusion of parison with sterile air
Transfer in mould and cutting (overpressure of sterile air)
Container blow moulding with sterile air & filling
Container closing

1. Sterile Air
2. Sterile Formulation

Med. Grade Polymer
Sterile Air
Sterile Air
Sterile Air
VIDEO SHOWING BFS PROCESS 430
1962 – GERHARD HANSEN AND BLOW FILL SEAL
MODERN BLOW/FILL SEAL TECHNOLOGY
WHY BFS TECHNOLOGY
ASEPTIC RISK REDUCTION

• Operators = Contamination Sources

“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...”¹.

ASEPTIC RISK REDUCTION – ADVANCED ASEPTIC PROCESSING

The FDA view…

• BFS, Isolators, cRABS

• Increased Quality

• Decreased Aseptic Risk

• Isolators and RABS increase separation

• BFS automation reduces contamination sources
# COMPARING RISK: BLOW/FILL/SEAL TO CONVENTIONAL GLASS SYSTEMS

<table>
<thead>
<tr>
<th>Conventional Glass</th>
<th>Blow/Fill/Seal Plastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass Breakage</td>
<td>Robust container</td>
</tr>
<tr>
<td>Silicone contamination</td>
<td>Silicone not required</td>
</tr>
<tr>
<td>Preformed container, stopper, cap</td>
<td>Newly Created Container</td>
</tr>
<tr>
<td>Transport to facility</td>
<td>N/A</td>
</tr>
<tr>
<td>Storage – days/months prior to fill</td>
<td>N/A</td>
</tr>
<tr>
<td>Decontamination step</td>
<td>N/A</td>
</tr>
<tr>
<td>Aseptic filling</td>
<td>Aseptic filling</td>
</tr>
<tr>
<td>Capping in classified area</td>
<td>N/A</td>
</tr>
<tr>
<td>Known particle contamination</td>
<td>Very low particle load (10x &lt;)</td>
</tr>
<tr>
<td>Multiple integrated systems</td>
<td>Single automated system</td>
</tr>
</tbody>
</table>
TRADITIONAL INJECTION METHODS WITH BFS
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 Lense Cleaning
- Ointments, Enemas, Gels
COMMON BFS PRODUCTS
COMMERCIAL CONTAINERS FOR INJECTABLE PRODUCTS
LUER CONNECTION FOR SYRINGE

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• <1 mL

• Advanced Aseptic

• Other designs being developed

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

### Post Dose Ratio of Geometric Mean Titers (GMTs) of Hemagglutination Inhibition (HAI) Antibody

<table>
<thead>
<tr>
<th>Strain</th>
<th>Q/LAIV</th>
<th>T/LAIV</th>
<th>GMT Ratio (T/LAIV / Q/LAIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>GMT</td>
<td>N</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>1176</td>
<td>8.1</td>
<td>586</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>1176</td>
<td>8.3</td>
<td>586</td>
</tr>
<tr>
<td>B Yamagata</td>
<td>1176</td>
<td>60.3</td>
<td>294</td>
</tr>
<tr>
<td>B Victoria</td>
<td>1176</td>
<td>27.4</td>
<td>292</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.

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 – 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
PATH DEVELOPED PRODUCTION COSTS

Total cost of delivery – Rotavirus vaccine

Abbreviations: BFS, blow-fill-seal; MMD, multi-mono-dose.

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
BILL AND MELINDA GATES FOUNDATION GRANTS
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
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

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• Successful stability trial
• Injectable vaccine
• Containing adjuvant

• Supported by Global Good
NEXT STEPS

Global Good next generation design

- cGMP system being built
- Capable of human trials
- Increased processing capability
- Cold chain capabilities
- Available to everyone
NEXT STEPS – NEW GRANT WORK
CPAD DEVICE – COMPACT AUTO DISABLE DEVICE

ApiJect development
NEXT STEPS
ROMMELAG CMO – DEDICATED TESTING SITE

FDA inspected facility

• Platform for trials
  ▪ Clinical
  ▪ Technical

• Dedicated biological facility

• Disposable filling system

• Commercial production capability
NEXT STEP
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