

**CEPI**



# **COVID-19 Vaccine Manufacturing Presentation for DP Workshop**

27 July 2020

# Need for Workshop

The COVID-19 pandemic is creating unprecedented challenges for the rapid development of vaccines. Billions of doses of vaccine will be needed over the next 12-24 months, and this scale-up has the potential to create bottlenecks in some areas (e.g. fill/finish) and shortages in the supply chain (e.g. vials & stoppers). As such, CEPI has initiated the creation of a DP Network to ensure sufficient fill/finish and glass vial capacity for vaccine developers. The vaccines developed will be deployed across the globe in high resource settings, as well as low resource settings. Thus, it is important that developers understand and align on the key images and presentations suitable for use in these settings.

The COVAX Vaccine Manufacturing SWAT team is inviting representatives from key vaccine developers who indicated a commitment to global distribution to a half-day workshop to determine interest in participation in the DP Network and to align on key DP images and presentations.

# Objectives of DP Workshop

- Present to vaccine developers the various DP image options (20R glass vials, smaller glass vials, bags and BFS) and share user needs (GAVI, MSF, UNICEF) and available regulatory feedback.
- Present to developers the proposed Drug Product network
- Listen to the developers for feedback on the proposed options for the DP image
- Obtain specific feedback from the developers on:
  - the interest and commitment to use the 20R multidose glass vials / stoppers or other back-up product images
  - the interest and commitment to use the DP network
- Invite the developers committed to use the DP network to the second workshop (3<sup>rd</sup> August)
- Propose what studies COVAX facility might fund to address concerns (Example: study on coring and container closure integrity if value added; human factors studies on BFS and bag images)

# Agenda

- Teleconference Setup, Introductions & Meeting Guidelines/Goals - 20 min
- [COVAX: Overview](#) – 10 min.
- User Needs/Preferences – 30 min.
- *Break – 15 min*
- [Lead presentation](#) (preservative-free, 20 dose multi-dose glass vial/MDV) – 40 min
- [Examples of alternative backup presentations](#) – 30 min
- *Break - 15 min*
- [Overview of DP Network](#) – 30min
- [Stability, Shelf-Life & Cold-Chain requirements](#) – 20 min
- Closing/next steps – 15 min

# Roles and expectations of workshop participants

## Role:

- Represent your organization in the context of the global vaccine response to COVID-19
- Enable and support decisions so that we can quickly settle issues and continue to make progress. You should be empowered to represent the position of your organization during the meeting. Note: August 3rd meeting is where most decisions/commitments will be codified.

## Expectations:

- Come prepared: Ready to discuss specific assignments, if any have been assigned to you
- Be engaged: Ask questions; State any significant objections so that they can be noted/addressed
- Accept guidance/decisions from the meeting leader:
  - Some topics may be moved to a 'parking lot' for follow-up;
  - Discussions may need to be curtailed to allow for new topics to be discussed;
  - Decisions rarely have 100% support; follow-up off-line if there are lasting concerns about a decision

# Meeting Goals

**Determine if your organization wants to participate in one or more of the following programs**

- DP Network
- Access to glass vials
- MEDinstill Bags
- Blow-Fill-Seal (BFS)

**Product Image:**

- Assuming glass vials, is a 20-dose vial presentation acceptable?

# Introductions

We will designate one representative from each organization to introduce all their participants

Organizers: BMGF: David Robinson; CEPI: Ingrid Kromann and Nicolas Havelange

# Meeting rules & guidelines

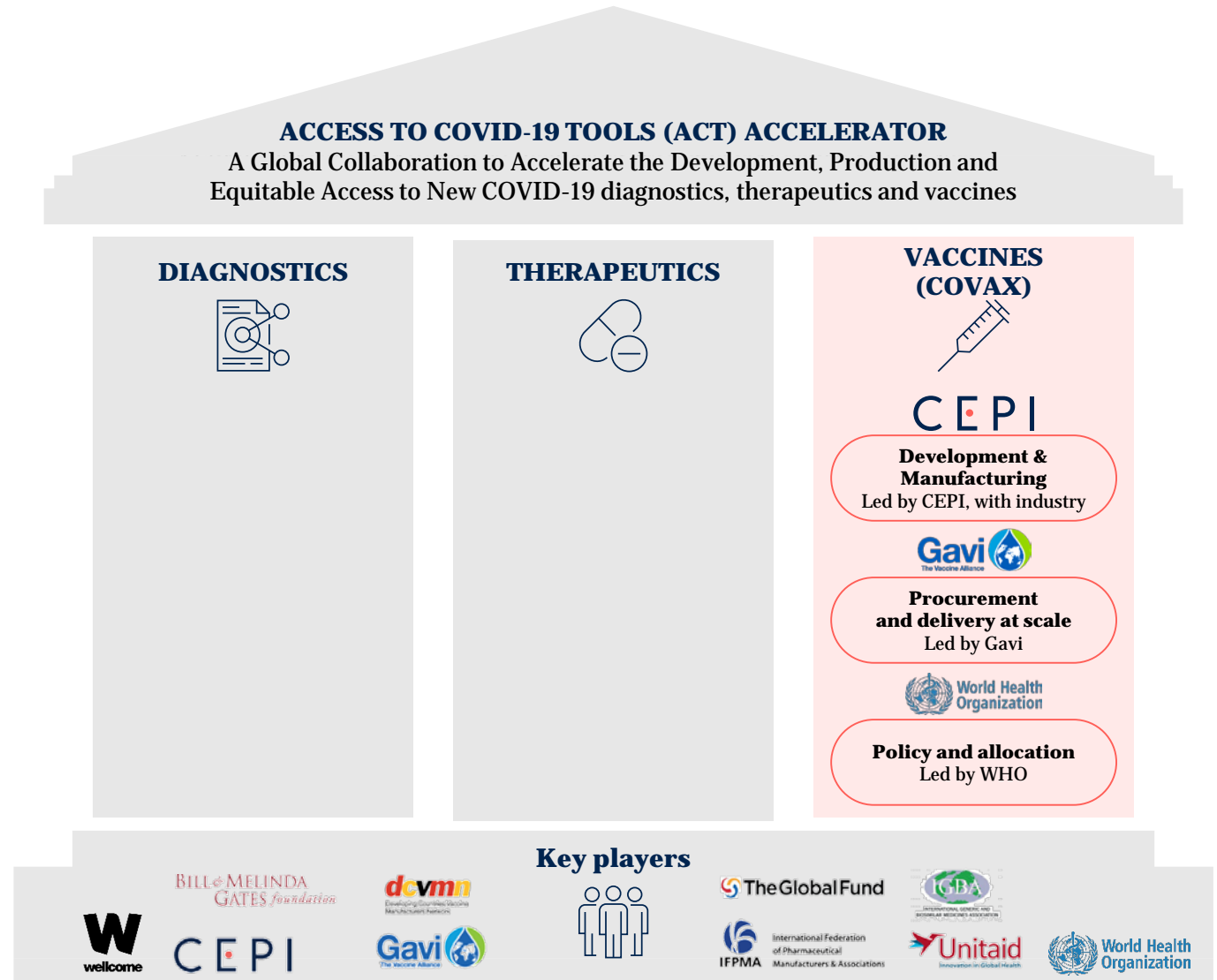
- Stay on mute unless you are presenting or asking a question
- Please click the 'raise your hand' button if you would like to speak. We ask participants to share questions/comments verbally during the Q&A as much as possible
- Please state your name before sharing a comment or question
- Use the Chat function for short questions. Moderators will monitor the Chat & raise questions for you
- Please save questions for the relevant part of the agenda, focusing comments on the topics currently being discussed
  - Specific regulatory questions will not be addressed at this workshop – however, if you type your regulatory questions using the “Chat” function, we will collate these and present them to the Regulatory Advisory Group (RAG) so that they are aware of the regulatory questions that the group has.
- Note that we will be capturing decisions and action items arising from the discussions; we will not be capturing detailed meeting minutes for a 4 hour-long session.





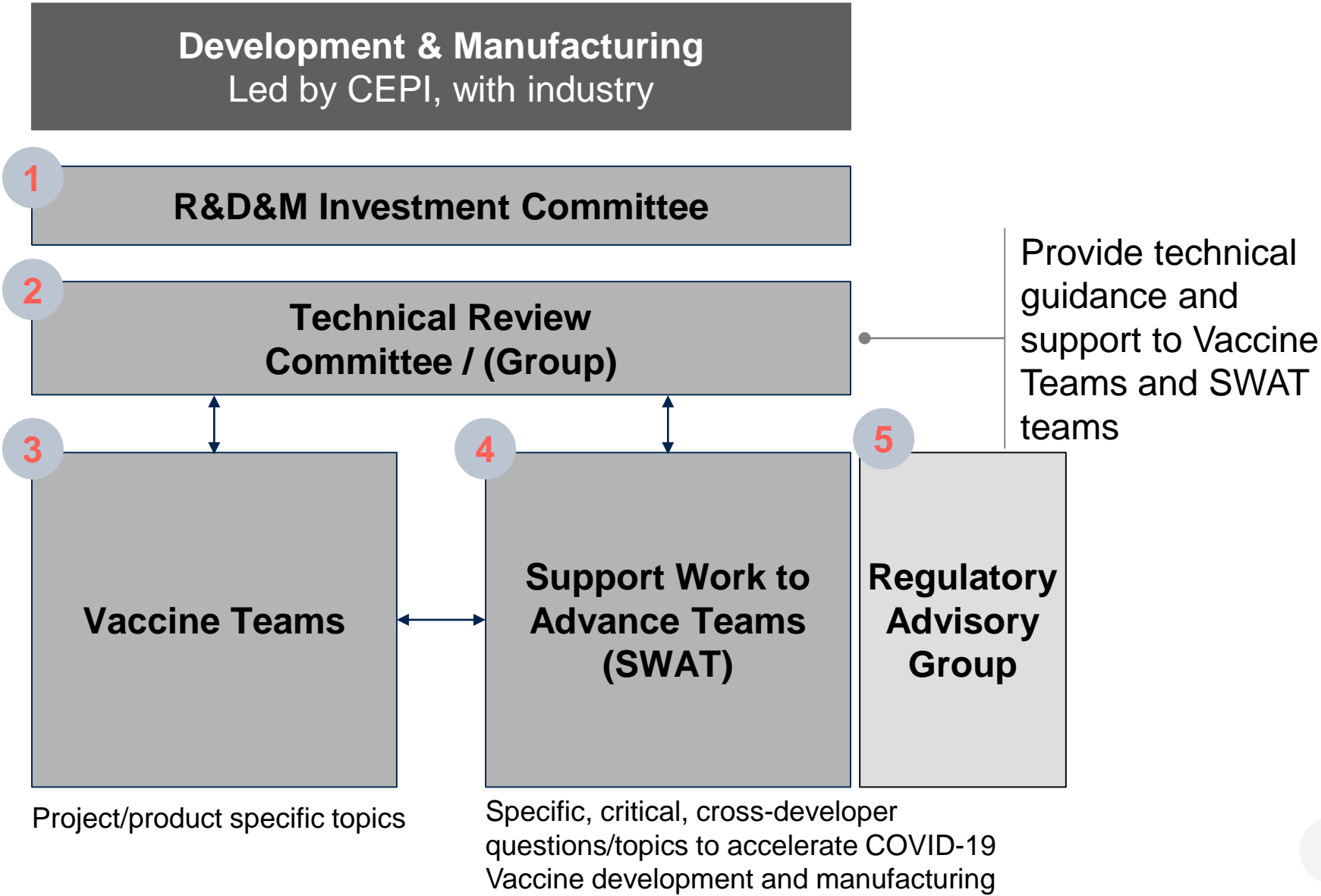
# **ACT-Accelerator: COVAX pillar (vaccines)**

# Access to COVID-19 tools (ACT) accelerator



# The COVAX Development & Manufacturing workstream has 5 functional groups

Manage allocations of funds for R&D and manufacture  
Multidisciplinary group with industry expertise



# SWAT teams – Manufacturing : working groups and activities

Working groups	Proposed activities [targeted due date (for first version)]
DP/DS Scale up and out	<ul style="list-style-type: none"><li>• <b>Drug Product strategy:</b><ul style="list-style-type: none"><li>– DP facilities identified and strategy described [Aug 2020]</li><li>– CMC: e.g., validation strategy (process)</li></ul></li><li>• <b>Drug Product capacity:</b><ul style="list-style-type: none"><li>– manufacturing network established and capacity booked (F&amp;F activities) adjuvant and LNP capacity identified</li></ul></li><li>• <b>Drug Substance strategy:</b><ul style="list-style-type: none"><li>– antigen scale-up and scale-out plans [Oct 2020]</li><li>– CMC: e.g., validation strategy (process)</li></ul></li><li>• <b>Drug Substance capacity:</b><ul style="list-style-type: none"><li>– manufacturing sites matched and capacity booked</li></ul></li><li>• <b>Manufacturing requirements for emergency use</b><ul style="list-style-type: none"><li>– regulatory advices</li></ul></li><li>• <b>Addressing regulatory challenges</b> related to DP and DS scale up and out</li></ul>
Supply Chain/labelling/barcoding	<ul style="list-style-type: none"><li>• <b>Supply chain strategy</b> [Sep 2020]<ul style="list-style-type: none"><li>– Labelling strategy, raw materials secured (i.e. vials, stoppers, single use items, media, resins)</li><li>– PQ/EUL Labelling/counterfeit countermeasures</li></ul></li><li>• <b>Addressing regulatory challenges</b> related to supply chain</li></ul>
Release assays – OMCL and Authority Batch release	<ul style="list-style-type: none"><li>• <b>Potency assay requirements</b><ul style="list-style-type: none"><li>– approach regulatory agencies for advice [Q2 2020]</li></ul></li><li>• <b>Procedure to allow timely national batch release</b> – Mutual recognition [November 2020]</li><li>• <b>Support setting up analytical capacity</b></li><li>• <b>Addressing regulatory challenges</b> related to release assays and Authority Batch release</li></ul>

# User Needs/ Preferences

*Delivery Team Feedback to DP Image Questions  
Feedback from 14 July and 21 July 2020*

# General Feedback and Concerns

- Appreciation for the early engagement
- Many unknowns on cold chain requirements
- Need for data-driven decision making (like cold chain capacity build)
- Availability of syringes
- Demand dynamics – different images may be needed for different phases & populations – HCW, mass immunization, on-going routine immunization, remote villages
- Multiple images will be used by manufacturers (1, 5, 10, 18 doses/vial)
  - request for multiple of 5 for ease of tracking/accounting/planning
  - higher MDV images possible with preservative
- Co-formulation of some products may be challenging in field (training); cold chain footprint for “bundled vials”, safety concerns for reconstitution errors.

# General Feedback and Concerns

- VVM preferred
- Bar-coding preferred
- Information on various images in field and how to use
- For product requiring ultra-low cold chain, is the image/packaging compatible with our shipping containers?
- Early engagement with WHO team and PSPQ requirements
- It is not yet clear exactly how mass immunization will be done (possible exception is school-aged children).
- Delivery of 1BN doses in LMIC/LIC in <12 months is unprecedented (2.7 M doses per day for 365 days)

# Multi-dose vials

- MDV are generally accepted in LMIC/LIC as a standard image.
- There are PQ-approved 20-dose vial images
- There is always a concern of wastage with larger MDV images, but this should be manageable for the short term for COVID19 due to the high demand and mass vaccination needs.
- There has been prior use of 50 dose vials, but these are largely discontinued
- There is a preference to 18 doses in a 10R vial vs. 20 – 45 doses in a 20R vial. (Multiples of 5 may be better.)
- Some questions on coring, but generally manageable
- After mass vaccination, smaller, preserved MDV images are preferred.
- Can there be a mix of vial size options?



## 200-dose bags

The bag may be interesting to support mass vaccination but creates multiple questions/concerns:

- Lack of compatibility with current auto-disable syringes.
  - Wastage (if it must be used within 6 hours)
  - Training – new device during a chaotic time will be challenging
  - Time out of cold chain (standard practice is to not return product to cold chain after use)
  - Container closure validation potential to allow use for > 6 hours
  - Risks of cross-contamination between patients
  - Lack of PQS standard
  - Perception of different presentations being used in different country groupings
  - Concern about use of completely novel technology during a pandemic
- 
- It would be helpful to have samples to better understand the device and its use. → samples being produced.
  - Disposal of bags (different than vials/syringes)

# CEPI supporting gap resolution

- Transparency on planning, product availability, cold chain requirements, etc., as the portfolio evolves
- Data collection/validation for 200-dose bag:
  - Auto-disable needles
  - CCI data over 200 uses and several days
  - In-use stability with products (40C for several days)
  - Development of training materials
- Alternate approaches to increasing supplies
  - BFS, plastic vials, additional glass capacity



# Lead Presentation

# CEPI's early learnings regarding capacity



- **>10BN doses of DS capacity**
- **>4BN doses of capacity for glass vial filling** at 20-dose/vial
- **Global shortage of tubing glass** – used for pharmaceutical vials
  - CEPI have procured the remaining global capacity
- Chosen 20R vials to maximize doses during high demand vaccination campaigns
- **Agreed to develop smaller MDV images after peak demand for vaccine**
- Not all partners will use CEPI's vial/DP network. **Multiple MDV images may be deployed**, depending on which vaccines succeed (5-dose, 10-dose, 18-doses in a 10R vial – preserved).

## Capacity options with current glass supply contract

Vial	Qty (M)	Doses per vial (nominal)	Doses per vial (max)	Doses (nominal/BN)	Doses (max/BN)
20R	100	20	45	2.0	4.5
10R	125	10	18	1.3	2.3
6R	144	5	15	0.7	2.2
4R	150	5	8	0.8	1.2

**COVAX Goal: 20R selected to maximize doses delivered**

# Multi-dose vials

## Glass Vials

- Initial response: **20-dose tubing glass vials** for drug product (no preservative); use within 6 hours of first dose per WHO policy
- After 12-18 months: **MDV with preservative (5-10 dose/vials to be determined) for routine use/stockpile**
- CEPI has secured vials for 100M 20R vials for vaccine developers (can be used for up to 45 doses)
  - Vials sourced from 4 new production lines (3 in Italy, 1 in Mexico)
- Low-coring stopper design chosen
- Vial adapter option

## Bags

- Can support supply above the availability of MDV
- Rapid filling and dispensing could benefit mass-vaccination efforts
- Maintains container closure through 200 doses removed; can be used for multiple vaccination sessions over several days.
- May be an image of choice for some settings (e.g., drive-through immunization clinics in HICs)

# WHO multi-dose vial policy (preservatives)

- “If the vaccine does not contain an effective preservative, and if there is no evidence that data on preservative efficacy have been rigorously reviewed, opened multi-dose vaccine vials should be discarded at the end of the immunization session, or within six hours after opening, whichever comes first. The six hour time-limit corresponds to the average time frame over which an immunization session is ordinarily conducted.”
- “The WHO policy position is that thiomersal has been proven safe and effective and that there is no scientific justification to remove its presence from vaccines. In addition, many countries rely on the use of thiomersal in multi-dose vials to allow opened vials to be kept for up to 28 days, thus reducing cold-chain capacity and cost constraints, and thereby assuring a sufficient supply of safe vaccines.”
- Importance of VVM as a visual signal in standard use and during campaigns

**Discussion point: Is a preservative required for initial presentations?**

# Vial Adapter Options

**Background:** Vial adapters have been proposed to mitigate concerns about septum integrity and vaccine wastage for 20 dose vials.

**Test results:** Previous PATH testing of vaccine stoppers found they were within acceptable USP limits for fragmentation and self-sealing for 50+ piercings.\*

## Programmatic fit

- **LMICs:** Vial adapters cannot be used with AD syringes due to their fixed needles. Use of Luer syringes with separable needles is considered a step backward in injection safety, and will have significant supply, training, and policy implications.
- **HICs:** Luer syringes with separable needles are commonly used for vaccination, and vial adapters are likely a more familiar technology for HCW.

**Wastage:** Vial adapters, even those with integrated valves/air filters, do not extend open-vial use window of unpreserved vaccines (vaccine could be contaminated at first piercing.)



## Discussions with West Pharma:

- "Swabbable vial adapter" validated for 28 actuations over 7 days. (Multiple examples at higher actuations by specific customers).
- Significant recent spike in demand limits the available quantities.
- Proposing a capital investment to increase capacity to 20-40M units/year. (400 – 800M doses at 20 dose/vial)
- Alternate vendors exist, but likely also limited in supply

\*Jarrahian et al. Vaccine vial stopper performance for fractional dose delivery of vaccines. Human Vaccines and Immunotherapeutics. 2017.  
Available at: <https://doi.org/10.1080/21645515.2017.1301336>

**Would a vial adapter be acceptable to improve CCI risk, but allow usage over >6 hours?**



# Points to consider



## Product allocation:

- 50% LMIC – prefers and routinely uses MDV; most require auto-disable syringe
- 50% HIC/UMIC – prefers Unit dose; MDV generally  $\leq 5$  dose
  - may more easily implement 200 dose-bag (drive-thru clinics)

## Initial products unpreserved:

- More stable/preserved images available in year 2/3
- Propose use within 6 hours of first dose (can this be enforced?)
- Vial adapter/200-dose bag validated for use without losing CCI
  - Can these be used over several days (based on in-use stability, VVM monitored)

## Wastage:

- During high demand (mass vaccination)
- As demand decreases (alternate images to follow in year 2/3)

## Question to developers: How likely are you to use a 20-dose MDV; what other presentations are you developing?

- Single presentation?
- Multiple presentations? If more than one, what would be the potential “split” among the images?
- When committing to doses, are you accounting for filling lines and glass availability or is this an unresolved issue?
- CEPI has reserved a large quantity of tubing glass -- Would you like to participate in our meeting on August 3<sup>rd</sup> where we will be looking for input on which developers would like to make a commitment to access these glass vials?



# Examples of Alternate Backup Presentations

# Alternatives to glass vials

CEPI/BMGF have considered multiple alternative images due to the glass and sterile fill capacity limitations:

- **200-dose bag by MEDInstill/Intact Solutions**

- Independent filling network with closed-system filling (room requirements ISO 8 vs ISO 5)
- Container Closure Integrity maintained through 200-400 doses delivered
- FDA approved for filling bags for critical medical supplies (delivery of 0.5 mL doses from bags is novel).

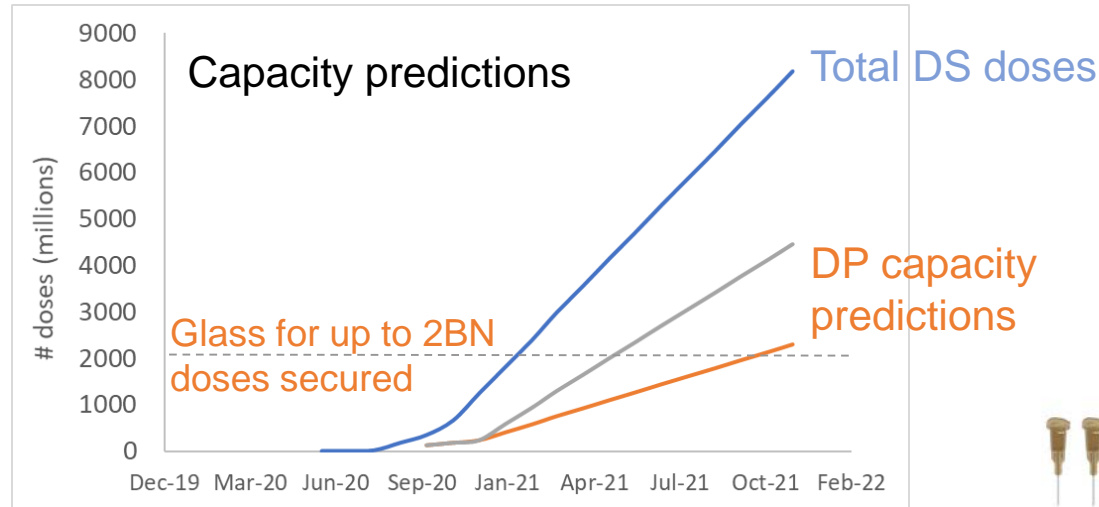
- **Blow-fill-seal (BFS)**

- Demonstrated for a variety of vaccines previously
- Network capacity can be available, but after development and validation (impacting second half of 2021)
- Mono-dose and multidose options

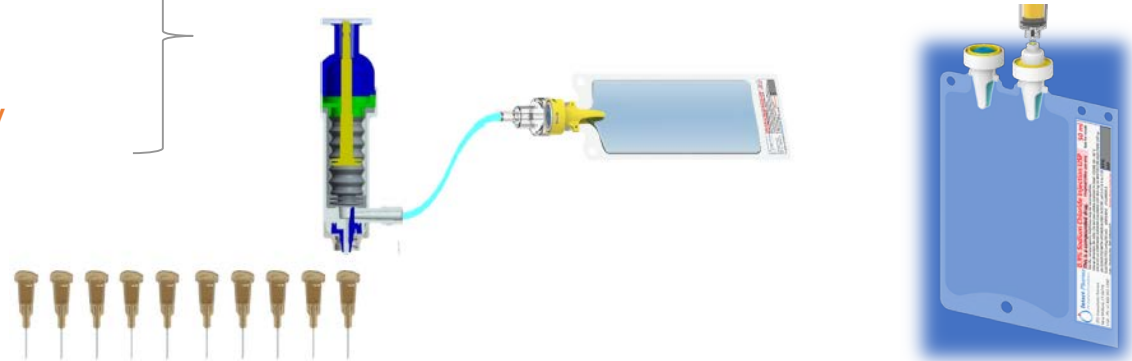
- **Plastic vials**

- Silicone-dioxide coated for glass-like properties; reduced weight/shipping costs, reduced breakage
- Still requires sterile filling capacity

# Why MEDInstill multi-dose bags?



DS-DP gap to be filled by MEDInstill 200-dose bags with sterile filling and dispensing



- **Fill/finish capacity:** fillers can be installed flexibly at existing CMOs, low environmental requirements and high capacity
- **Filling speed:** one filler can fill 38k pouches (= 7.7M doses) per day (3 shifts); 40x faster than 1-dose vial filling
- **Costs:** COGS is estimated at \$0.03-0.06/dose (at >1.5BN doses, equipment and consumables); 20-dose vials \$0.10/dose
- **Storage and distribution:** much reduced cold-chain footprint for (frozen) storage and shipment; important for LMIC
- **Low wastage:** sterility maintained during dosing, so time of use only limited by product stability
- **Suitable for mass vaccination:** fast administration, no need for separate syringes (for multiuse syringe option)

# Global use of Medinstill Bags



Measles vaccination in Yida refugee camp  
Source : MSF



A vaccination against measles and rubella is given to a child in India



Drive-through COVID-19 vaccination service envisioned in healthcare centers in Abu Dhabi

## Key advantages for LMIC:

- Low cost/dose
- Low cold chain footprint
- Sterility guaranteed in challenging environments
- Fast mass vaccination, fewer healthcare workers required
- Capacity increase makes vaccines available to the world

## Key advantages for HIC:

- Sterility maintained, reduced wastage
- Faster vaccination, less waiting
- Capacity increase makes vaccines available to the world
- Fewer concerns around training and reuse prevention

# BFS in multi-monodose or multi-dose vial



## Single-dose/Multi-monodose (MMD)

- Requires forming container (blow molding), filling container and sealing, twist off top (no scoring) / not resealable
- Requires separate syringe which could be auto-disable (AD)
- Compatible with machines that use mixing to suspend adjuvants and/or add cooling to formulation tank and filling mold
- Two presentation/ secondary packaging options
  - To save cold chain space, ampoules stay attached and overwrapped as 5- or 25-pack bricks, user tears off ampoules as needed at point of use.
  - Can separate ampoules at the factory with punch tool and individually package (lose most of cold chain space saving)



## Multi-dose vial (MDV)

- Requires forming container (blow molding), inserting a rubber septum and sealing
- Requires separate syringe which could be auto-disable (AD)
- Lower throughput due to need to add septum but multi-dose filling compensates for this lower throughput
- Compatible with machines that use mixing to suspend adjuvants and/or add cooling to formulation tank and filling mold
- Further behind in development (~4-6 mo. delay)

- Both formed in a single process/machine (takes plastic pellets and liquid vaccine as inputs and gets sealed/ crimped)
- Both require design optimization for COVID over the next 2-4 months, with MDV further behind in development; need to decide on MMD vs. MDV to proceed

# Understanding lead & back-up presentation options for COVID

Option	Technical/ Regulatory Risk	Delivery Risk	Supply Risk	Wastage risk	Cold Chain	Cost
Glass vials (20 dose)	Proven method; 20-dose may not be acceptable by all relevant regulatory authorities	User feedback req'd	2BN doses secured	20-dose vials could lead to wastage if not large campaigns	1.0X	Lowest cost option
Glass vials (1, 5, 10 dose)	Proven method	User feedback req'd	Supply will most likely not meet LMIC needs	Minimized risk	8x	10-dose = Cost 2-3x of 20-dose for same # of doses
BFS	No validated designs for vx delivery	User feedback req'd	High throughput machines w/ global distribution	Single dose means low wastage if design is optimized	2x	Costly compared to glass MDV, favorable for single dose
MEDInstill	Initial lukewarm response from regulatory, new unproven technology	User feedback req'd Innovation, training	New technology and company some supply risk; proven subcontractors	Only favorable in very large campaigns	0.66X	High doses/vial imply v low cost

**Hypothesis: Glass vials preferred, but may only be feasible in 20-dose presentation**



## Question for developers?

- What questions do you have around use of these alternate images?
- How likely are you to consider using either of these alternate presentations (bags and/or blow-fill-seal)?
- Would you like to participate in our meeting on August 3<sup>rd</sup> where we will be looking for input on the extent to which either CEPI or the foundation should continue to invest in these alternate presentations or use in the response to COVID-19?



# Overview of DP Network

# COVID-19 Manufacturing Summary

- CEPI is proactively preparing for production (at risk) of **billions of doses of vaccine in 2020 and 2021** for COVID19.
- **We continue to add to the 9-product portfolio to support 3-5 licensed products.** The approaches include recombinant proteins (with lipid-based adjuvants), DNA with electroporation, mRNA with lipid nano particle adjuvant, and viral vectors. Considering additional viral vectors and inactivated vaccines.
- **Formulation and Filling have a high potential to be the bottleneck** by the end of 2020. A strategy has been developed. Mitigations are planned.
- The current global annual production of commercial vaccines is currently about 20BN doses (4-5 Bn doses of multi-valent vaccine). **Our goal is to find new capacity, and not de-prioritize current critical vaccines and therapeutics.**
- The locations for **DS and DP capacity will be where capacity currently exists** or where it can be created quickly.
- Ideally, the **capacity is aligned with dose allocations to streamline supply chains and reduce regulatory complexity.**

# COVID-19 Allocation Principles

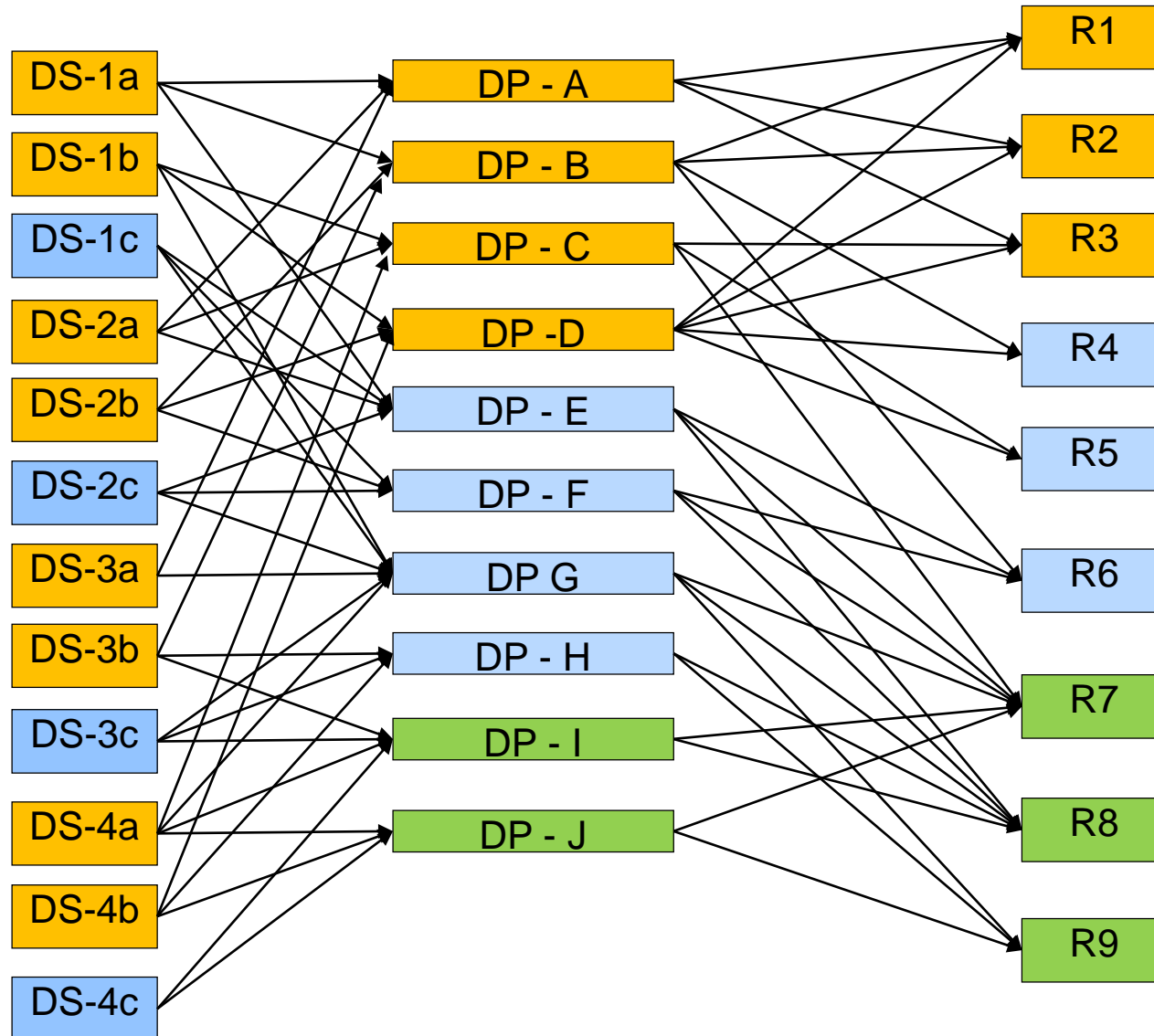
- During the 2009 H1N1 pandemic, product was distributed based on people's ability to pay. **Many lower income countries were not able to access vaccine.**
- The COVAX facility for purchase of vaccines leverages tiered pricing such that HIC/UMIC product sales at a premium subsidize LMIC/LIC sales. Vaccine is distributed based on medical need vs. ability to pay with an initial target of 20% of each participating countries' population.
- The tiered costs are based on estimated allocations of 30% HIC sales, 20% UMIC sales, 50% LMIC/LIC sales.
  - LMIC/LIC costs also subsidized by Overseas Development Assistance (ODA)
- HIC/UMIC product commitments and down-payments support costs of manufacturing at risk across the network. The ability to deliver **balanced HIC/UMIC/LMIC/LIC doses is critical to the success of COVAX.**

# Drug Product Network

## Confounding Factors to Network Design

- **Regulatory acceptance** by manufacturing region
  - WHO PQ status, Status with stringent NRAs
  - General “one-way flow” HIC → HIC → UMIC → LMIC impacts flexibility of supply; supply balance is key for global allocation
  - HIC siting favors flexibility; UMIC/LMIC siting favors cost and access; **the right mix is a key to success for COVAX**
- **Nationalism** (commitment to **fair allocation is paramount** to balance supply and demand)
  - Some countries may block borders until local demand is satisfied, or retain a high share (~50%) of doses
  - Nationalism counter-strategy could be **low-population countries with good technical capabilities**.
- Independent government vaccine purchases
  - Many deals outside of COVAX **confound demand by country/region and hence allocations**
  - Some bi-lateral deals are contingent on vaccine success and can shift demand accordingly
- **Independent product supply** and supply chains
  - Within COVAX, but not within CEPI network; various product images
- Acceptability of **various drug product images** in different countries (MDV well accepted in LMIC, more challenging in HIC)

# Supply Chain Design



- DS located in HIC and UMIC
- DP distributed in HIC/UMIC/LMIC
- May launch with limited supply chains per region with more added over time as options are approved
- Focused/streamlined supply chains favors regulatory approvals
- Flexibility added over time with cross-licensing products/facilities/networks
- Managing the complexity will be an extreme challenge as noted, not just due to the network shown, but by non-COVAX suppliers and demand as well.
- Good S&OP depends on good data. The data for COVID19 vaccines is not designed to flow to a central location or "control tower" to adjust plans to perturbations in the supply/demand
- Partners and COVAX members will need to participate in the S&OP process

# Managing Allocations

- The DP network design will drive ultimately to **a broad regional network** with all regions covered
- **Country participation within allocation framework** (avoid nationalism by policy or network structure)
- **Regulatory harmonization and guidance** to partners
  - By region, by product type
  - Streamline network, build flexibility over time.
- **S&OP process development**; engagement by COVAX pillars (and non-COVAX partners?)
  - Routine “re-balance” of production plans to align with allocations as supply/demand evolves
- For firms choosing to build their own DP network, consider how your network can support these critical COVAX allocation principle

# CEPI's DP strategy

- CEPI has developed a global DP strategy
- CEPI is setting up a DP Network for 2 to 4BN doses of 2-3 COVID-19 vaccines (9 in portfolio)
- Access to this network is open to all vaccine developers intending to participate in the COVAX Facility regardless of whether they are a recipient of funding from CEPI or the foundation
- Network capabilities:
  - Able to manufacture all vaccine modalities (RNA, pDNA, recombinant protein, viral vectors, adjuvants)
  - Able to produce DP starting Sep/Oct 2020
  - Established around the globe
  - Able to fill multidose vials and multidose bags
- CEPI will set up the network, so vaccine developers can leverage the network capabilities
- CEPI has already secured DP vials for 2-4 BN\* doses (\*depending on fill volume in 20R vial)



# Key Characteristics of the DP Network

## DP Site Selection Process

- CEPI, together with BMGF and CHAI, conducted a survey of over 200 companies, institutions and CMOs of available DP capacity
- CEPI shortlisted 23 companies which were then interviewed using a structured interview process
- CEPI has selected companies with appropriate geographical distribution to supply vaccines in 2020 and 2021 (and beyond)

## DP Sites

- CMOs and/or Pharmaceutical companies, global footprint
- Will be able to process RNA, DNA recombinant proteins, live viral vectors and adjuvants
- Will cover formulation, filling, visual inspection, labelling, packaging, analytical testing and QA release
- Are able to allocate sufficient capacity to the manufacturing of COVID-19 vaccines for a duration of at least 18 months/until all 4BN doses have been produced and delivered worldwide.

## Capacities

- In 2020, the selected sites can fill more than 400 Mn doses in vials
- In 2021, the selected sites can fill more than 4 Bn doses in vials
- The sites are also interested in filling MedInstill multidose bags
- If more capacities are required, CEPI can expand the network

## Raw Materials

- DP Network will have access to glass vials, rubber stoppers and crimp caps that have been reserved by CEPI

## Regulatory

- The network sites will preferably be approved by major health authorities and/or have WHO/PQ
- WHO is considering an EUL process for sites which do not yet have WHO/PQ

# Contractual and Network Management Considerations

## Capacity Reservations / Contracting

- CEPI will reserve capacities at the DP Sites
- The Capacity reservations will depend on the Interest and Commitment of the Vaccine Developers
- Final Answers would be needed on August 3<sup>rd</sup>
- CEPI will agree with DP Companies on Key Contractual Terms
- Vaccine Developers can then contract with the DP Companies under these conditions and at reduced risk (if your vaccine fails)
- Sufficient capacities for vials, stoppers etc, will also be secured at attractive conditions
- If we are reserving the capacities for the vaccine portfolio, the risk of “unused capacity” is going to be reduced

## Network Management

- The global vaccine manufacturing and distribution efforts will require excellent coordination of all steps in the Supply Chain
  - Procurement and logistics for vials, stoppers, caps, labels, cartons, etc.
  - Tracking materials through supply chain, including through release at CMO, by development partner, and NRAs
- Vaccine Developers will be responsible for product quality and release; quality agreements with DP network partners.
- CEPI is in touch with several Multinational Companies which expressed willingness to support these global coordination efforts

# Questions to developers

- How likely would you want to access the DP Network for fill/finish capacity?
- How soon would you need access?
- Are there any special requirements other than those already noted?
- Would you like to participate in our meeting on August 3<sup>rd</sup> where we will be looking for commitments to access the DP Network?
- We are happy to have 1:1 Calls with you before August 3<sup>rd</sup>



# Stability, Shelf-life and Cold Chain Requirements

# Summary of key iTPP parameters (Part 1)

- Intervention TPP (iTPP) is a guidance document to help facilitate product development decisions
- Minimal parameters are used in Stage Gate Go/No go decisions. Optimistic parameters are used to signal areas where innovation or improvements are desired. These can include efficacy, storage conditions & COGS
- Following parameters are a compilation of the parameters proposed by CEPI, BMGF and the WHO\*

## **COVID-19 Vaccines**

### **Stability and Shelf Life**

- Minimal: If required, shelf life of at least 12 months at temperatures as low as -70°C with sequential stability of at least 2 weeks to 3-months\* at 2-8°C and/or the potential for storage at -20°C for one year, Long-term: Storage at -20°C or warmer
- Optimal: Shelf-life of 5 years at 2-8°C. Higher storage temperatures will enhance distribution. Proof-of-feasibility and intent to apply a VVM (Vaccine Vial Monitor)

\* Ranges are shown to accommodate differences in the parameters between the different iTPPs

# Summary of key iTPP parameters (Part 2)

## Presentation

- Minimal: Multi- or single-dose presentations are acceptable, Maximum parenteral dose volume: 1 mL
- Optimal: Multi- or single-dose presentations are acceptable, Maximum parenteral dose volume: 0.5 mL
- Both (WHO): Lyophilized vaccine will need to be paired with a separate vial of the appropriate diluent\*

## Multi-dose Vials

- Both: Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy (MDVP)\*\*.

\* Presentations with antigen in one vial and adjuvant in a separate vial are not covered in the iTPPs but likely that the guidance would be similar to that for a lyophilized vaccine

\*\* Briefly: opened vial can be used for up to 28 days after opening if it meets criteria set forth by the WHO MDVP and has been approved via WHO PQ process. Vials without preservative should be discarded 6 hours after opening

# Vaccine Vial Monitors (VVM)



- VVM is a heat-sensitive material affixed to the primary container to register cumulative heat exposure over time
- The combined effects of time and exposure to higher temperatures cause the inner square to irreversibly darken
  - If the inner square is lighter than the outer circle, the vaccine may be used
  - If the inner square is the same color or darker than the outer circle the vaccine may not be used

**Table. VVM reaction rates by category of heat stability**

Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
<b>VVM 30:</b> High Stability	30	193	> 4 years
<b>VVM 14:</b> Medium Stability	14	90	> 3 years
<b>VVM 7:</b> Moderate Stability	7	45	> 2 years
<b>VVM 2:</b> Least Stable	2	N/A*	225 days

\*VVM (Arrhenius) reaction rates determined at two temperature points



Vaccine Vial Monitor  
(showing no heat exposure)

- There are four different types of VVMs designed to be used for different groups of vaccines according to their heat stability

# Discussion

- Discuss potential limitations for cold-chain delivery, including use of VVM
- Question to developers: What shelf-life do you anticipate being able to get approved at the time of distribution?



# Closing and next step

# Topics for future meetings

- August 3<sup>rd</sup> meeting will be focused on the specific needs of the DP Network and follow-up from this meeting.
- Manufacturing topics for future Workshops?
- Final questions/comments from each entity attending?



# **Additional Details/Back-up slides**

# CEPI's options to consider

Base case 20R vial, filled to deliver 20 doses=2BN doses (before wastage), additional doses to 200-dose bag

- Upside case 1 – 20R vial, filled up to 45 doses/vial = 4.5BN doses, plus 1.5BN in 200-dose bags
- Upside case 2 – 20R vials, add 20R vials of molded glass (vs tubing glass) = up to 4BN doses
  - Concerns of machinability and delamination

10R vial – filled to deliver 10 doses = 1.2BN doses (before wastage), additional doses to 200-dose bag



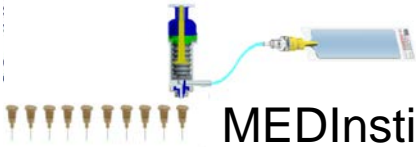

- Upside case 1 – 10R vial, filled up to 18 doses/vial = 2.1BN (up to 4.0BN with molded glass)
- Upside case 2 – 10R vial, filled to 10 dose add 10R vials of molded glass = 2.0BN (limited by total sterile fill capacity)

Supplement 20R/10R quantities with other DP images:

- Invest in more tubing glass capacity (~25M USD upfront) = 2BN additional doses (capped by fill capacity)
  - Could be 20R or 10R
- 200-dose bags = 1.5 to 3BN additional doses (3BN dose in 200 dose bags)
- Blow-fill-seal (\$100-300M upfront to validate lines) = 400M – 1.2BN additional doses by end 2021

10R with 18 doses has an improved cold chain footprint over a 20R with 20 doses and was proposed by delivery team.

# Drug Product approach: towards BNs of doses

		Capacity and costs	Usability and acceptance	Access
Single-dose vial		Insufficient capacity (vials, F/F, cold chain, ...)	Standard, high quality solution	Limited F/F and cold chain capacity
Multi-dose vial (20 doses)		Up to 2BN doses Issues: wastage and need for syringe	Standard accepted solution, limited time of use	Global DP manufacturing network
MEDInstill 200-dose bag		Up to 1.5BN doses Low wastage, no need for syringe, low cold-chain footprint	Novel solution, introduced to users and regulators	Flexible and fast placement of fillers in region of choice
Blow-fill-seal		Requires Investment Under Evaluation by BMGF	Requires compatibility testing, significant process development	COGS well suited for worldwide access

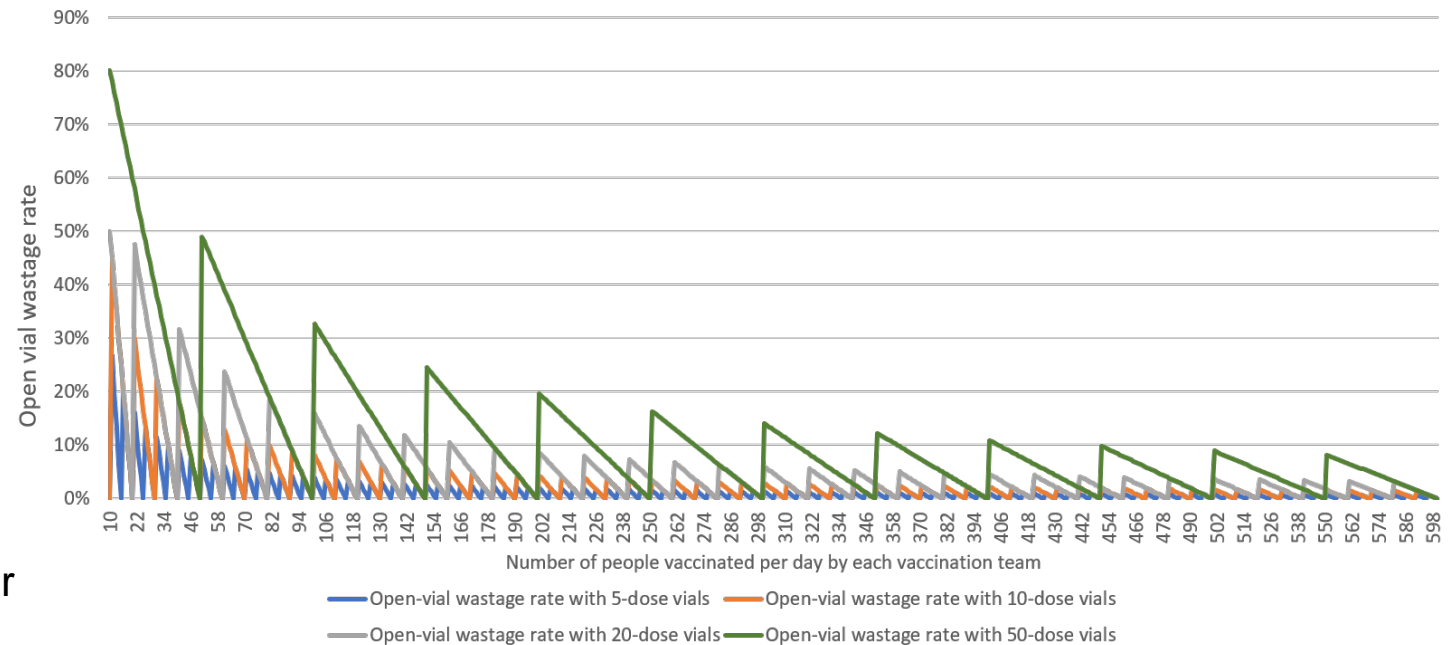
# Programmatic wastage analysis

**Objective:** To gain understanding of the potential programmatic vaccine wastage implications of alternative multi-dose vials for a COVID-19 vaccine.

- Vial sizes included: 5, 10, 20, 25, 30 and 50-dose vials.

## Key findings:

- If the number of people expected to be vaccinated per location per day is **<80 people, then using 20-dose vials** will result in the lowest wastage-adjusted vaccine price per dose for most session sizes.
- The per-dose price premium associated with lower dose vials is an important driver of the results – the higher the per-dose price premium associated with lower dose vials; the better value of money associated with higher dose vials.



# DP image options Pre-read only

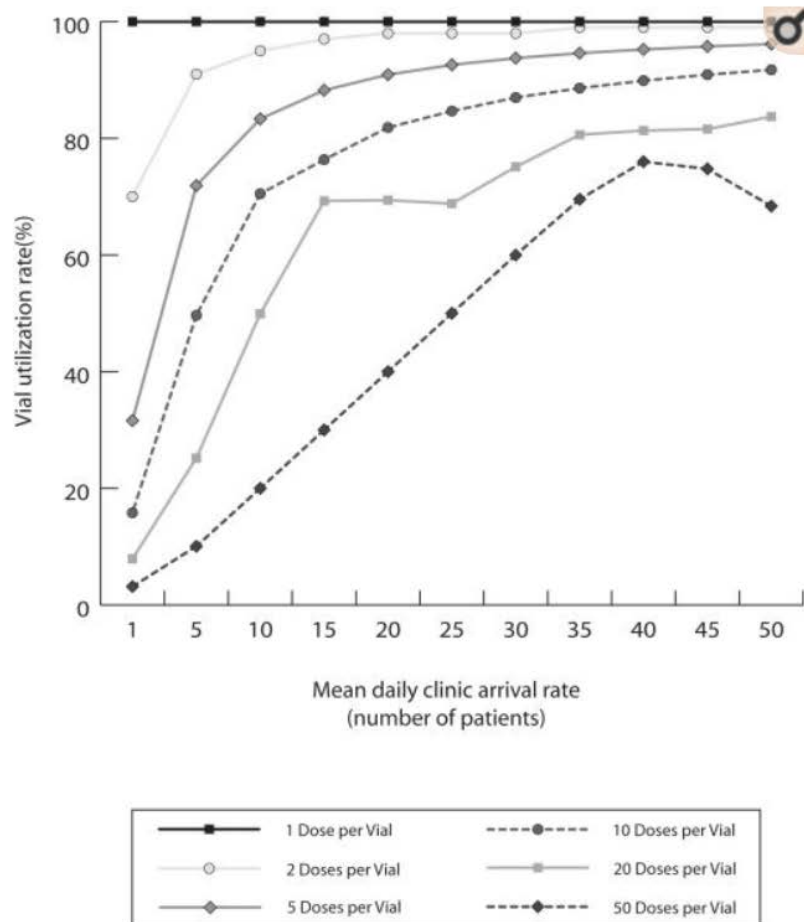
Option considered	Doses 2021 (M)	Concerns	Mitigations	Comments
1	173	1. Capacity, cost/dose, # batches 2. cold chain footprint (8x 20-dose)	1. no mitigation for low capacity until 2022 with large investment. 2. no mitigation of cold chain capacity until 2022	limited sterile capacity for single dose vials/syringes and limited tubing glass capacity.
5	720	1. Capacity, cost/dose, # batches 2. cold chain footprint	1. no mitigation for low capacity until 2022 with large investment. 2. no mitigation of cold chain capacity until 2023	limited sterile capacity for this image and limited tubing glass capacity.
10	1,200	1. Capacity, 2-3x cost of 20-dose to fill 2. FDA limit 5 doses w/ preservative 3. Wastage 4. Non-preserved product	1. invest in more tubing glass capacity & vial capacity to match DP capacity (30-50M USD) 2. Coring studies show acceptable for 20+ punctures (low coring stopper design). Limit use to 6 hours after first withdraw. 3. Limited wastage during mass vaccination campaigns	In this format, only 2BN doses of filling capacity has been identified.
20	2,000	1. FDA limit 5 doses w/ preservative 2. wastage 3. Coring/loss of container closure 4. Non-preserved product	1. Coring studies show acceptable for 20+ punctures (low coring stopper design). Limit use to 6 hours after first withdraw. Consider vial adapter. 2. Limited wastage during mass vaccination campaigns. 3. Coring studies confirm feasibility. Option for vial adapter.	In this format, up to 4BN doses of capacity has been identified. Transition to 5/10 dose with preservative in 12-18 months. (not compatible with AD syringes)
50	3,750	1. FDA limit 5 doses w/ preservative 2. wastage 3. coring	1. Consider vial adapter. 2. Limited wastage during mass vaccination campaigns. 3. User vial adapter. (not compatible with AD syringes)	Capacity exceeds needs, but concerns over wastage without preservative, particularly in remote settings.
100	5,000	1. FDA limit 5 doses w/ preservative 2. wastage 3. coring	1. Consider vial adapter. 2. Limited wastage during mass vaccination campaigns. 3. User vial adapter. (not compatible with AD syringes)	Capacity exceeds needs, but concerns over wastage without preservative, particularly in remote settings.
200 dose bag	1,500-3,000	1. Novel, regulatory and user risks 2. auto-disable syringe not compatible 3. time at temperature risk for extended use (> 1 day)	1. User training and education. 2. seek auto disable alternative. 3. in-use stability studies at elevated temp. Less problematic during mass vaccination. VVM will be used.	Tremendous rapid response capabilities in that the filling unit can finish 10M doses/day per unit (6 units planned). Integrated multi-use syringe eliminates the need for syringes in the field.
single dose BFS/ Multi-monodose	~400-1,200	1. novel design 2. user stability studies required 3. balance b/w cold chain volume and wastage	1. BMGF planning to fund container design work 2. Initiate stability studies with viable candidates early 3. Looking at single dose as backup option/option when volumes are small and wastage is important consideration	Well-established technology that would be new for sterile injectables; could be important backup if there are glass shortages, and/or it is important to have widespread single dose presentation.

Doses/vial	Capacity(*) (million doses)	Waste	Immunisations
5	720	0.02	706
10	1200	0.1	1080
20	2000	0.2	1600
35	3500	0.4	2100

(\*)OMPI Capacity

Doses/vial	Vial type	Vial volume (ml)	Volume/dose (ml)	Relative Vol/dose
5	4R	6	1.20	0.96
5	6R	10	2.00	1.60
5	10R	13.5	2.70	2.16
10	10R	13.5	1.35	1.08
10	20R	25	2.50	2.00
20	20R	25	1.25	1.00
35	20R	25	0.71	0.57





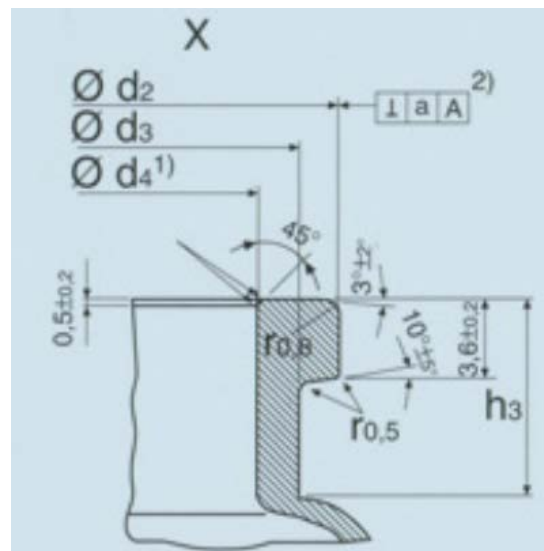
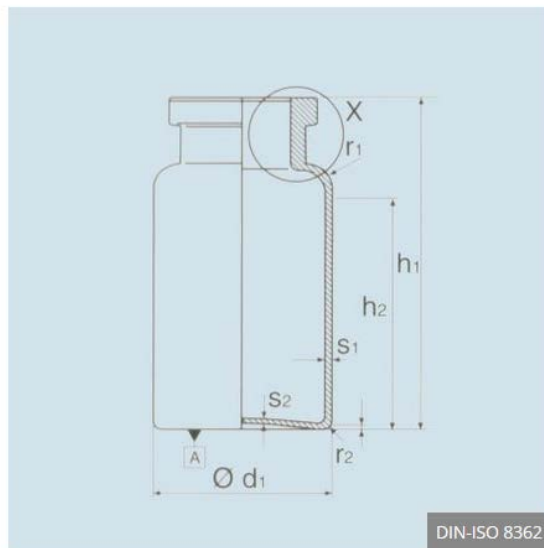
The Figure shows how percentage of doses wasted (i.e., number of doses wasted/total number of doses) varies by the patient arrival rate.

Each line represents a different vial presentation.

As the patient arrival rate increases, the wastage rate for the multi-dose presentations decreases while the wastage rate for the single dose presentation remains constant

#### Single versus Multi-Dose Vaccine Vials: An Economic Computational Model

[Bruce Y. Lee](#), MD, MBA,<sup>1,2</sup> [Bryan A. Norman](#), PhD,<sup>3</sup> [Tina-Marie Assi](#), MPH,<sup>1,2</sup> [Sheng-I Chen](#),<sup>3</sup> [Rachel R. Bailey](#), MPH,<sup>1,2</sup> [Jayant Rajgopal](#), PhD,<sup>3</sup> [Shawn T. Brown](#), PhD,<sup>4</sup> [Ann E. Wiringa](#), MPH,<sup>1,2</sup> and [Donald S. Burke](#), MD<sup>2</sup>  
[Vaccine. 2010 Jul 19; 28\(32\): 5292–5300.](#)



Tipo Type Type Typ	Cap. raso bocca • Cap. ras-board • Brim. capacity • Rand.-volumen		d <sub>1</sub>		d <sub>2</sub>	d <sub>3</sub>	d <sub>4</sub>	h <sub>1</sub>		h <sub>2</sub>	h <sub>3</sub>		r <sub>1</sub>	r <sub>2</sub>	s <sub>1</sub>		s <sub>2</sub>	t							
	ml	Tolleranza Tolerance Toleranz		Tolleranza Tolerance Toleranz	+0,2 -0,3	max	±0,2		Tolleranza Tolerance Toleranz	min.		Tolleranza Tolerance Toleranz	-	-		Tolleranza Tolerance Toleranz	min.	max							
2R	4	±0,5	16	±0,2	13	10,5	7	35	± 0,5	23	8	± 0,5	2,5	1,5	1	± 0,04	0,7	0,7							
4R	6							45		33															
6R	10		22		16			40		27	8,5		3,5	2					9						
8R	11,5							45		32															
10R	13,5	±1	24		20	16,5	12,6	45		31	10	± 0,75	5,5	2,5	1,2	± 0,05	1	1							
15R	19							60		46															
20R	25	±1,5	30	±0,3		17,5		55	± 0,7	35															
25R	30,5							65		45															
30R	36							75		55															

# Glass vial supply more likely to be constrained in 5- or 1-dose format

- How many investments do we have? What information are we missing?
- For other deals with companies, are they already accounting for filling and glass supply/ will we be procuring finished product?

Vial size	Vial Volume Scenarios (2021)		Amount secured
	CEPI 1B for LMICS*	Populationx2 13.2B for LMICS**	
20-dose vials (10R)	50M	660M	100M year (CEPI) from OMPI; considering proposal from Corning
5-dose vials (5R?)	200M	2.7BN	None; could transfer OMPI 10R to 5R
Single-dose	1BN	13.2BN	None; could transfer OMPI 10R to 2R

\*Based on CEPI commitment to 1BN doses for LMICS

\*\*Based on populations in LMICS (incl. China and India) x 2 doses (will be revised/used here as preliminary figure)

# Updates main glass vial manufacturers – capacity

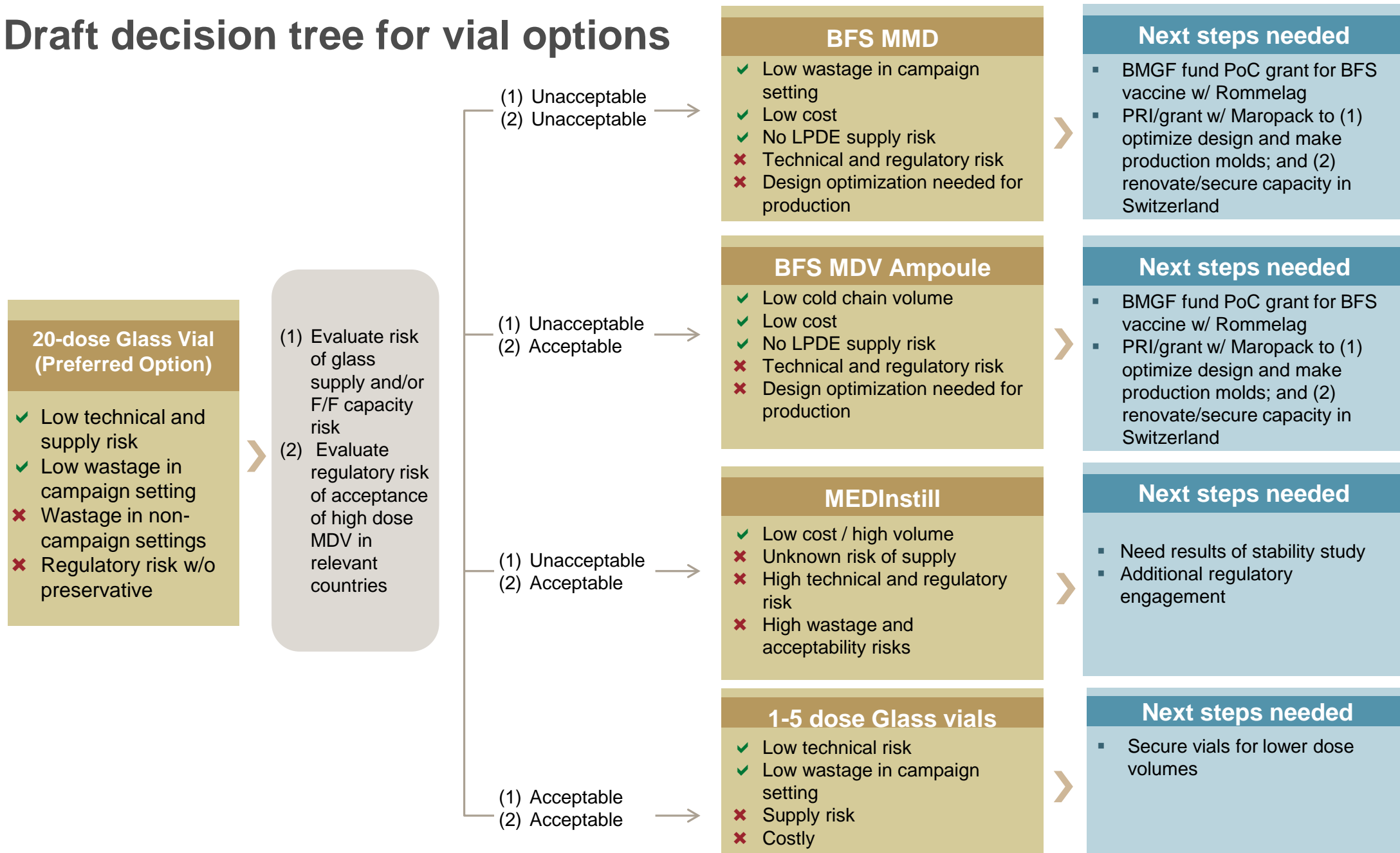
*Additional 5 manufacturers in backup slide*

Manufacturer	Tubular Glass Capacity	Molded Glass Capacity Type I (improved quality)	Notes (Lead time to order, cost of additional glass line, etc.)
SGD		60 M this year 80M next year	
OMPI	6M This year (oct 2020) 10R 18M next year 10R		CEPI approval of investment. Increase capacity x5 with additional investment from CEPI required about 4.8M (2.4+2.4) for 138M vials.
SCHOTT	No free capacity	-	Additional capacity option: <ul style="list-style-type: none"> <li>• 2.3m EUR investment per machine</li> <li>• Capacity: 25-30M units 10R/20R per year per machine</li> <li>• Lead time: 12 months</li> </ul>
NIPRO	Around 90 M 20R vials in 2021 (see details in backup slide)  (relative flexible on standard vial sizes: 2R, 6R, 10R and 20R)		Production sites: Germany, India, US Lead time for <ul style="list-style-type: none"> <li>• normal size orders: 14-18 wks.</li> <li>• high volume orders: 6-8 ms</li> </ul> Pricing: <ul style="list-style-type: none"> <li>• GER/IND: 142 EUR / 1k vials</li> <li>• US: 155 USD / 1k vials</li> </ul>
Gerresheimer		40M 25R or 200M 6R or 100M 10R or 400M 2R	Possible. Further discussion required for costs and glass specification
Bormioli		2020: 30M 20R 2021: ≥30M 20R	Can provide in either improved or standard molded glass
Corning	Around 40 M 20R vials in 2021 (see details in backup slide)		Production sites: US, Italy Pricing: <ul style="list-style-type: none"> <li>• US: 730 EUR / 1k vials</li> </ul>

# Glass vial manufacturers – monthly potential delivery

Manufacturer	4Q 2020 (monthly) in M vials	1Q-4Q 2021 (monthly) in M vials												Notes
		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
Nipro Germany	TBD	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	20R Type 1 clear, Standard Nipro Packaging, Standard Nipro Quality Order commitment needed ASAP 4Q2020 supply to be updated
Nipro US	TBD	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3	
Nipro India	TBD	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	
Corning	4.0	3.6	3.3	3.7	3.6	3.6	3.6	3.4	3.7	3.6	3.7	3.3	3.1	Borosilicate, Coated, 20R vials

# Draft decision tree for vial options





# MEDInstill Bags As an Additional DP Option

*High capacity and speed at low costs for global access*



# Fast administration for mass vaccination



## Glass Vial: ~60 sec

1. Open syringe packaging
2. Open needle packaging
3. Attach needle
4. Scrub skin
5. Wipe vial surface
6. Pull air into syringe
7. Uncap syringe
8. Pierce vial
9. Inject air in vial
10. Withdraw dose
11. Eject air
12. Vaccinate



## Intact™ Luer bag: ~30 sec

1. Open needle packaging
2. Connect to luer bag
3. Withdraw dose
4. Attach needle
5. Scrub skin
6. Uncap syringe
7. Vaccinate
8. Recap and discard needle



## Intact™ MD Syringe: ~20 sec

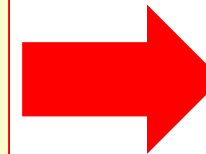
1. Scrub skin
2. Open needle packaging
3. Attach needle
4. Uncap syringe
5. Vaccinate
6. Recap and discard needle

MD Syringe is at least 3x faster

No air injected: no risk of contamination, safer and less wastage

No risk of mistakes in the dosing (metered dose)

Fewer repetitive steps means less burden and stress on the healthcare worker (6 steps instead of 12)



**With the same size  
healthcare team,  
vaccination programs can  
be deployed in half the time,  
saving more lives**

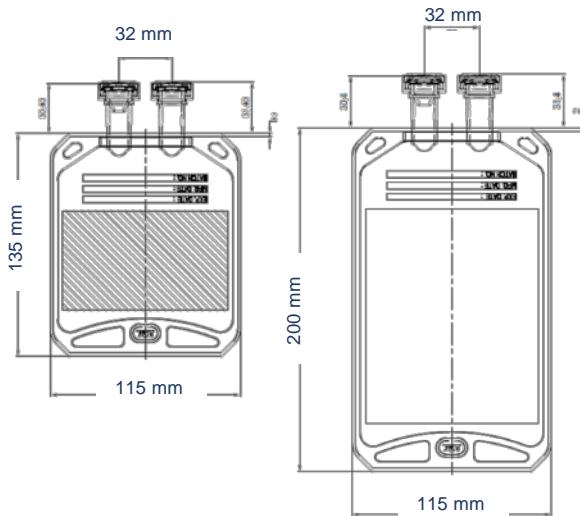
[CDC handling procedures for Single Dose vials](#)

[CDC handling procedures for Multi Dose vials](#)



# Low cold chain footprint

- Cold chain volume 0.5 – 0.7x the dose volume in 20-dose vial
- Several WHO-approved vaccine carriers for these pouches
- Because of the short development timelines, several vaccines might require (deep) frozen storage conditions



Presentation	Cold chain volume (cm <sup>3</sup> /dose)*
1-dose vial	15.2
5-dose vial	4.6
1-dose BFS	~4
10-dose vial	3.3
20-dose vial	2.1
<b>200-dose pouch</b>	<b>1.4</b>
<b>400-dose pouch</b>	<b>1.0</b>

\*Glass vial averages from current WHO prequalified vaccines.

# High capacity and speed at low costs

- Filler can be installed in 3 months in ISO 8 / class D environment, multiple fill sites have expressed interest
- 1 filler running at 2 shifts/day can fill 4M doses/day or 1.5BN doses/year
- Bag and syringe supply consumable partners deliver in ~6 months
- Costs are \$0.03 – 0.06/dose, vs \$0.10/dose in 20-dose vials



It takes only a few seconds to fill 200 doses.



	Risk	Mitigation
Technical	Compatibility issues with COVID-19 candidate vaccines: adsorption, instability, leachables	<ul style="list-style-type: none"> <li>• It does not have to work for every product</li> <li>• Bag material widely used for e.g. DS storage</li> <li>• Bag film can be changed, product can be stored frozen</li> <li>• Leachable data available from St Gobain</li> <li>• Include bags early in stability studies for COVID-19 vaccines</li> <li>• Compatibility studies ongoing; initial results promising</li> </ul>
	Frozen storage might be required because of limited stability data at 2-8°C	<ul style="list-style-type: none"> <li>• Low cold chain footprint</li> <li>• Product may require frozen storage anyway (e.g. mRNA vaccines, Measles)</li> </ul>
	Homogeneity of dosing needs to be ensured, especially after overnight storage	<ul style="list-style-type: none"> <li>• In-use stability studies will be performed to cover this issue</li> <li>• Needs to be ensured for multidose vials as well</li> <li>• Already demonstrated for alum-adsorbed product</li> </ul>
	Container-closure integrity needs to be proven during dispensing	<ul style="list-style-type: none"> <li>• Sterility shown by MEDInstill with syringe immersed in 8 Log CFU/ml broth</li> <li>• Microbial challenge / CCIT study under worst-case conditions planned</li> </ul>
Acceptability	User acceptance	<ul style="list-style-type: none"> <li>• Usability study ongoing at PATH, including prototype testing</li> <li>• Flexible technology: could change to pouch with luer lock to fill separate syringes, which is more familiar to users</li> <li>• Positive initial feedback from stakeholders</li> </ul>
	Regulatory acceptance, especially of using a non-preserved multidose DP longer than six hours after first dose	<ul style="list-style-type: none"> <li>• Technology already introduced to FDA and EMA</li> <li>• Filling process accepted as closed manufacturing method</li> <li>• Scientific advice sought on time of use</li> </ul>

# Intact Solutions multidose pouch – PATH stakeholder interview results



## 200-dose and 400-dose pouches

### Designs assessed:

- Luer port pouch with separate needle & syringe
- Pouch with attached multidose syringe
- Pouch with attached multidose syringe and non-reusable plastic needle

### Advantages

- Small cold chain volume.
- Speed of use.
- Innovative.
- Increased vaccine production capacity at high speed and low production cost.
- Alignment with mass campaign strategies.
- In a mass campaign setting, wastage is expected to be low (similar to a 20-dose glass vial).

### Design recommendations

- Prioritize Luer port pouch due to likelihood of lesser challenges with acceptability, training, safety, and regulatory approval.
- Contact regulatory authorities early to confirm approach to data on contamination risk specifically for vaccine delivery indication.
- Use RUP syringes/needles and develop HCW training approach to mitigate injection safety risks (AD syringes not compatible.)
- Conduct vaccine stability testing at CTC conditions (at least 40°C for at least 3 days at end of shelf life) or develop a holder for the pouch to keep vaccine cold during use.
- Align with global/national stakeholders on strategies for use of mass campaigns for COVID-19. Focus also on HIC use and avoid targeting use of COVID-19 vaccines in pouch presentations exclusively in LMICs.
- Develop communications strategies and test in-country to understand and mitigate impact on COVID-19 specific and overall vaccine hesitancy and introducing new/innovative products in a pandemic context.
- Align secondary packaging with existing cold chain equipment.

**Next steps:** PATH will conduct human factors evaluation of physical prototypes once received (in Seattle and in Zambia with Living Labs).

# Some stakeholder and user feedback

It would increase availability and access – *UNICEF*

Healthcare workers will like this new tool, best  
suites for campaign use – *PATH Senegal*

Excited about this new presentation, it has potential  
for other vaccines as well - *MSF*

Obvious advantages for mass vaccination,  
logistics, transport, cold chain - *MSF*

Lightweight, flexible, good for fast mass vaccination,  
can address vaccine shortages, easier to  
carry/transport – *PATH India*

Innovative device, good training  
will be required – *PATH Senegal*

Stability of the vaccine needs to be  
ensured, temperature and light,  
VVM is key - *MSF*

Autodisable syringe/needle might be  
required in some areas - *WHO*

## Appendix – details from iTPPs

- Comparison of iTPP data from BMGF, CEPI & WHO documents related to storage, presentation and MDVs

# Stability/ shelf life

*Italics indicates areas where iTPPs diverge*

Organization	BMGF	WHO	CEPI
<b>Minimum</b>	<p>If required, shelf life of at least 12 months at temperatures as low as -70°C with sequential stability of <i>3-months</i> at 2-8°C and/or the potential for storage at -20°C for one year.</p> <p>Long Term: Storage at -20°C or warmer</p> <p>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.</p>	<p>Outbreak: Shelf life of at least 12 months as low as -60—70°C*, and demonstration of at least 2-week stability at 2-8°C.</p> <p>LT: Storage at -20°C or higher;</p> <p>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.</p>	<p>Shelf life of at least 12 months at up to -70°C. Stability of at least <i>1 month</i> at 2-8°C should be demonstrated.</p> <p><i>The need for a preservative is determined and any issues are addressed.</i></p> <p>VVM: Proof of feasibility and intent to apply a VVM to the primary container.</p>
<b>Optimistic</b>	<p>Higher storage temperatures and greater thermostability will enhance vaccine distribution and availability.</p> <p>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.</p>	<p>Higher storage temperatures and higher thermostability will greatly enhance vaccine distribution and availability, and are thus strongly preferred.</p> <p>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.</p>	<p>Shelf life of 5 years at 2-8°C.</p> <p>Additional data on thermostability at higher temperatures.</p> <p><i>The need for a preservative is determined and any issues are addressed.</i></p> <p>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container for multi-dose vials.</p>

BMGF NOTES: mRNA vaccines may not be able to be stored refrigerated for extended periods. As such, initial storage at temperatures as low as -70°C with shipment at higher temperatures (-20°C or refrigerated) and/or subsequent storage refrigerated or at -20°C is acceptable.

In all cases, attempts should be made to alter storage requirements to leverage existing infrastructure in LMIC settings.

While it is feasible to deliver vaccines at -80, the planning, supply procurement, installation and training required for a large-scale COVID-19 roll-out would be unprecedented (additional costs estimated at minimum to be \$0.35 - \$0.70/dose delivered).

WHO NOTES: \* For drug product, storage at temperatures below -20°C would require additional infrastructure and may impede distribution of vaccine, and would thus need to be addressed.



# Presentation

*Italics indicates areas where iTPPs diverge*

Organization	BMGF	WHO	CEPI
<b>Minimum</b>	<p>Multi- or single-dose presentations are acceptable.</p> <p>Maximum parenteral dose volume: 1 mL</p>	<p>Multi- or mono- dose presentations are acceptable.</p> <p>Maximum parenteral dose volume: 1 mL</p>	<p><i>Vaccine provided as a liquid or lyophilized product in mono- dose or multi-dose presentations with a maximal dose volume of 1.0 mL.</i></p> <p><i>Lyophilized vaccine will need to be paired with a separate vial of the appropriate diluent.</i></p>
<b>Optimistic</b>	<p>Outbreak: Multi-dose presentation is preferred for ease of use in campaigns.</p> <p>Long Term: Single-dose or multi-dose presentations are acceptable</p> <p>Maximum parenteral dose volume: 0.5 mL</p>	<p>Outbreak: Multi-dose presentation is preferred for ease of use in campaigns.</p> <p>LT: mono-dose or multi- dose presentations are acceptable</p> <p>Maximum parenteral dose volume: 0.5 mL</p>	<p>Vaccine provided as a liquid or lyophilized product in mono- dose or multi-dose presentations with a maximal dose volume of 0.5 mL.</p> <p>Lyophilized vaccine will need to be paired with a separate vial of the appropriate diluent.</p>

BMGF NOTES: WHO document, “Assessing the programmatic suitability of vaccines candidates for WHO prequalification”



# Multi-dose vials

*Italics indicates areas where iTPPs diverge.*

Organization	BMGF	WHO	CEPI
<b>Minimum</b>	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's MVDP (briefly: opened vial can be used for up to 28 days after opening if it meets criteria set forth by MDVP). <sup>7</sup>
<b>Optimistic</b>	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. <i>If feasible, vaccines consistent with an "open vial" policy may have additional advantages</i>	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy <sup>9</sup> .	Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy (MVDP) (briefly: opened vial can be used for up to 28 days after opening if it meets criteria set forth by MDVP). <sup>7</sup>

BMGF NOTES: WHO Policy Statement: Multi-dose Vial Policy (MDVP)

Selection of exact number of doses for a multi-dose vial will depend upon:

- 1) Stability data;
- 2) Anticipated use-case;
- 3) Impact on COGS;
- 4) Availability of pharmaceutical-grade glass/vials.

It should be noted that larger (e.g. 100-dose) presentations may require the use of a vial adapter or other measures to demonstrate container closure integrity and in-use stability through the anticipated period of use (likely 8 hours in outbreak settings). Regarding preservatives: Not a requirement given the constraints of rapidly developing multi-dose formulations.

WHO NOTES: 9) If feasible, vaccines consistent with an "open vial" policy may have additional advantages

CEPI: 7) WHO 2014. [https://apps.who.int/iris/bitstream/handle/10665/135972/WHO\\_IVB\\_14.07\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/135972/WHO_IVB_14.07_eng.pdf).



# Other Components

# Stoppers & aluminum caps

- CEPI has completed an open tender for rubber stoppers and aluminum caps
- The preferred stopper is a low-coring, bromobutyl stopper (Aptar)
- The stopper/cap for the 20R vial was competitively bid; a change in vial will require re-bidding

# Rubber stopper manufacturers update

- Specifications: Stopper for Blow Back Vial , resistant to +40°C -20°C, possibly at -70°C. Coated stopper for use of oil adjuvants
- Initial contact with manufacturers established (80% of market):
  - West: contact ongoing
  - Datwyler: 500M-1BN caps available in target time frame
  - Aptar: CEO contact ongoing, no capacity issues
- Requests for contracting mechanisms / capacity booking

# Autodisable syringe supply

- To understand potential capacity for AD syringes for COVID-19 vaccine delivery, PATH contacted three prequalified AD syringe suppliers in April 2020.
- Even without surveying the entire landscape of suppliers, sufficient capacity for AD syringes appears feasible by 2021. However, the additional scale-up capacity referenced below assumes syringe purchase commitments from UNICEF by May 2020 to enable new equipment purchase and installation.

Note: Some packaging technologies under consideration for COVID-19 vaccines are not compatible with AD syringes (which have fixed needles) and will require supply of different delivery devices.

- MEDInstill pouch with reusable syringe (Luer needle)
- MEDInstill pouch with Luer port (RUP syringe with separable needle)
- BFS Luer ampoule (RUP syringe with separable needle)
- BFS prefilled device (custom needle hub)

Company	Location	WHO PQ	Currently on UNICEF procurement list	Currently uncommitted capacity for 2020	Potential scale by September 2020	Potential scale by March 2021
HMD	India	Yes	Yes	270M	455 M/year	960M/year
ADMD	UAE	Yes	Yes	50M		100M/year
Oneject	Indonesia	Yes	No	100M	500M/year	1180M/year

# Country and commercial readiness

## Demonstrated country interest



- At least 4 LMICs have proactively piloted introduction of barcodes on secondary packaging along with electronic inventory systems and many countries are adopting electronic immunization registries that could benefit from the to enter data by scanning barcodes.
- Turkey has successfully used barcodes since 2010 on all pharmaceuticals and packaging levels, including vaccine primary containers, and all their vaccine suppliers have complied with their request for barcodes on labels.
- In the VIPS Phase II online survey, 96% of LMIC respondents reported that a transition from a paper-based system to an electronic system to inventory vaccines would benefit their immunization program and 95% of respondents reported that such a transition for patient record keeping would benefit their immunization program. Thirty-three percent of respondents stated that their country already uses electronic patient recordkeeping systems.

## Large target market and significant interest in supporting development and commercialization

- Some vaccine manufacturers have moved forward with barcodes on primary packaging to meet the demand from particular countries and/or to comply with their national regulatory authorities (e.g., GSK, Merck, Sanofi, and Wyeth/Pfizer). Some manufacturers will require upgraded labelling equipment and QC procedures to add barcodes.
- Four out of five vaccine manufacturers responding to a recent Delivery Technologies Working Group survey are interested in applying 2D barcodes to vaccine primary containers for LMICs in the future with one specifying that the approach should be phased (with higher packaging levels first). The fifth manufacturer that is not interested has capability but stated that they comply as required by customers.

# Barcodes on primary containers were prioritized by VIPS

- Track and trace is considered a priority for vaccines and 2D barcodes on primary containers would **support the transition to electronic record keeping, in line with the objectives of advancing digital health in Primary Health Care.**
- While this is a mature technology in general, analysis of the added value of barcodes on primary packaging and a 'push' for implementation if warranted by the results could build upon the existing efforts of UNICEF and Gavi to place barcodes on vaccine secondary packaging and spur wider implementation of systematic monitoring and surveillance systems.
- Barcodes could **be highly valuable for COVID-19 vaccine deployment in terms of tracking inventory, immunization coverage, and AEFIs.**
- The COVID-19 crisis may be an opportunity to leverage investment to catalyze barcode implementation for immunization programs more generally. Implementation of barcodes for COVID-19 vaccines is likely not feasible for the current pandemic and the first vaccine deployments, but they may be for later phases of vaccine deployment.
- While it will take time to ensure country readiness, a few countries with advanced electronic recordkeeping could benefit from their availability on secondary packaging almost immediately and on primary packaging in the coming years.
- Clear recognition that barcodes themselves are not an innovation but part of a broader innovation ecosystem that will need coordination and integration within the realms of vaccine standards, manufacturing, regulatory, procurement, distribution, and in-country recordkeeping.



# Ongoing barcode work

- UNICEF has launched a GS1 impact evaluation, outsourced to Movilitas, with the objective of conducting due diligence on the wide ranging operational, economic and programmatic impacts of mandatory GS1 labelling on secondary packaging for vaccines.
  - This work is carried out through a comprehensive consultation with UNICEF Supply Division, regional and country offices, industry, manufacturers, national governments, WHO, UNFPA, national regulatory authorities, industry experts, development partners and donors.
- VIPS is developing a 5-year action plan to consider the impacts of GS1 labeling on primary packaging of vaccines, create an enabling environment to advance this innovation, and to build on the secondary packaging work as appropriate.
  - This work is meant to be complementary to the work of other stakeholders.





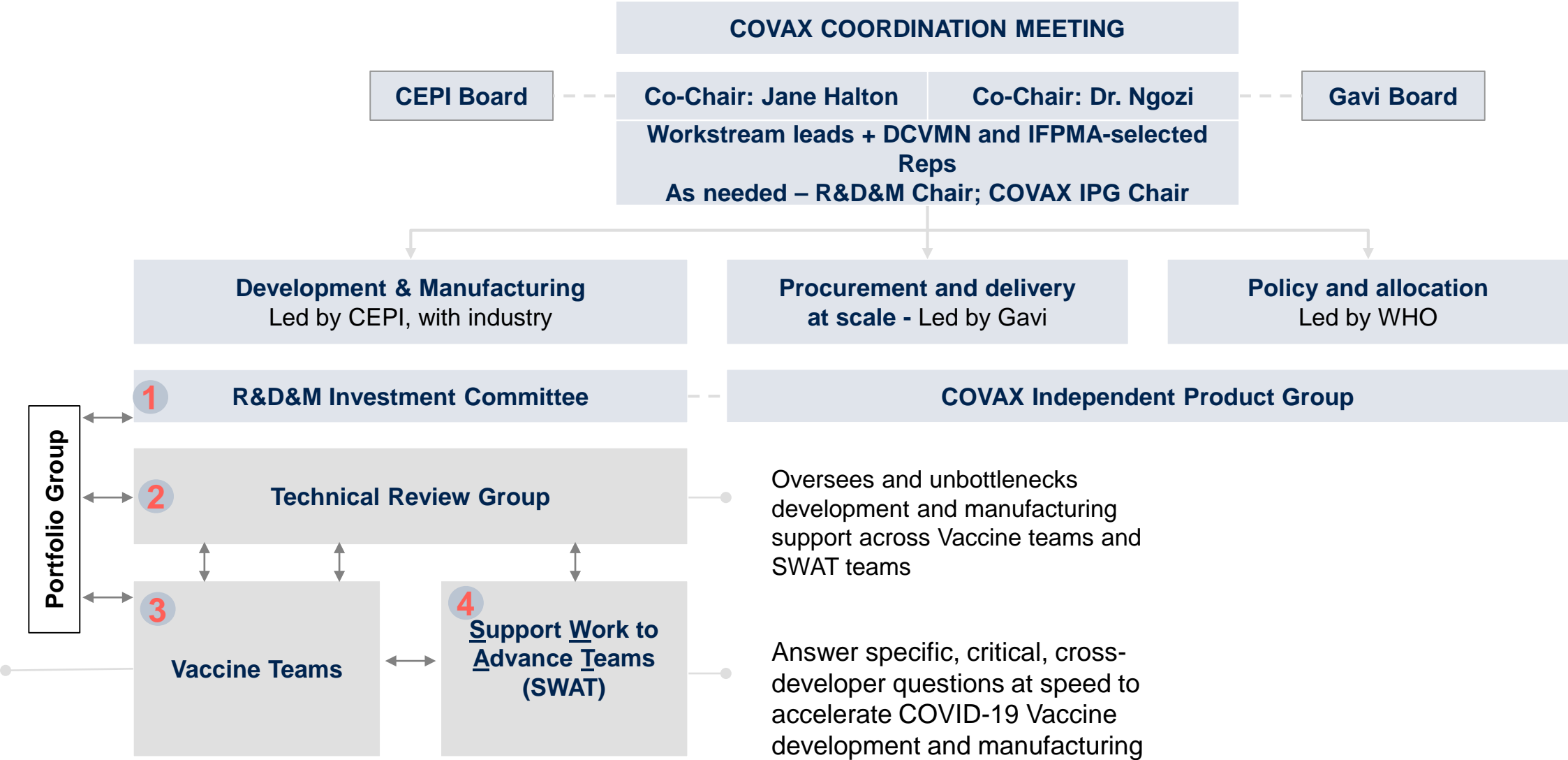
# **ACT-Accelerator: COVAX pillar (vaccines)**

## **Back-up slides**

# Access to COVID-19 tools (ACT) accelerator

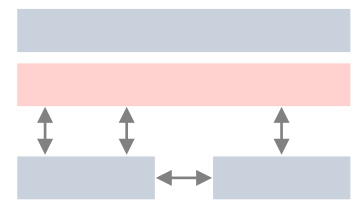


# ACT-A / COVAX governance



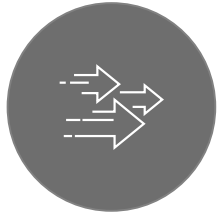
# Technical Review Committee / (Group)

PRELIMINARY



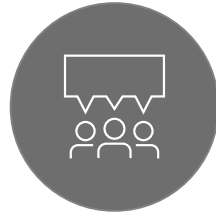
<b>Objectives</b>	<ul style="list-style-type: none"> <li>• Provide end-to-end oversight</li> <li>• Provide technical support and guidance</li> <li>• Ensure optimal integration between teams</li> </ul>	<ul style="list-style-type: none"> <li>• Provide end-to-end oversight</li> <li>• Ensure optimal integration between teams</li> <li>• Provide technical support and guidance to Vaccine Teams</li> <li>• Raise questions from Vaccine Teams to be addressed by SWAT teams</li> <li>• Make stage gate recommendations</li> </ul>
<b>Members</b>	<div>Chair: CEPI Director R&amp;D &gt;&gt;&gt;</div> <div>Core members:</div> <ul style="list-style-type: none"> <li>• Head of Programmes, Function leads, portfolio management member, Director of Finance WHO, Gavi, BMGF &gt;&gt;&gt;</li> <li>• SWAT Team co-leads, IFPMA, DCVMN, other partners</li> </ul> <div>Extended members:</div> <ul style="list-style-type: none"> <li>• External experts – invitation only</li> <li>• Vaccine teams PLs – invitation only &gt;&gt;&gt;</li> </ul>	
<b>Approval authority</b>		<ul style="list-style-type: none"> <li>• Delegated approval authority for budget change requests of up to \$5M</li> </ul>
<b>Format</b>	<ul style="list-style-type: none"> <li>• 1h weekly meeting</li> </ul>	<ul style="list-style-type: none"> <li>• 1h weekly meeting</li> </ul>

# COVAX SWAT teams are being set up as a **joint platform** to accelerate COVID-19 Vaccine development and manufacturing by **addressing common challenges together**



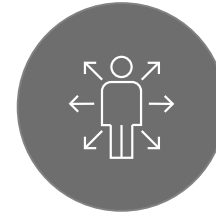
## Timely and targeted

Addresses specific cross-developer technical challenges as they are raised and/or identified on an ongoing basis



## Multilateral

Establishes a dialogue and global joint effort across different COVID-19 vaccines organizations (incl. Industry and other global networks)



## Knowledge-based

Identifies and collates most relevant materials and insights across the broader COVID-19 ecosystem to accelerate vaccine development and manufacturing



## Resource-efficient

Coordinates between different organizations/initiatives to limit duplications and ensure expertise is efficiently leveraged

**SWAT teams**

**Enabling sciences**

**Clinical Development & Operations**

**Manufacturing**

**Regulatory Advisory Group**

# TERMS OF REFERENCE | SWAT Teams

Objectives		<ul style="list-style-type: none"><li>▪ Focus on resolving common technical cross-project questions and challenges at speed</li><li>▪ Act as an open source of information for Vaccine Teams and more widely</li><li>▪ Promote harmonization and comparability across projects</li><li>▪ Bring together different stakeholders and coordinate with other players in the ecosystem to maximize efforts (e.g., ACTIV)</li></ul>
Approval authority		<ul style="list-style-type: none"><li>▪ Small budget allowance will be set up for workshops and will require approval of the CEPI SWAT team lead</li></ul>
Role description	Lead	<ul style="list-style-type: none"><li>▪ Identify key questions, deliverables, timelines, core team and extended team membership, and ways of working for the SWAT team</li><li>▪ Develop and assess work packages as per deliverables description</li><li>▪ Accountable for progress of each deliverable</li></ul>
	Core team	<ul style="list-style-type: none"><li>▪ Help with definition and revision of key questions, deliverables and timelines as needed</li><li>▪ Drives SWAT team work according to work packages/ deliverables description</li><li>▪ Involved with decision-making on topic of expertise (e.g., Regulatory)</li></ul>
	Extended	<ul style="list-style-type: none"><li>▪ Additional experts and representatives of institutions / organisations may attend as standing observer or ad hoc as required, to provide expertise in knowledge-specific items</li></ul>
Decision making principles		<ul style="list-style-type: none"><li>▪ SWAT Team lead is responsible for developing timed deliverables &amp; work packages to be reviewed by the Technical Review Committee</li><li>▪ Core team experts are involved with decision-making on topic of expertise; Extended members do not have decision rights</li><li>▪ If consensus cannot be reached on a topic and further expertise required, SWAT Team lead to escalate to Technical Review Committee</li></ul>
Format		<ul style="list-style-type: none"><li>▪ <b>Forum:</b> Multi-lateral discussions</li><li>▪ <b>Frequency:</b><ul style="list-style-type: none"><li>▪ Bi-weekly check-ins (15 mins) on critical topics</li><li>▪ Working sessions once a week (1.5h each with prep time)</li><li>▪ Weekly check-ins with Vaccine teams Project Leaders</li><li>▪ Cross SWAT team check-ins to solve interdependencies scheduled as needed</li></ul></li></ul>

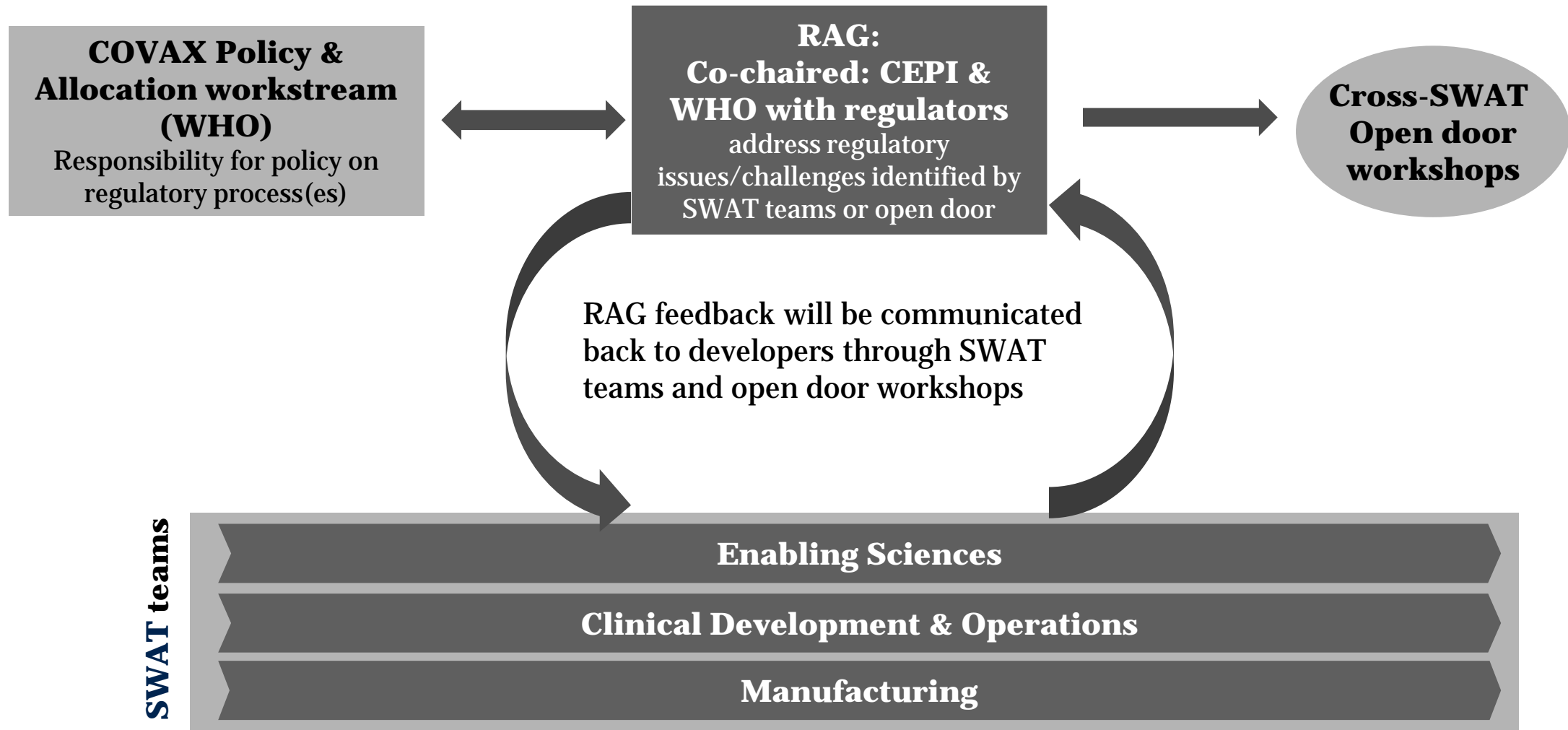
SWAT

(Vaccine Manufacturing Cross-Product Support Team)

teams membership

	Leads	Core team members	Extended team members
Enabling sciences	Paul Kristiansen (CEPI) & (WHO)	IFPMA, DCVMN, BMGF, CEPI Task Force Leads, CEPI regulatory (Deb Yeskey/ Svein Rune Andersen)	CEPI participants and additional experts
Clinical Development and Operations	Jakob Cramer (CEPI) & Peter Dull (BMGF)	NIH/NIAID, WHO, IFPMA, DCVMN, SPEAC/BC, Statistics, CEPI Reg. Affairs, CEPI Epi, CEPI regulatory (Deb Yeskey/ Svein Rune Andersen), AVAREF, Africa CDC, ASEAN-NDI, Ana Maria Henao Restrepo (WHO)	CEPI participants and additional experts
Manufacturing	Ingrid Kromann /Nicolas Havelange (CEPI) & David Robinson (BMGF)	Adriansjah Azhari (DCVMN), Carmen Rodriguez Hernandez, (WHO), Jim Robinson (CEPI CMC-SM), Deb Yeskey/ Svein Rune Andersen (CEPI regulatory) Dominique Maugeais (GAVI), Michael Thien (IFPMA), Diane Wilkinson (Vaccines Europe)	CEPI participants and additional experts
Regulatory support			
Regulatory Advisory Group (RAG)	Deb Yeskey/ Svein Rune Andersen (CEPI),WHO & regulators		

# A Regulatory Advisory Group (RAG) will support SWAT teams



**RAG monthly meeting:** SWAT team leaders will bring relevant topics to CEPI regulatory, who will aggregate material and make available to the RAG prior to meetings



# Regulatory Advisory Group

Generic topics that would warrant regulatory feedback:

## Clinical development:

- Minimum data package requirements for entering in rolling review with stringent regulatory agencies
- Clinical trial designs, clinical endpoints, correlate of protection, special populations, safety monitoring/follow-up
- Requirements for post-licensure efficacy and safety studies

## Manufacturing:

- Manufacturing requirements for emergency use – level of maturity expected
- Strategy for validation/validation of manufacturing processes across sites.
- Specifications and Analytical methods
- Authority batch release requirements + procedure

## Enabling sciences

- Animal models – requirements for standardisation
- Clinical assays and reference standards

# SWAT teams – Enabling Sciences

## Task Forces

### Proposed activities [targeted due date (for first version)]

#### Assay Standardization

- **Antibody standard available**
  - Research grade antibody standard and panel [Completed April 2020]
  - International antibody standard [material available by end of May 2020 and target WHO ECBS endorsement by February 2021]
- **Centralized testing capacity** for uniform performance within identified consortium of labs set up to analyze pre-clinical and clinical Phase 1 and 2 samples. Plans to include in ELISA (total IgG binding to full S, RBD, NP), pseudoviral neutralization, wild type neutralization, ELISPOT [First laboratory contract signed beginning of July 2020]
- Define the **type and required performance of Diagnostic assays** for clinical trial use, as a basis for assay evaluation and validation
- **Addressing regulatory challenges** related to assay standardization

#### Animal models

- **Establishment of animal testing network to**
  - Develop appropriate animal models
  - Ensure high quality testing capacity for supported vaccine candidates
- **Scientific evidence on appropriate animal models** for safety and efficacy
- **Guidance on VMED evaluation work**, based on summary of research
- **Guidance on CoP** for Covid-19 before late stage clinical trials based on summary of research [September 2020]
- **Addressing regulatory challenges** related to animal models

# SWAT teams – Clinical Development & Operations

Task Forces	Proposed activities [targeted due date (for first version)]
Clinical-operational readiness	<ul style="list-style-type: none"> <li>• <b>Trial site readiness</b></li> <li>• <b>Landscape analysis:</b> which developer will join i) Solidarity III, ii) NIH/ACTIVE, iii) individual efficacy trial approaches</li> <li>• Create <b>open access database / repository</b> with information on regulatory requirements for <b>CTA</b></li> <li>• <b>Clinical trial site network set-up</b> with mapping of ability (capacity &amp; capability) to hold trials with a focus on countries / regions that may require capacity building support</li> </ul>
Vaccine safety	<ul style="list-style-type: none"> <li>• <b>Case definition</b> for relevant <b>AESIs</b> [July 2020]</li> <li>• <b>Case definition on vaccine-mediated disease enhancement (VMED)</b></li> <li>• <b>Planning of post roll-out vaccine safety surveillance</b></li> <li>• <b>Maternal immunizations / pregnant women in clinical trials</b></li> </ul>
Clinical science	<ul style="list-style-type: none"> <li>• <b>Standard clinical trial elements</b> including endpoint case definitions for disease and infection (primary / secondary endpoints) [July 2020]</li> <li>• <b>Adaptive</b> (case-driven) <b>trial design</b> [July 2020]</li> <li>• <b>Correlate of Protection in clinical trials</b></li> <li>• <b>Alternative / supportive evidence</b> in case conventional vaccine efficacy trials are not possible (e.g. passive transfer, CHIM)</li> <li>• <b>Discuss optimization options</b> e.g., seamless / expansion trial designs, e.g. combining two (or more) phases into a single trial, adapting after an interim readout (e.g., after dose-finding portion, ineffective dose groups are stopped while effective dose groups are expanded to show efficacy)</li> </ul>