FILLING YOUR NEEDS

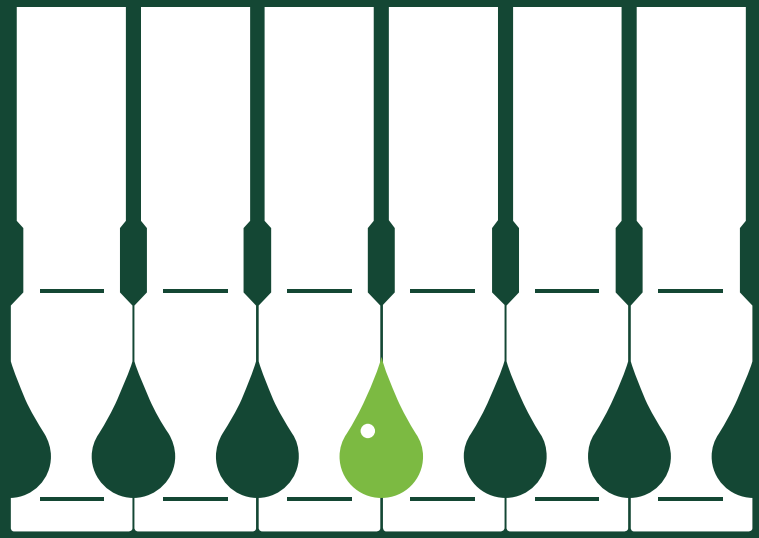
ROMMELAG CMO

BLOW-FILL-SEAL TECHNOLOGY BENEFITS: AUTOMATED MONITORING OF CRITICAL PRODUCT FEATURES WITHIN IN-PROCESS CONTROL: LOWERING ASEPTIC RISK

Developing Countries Vaccine Manufacturers' Network

Vaccine Safety Monitoring
DCVMN Regional Training Workshop
Sao Paulo, February 2019

Tim Kram, General Manager,
Rommelag USA, Inc.



Disclaimer:
This presentation reflects the views of the author and should not be construed to represent Rommelag's views or policies

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**

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

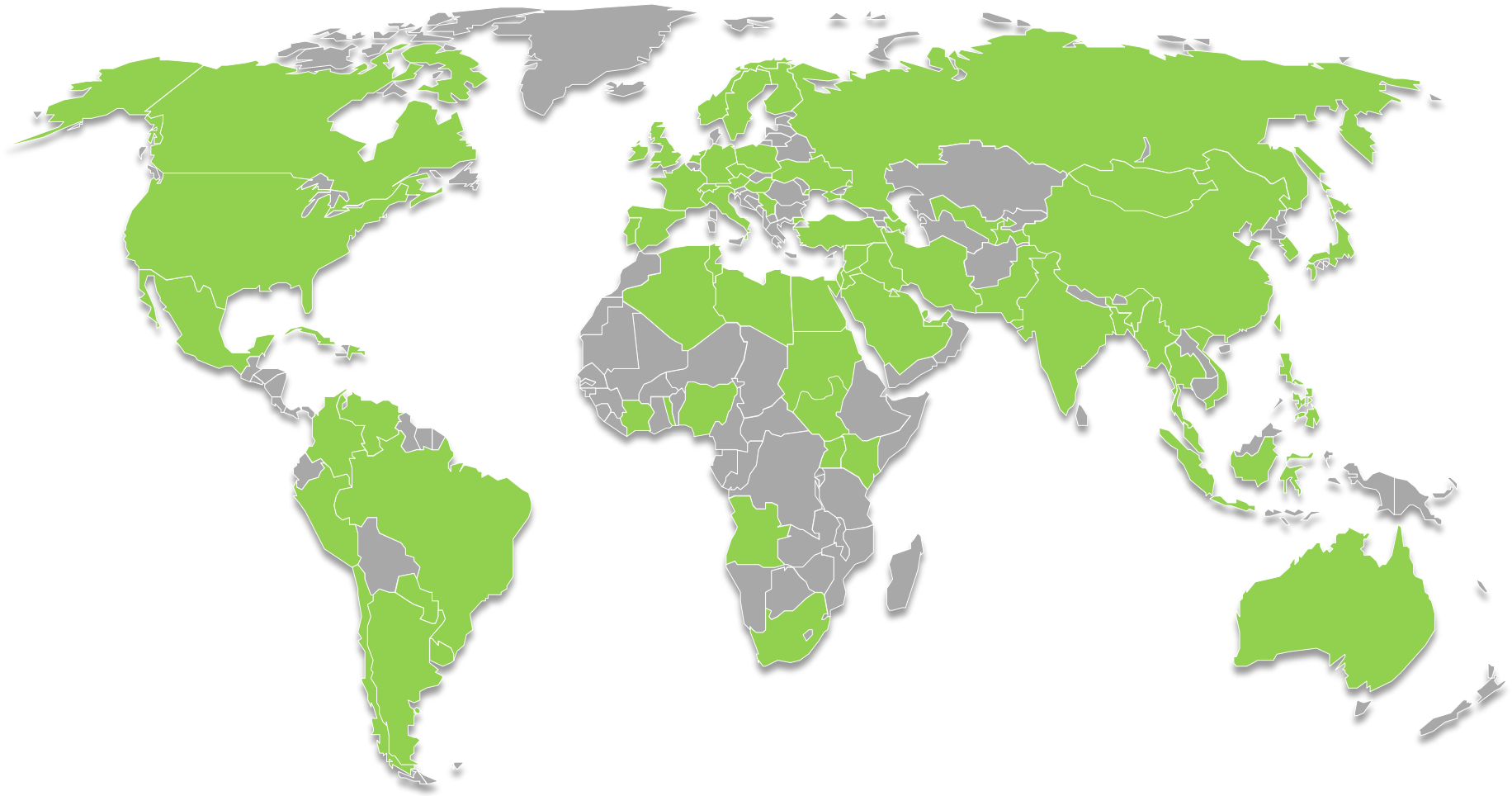
dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG CMO

ROMMELAG ENGINEERING

dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG - WORLD WIDE PRESENCE

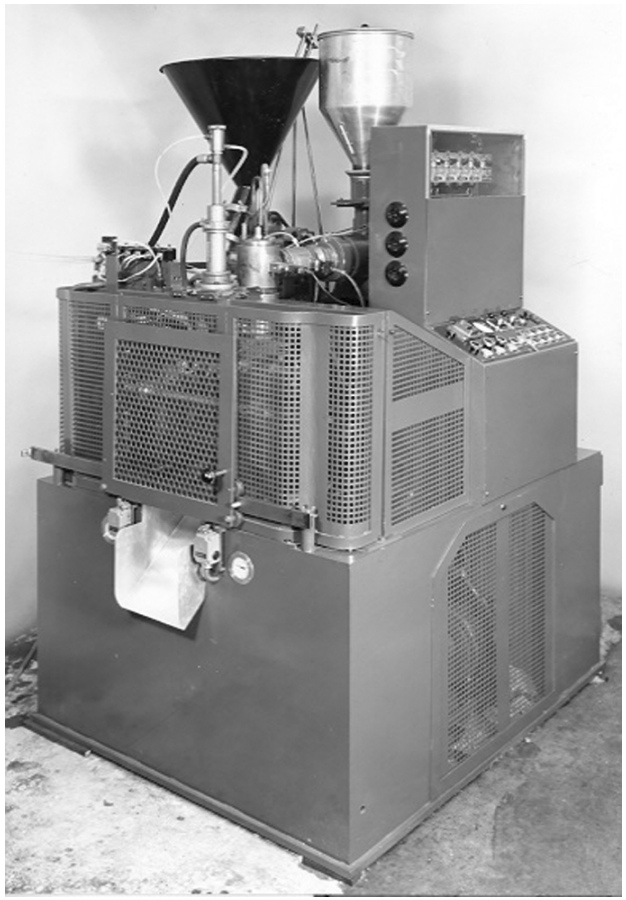


Blow/Fill/Seal system locations

ROMMELAG CMO

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.

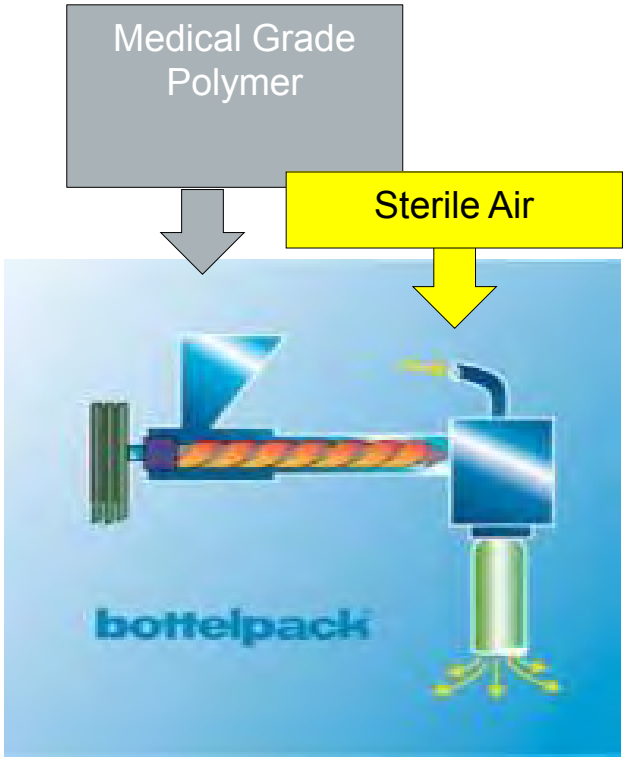
Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004

dcvmn
Developing Countries Vaccine Manufacturers Network

BLOW-FILL-SEAL (BFS) PROCESS: PARISON FORMATION

Blow/Fill/Seal Process: 4-13 seconds

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

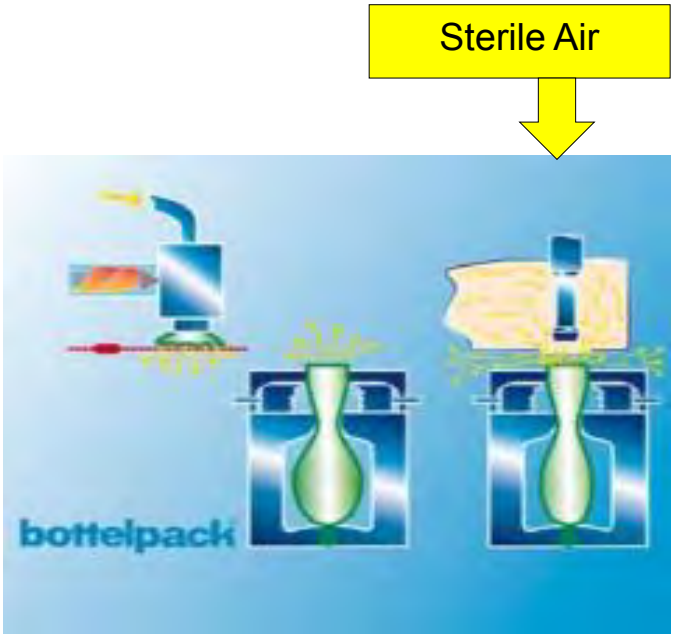


Melting polymer & extrusion of parison with sterile air

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



Transfer in mould and cutting (overpressure of sterile air)

BLOW-FILL-SEAL (BFS) PROCESS: BLOWING

Blow/Fill/Seal Process: 4-13 seconds

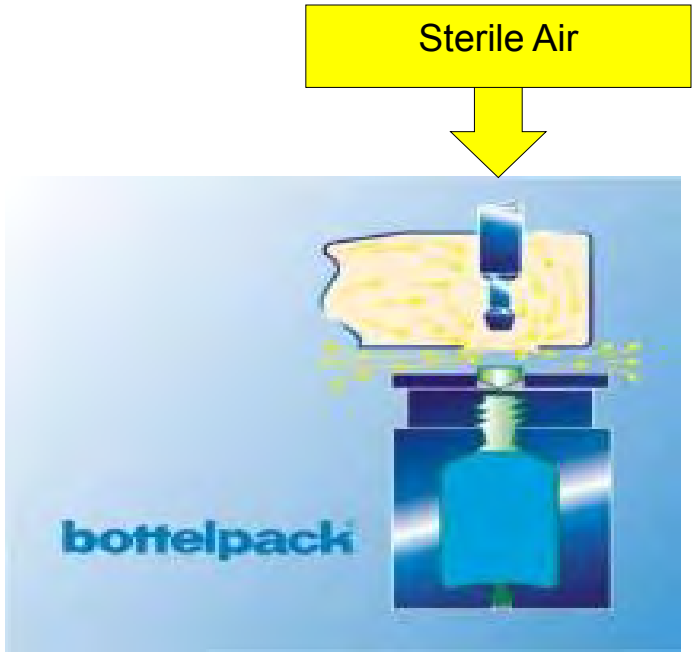
- Sterile filtered air blown into bottle to complete formation

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

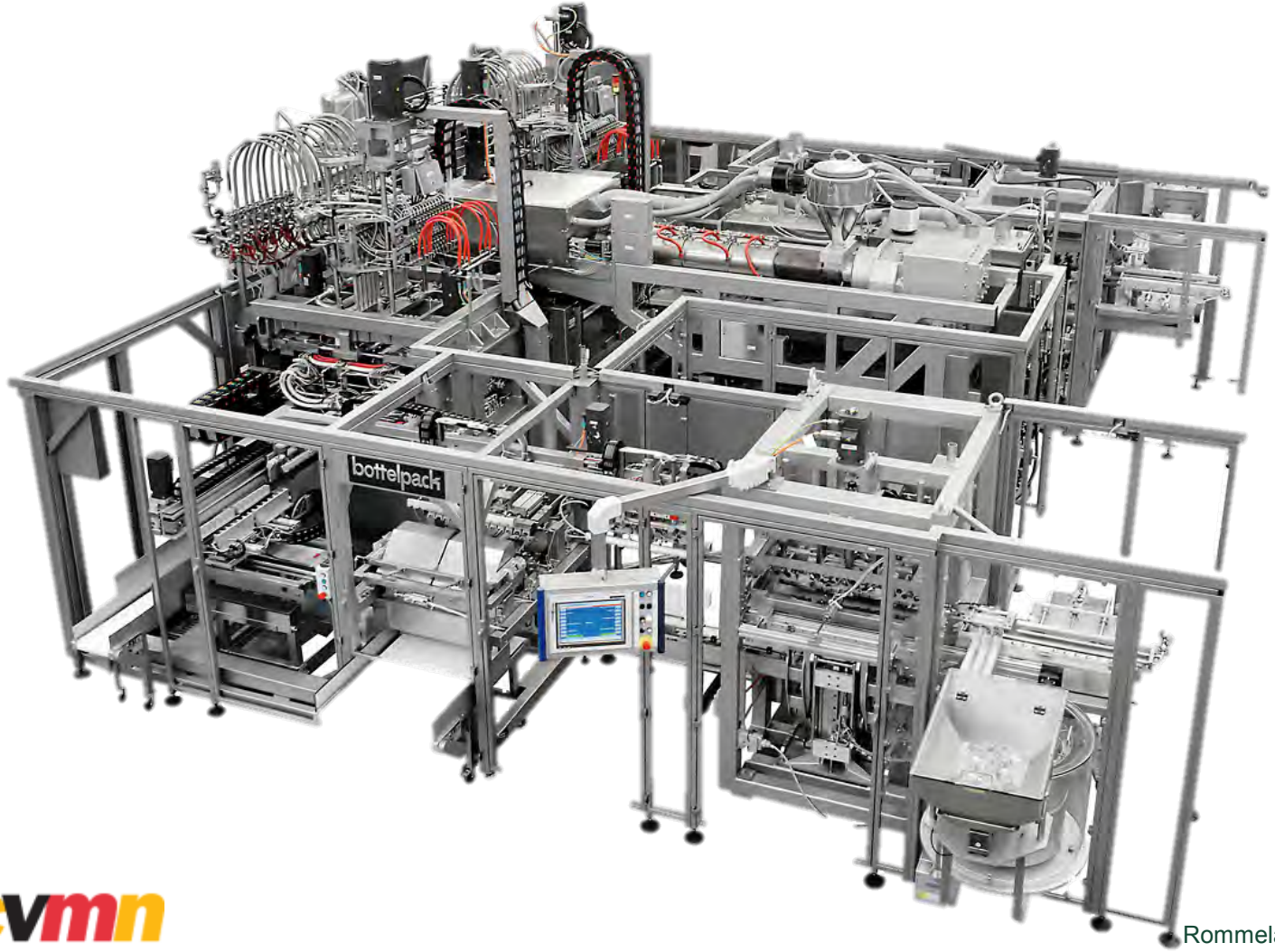


Filling and Container closing

VIDEO SHOWING BFS PROCESS 430

ACTUAL OPERATING ASEPTIC FACILITY TRC – COLUMBIA SC USA

MODERN BLOW/FILL SEAL TECHNOLOGY



dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG CMO

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].

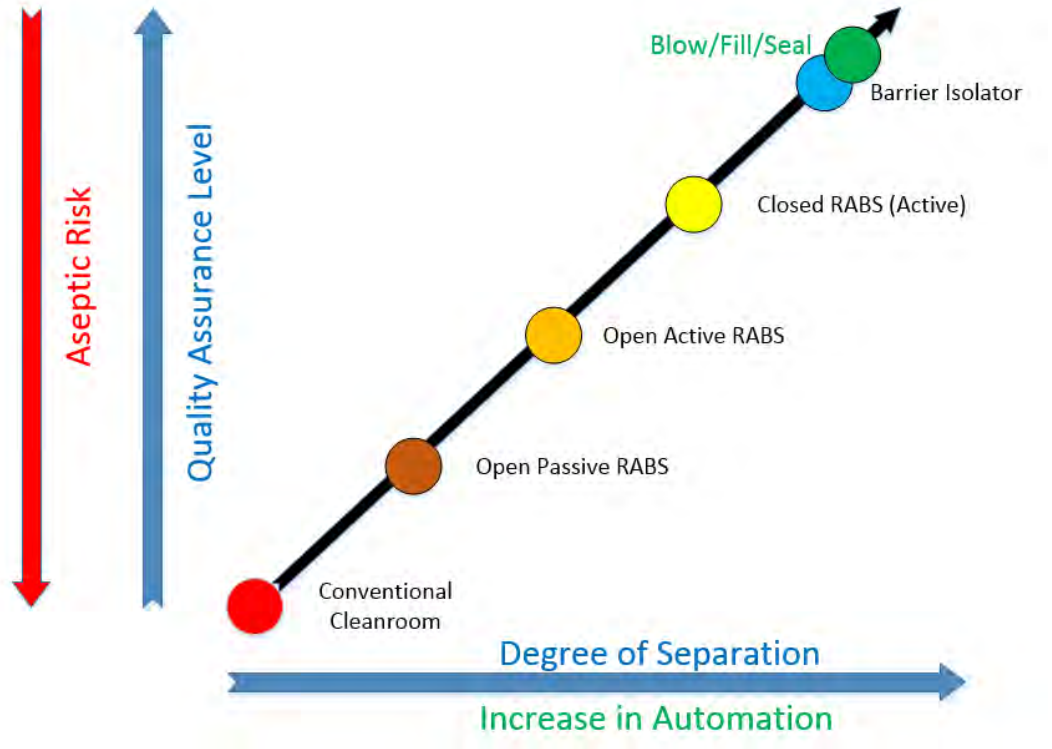
[1]FDA *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, 2004, Appendix 1, APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY

dcvmn
Developing Countries Vaccine Manufacturers Network

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



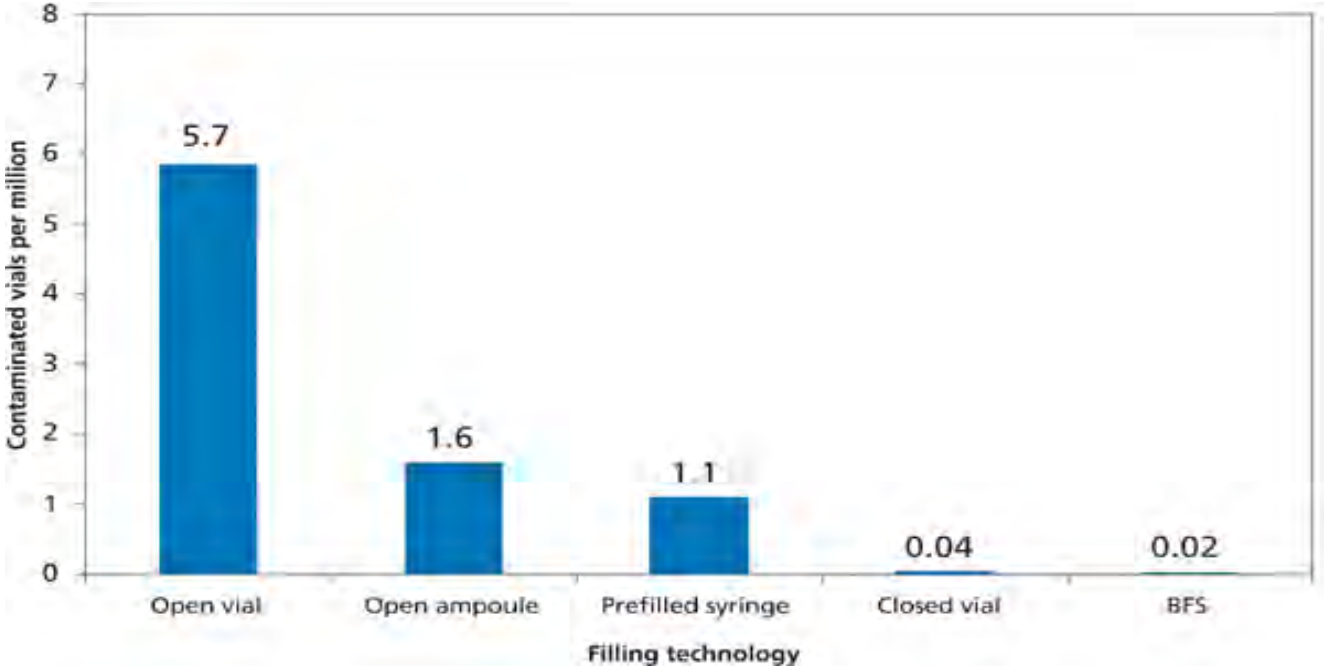
dcvmn
Developing Countries Vaccine Manufacturers Network

COMPARING RISK: BLOW/FILL/SEAL TO CONVENTIONAL GLASS SYSTEMS

Conventional Glass	Blow/Fill/Seal Plastic
Glass Breakage	Robust container
Silicone contamination	Silicone not required
Preformed container, stopper, cap	Newly Created Container
Transport to facility	N/A
Storage – days/months prior to fill	N/A
Decontamination step	N/A
Aseptic filling	Aseptic filling
Capping in classified area	N/A
Known particle contamination	Very low particle load (10x <)
Multiple integrated systems	Single automated system

MINIMIZED RISK OF CONTAMINATION BY REDUCING PARTICLES, PROCESS STEPS & HUMAN INTERACTION

Potential risk of contamination by filling technology based on air quality and exposure time



Verjans, B. Reed, C. (2012). "Assessing Filling Technologies for Contamination Risk." Biopharm International. 25(3), pp. 46-58.

dcvmn
Developing Countries Vaccine Manufacturers Network

STERILE PRODUCT PATHWAY

Automated CIP + SIP

- *As with any aseptic processing operation, it is critical that product contact surfaces be sterile. A validated steam-in-place cycle, or equivalent process, should be used to sterilize the equipment path through which the product is conveyed.*

FDA *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, 2004, Appendix 1, APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY

STERILE PRODUCT PATHWAY

Automated CIP SIP

- Standard Stainless Steel
- Automated CIP
- Automated SIP
- No manual operations
- Records maintained by the machine

dcvmn
Developing Countries Vaccine Manufacturers Network

PREVENTIVE MAINTENANCE

A well maintained machine is necessary

- *In addition to suitable design, it is important to establish an adequate preventative maintenance program. For example, because of its potential to contaminate the sterile drug product, the integrity of the cooling, heating and other utility systems associated with the BFS machine should be maintained and routinely monitored.*

- Highly automated and reliable machine. But it requires regular maintenance to ensure proper automation

FDA *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, 2004, Appendix 1, APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY

dcvmn
Developing Countries Vaccine Manufacturers Network

PRODUCT COMPATIBILITY

Common materials of construction

- LDPE and PP are the most commonly used materials with BFS technology
- Standard material Extractable studies available for common materials
- Stability trials used to show compatibility with plastic material
- Secondary barrier foils can be added to improve stability

PRODUCT COMPATIBILITY

Qualified Polymer

- LDPE is the most commonly used for Vaccines
- USP qualified
- DMF
- Qualified vendor
- Incoming QC checks
- Qualified storage area

VACCINE FACILITY CONSIDERATIONS

- Biosafety complies with the CDC requirements and the EU directive
- Environmental requirements for the clean rooms and BFS aligned with FDA and EU guidance.
- Room classification reflects ISO 14664 (international standard organization)

BIOSAFETY	GMP
Protect the employees	Protect the product
Minimize cross contamination	Prevent escape of materials
Production flow: Dirty to clean!	Production flow: Clean to dirty!

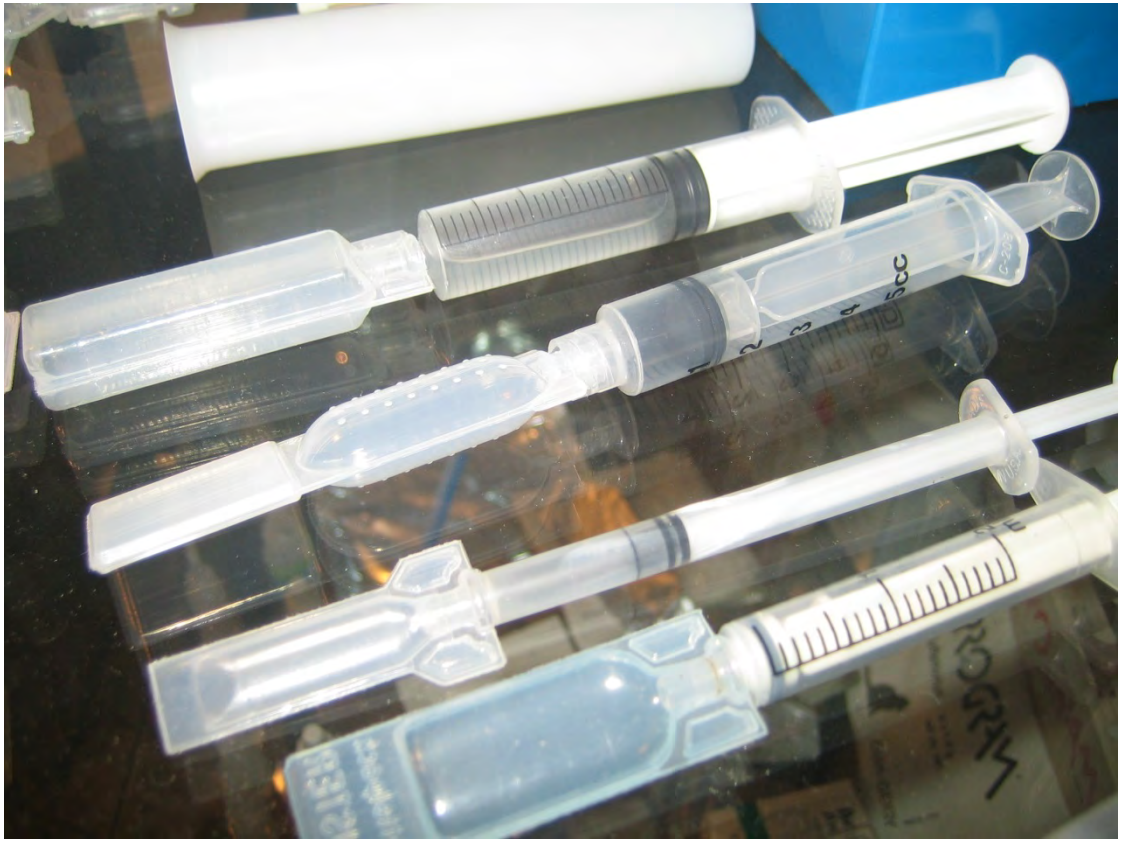
Bio Safety

dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG CMO

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

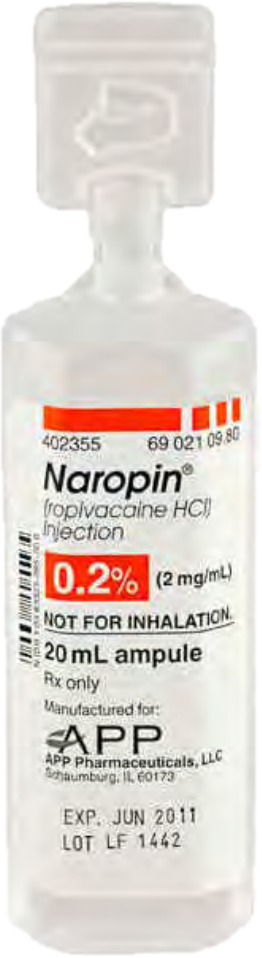
Multi-dose Ampoules
Unit-dose Ampoules

Eye Care, Nose Care, Ear Care, Contact Lense Cleaning

Ointments, Enemas, Gels

dcvmn
Developing Countries Vaccine Manufacturers Network

COMMON BFS PRODUCTS



Developing Countries Vaccine Manufacturers Network

COMMERCIAL CONTAINERS FOR INJECTABLE PRODUCTS LUER CONNECTION FOR SYRINGE

Rommelag CMO

- <1 mL
- Advanced Aseptic
- Other designs being developed
- Glass ampoule replacement

ROMMELAG CMO

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

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

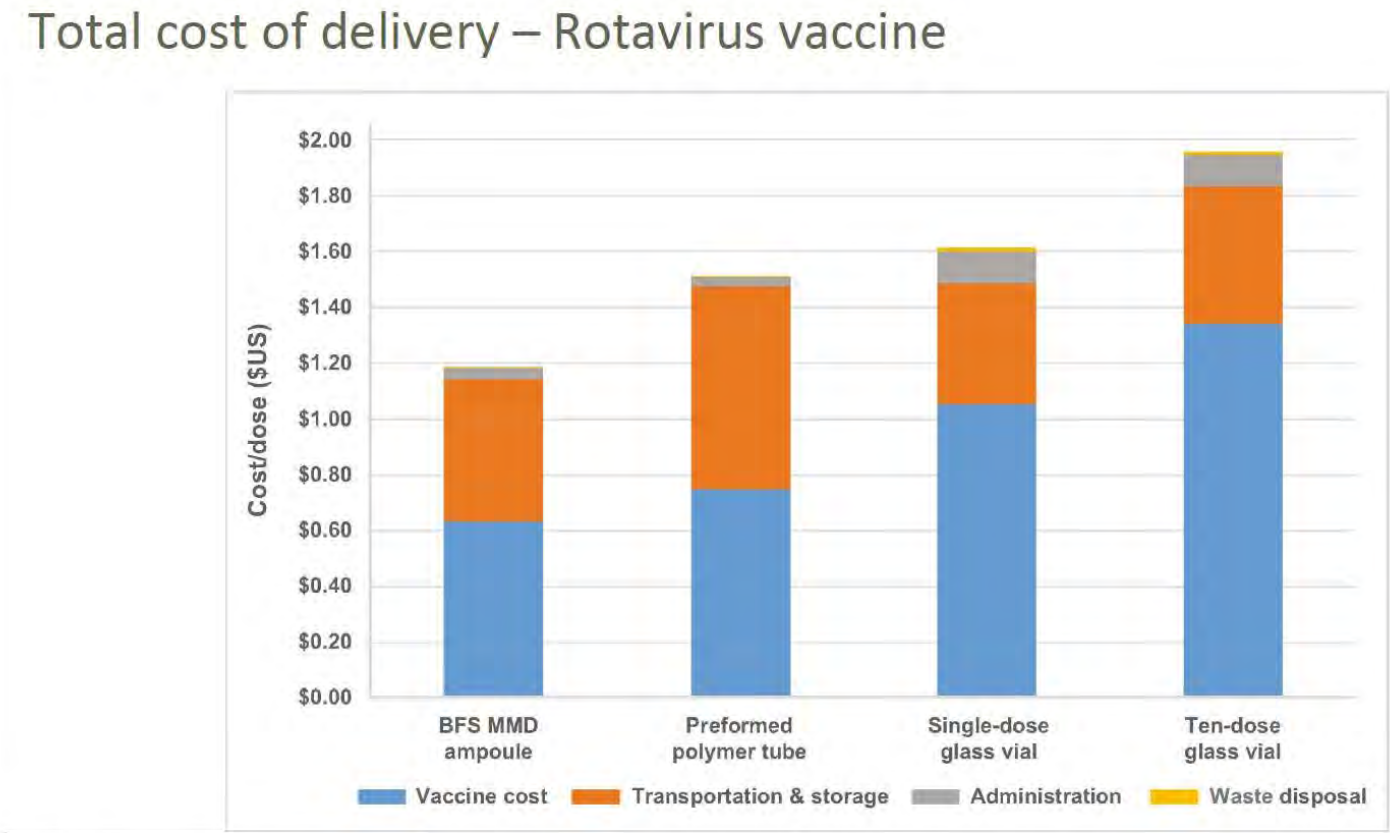
2012

- 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

PATH DEVELOPED PRODUCTION COSTS



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

dcvmn
Developing Countries Vaccine Manufacturers Network

ROMMELAG CMO

BILL AND MELINDA GATES FOUNDATION GRANTS

VACCINES: WHY BLOW FILL SEAL

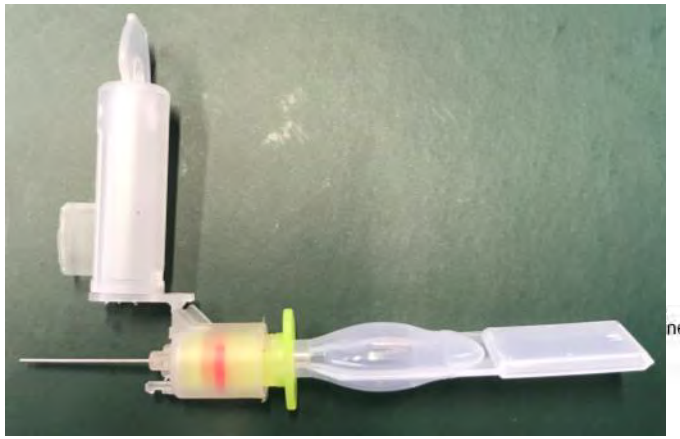
Container development grant

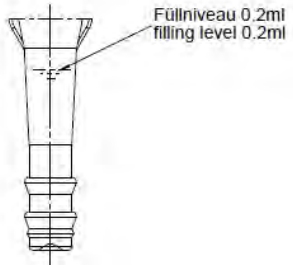
- Single dose per container:
  - No preservatives
  - Low wastage
  - Low breakage
  - Small cold chain footprint
- Low Cost of Goods
- Vaccine compatibility

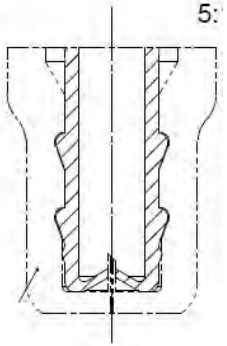
dcvmn
Developing Countries Vaccine Manufacturers Network

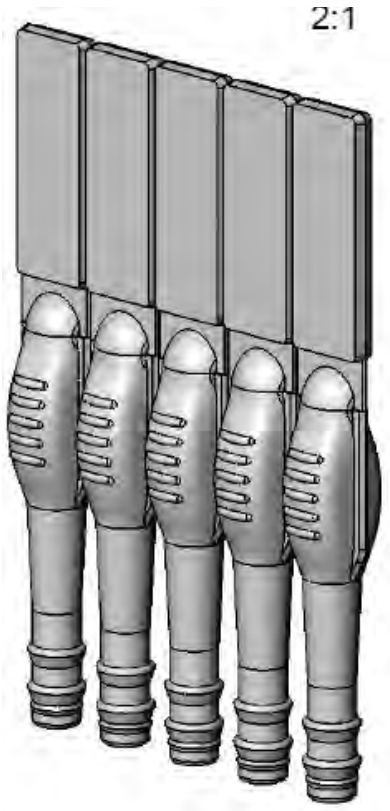
CPAD DEVELOPMENT GRANT

- **ApiJect Concept container**
  - Double needle design
  - Existing BFS container design









dcvmn
Developing Countries Vaccine Manufacturers Network

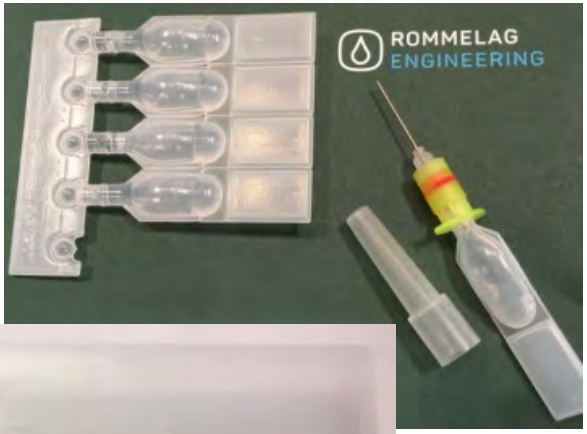
GLOBAL GOOD DESIGN – REDUCED CONTAINER SIZE OPTIMIZED FOR COLD CHAIN

dcvmn
Developing Countries Vaccine Manufacturers Network

GRANT TO DEVELOP NEW DELIVERY FORMS

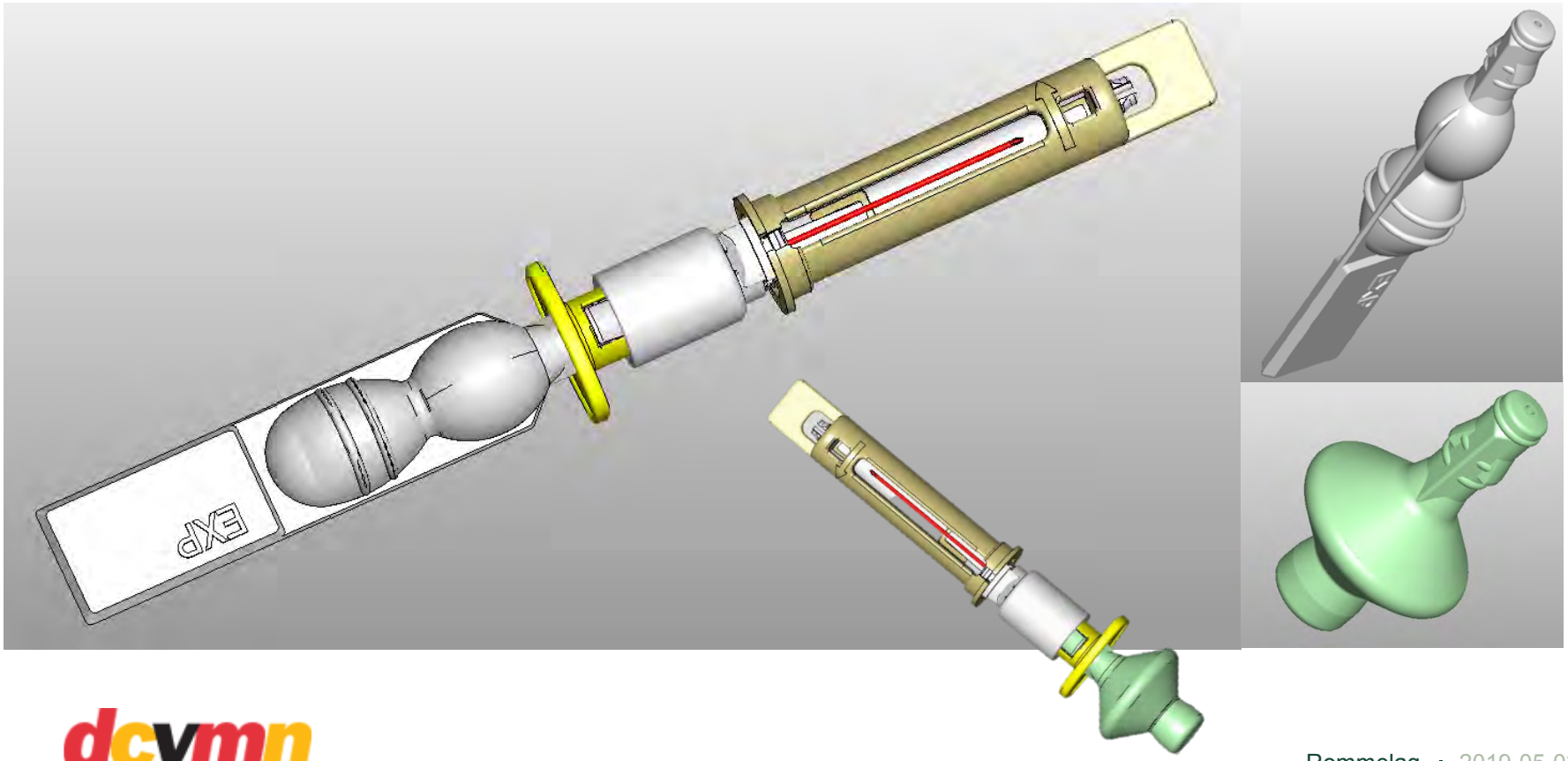
Rommelag Engineering

- 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



dcvmn
Developing Countries Vaccine Manufacturers Network

GRANT TO DEVELOP NEW DELIVERY FORMS

Rommelag Engineering

- ApiJect current design

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

INVENTPRISE VACCINE TESTING

Rommelag CMO

- Successful stability trial
- Injectable vaccine
- Containing adjuvant

- Supported by Global Good

Developing Countries Vaccine Manufacturers Network

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
ROMMELAG CMO – DEDICATED TESTING SITE

FDA inspected facility

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

dcvmn
Developing Countries Vaccine Manufacturers Network

NEXT STEP

ROMMELAG CMO

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.

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