Plenary Session 2: Landscape

Clinical Trials of Inhalable Dry Powder Aerosols of Vaccines Using Puffhaler® or Solovent® Active Dry Powder Inhalers

Robert E. Sievers, Scott E. Winston, Stephen P. Cape, Jessica M.H. Thrall, Nisha K. Shah, Jane Duplantis, Diane E. Griffin, Wen-Hsuan Lin, Sharad Agarkhedkar, Rajeev Dhere, Vivek Vaidya, Ravindra Muley, Prasad Kulkarni, Subhash Kapre, Ken Powell, Mark Papania and Paul Rota

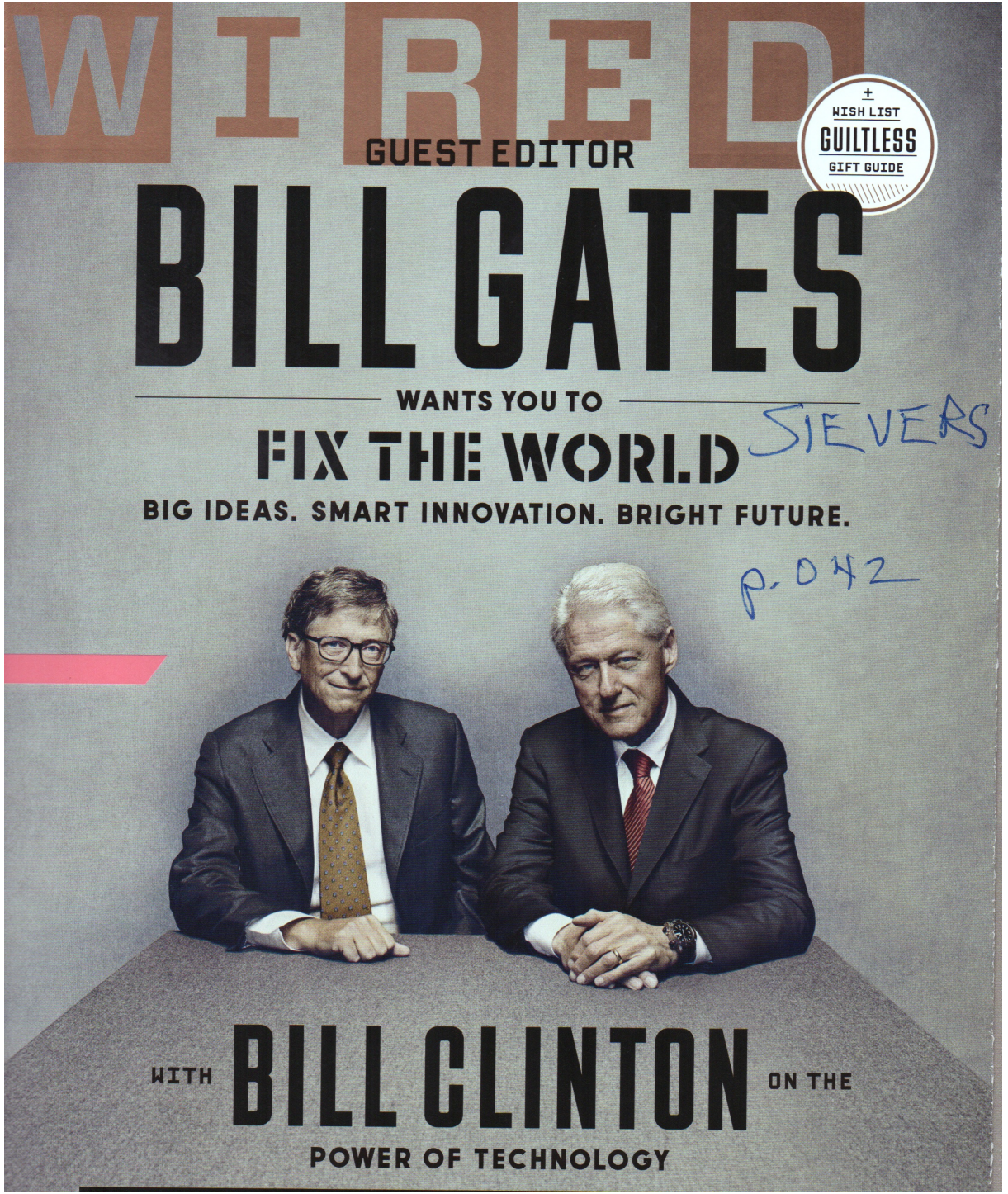
Next-Generation Vaccine Delivery Technology Meeting
Geneva, Switzerland

Name: Robert E. Sievers

Email: Bob.Sievers@colorado.edu

Title: Professor of Chemistry

Date: February 18, 2014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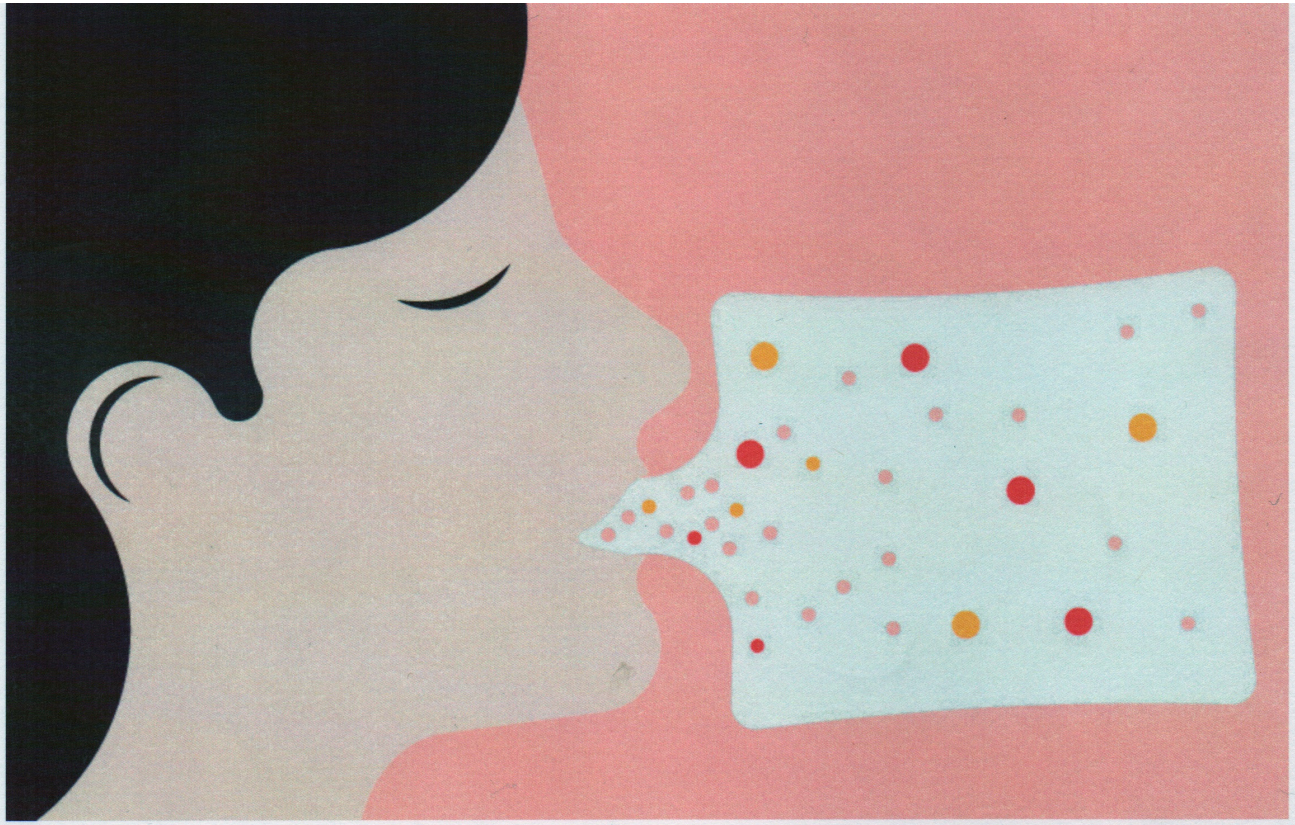
P. 042
WITH BILL CLINTON ON THE
POWER OF TECHNOLOGY



METHOD: Inhalation

COMPANY: Aktiv-Dry

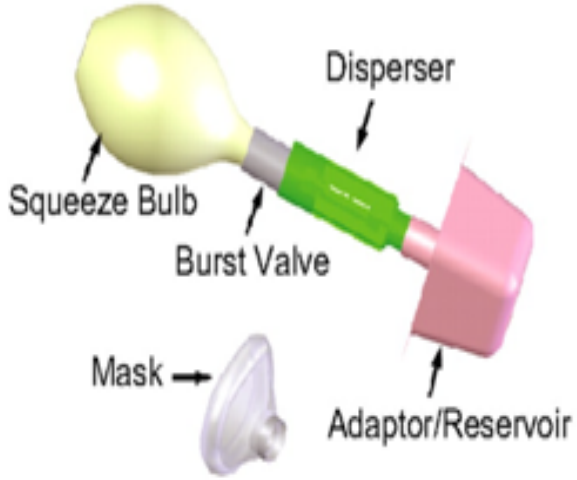
PRODUCT: PuffHaler

Bundled in blister packs and inhaled, the dry-powder measles vaccine targets the respiratory system—just like the virus. It's transportable and stable for six months without refrigeration.

STATUS: Inhalers conferred measles protection on monkeys; a trial with 60 human volunteers in India recently wrapped up.

Dry Powder Inhalers (DPIs)

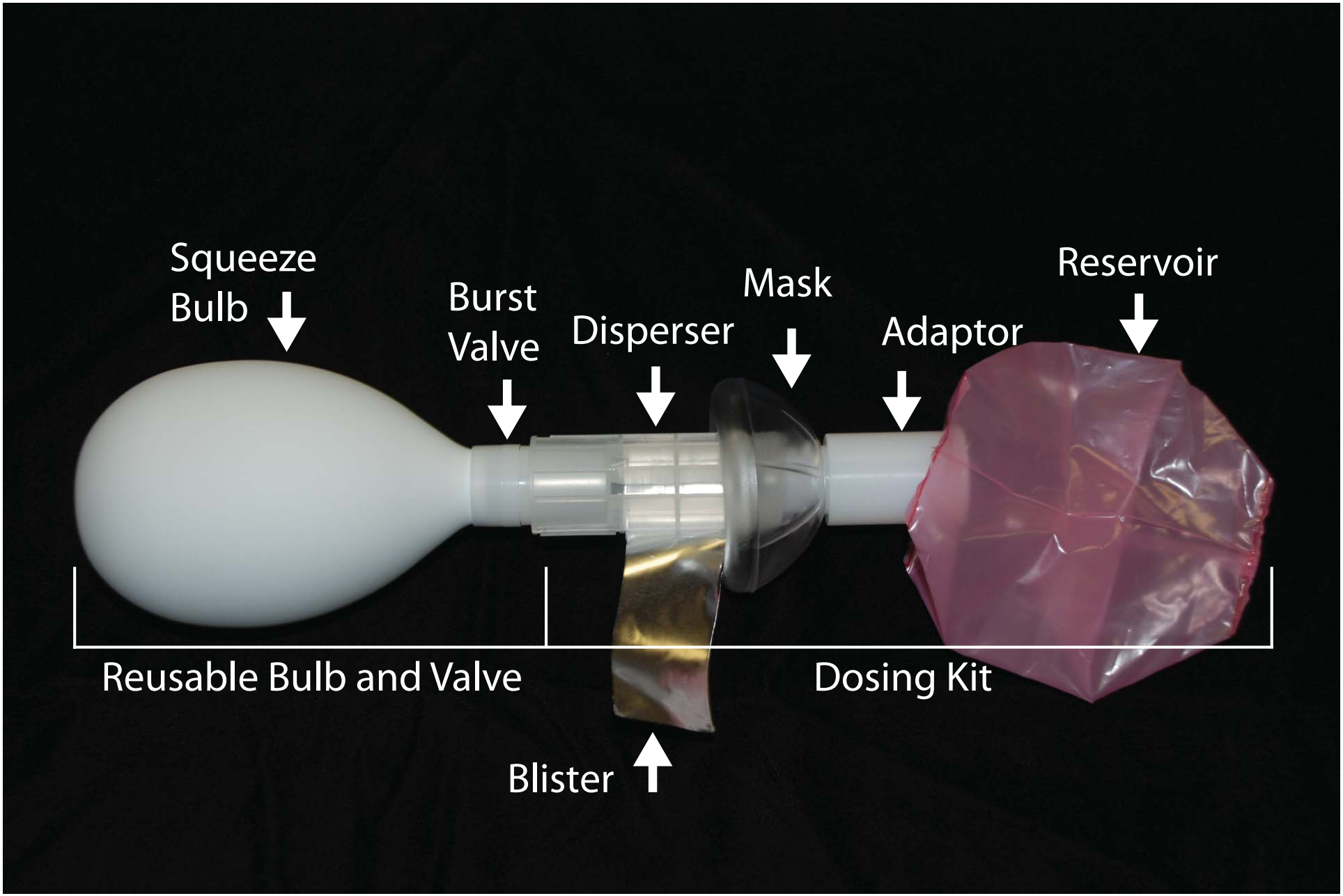
PuffHaler®



Solovent

PNAS

- Basic designs are usually dependent solely on the indrawn breath of the user to generate an aerosol. Modifications such as the PuffHaler® or Solovent may be used to disperse the aerosol into a spacer or reservoir from which the recipient can inhale the aerosol.
- A mask or a nasal adapter can also be attached when necessary.


Squeeze Bulb
Burst Valve
Disperser
Mask
Adaptor
Reservoir
Reusable Bulb and Valve
Dosing Kit
Blister


Peel blister containing dry powder…
PuffHaler®


Squeeze to load powder into reservoir…
PuffHaler®

Reservoir filled and ready to administer

PuffHaler®

Younger subjects may use mask with the reservoir

PuffHaler®

Grand Challenges in Global Health

AKTIV-DRY

DRY POWDER MEASLES VACCINE:

Macaque Study

Confirmation of protection by challenge with live virus:

- 14 months after immunization were challenged with wild-type measles virus and found protected against measles (at Johns Hopkins).
- Unvaccinated macaques developed rash and measles virus present in their bloodstream.
- **Immunized macaques exhibited strong measles-specific immune (memory T-cell) responses in contrast with the controls, which showed none.**

Grand Challenges in Global Health

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DRY POWDER MEASLES VACCINE:

Phase I Clinical Trails

- Project taken from conception (2005) to IND filing (2010)
- Technology developed at AD, CU, and BD transferred to SIIL
- Designed, installed, and qualified a GMP CAN-BD at SIIL for production of MVDP for clinical trials and multiple batches manufactured

- **Stability Studies:**
  - The myo-inositol-stabilized dry powder measles vaccine has a shelf-life of 4 years at 2 to 8°C
  - Serum Institute of India has shown stability at 25°C for 6 months.

- **Human Studies:**
  - As of March 2012, 60 adult volunteers inhaled dry aerosol vaccine using the PuffHaler or Solovent, or received the traditional measles injection.
  - No serious adverse events have been recorded to date.

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Aerosol Dry Powder Advantages over Liquid Vaccines

- Powders inherently more stable than liquids
- No water to transport or keep sterile
- Less chance of vaccine contamination
- Less vaccine wastage with single-dose packaging
- No needles and therefore no re-use, including lower risk of disease transmission
- No electricity/refrigeration or batteries required for delivery
- Potentially lower dose and therefore lower side-effects by vaccinating through the same route the disease uses.

Grand Challenges in Global Health

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Projected Savings Over 40 Years

WHO: $50M*

- Aerosolized Wet Mist

  = 20% savings by not using sharps

PATH: $100M*

- Needle-free, Jet Injection of current lyophilized vaccine

  = savings through waste management

Aktiv-Dry and CU: $700M

- Aerosolized Dry Powders = cut vaccine wastage, do not need sterile water for reconstitution, and cut needle-use, hazards and disposal problems

*Louis P. Garrison, Jr. (University of WA)

	MVDP Puffhaler® (n=20)		MVDP Solovent™ (n=20)		SMV (n=20)	
Days	28	84	28	84	28	84
Seroconverted (≥ 2 fold rise) n (%)	9 (45.00)	11 (55.00)	4 (20.00)	9 (45.00)	5 (25.00)	7 (35.00)
p-value*	0.1848	0.2036	0.7050	0.5186	-	-

*comparing MVDP with SMV

The safety evaluation looked at incidence of adverse events, rate of notable vital sign abnormalities, abnormal clinical laboratory test values, and unusual findings in physical examinations.

- Serum concentrations of measles antibody activity were determined by ELISA and summarized for each group by a commercial ELISA kit (Trinity Biotech Captia™ Measles IgG).
- The following immunogenicity parameters were reported:
  - Proportion of subjects on Day 28 and Day 64 showing seroconversion defined as a 2-fold rise in IgG titers with respect to baseline
  - Geometric mean concentration (GMC, IU/L on Days -7, 28 and 84) of measles IgG antibodies

Grand Challenges in Global Health

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CAN-BD

Carbon Dioxide Assisted Nebulization with a Bubble Dryer®

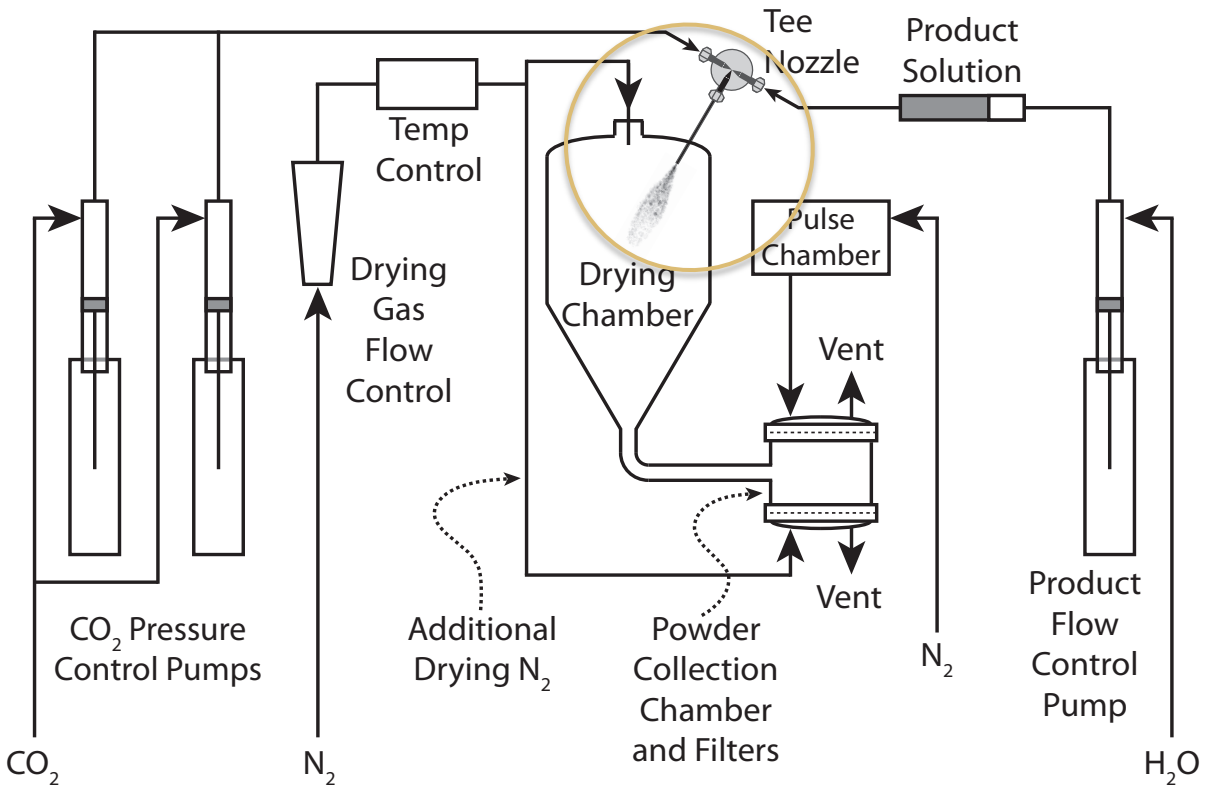
Gentle spray drying process variant that utilizes pressurized CO_2

- ✓ Fine dry micro-particulates
- ✓ Lower processing temperatures
- ✓ High throughput (400 million doses)

Grand Challenges in Global Health

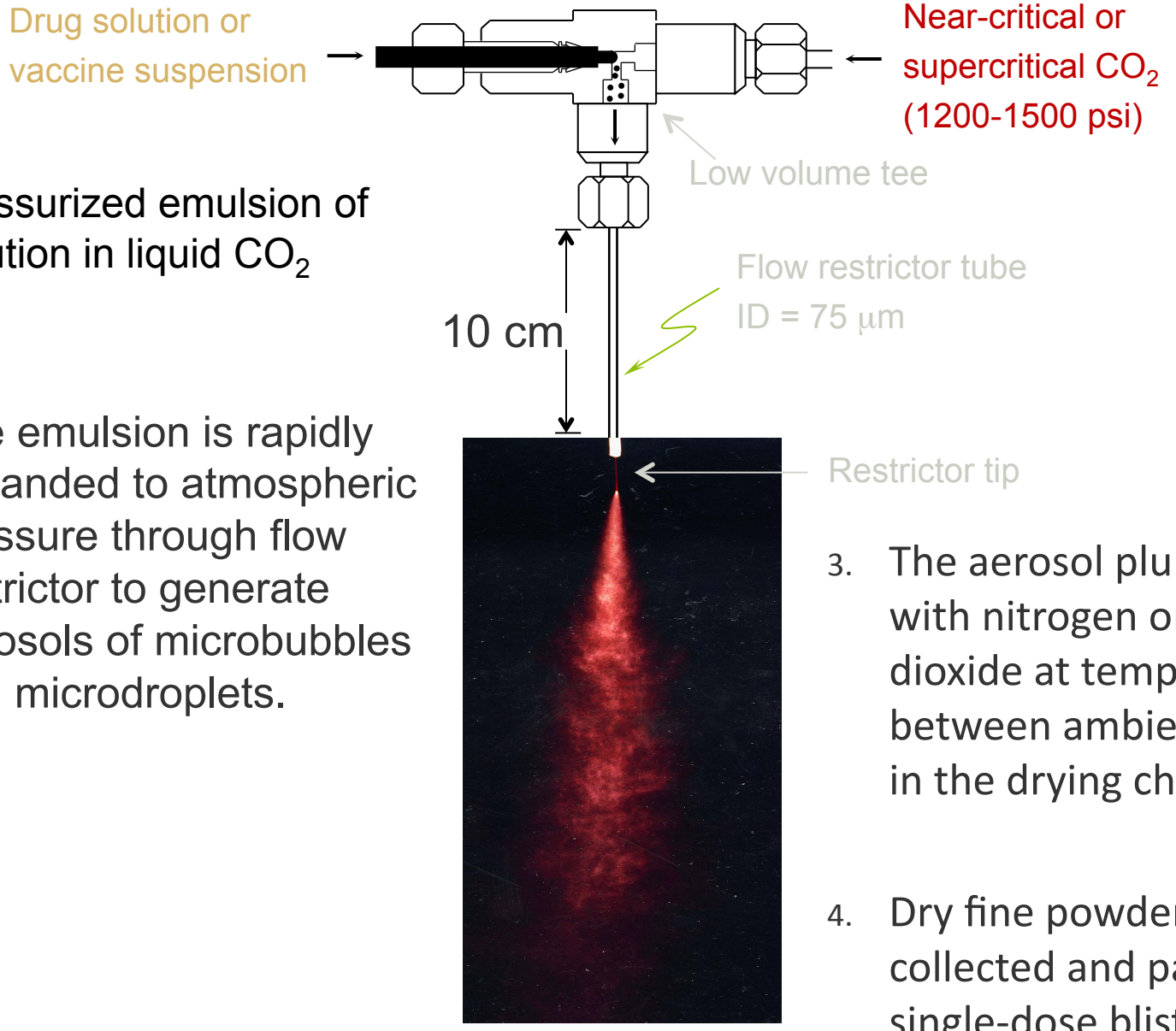
AKTIV-DRY

Carbon Dioxide Assisted Nebulization with a Bubble Dryer®



AKTIV-DRY

CAN-BD Nebulizer



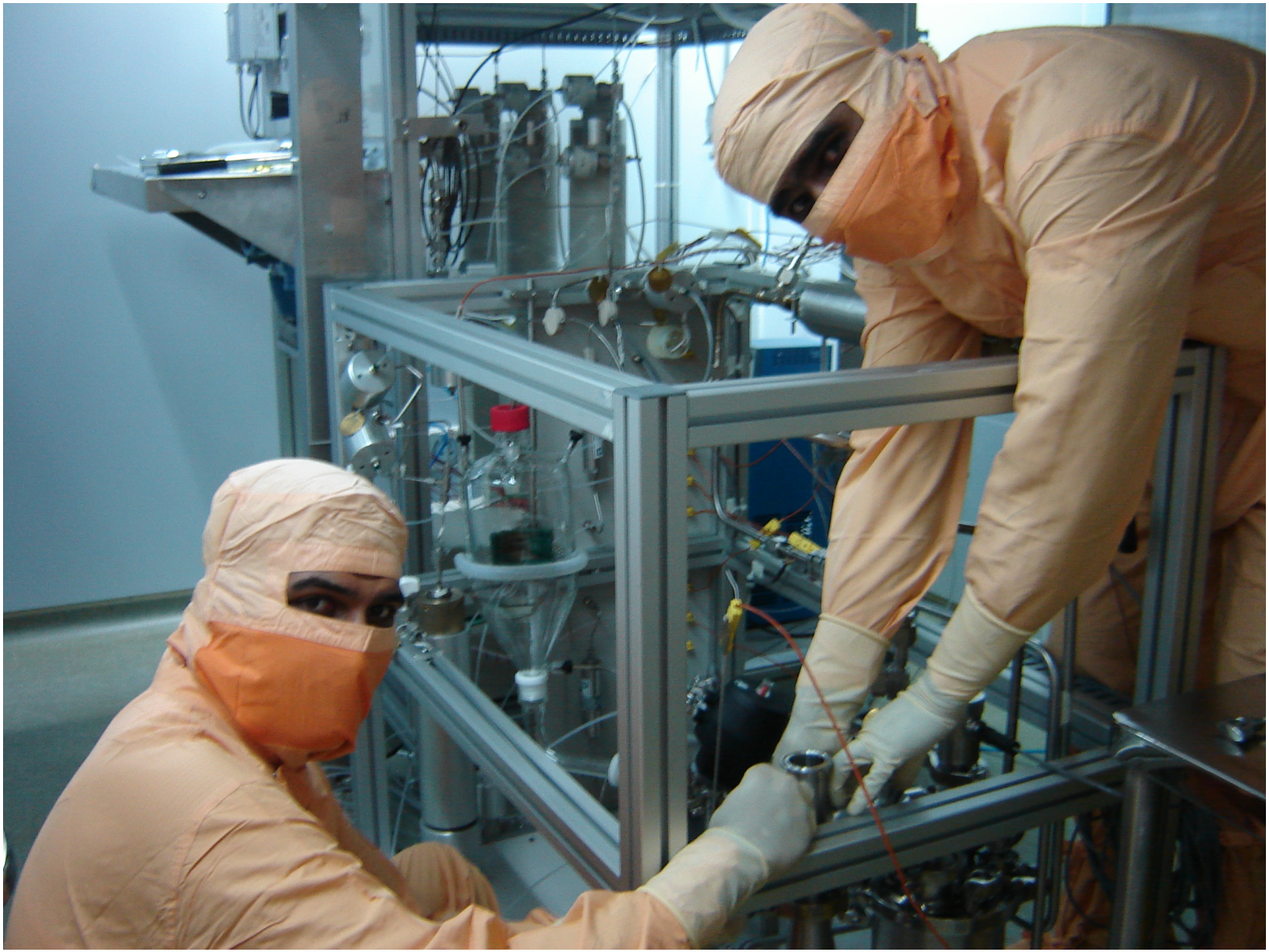
1. Pressurized emulsion of solution in liquid CO_2

2. The emulsion is rapidly expanded to atmospheric pressure through flow restrictor to generate aerosols of microbubbles and microdroplets.

3. The aerosol plume is dried with nitrogen or carbon dioxide at temperatures between ambient and 70°C in the drying chamber

4. Dry fine powders are collected and packaged in single-dose blister packs or capsules

GMP Bubble Dryer at Serum Institute of India



Grand Challenges in Global Health

AKTIV-DRY

FNIH Grand Challenges in Global Health Initiative:
Inhalable Measles Vaccine Dry Powder

- $20 M International collaboration
- Aktiv-Dry led a 30-member interdisciplinary team of immunologists, engineers, scientists, physicians, consultants, business, and regulatory specialists

- Aktiv-Dry (AD)
- University of Colorado
- Serum Institute of India Ltd
- CDC
- Sristek
- Becton-Dickinson Technologies
- Avanza Laboratories
- Johns Hopkins
- University of Kansas

<Technology Name>: Mechanism of Action

Overview:

- <As required describe technology mode of action from performance perspective both engineering / immunological>
- <Historical reference of use could also be included on this slide>

Insert representative photo / data summary as applicable / video of action

<Technology Name>: Specific Example

Description:

- <Overview of technology – to include manufacturer name>

Insert technology photo

Status:

- <brief overview – technical status, data overview (preclinical/clinical), regulatory, market availability, pricing/cost)

<Technology Name>: Benefits and Challenges

Benefits:

- <highlight benefits and strengths of technology>

Insert representative technology photo

Challenges:

- <highlight challenges facing technology class – include potential barriers to programmatic use, technical weaknesses , etc. as applicable>

<Technology Name>: Opportunities and Way Forward

Global Public Health Challenge:

- <Highlight global public health challenge that technology address>

Technology Availability:

- <Probability of technology availability for program use in the next 10 – 20 years if not sooner>
- <What is needed to realize availability of technology?>
- <Suggestions for the way forward>

Insert representative photo / data summary as applicable / video of action