FILLING YOUR NEEDS

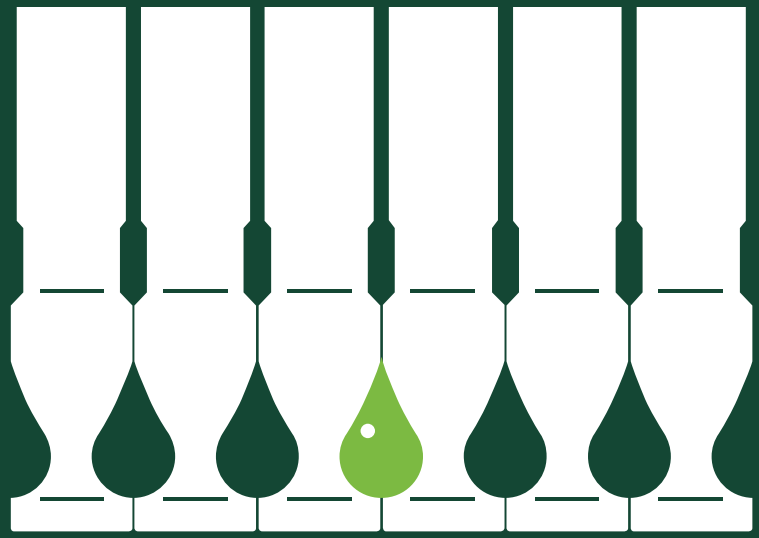
ROMMELAG CMO

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

Developing Countries Vaccine Manufacturers' Network

DCVMN 20th Annual General Meeting
Virtual Meeting
3-5 November 2020

Tim Kram, General Manager,
Rommelag USA, Inc.



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

dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG BLOW/FILL/SEAL TECHNOLOGY TIM KRAM

Commitment to Aseptic Fill/Finish Technology

ROMMELAG ENGINEERING

Innovators Blow/Fill/Seal Technology

850 People

ROMMELAG CMO

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

dcvmn
Developing Countries Vaccine Manufacturers Network

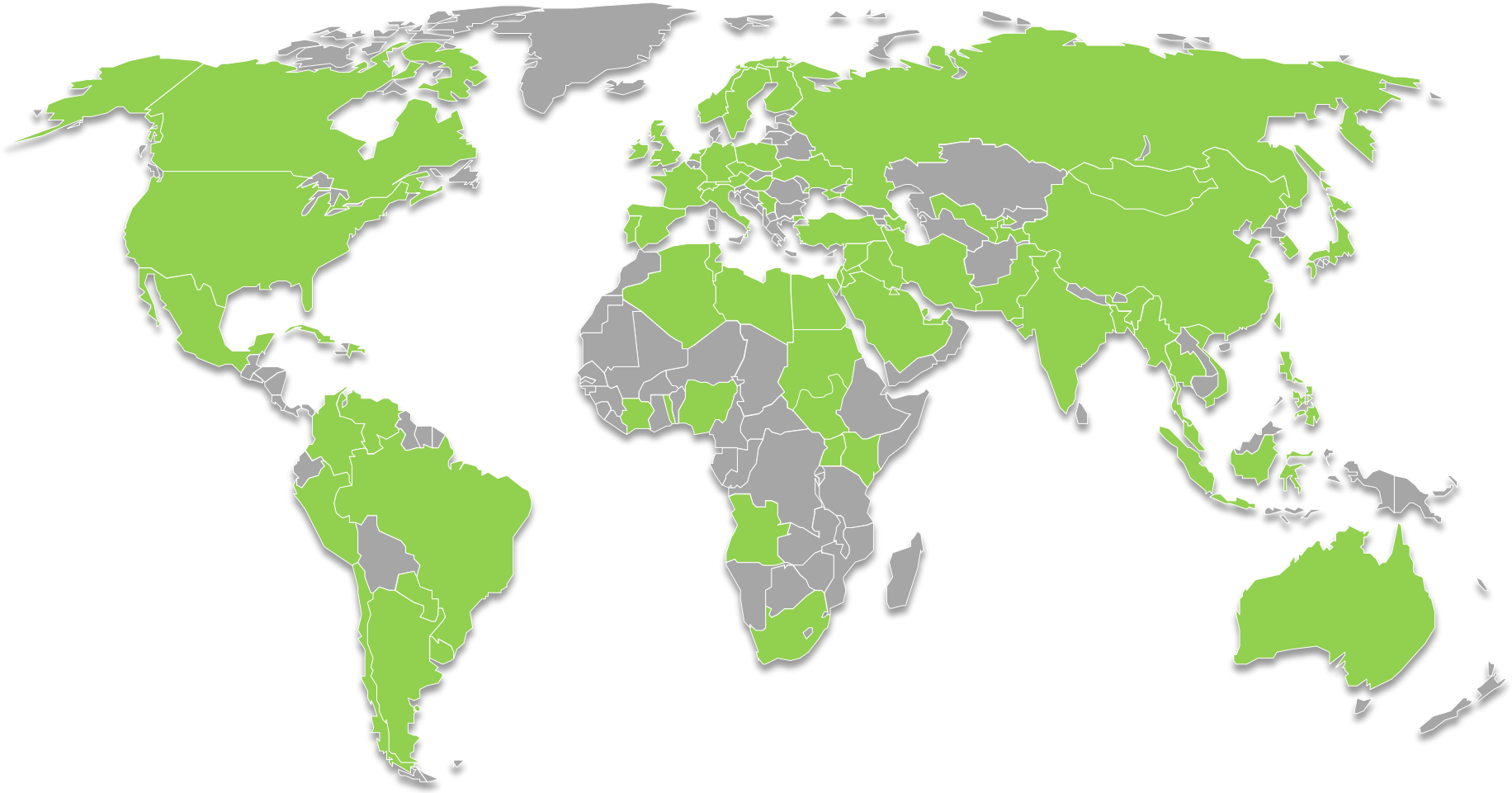
ROMMELAG CMO

Manufacturers Network

ROMMELAG ENGINEERING

dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG - WORLD WIDE PRESENCE



Blow/Fill/Seal system locations

ROMMELAG CMO

BLOW/FILL/SEAL BASICS

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

dcvmn
Developing Countries Vaccine Manufacturers Network

VIDEO SHOWING BFS PROCESS 430

Rommelag Closed Parison Technology – 430

https://vimeo.com/188628707

ROMMELAG CMO

HISTORY OF BLOW/FILL/SEAL WITH VACCINES

DILUENT PRODUCTS

Sterile Water for Injection

VACCINE COMPATIBILITY – NASAL LAV VACCINE

2007-2010

DOI:10.1111/irv.12027
www.influenzajournal.com

Original Article

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. Rousculp,[e,†] Filip Dubovsky,[f] Raburn M. Mallory[f]

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

Developing Countries Vaccine Manufacturers Network

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

Strain	Q/LAIV		T/LAIV		GMT Ratio (T/LAIV / Q/LAIV)	
	N	GMT	N	GMT	Ratio	95% CI
A/H1N1	1176	8.1	586	7.7	0.95	0.87, 1.03
A/H3N2	1176	8.3	586	7.7	0.93	0.85, 1.00
B Yamagata	1176	60.3	294	54.1	0.90	0.79, 1.02
B Victoria	1176	27.4	292	26.7	0.97	0.87, 1.10

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

Developing Countries Vaccine Manufacturers Network

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

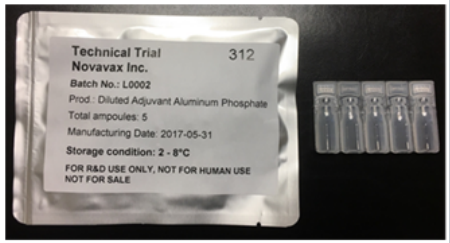
GlaxoSmithKline Australia VP and General Manager Geoff McDonald in the new vaccine facility. Picture Aaron Francis

dcvmn
Developing Countries Vaccine Manufacturers Network

VACCINE COMPATIBILITY – INJECTABLE

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

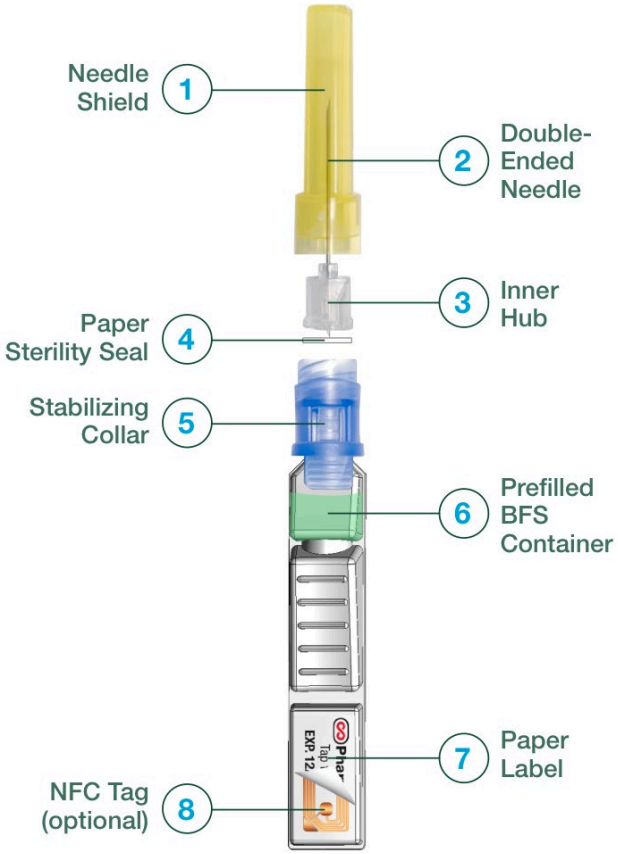
Feasibility Assessment of Novavax RSV F vaccine with Maropack Cold BFS Process in Global Good Design Ampule

- 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

APIJECT 510K DEVICE

- Device based on insulin needle design
- 0.5 mL BFS primary packaging
- Assembled prior to administration



dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG CMO – DEDICATED BIOLOGICS SITE

- Platform for trials
  - Clinical
  - Technical
- Dedicated biological facility
- Disposable filling system
- Commercial production capability

dcvmn
Developing Countries Vaccine Manufacturers Network

CONTACT INFO

Tim Kram
Rommelag USA, Inc.
tim.kram@rommelag.com
303-674-8333

Yves Schwander
Director Development
Rommelag CMO / Maropack AG
Industriestrasse Briseck 4 · 6144 Zell · Switzerland
T +41 41 989 74 60 · F +41 41 989 74 01
Yves.Schwander@rommelag.com

ROMMELAG
CMO

END

GLOSSARY

- **Advanced Aseptic Process -** A process in which direct intervention with open product containers or exposed product contact surfaces by operators wearing conventional cleanroom garments is not required and never permitted (1).
- **Air Shower -** A device fitted to a B/F/S machine which provides, as a minimum, a continuous flow of Grade A quality air supply over the filling needles and the point-of-fill. The Air Shower is also known as a Nozzle Shroud .
- **Aseptic Processing Area (APA) -** Classified environment used for aseptic filling of sterile containers with sterile products, e.g., liquid solutions. The APA has a HEPA-filtered air supply and materials; equipment and personnel are strictly controlled to minimize/remove any potential risk of microbial/particulate contamination transfer into the sterile product .

1. *General Chapter <1116> Microbiological Control and Monitoring of Aseptic Processing Environments USP38/NF33.* **U.S Pharmacopeia.** 2015. www.usp.org.

GLOSSARY

- **Critical Processing Zone -** Location within the aseptic processing area in which product and product contact surfaces are exposed to the environment. The Critical Processing Zone is dependent upon machine design and includes, but is not necessarily limited to the parison extrusion and cutting area (only for shuttling machines), mould transfer area (only for shuttling machines), air shower (only for shuttling machines), and point-of- fill.
- **Dynamic (in operation) -** B/F/S machine line fully operational and filling, with the number of allowed operating personnel present as during normal running conditions.
- **Mandrel -** Specialized filling needles on certain B/F/S machines which also can act to form the container
- **Parison -** The “tube” of polymer extruded by the B/F/S machine from which the containers are formed.

GLOSSARY

- **Static (at rest) -** B/F/S machine line with conveyor belts at rest but with air shower and room ventilation in operation; extruder (heated; not running), and mould carriage in standby. No operating personnel present. (2; 3)
- **Zone of Protection/Machine Shroud** - A system fitted to a B/F/S machine to direct a flow of HEPA-filtered air over the Critical Processing Zone of the machine (For open parison/shuttle machines only)

2. *EU Guide to Good Manufacture Practice: Annex 1, Manufacture of Sterile Medicinal Products.* **European Commission.** 2009.

3. *Guidance for Industry. Sterile Drug Products Produced By Aseptic Processing – Current Good Manufacturing Practice.* **U.S. Food and Drug Administration.** 2004.