Manufacturing, tech transfer and release challenges

Ingrid Kromann
Head CMC, CEPI

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A global partnership

Vision

A world in which epidemics and pandemics are no longer a threat to humanity.

Mission

To accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be accessible to all people in need.

The COVID-19 pandemic

Over 3.3 million lives now lost.

Expected to cost the global economy **USD 28 trillion by 2025.**

Destroyed the livelihoods of hundreds of millions, fractured societies, and broken the very essence of ‘normal life’.

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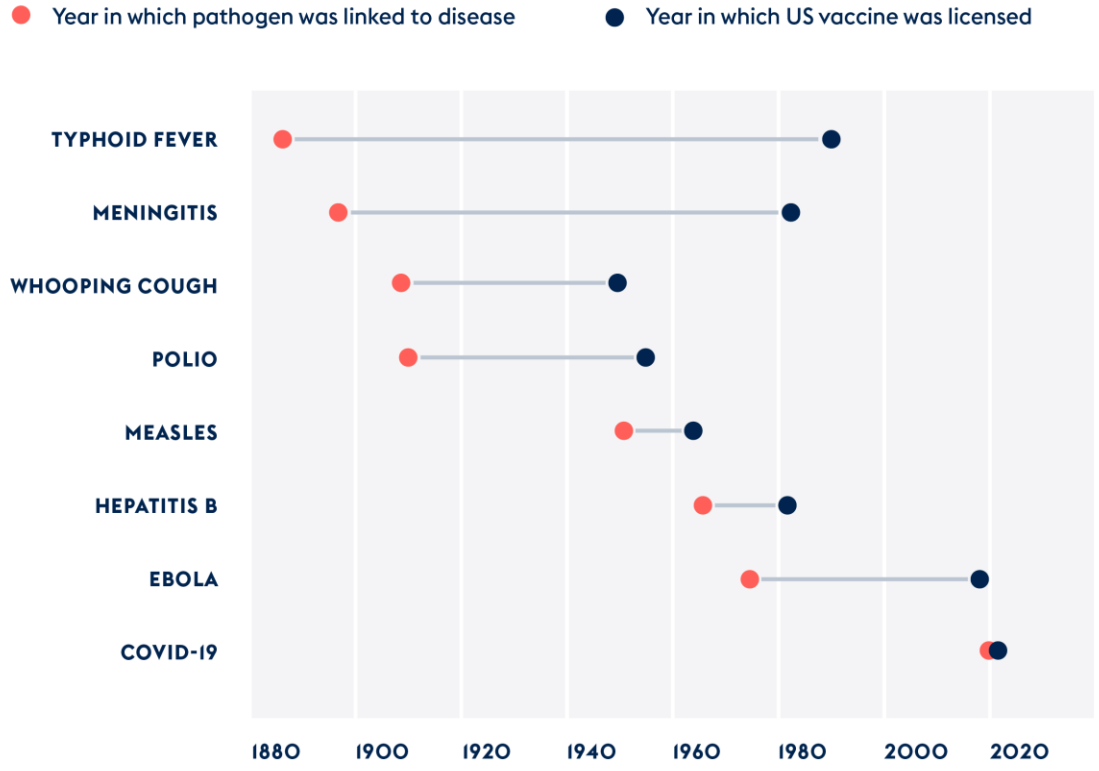
Rapid progress in vaccine innovation



Data source: Our World in Data

“We are not only experiencing a period of catastrophe but this era in history will also be remembered for the incredible advances in vaccine technology and medicine more generally.”

CEPI CEO, Richard Hatchett

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Early MERS and Disease X investments

The beta coronavirus causing **Middle Eastern Respiratory Syndrome** (MERS) was on CEPI's list of priority pathogens

Preparing for **Disease X** by developing rapid-response platforms was one of CEPI's top priorities

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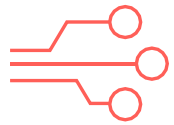
Today - 10 CEPI-supported vaccines

	DNA / mRNA			Viral vector		Protein				
COVID-19	**Inovio**	**Moderna**	**CureVac**	**University of Hong Kong**	**AstraZeneca / Univ. Oxford**	**VBI Vaccines**	**Novavax**	**Clover BioPharma**	**Biological E**	**Sk Bio**
Location	USA	USA	Germany	China	UK	US/ Canada	USA	China	India	South Korea
Platform	DNA	mRNA	mRNA	Viral Vector	Viral Vector	VLP	Protein	Protein	Protein	Protein
Antigen / Adjuvant	Full-length S protein	Full-length S protein	Full-length S protein	Receptor Binding Domain	Full-length S protein	Full-length S protein/ alum	Full-length S protein / saponin-based Matrix-M	Full-length S protein/CPG10 18	Monomer RBD /CpG-alum	Recombinant RBD / Alum, AS03, or CpG+Alum
Current phase	Phase II/III	Phase III ongoing. WHO EUL granted	Phase II/III	Phase I	Phase III ongoing. WHO EUL granted	Preclinical	Phase III	Phase II/III	Phase I/II	Phase I/II

Speed



Scale

Access

CEPI's preliminary COVID-19 vaccine portfolio

COVID-19

	Moderna	Inovio	University of Queensland / CSL	CureVac	Clover BioPharma	Merck / Themis	Novavax	AZ / Univ. Oxford
Platform	mRNA	DNA	Protein	mRNA	Protein	Viral Vector	Protein	Viral Vector
Weeks from ID of pathogen to start of the clinical trial	9	12	26	23	23	35	20	15

Platform	Protein	RNA	Viral Vector	DNA
Weeks from ID of pathogen to manufacturing 100.000 doses	< 20	< 20	< 22	< 30

Adjuvants

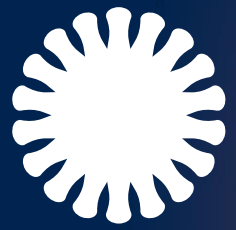
gsk

DYNAVAX

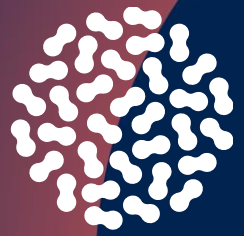
Seqirus

Speed **Scale** **Access**

CEPI response to COVID-19

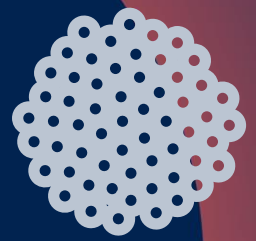


Early MERS and Disease X investments

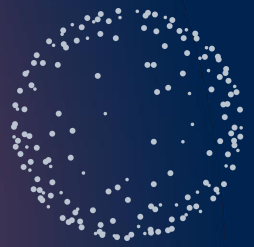


Establishing one of the largest vaccine portfolios

Harmonising assessment of COVID-19 vaccine data



Tracking SARS-CoV-2 variants



Advancing broadly protective coronavirus vaccines

Enabling equitable access through COVAX

The solution: COVAX

COVAX is the only solution which will deliver fair, equitable and necessary access to vaccines for every country that participates.

Together we aim to produce 2 billion doses of vaccine and distribute them globally and fairly in 2021.

COVAX works by pooling financial resources to purchase vaccines at scale, sharing the risks associated with developing vaccines and investing up-front in manufacturing so that vaccines are ready to be distributed as soon as they are licensed.

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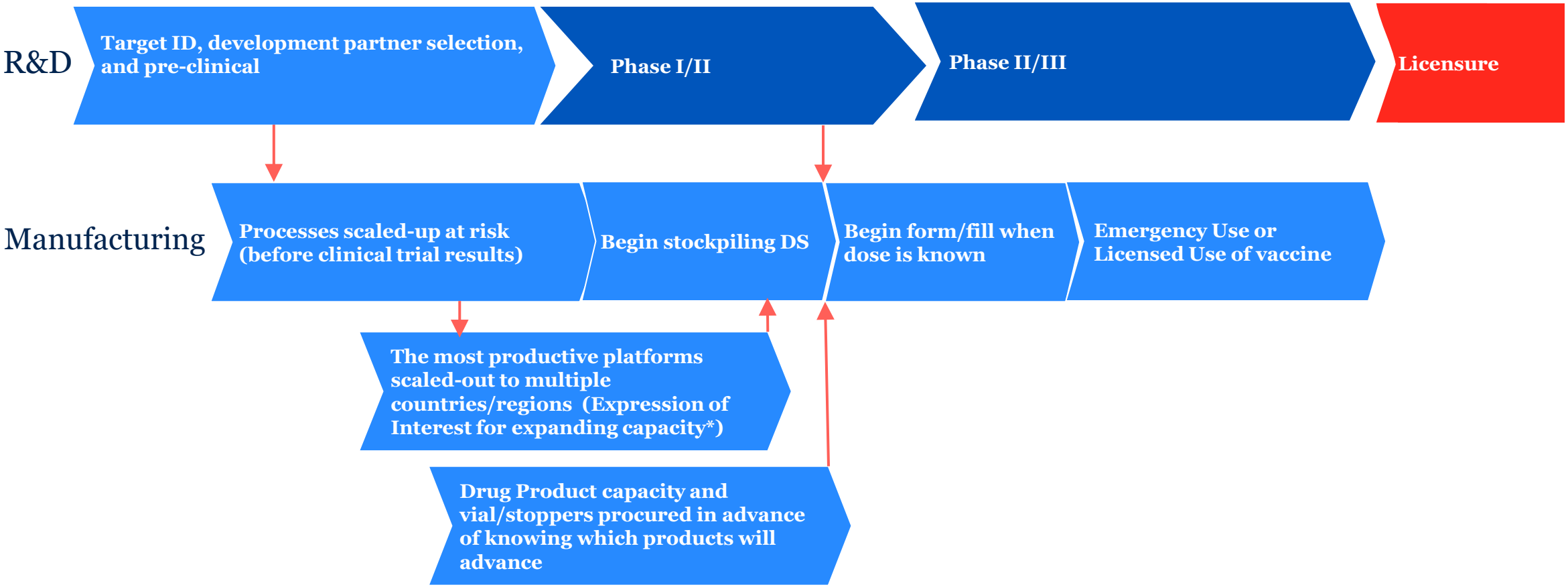
COVAX – Manufacturing working groups and activities

Working groups	Activities and workshops
DP/DS Scale up and out	• **Drug Product strategy and capacity:** – DP facilities identified and strategy described – CMC: e.g., validation strategy (process) – manufacturing network established and capacity booked (F&F activities) adjuvant and LNP capacity identified • **Drug Substance strategy and capacity:** – antigen scale-up and scale-out plans – CMC: e.g., validation strategy (process) and comparability – manufacturing sites matched and capacity booked • **Manufacturing requirements for emergency use** – regulatory advices • **Addressing regulatory challenges** related to DP and DS scale up and out
Supply Chain/labelling/barcoding	• **Supply chain strategy** • Labelling strategy, raw materials secured (i.e., vials, stoppers, single use items, media, resins) – PQ/EUL Labelling/counterfeit countermeasures • **Addressing regulatory challenges** related to supply chain
Release assays	• **Potency assay requirements** – approach regulatory agencies for advice • **Procedure to allow timely national batch release** – mutual recognition • **Addressing regulatory challenges**

Manufacturing scaled-up and out at risk to maximize doses available in 2021



- Scale-out of Drug Product aimed to distribute manufacturing across multiple countries/regions.

Process Deliverables for COVID-19

	Ph1/2a (early stage)	Ph2b/3 (late stage)	Final scale for outbreak use and licensure
High level definition	Process defined and transferred to manufacturing site	Process fit for purpose, capacity > 100M doses/year	Process validation
Quality	• Process developed & basic consistency demonstrated • FF process in place • Process description and MBR • Ph1 CTM released • CQAs & CPPs defined based on risk assessment • RA & CMC strategy discussed	• Process optimized, scaled up, and fixed (intermediate or final scale) • Process robustness demonstrated (#CTMs) • Process characterization • Updated CQAs & CPPs • Final MBR • In process hold times established	• Process validated, or Validation Master Plan defined for validation after licensure for outbreak use • Scale up and comparability between intermediate and final scale (if applicable)
Viability	• Process scale up approach defined • Estimated # doses/year • TT strategy and protocol • Development cost and COGS estimated	• Final COGS confirmed within range suitable for global access • Final scale-up and scale-out strategy and sites defined, capacity > 100M doses/year • DP strategy defined • regulatory authority(ies) agreement on the Process and the Analytical Plan?	• Confirmation of capacity and COGS

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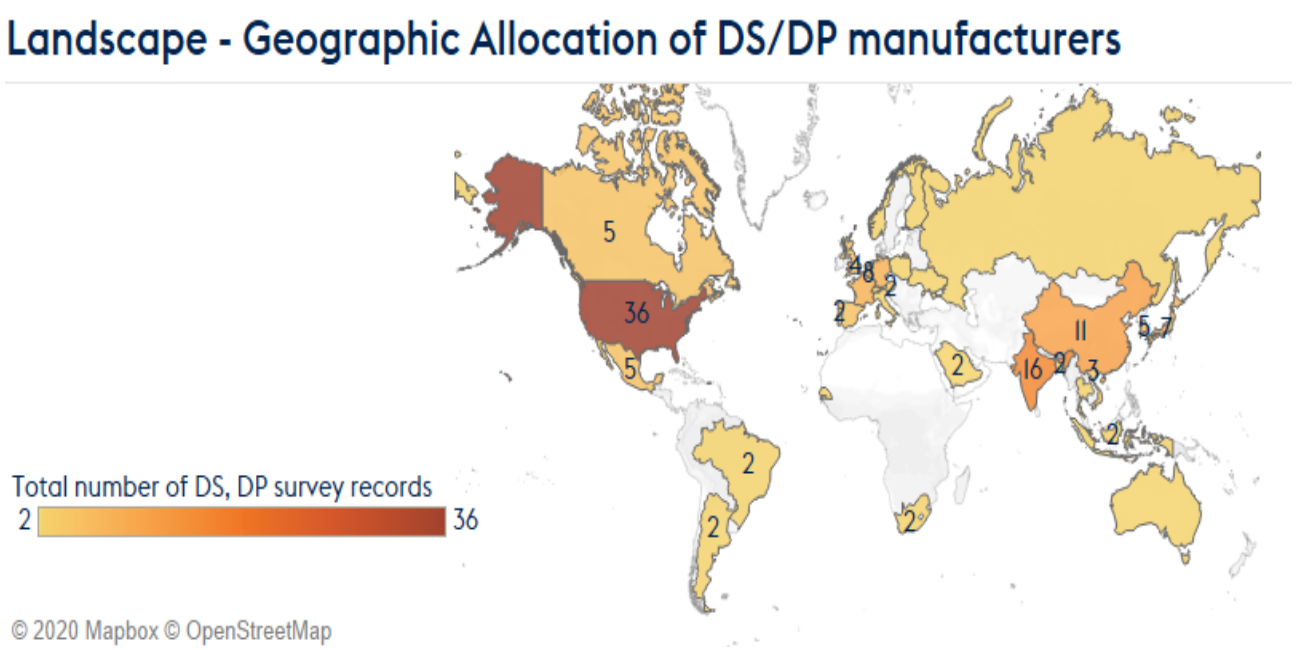
Process

Strategic investments to support producing 2 billion COVID-19 vaccines by end of 2021



Each number reflects the quantity of DS and DP manufacturers and their location

This does not take into account how many facilities each manufacturer operates

52 **DS** manufacturers reviewed

20 Groups contacted

1 Reservation agreement signed with SK Bio (S. Korea)

6 Deals signed between vaccine manufacturers & developers based upon CEPI introduction

Feb'20: DS capacity built at risk to scale out most productive platforms

Feb'20: DP capacity & vials procured in advance of knowing which vaccines to progress

89 **DP** manufacturers reviewed

23 Groups contacted

7 Companies shortlisted

2 Reservation agreements signed with GC Pharma (S. Korea) & BioFabri (Spain)

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Tech Transfer workshop – key take aways

Strategy

Facilities and Engineering

Analytical QC Testing

Process riskmanagement

Regulatory

Raw materials & supply chain

Communication

1. **Supply** – Focus on raw materials and consumables early (“have a mass balance”). Build in a plan for “worst case” such as low yields and ensure proper mitigation strategies.
2. **Cultural and language** - assign project manager with right language skills and consider implementing mechanisms to monitor preferences and collaboration between member states
3. **Documentation** - Have a clear documentation strategy with in the “end in sight”— write each report with a focus on what needs to go into regulatory submissions to reduce redundancy of technical writing.
4. **Teamwork** - Identify decisions and decision-makers upfront and empower them. Think out of the box — unite, collaborate and cooperate.
5. **Leverage prior knowledge** (in this case of similar platforms) for risk-based approach to prioritize experiments on unit ops and parameters that are at high risk or with little understanding.
6. **Regulatory** – Early and frequent regulatory communications and engagement throughout tech transfer facilitates compliant transfer process and final approval

Analytics Deliverables for COVID-19

	Ph1/2a (early stage)	Ph2b/3 (late stage)	Final scale for outbreak use and licensure
High level definition	Key Analytical methods scientifically sound	Key analytical methods qualified	Key analytical methods validated
Quality	• TPP and initial specifications defined • Key analytical methods in place for release and stability (potency, identity, purity) • Qualified assays for dose selection • Ph1 and Tox material shown to be comparable • IPCs identified • Analytical and regulatory strategy defined	• Ph1/2a material shown to be representative of Ph2b/3 material • Potency assay qualified at selected dose • Release and stability methods qualified (antigen & adjuvant)	• Specifications fully justified • Potency assay validated at selected dose • Release and critical stability assays validated • Other CQA assays qualified • Ph2b/3 material representative of material for outbreak use • Correlation *in vitro* / *in vivo* potency
Viability	• Need for adjuvant and related analytical methods identified	• Assay throughput not rate-limiting for Ph2 • Capacity and throughput needs for Ph3 defined • Identify qualified vendors for supply of all reagents at scale • Identify potential preservative need • regulatory authority(ies) agreement on the Process and the Analytical Plan	• Ensure compatibility of assays with preservative and final container material

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Process

Assay- release


This text was drafted by the EDQM in collaboration with Group of Experts 15 (vaccines for human use) of the European Pharmacopoeia (Ph. Eur.) Commission, composed of experts from licensing authorities, national control laboratories, academia and industry, from Europe, the USA, Canada and Australia. It is not an official text of the Ph. Eur. and is not binding.

RECOMBINANT VIRAL VECTORED VACCINES FOR HUMAN USE

https://www.edqm.eu/sites/default/files/medias/fichiers/COVID-19/recombinant_viral_vectored_vaccines.pdf

Full OCABR Guideline for Pandemic COVID-19 vaccine (mRNA) now available

NEWS | 07 APRIL 2021 | STRASBOURG, FRANCE

https://www.edqm.eu/en/news/full-ocabr-guideline-pandemic-covid-19-vaccine-mrna-now-available

npj | Vaccines

www.nature.com/npjvaccines

PERSPECTIVE OPEN

Check for updates

Considerations for bioanalytical characterization and batch release of COVID-19 vaccines

Gautam Sanyal[1]✉, Anna Särnefält[1] and Arun Kumar[1]

The COVID-19 pandemic has prompted hundreds of laboratories around the world to employ traditional as well as novel technologies to develop vaccines against SARS-CoV-2. The hallmarks of a successful vaccine are safety and efficacy. Analytical evaluation methods, that can ensure the high quality of the products and that can be executed speedily, must be in place as an integral component of Chemistry, Manufacturing, and Control (CMC). These methods or assays are developed to quantitatively test for critical quality attributes (CQAs) of a vaccine product. While clinical (human) efficacy of a vaccine can never be predicted from pre-clinical evaluation of CQA, precise and accurate measurements of antigen content and a relevant biological activity (termed "potency") elicited by the antigen allow selection of potentially safe and immunogenic doses for entry into clinical trials. All available vaccine technology platforms, novel and traditional, are being utilized by different developers to produce vaccines against SARS-CoV-2. It took less than a year from the publication of SARS-CoV-2 gene sequence to Emergency Use Authorization (EUA) of the first vaccine, setting a record for speed in the history of vaccine development. The largest ever global demand for vaccines has prompted some vaccine developers to enter multiple manufacturing partnerships in different countries in addition to implementing unprecedented scale-up plans. Quantitative, robust, and rapid analytical testing for CQA of a product is essential in ensuring smooth technology transfer between partners and allowing analytical bridging between vaccine batches used in different clinical phases leading up to regulatory approvals and commercialization. We discuss here opportunities to improve the speed and quality of the critical batch release and characterization assays.

npj Vaccines (2021)6:53; https://doi.org/10.1038/s41541-021-00317-4

OMCL – NCL test and release

- **IDENTIFY AN OMCL FOR OCABR**: To help manufacturers identify OMCLs for the conduct of OCABR a list of OMCLs with capabilities relevant for OCABR of COVID-19 vaccines has been established and is available to manufacturers on request at BatchRelease@edqm.eu.
- **FACILITATING TIMELY TEST TRANSFER**: Recommendations for early transfer to OMCLs of methods for potential EU OCABR tests of COVID-19 vaccines candidates to comply with the accelerated vaccine development timelines; available to manufacturers on request at BatchRelease@edqm.eu. Elements of this recommendation are also relevant for blood derived medicinal products.
- **PRODUCT SPECIFIC GUIDELINES: NEW:** Pandemic COVID-19 Vaccine (Non-Replicating Adenovirus-Vectored Vaccine) and Pandemic COVID-19 Vaccine (mRNA Vaccine) guidelines are available in the full version and include an update with the model protocol for manufacturers. A **NEW** Pandemic COVID-19 Vaccine (Recombinant Spike protein) guideline containing section 2 only is also available. It was prepared based on knowledge available at the time of drafting. It will be updated accordingly including addition of a model protocol for the manufacturer's data submission, in line with the relevant approved marketing authorisations when available.

Document title	Last web update	In force from
Pandemic COVID-19 Vaccine (Non-Replicating Adenovirus-Vectored Vaccine) (full version)	20/04/21	01/05/21
Pandemic COVID-19 Vaccine (mRNA Vaccine) (full version)	06/04/21	01/05/21
Pandemic COVID-19 Vaccine (Recombinant Spike protein) (section 2 only)	20/04/21	20/04/21

https://www.edqm.eu/en/ocabr-activities-related-covid-19-vaccines

World Health Organization

National Control Laboratories

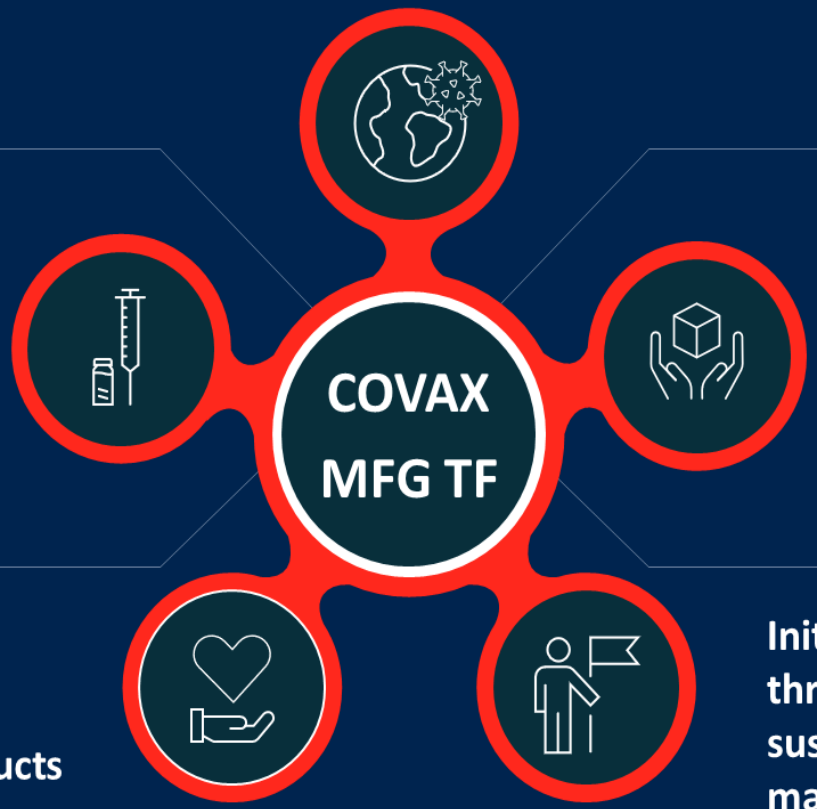
Manufacturers can apply for prequalification of a vaccine only if their national regulatory authority (NRA) (or the NRA of the vaccine-exporting country) is "functional" or a WHO-listed Authority operating at maturity level 3 or above. One of the critiera for such NRAs is that they operate a national control laboratory that can perform lot release testing of prequalified vaccines.

Current CMC Challenges

- Raw material supply – single use filters, bags etc
- Multiple tech transfers – complex comparability studies
- QC/Assay robustness and validation
- Appropriate stability program to support shelf life through release and distribution/administration
- QA resources for release of product
- Shipment – import/export of raw materials and vaccine components

COVAX supply chain & manufacturing task force

Support COVAX mission to end acute phase of the pandemic by end 2021



Optimize the number of Vx doses manufactured in the short term

Prioritize doses for COVAX with a special emphasis on AMC92 to ensure greater equity

Mitigate unintended impact on other vaccines and health products

Initiate regional health security through establishment of sustainable regional long-term manufacturing of vaccines

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World Health Organization
Gavi The Vaccine Alliance
unicef
Bill & Melinda Gates foundation
IFPMA
dcvmn Developing Countries Vaccine Manufacturers Network
Bio Biotechnology Innovation Organization

Status

COVAX original aim is to deliver at least 2 billion doses of vaccines in 2021, including 1.8 billion doses to low- and middle-income countries.

To date, COVAX has delivered nearly 78m doses of COVID-19 vaccine to 127 countries since its launch in February. Designed and implemented in the midst of an unprecedented global public health crisis, COVAX has proven it works.

COVAX partners are now urgently calling on countries to fund the COVAX AMC, share doses, and free up supply chains.
COVAX will also continue to diversify its portfolio further and will announce new agreements with vaccine manufacturers in due course.

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Another pandemic need never happen

100-day vaccine development timeline moonshot

Vaccine libraries for whole virus families

CEPI has an important role to play in the post-pandemic architecture

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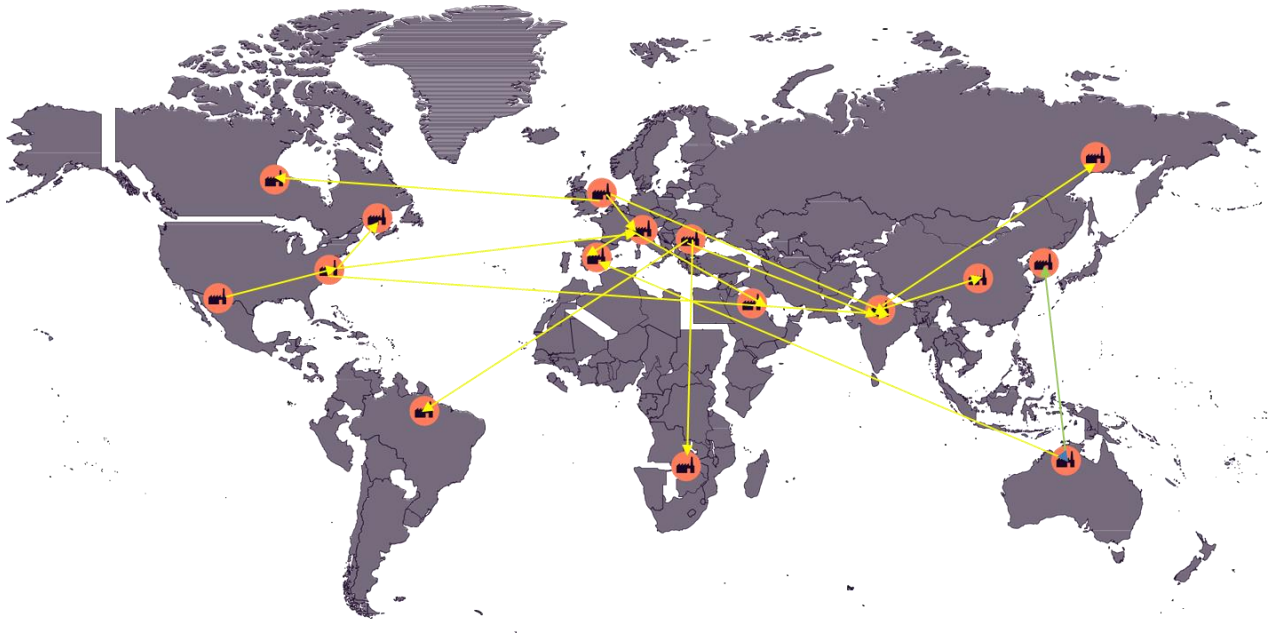

Request for Information: 2021 CEPI Vaccine Manufacturing Landscape Assessment

CEPI together with BMGF are requesting information to identify countries/regions in Africa, South East Asia, Latin America, and Middle East with either:

- Existing vaccine capacity/capability and requirements to develop these further to improve epidemic/pandemic preparedness and response options in future…or…
- Countries or regions with aspirations to establish &/or improve vaccine capacity/capability that may currently be absent or limited

Note: Call open 29Mar-31May 2021

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CEPI: New vaccines for a safer world