

Accelerated vaccine development and experiences with regulatory pathways for vaccines in emergency situations

October 26th 2020



Agenda

- Introductions of the organizers, meeting overview and rules 5 min
- "Overview of EUL/PQ and regulatory alignment to facilitate approvals at global level" (20 min. and 20 min. Q&A
 - o Carmen Rodriguez-Hernandez, WHO
- "Lessons Learned in the Development of an Ebola Vaccine" (20 min. presentation and 20 min. Q&A)
 - o Jayanthi Wolf; Executive Director, Global Regulatory Affairs, Merck MSD
- "Bio Farma and Development of a novel oral polio vaccine (nOPV2)" (5 min. presentation and Q&A)
 - o Erman Tritama, PT Bio Farma
- "Accelerated development and WHO EUL submission for nOPV2" (15 min. presentation and 15 min. Q&A)
 - o Ajoy Chakrabarti & David Robinson, Bill & Melinda Gates Foundation

Regulatory alignment and authorization of vaccines under EUL/PQ

SWAT manufacturers workshop

"Accelerated Vaccine Development and Experiences with regulatory pathways for vaccines in emergency situations"

Carmen Rodriguez Team lead vaccines Prequalification

Department of Regulation and Prequalification (RPQ)

26 October 2020



WHO's ongoing COVAX regulatory work



- Alignment ongoing (Regulatory Advisory Group, ICMRA*, regional regulators)
- Biweekly regulatory updates, 15 regional update webinars
- Documents published
 - EUL procedure (Jan), Q&A (Jul)
 - Draft consideration criteria (Sep)
 - Expression of Interest (EoI) (EUL/PQ) (Oct)
- >10 dedicated company meetings hosted prior to EoI publication
- Roadmap template (expected publication 30 Oct)
- Safety preparedness manual
 - PV Preparedness checklist, AESI definitions, active surveillance methods, guidance on RMPS, PSURs, data sharing platforms, reliance, work-sharing and risk communications

Features of PQ and EUL



Prequalification (PQ) 1987

- Review of extensive quality, safety and efficacy and PSPQ for international supply
- Assessment performed by WHO independent experts
- Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- Post-PQ monitoring
- Reassessment/requalification

Emergency Use Listing (EUL) 2015

- Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs
- Rolling review of data
- Assessment performed by WHO independent experts in collaboration with National Regulatory Authorities (WLA)
- Reliance on WLA abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- Post- deployment monitoring
- Time limited recommendation
- Development should continue for MA/PQ

WHO EUL/PQ submission requirements for evaluation of COVID-19 candidates & areas of specific guidance (examples)

Non-clinical & Clinical assessment

- Non-clinical information
- Clinical development programme
- Ethics Committee approval of clinical trials
- Evidence of GLP/ GCP conduct
- Evidence for registration
- Clinical trial design
- Statistical Considerations
- Clinical trial end-point assays
- Vaccine lots used in clinical studies and lotto-lot consistency studies
- Subject exposure to a new vaccine in trial

- Follow-up in clinical trials
- Requirement for a risk management plan
- Specific data:
 - Clinical efficacy data
 - Immunogenicity data
 - Duration of protection
 - Indirect effect
 - Target populations
 - Safety data
 - Benefit risk assessment report

Manufacturing, QC & labelling

- Characterization of cell banks
- Characterization of master and working seed organism(s)
- Process validation (based on risk assessment, incl. production lot consistency & post-listing commitments)
- Justified specifications
- Stability data
- GMP inspection reports
- Process change
- Labelling

WHO's assessment decision will be guided intra alia by **status of clinical development**, extent of the **available quality, safety and efficacy data**, evidence of **compliance**, **process validation** and reference NRA **regulatory approvals**

Relevant information for estimating timelines to EUL/PQ

Estimated best case scenarios:

- First full EUL/PQ application submission Jan 2021
- Timely EUL/PQ recommendation (contingent on parallel review) – within days of approval by NRA / SRA in charge of oversight
- Translation to in-country decisions or approval 1 month post EUL/PQ

& Next steps



- Identify risks and provide advice for addressing potential issues that arise in the course of assessing timelines & product acceptability
- Progress on regulatory agreement on single label (model) –WHO position on QR/barcodes
- Flag potential issues that affect interfaces with policy, allocation & communication work

Regulatory alignment, authorization and country processes



1 Context & need for global regulatory alignment



- **Rapid globalization** of supply chain of medical products & technologies (clinical trials, manufacturing, marketing, distribution)¹
- Patchwork of regulatory requirements & processes globally
- Uneven global regulatory capacity for new drug approval
- Duplicated efforts for a given product submitted to agencies in different countries¹
- Increased time and cost to bring new drugs to market¹
- Barriers to assurance of drug efficacy/ safety & efficient dev. of novel treatments²
- **COVID-19 context** calls for greater scale of cooperation (large number of vaccines under development and large number of countries to benefit from such vaccines)

Need for multilateral strategic coordination of regulatory efforts

1 "International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary." Forum on Drug Discovery, Development, and Translation. V. Weisfeld and T.A. Lustig, Eds. National Academies Press (US), Washington (DC). 24 Oct. 2013. Web.

2 Zerhouni, Elias and Margaret Hamburg. "The need for global regulatory harmonization: A public health imperative," Science Translational Medicine. 8:338 (2016).

WHO regulatory alignment roadmap for COVID-19 vaccines: overview of recognized pathways, and summary of related alignment activities





- Aligned requirements with
 NRA / SRA in charge of
 oversight
- Participant NRA requirements
 captured
- Single format for application
 submitted by manufacturers
- Interactions & agreements with NRAs/ SRAs in charge of oversight early in process (incl. report sharing, aligned requirements)
- **Global assessment** with region-designated national authority representatives
- Transparent sharing of reports with all regulatory authorities for decision making process
- **Promotion of reliance principles** in countries based on facilitated pathways (direct, through regional networks, via regional champions/NRAs of reference)

In-country expedited approval for use & post-listing monitoring: the WHO regulatory alignment roadmap*



1. Preliminary activities	2. Launching of EOIs	3. Submissions & assessment	4. Recommendation for listing	5. Post-listing monitoring
 Global regulatory cooperation Establishment of strategies for expedited approval in participants & post-listing monitoring 	 Manufacturers EOIs (Phase IIb/III & approval by NRA/SRA in charge of oversight within 6 months & compliance with criteria for assessment) Discussions on rolling submission procedure 	 Establishment of assessment pathway according to NRA/SRA in charge of oversight Establishment of Review Committee (NRA/SRA in charge of oversight & regulators /reviewers from potential user participants) 	 Approval granted by NRA/SRA in charge of oversight Advisory committee convened (post-listing commitment) WHO EUL/ PQ recommendation with conditions 	 Implementation of strategies for safety, quality & effectiveness monitoring Validity of listing based on new data generated Possible conversion of EUL to PQ
COVAX EUL/PQ	NRA reliance on EUL/PQ	acilitated access to countrie	!S	
	• S • V	haring of assessment/ inspection VHO-facilitated national approve	on reports / lot release with r al process	regional-designated country reps



- Incorporate feedback on WHO roadmap and continue implementation discussions with regional networks & reference NRAs
- Finalize labelling recommendation
- Continue support for planning of **post-marketing / safety monitoring** in countries
- Respond to issues raised to the COVAX Regulatory Advisory Group (WHO co-chairs)
- Continue engagement & alignment with **regulatory bodies** (e.g. ICMRA, regional regulatory networks) incl. updates/webinars
- Update on best practice principles for regulatory "agility"



WHO's regulatory alignment roadmap* is based on collaborative principles & to be successful...

- o Regional networks must identify regional experts to take part in global assessment
- Agreements must be established with NRAs/SRAs in charge of oversight
- The **WHO reliance mechanism** must be adopted by participating countries
- National regulatory agencies must commit to sharing information & fast decision making

Estimated best case scenarios:

- First full EUL/PQ application submission Jan 2021
- Timely EUL/PQ recommendation (contingent on parallel review) within days of approval by NRA / SRA in charge of oversight
- Translation to in-country decisions or approval **1 month post EUL/PQ**

* Roadmap for WHO Assessment of vaccine x during the COVID-19 Public Health Emergency









Department of Regulation and Prequalification, WHO

WHO/Otto 8.

LESSONS LEARNED IN THE DEVELOPMENT OF AN EBOLA VACCINE



Jayanthi Wolf, Cathy Hoath, William Lapps BMGF Workshop Oct 26, 2020



Presentation Outline

- Introduction
- Lessons Learned:
 - The vaccine construct
 - Clinical trials
 - Manufacturing
 - Pre-licensure access
 - Innovative regulatory strategy
- Discussion



A Global Collaboration to Develop an Ebola Vaccine

A diverse set of public-private partners:

- African governments, researchers and volunteers
- Governments of Canada. United States, Europe
- Field response and service organizations
- Global public health entities
- Universities
- Private sector companies



The ERVEBO® (Ebola Zaire Vaccine) Construct



The vaccine is a live, attenuated, recombinant vesicular stomatitis virus (rVSV)-based, chimeric-vector vaccine, for which the <u>VSV</u> envelope protein was deleted and replaced (ΔG) by inserting only the envelope glycoprotein (GP) of Zaire ebolavirus (ZEBOV). There is no live Zaire ebolavirus in the vaccine.

The vaccine is considered a Genetically Modified Organism (GMO), and in some countries classified as biosafety level-2 (BSL-2). In addition, manufacturing technology is considered "dual-use" and controlled under the US Department of Commerce, Bureau of Industry and Security, requiring specific licenses for technology transfers to countries outside the United States.





The Vaccine Construct Impacts Development

Lesson #1

Performing clinical trials and manufacturing-testing for a vaccine that is considered a Genetically Modified Organism requires additional resources and time.

Lesson #2

BSL-2 classification complicates supply chain and limits options to support rapid response.

Lesson #3

VSV-based vaccines are subject to export licenses from the US Bureau of Industry and Security¹. An exemption from the Commerce Control List would help manufacturers.

¹Reference: Wolf J, et al. *Vaccine.* 2020; 38: 7198-7200.





Existing Preclinical Data Supported Start of Clinical Trials

- The vaccine demonstrated 100% protection against ZEBOV challenge (high dose/high virulence strain) in cynomolgus macaques following a single immunization^{1,2}
- The vaccine protected immunodeficient (SHIV-infected) monkeys³ and lacked neurovirulent properties in monkeys⁴
- rVSV-Filovirus vaccines induced durable protection against virulent, high dose challenge (proof of concept for multivalent ZEBOV and Marburg vaccine)⁵
- rVSV vaccines were well-tolerated in monkeys⁶

1. Geisbert et al., Vaccine (2008).	4. Mire, et al.,
2. Qui et al., PLoS One (2009).	5. Geisbert et a
3. Geisbert et al., PLoS Pathogens (2008).	Geisbert and

4. Mire, et al., PNAS (2012).
 5. Geisbert et al., J. Virol (2009).
 6. Geisbert and Feldmann, JID (2011).

Additional efficacy and toxicity studies, including developmental and reproductive toxicity studies, were conducted in parallel with clinical development with results included in BLA



Clinical Trials During an Ebola Outbreak (2014-2016)





Guinea (Patient database), Liberia (Situation report, as of 6 May 2015), Sierra Leone (Patient database up to 1 May 2015, Situation report from 8 March 2015)



Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Kone, Eewa Kuisma, Myron M Levine, Serna Mandal, Thomas Mauget, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Rattingen*, Marie-Paule Keny*

Methods We did an open-label, cluster-randomised ring vaccination trial (Ebola ca Suffit!) in the communities of

Summary

Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine Lancet 2017;389:505-18 expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus Aublished Online December 22,2016 December 24,2016 December 24,2016 December 24,2016 December 22,2016 December 24,2016 December

http://dx.doi.org/10.1016/ S0140-6736(16)32621-6 This online publication has

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Clinical Trials During an Outbreak: Managing Time and Complexity

Lesson #4: Existing preclinical data on the vaccine platform can accelerate start of Phase 1 trials.

<u>Lesson #5</u>: Clear communication with community leaders and government agencies is critical to ensure the purpose of clinical research is well understood.

<u>Lesson #6</u>: Clinical immunogenicity assays need to be standardized and validated prior to the start of late stage clinical trials.

<u>Lesson #7</u>: It takes time to convert different formats and languages used to collect the clinical data into standard formats required by regulatory agencies.



Manufacturing Scale-Up





Manufacturing Considerations

<u>Lesson #8</u>: It takes time to establish and approval for a new manufacturing facility; "right-firsttime" manufacturing execution has low/medium probability of success for new vaccines.

<u>Lesson #9</u>: Site selection needs to take into account the regulations in the country/region in which the manufacturing site is located (e.g., GMO, export, testing).

<u>Lesson #10</u>: Heterogenous regulatory requirements impact the goal of flexibility and speed; need harmonized, fit-for-purpose solutions (e.g. labeling/artwork, serialization).



Pre-licensure Response: Under Clinical Protocols



A small number of doses were donated to other countries under various regulatory frameworks to vaccinate health care workers being deployed to DRC for outbreak support.



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MERCK

Pre-licensure Response Mechanisms: Being Prepared to be Prepared

Lesson #11

Expanded access of an investigational product prior to approval requires careful consideration and thorough planning; need to anticipate and manage accordingly. Protocol implementation is very difficult, requiring cost and effort for responders in the countries.

Lesson #12

Heterogeneity in protocols can lead to uncertainties and potential inefficiencies for preparedness; should consider opportunities for standardization.

Lesson #13

Protocol design and approvals take time and can put speed of response at risk; should consider having relevant protocols developed and submitted to Ethics Committees and Ministries of Health in advance of outbreaks.



WHO's Emergency Use Listing Procedure was Not Used for Ebola Vaccines

and

EUAL Procedure - 2015-2018

Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency

Introduction

The 2014 Ebola outbreak is the largest Ebola epidemic in history, which affected multiple countries in West Africa. This epidemic has demonstrated the need for a WHO emergency use assessment and listing procedure (EUAL) for candidate vaccines for use in the context of a public health emergency. The purpose of this extraordinary procedure is to provide guidance to interested UN procurement agencies and national regulatory authorities (NRAs) of relevant WHO Member States. The present document describes the EUAL procedure for candidate vaccines and is primarily aimed at manufacturers of these vaccines in the context of use during a public health emergency. Participation in the procedure is voluntary.

EUAL is not WHO prequalification, and should not be thought of as such.

http://apps.who.int/medicinedocs/documents/s21987en/s21987en.pdf

EUL Procedure – 2018-2020

Emergency Use Listing Procedure

1. Background

The World Health Organization (WHO) developed the Emergency Use Assessment and Listing Updated (EUAL) mechanism in response to the 2014 – 2016 Ebola Virus Disease (EVD) outbreak. The EUAL is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro Replaced diagnostics (IVDs) for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies if appropriate.

> Two submissions for Ebola vaccines were received but none was listed. No therapeutic products that were in development were submitted during the 2014-2016 Ebola outbreak. Twenty- five applications for IVDs were received for Ebola assays of which seven were listed. Also, three out of thirty- three applications received for Zika assays were listed.

> Based on the above experience, vaccine developers and national regulators identified the need to revise and simplify the procedure, in order to improve clarity on procedural aspects, and to avoid overlap or gaps in their respective functions.

https://www.who.int/diagnostics laboratory/eual/200110 new eul procedure final.pdf?ua=1



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Lesson #14: EUL Requires Careful Planning and Implementation



Local country emergency use laws or frameworks needed Special permissions for exports needed

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Facilitated by independent benefit//risk assessment by National Regulatory Authority Requires clearly defined labeling and traceability



Mechanism for

safety data

collection must

be in place

Liability coverage for vaccine developers must be considered

Postauthorization manufacturing changes must be evaluated





Novel Regulatory Strategy to Accelerate Approval in At-Risk Countries

- **Objective**: Obtain approvals in at-risk African countries as quickly as possible, facilitated by WHO Prequalification, and supported by approvals from the European Medicines Agency and U.S. FDA.
- Mechanisms: Collaborative reviews* including EMA, WHO PQ group, AVAREF, and African country NRAs. Active
 communication with Regulatory Agencies and between Regulatory Agencies including real-time information sharing
 facilitated by Breakthrough Therapy and Priority Medicines Designations. Use of rolling submissions to support accelerated
 assessments.



*https://www.who.int/medicines/news/2019/roadmap_for_intro_roll_out_licensed_ebola_vaccine/en/



Regulatory Approach: Collaboration is Needed

Lesson #15

Expedited pathways can help accelerate development; but requires significant resources for both the manufacturer and the regulatory agency.



Food and Drug Administration (FDA) Breakthrough Therapy (BT) designation (granted for V920 on 29-Jun-2016)



European Medicines Agency (EMA) Priority Medicines (PRIME) Status (eligibility granted for V920 on 23-Jun-2016)

Note: V920 is the Merck designation for ERVEBO®

Lesson #16 – the most important factor

Global and/or regional harmonization and work-sharing/reliance is critical for efficient approval of such unique vaccines.





Goals for Global Regulatory Harmonization



Single dossier



Reduction in number of unique labels and use of eLabeling



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Reduction in Module 1 requirements

Reduction in number of facility inspections through sharing of assessment reports



|| ×- Reduction in number of health authority questions through sharing of assessment reports Streamlining post

approval changes



Five-Year Timeline of the Development of the Ebola Vaccine



Reference: Wolf J, et al. NPJ Vaccines. 2020;5:51.



Lessons Can Be Applied to Pandemic Vaccine Development

- In a pandemic there is a need for speed to develop and distribute a vaccine
- However, a clear demonstration of the safety and efficacy of the vaccine is needed
- Instead of sequential steps, activities are conducted in parallel
- Additional financial risk: pre-invest in commercial manufacture as soon as clinical development begins
- Regulatory collaboration through worksharing/reliance and harmonization is key to ensuring equitable global access







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THANK YOU





P.T. BIO FARMA: BANDUNG INDONESIA

Overview and importance to Polio eradication

- Bio Farma is one of the largest vaccine manufacturers in the world
 - Successful history of developing vaccines and therapeutics for many decades
 - Supplies World Health Organization several pre-qualified vaccines (WHO PQ) for the global market
- Bio Farma was has been working on the development of the new Oral Polio Vaccine (nOPV) for several years
 - Leverages experienced manufacturing, regulatory, and clinical teams from OPV manufacturing; important supplier in Polio eradication efforts for many years
 - Partnered with PATH for tech transfer and development of nOPV, type 2 (nOPV2) manufacturing processes
 - Filing for WHO Interim EUL and eventually PQ in order to supply nOPV2 to UNICEF for use in outbreak response





KEY MANUFACTURING DECISIONS WERE MADE TO CREATE A RAPID STOCKPILE OF nOPV2



Accelerated scale-up in 10 months

- Challenge: Current Polio outbreaks
 have driven demand for nOPV2 for
 near-term use
- **Decision:** Pursue EUL application process and at-risk manufacturing of commercial product to have stockpile ready



50 dose vial presentation

- **Challenge:** Need to ensure maximum possible doses available at earliest timeframe to address PHEIC while fill-finish capacity was limited
- **Decision:** Use 50-dose vial presentation



Pivot planned commercial facility

- Challenge: Accelerated timeframe required commercial facility scale-up prior to original planned production facility being available
- **Decision:** Convert existing measles facility to multi-use

BILL& MELINDA GATES foundation

ACCELERATED DEVELOPMENT AND WHO EUL SUBMISSION FOR NOPV2

October 26, 2020

Vaccine Development & Surveillance Team Bill & Melinda Gates Foundation

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- BMGF summarized learnings from the experience of supporting WHO Emergency Use Listing (EUL) interactions as part of our Polio program.
- Have also captured best practices from our collective experience of working in vaccine development with respect to accelerating the process
- Three areas of focus: CMC; Regulatory; and Post-deployment monitoring
- <u>Goal</u>:

Capture key recommendations/best practices that are most relevant for COVID-19 vaccine developers



There are several initiatives to expedite access to products through accelerated assessment; EUL is one of these. BMGF often lists an EUL submission or equivalent as a milestone for the Global Access Commitments Agreement section of our grants

COVID-19 vaccines may become widely available to high-income countries much earlier than LMICs, especially if manufacturers supplying high-income markets have insufficient capacity to supply LMIC markets simultaneously.

- Because Stringent Regulatory Authority (SRA)-approved frontrunner vaccines will likely meet only some of the global demand for vaccines, continued vaccine development by Developing Country Vaccine Manufacturers (DCVMs) will be needed to ensure access to affordable vaccines for LMICs
- EUL will be an important pathway for DCVMs who will produce vaccines for LMIC markets at low cost and whose first registration will not be with an SRA

High mortality rate and transmissibility of SARS-CoV-2 combined with the near-term shortage of cheap, effective therapeutics make rapid development and approval of vaccines crucial.

• EUL provides limited time accelerated access based on the nature of the public health emergency

REGULATORY

Strategy for pre-emergency phase: Establish platforms for collaboration between WHO, subject matter experts, and relevant NRAs.

- All impacted regulatory agencies should be involved in the early phases of product development and in the assessment process
- Early alignment on non-clinical models and clinical study design allows for quick commencement of phase 2 and 3 trials with appropriate assistance

Strategy for <u>emergency phase</u>: Align with WHO PQ team early on content and format of submission.

- Define the structure of data tables and develop document "shells" in advance of clinical data becoming available
- Articulate the level of authorization required in the manufacturing country prior to EUL filing
- Discuss timing and details of a rolling submission and review process in pre-submission meetings
- Include plan for post-deployment monitoring for safety and efficacy

Strategy for post-listing phase: Reach agreement with PQ on the nature of data needed for assessment post-listing to support full PQ.

- Data from EUL submission may provide primary and/or supplementary data for full licensure or removal from EUL
- Monitoring of safety and efficacy in the field must be implemented

Updates based on emergency status:

• Authorizations of other candidate vaccines will affect the definition of "unmet clinical need". Subsequent applicants must demonstrate that COVID-19 remains an emergency or that their product offers some superiority.

CMC

Strategy: Aim to achieve fastest possible path to EUL while maintaining a robust plan to manufacture at the scale required to address the pandemic

- No abbreviated CMC path to EUL, so manufacturers will be held to commercial standards
- CMC requirements for most COVID-19 vaccines will require large amounts of human and financial capital invested at risk because of the attrition in vaccine development.
- Regulatory alignment for clinical trials, initial doses, and subsequent use:
 - > CMC regulatory standards for EUL are based on routine GMP standards for both pilot and commercial plants.
 - Circumstances may require launching doses from a pilot or alternate commercial facility while commercial facilities, commercial processes, and presentations are being finalized, so early alignment with WHO PQ and other regulators on expectations for standards, documentation, inspection, and process- and analytical-comparability assays is key.
 - A rolling EUL submission that initially reviews pilot facilities and includes commercial production data as it becomes available may be useful
 - It is important to pre-establish parameters for demonstrating process and analytical comparability and mechanisms that can accommodate changes during product rollout because material used in clinical studies may be made in a different facility than the facilities planned for commercial production.

CMC

- Site selection and capacity planning should plan for factors such as:
 - Manufacturers' experience base
 - Developing Country Vaccine Manufacturers (DCVMs) have significant experience navigating WHO PQ, WHO programmatic utilization recommendation, and GAVI/UNICEF procurement, but may have less experience with novel vaccines.
 - Multinational corporations (MCs) often have experience with novel vaccines but may not have used WHO PQ and/or GAVI/UNICEF procedures before.
 - > Small biotech companies may need assistance operating outside their home country and scaling to global markets.
 - > For each type of manufacturer, planning for the right technical assistance to avoid issues in submission and rollout is key.
 - Inspection planning
 - Scheduling regulatory facility inspections has been made even more difficult by COVID-19 travel restrictions. Developers should discuss with WHO PQ if inspections could be partially virtual or if the facility can rely on a previous PQ or ML4 inspection under the EUL.



Presentation options must remain flexible based on the nature of the pandemic and consider:

Stability

It may be necessary to initiate stability studies for many dose-per-vial presentations up front. Because of the duration of stability trials, the team may need to register a limited stability claim that is modified as longer duration studies are completed.

Preservatives

If there is not enough time to assess different preservatives, may need to discuss the use of preservative-free multi-dose vials with WHO PQ and relevant regulatory authorities. Note: These vials would need to be discarded within 6 hours of initial use. Potential wastage needs to be considered.

Setting specifications and labelling requirements

- Simplified labeling and packaging with common language and agreed-upon minimal requirements across all jurisdictions would be ideal for globally-implemented vaccines. While countries want to set their own specifications and accommodate multiple languages, heterogenous requirements should be limited to avoid delayed deployment at country level. WHO is currently working on this issue.
- Discuss the possible use of QR codes for package labeling SPC/PI (Summary of Product Characteristics/Package Insert), and PIL (Patient Information Leaflet) under emergency circumstances with regulators.

POST-DEPLOYMENT MONITORING

Strategy: Discuss post-deployment product monitoring requirements with WHO PQ during pre-submission meetings for early alignment

- Product monitoring must include:
 - > Use of a reporting system for adverse events following immunization (AEFIs)
 - > Active surveillance to investigate specific safety concerns.
- Limited active surveillance
 - > Developers should consider conducting surveillance through sentinel sites, leveraging existing epidemiological networks, and implementing targeted cohort studies using trained local investigators to examine possible safety signals.



- Accelerated development is based upon conducting many activities at-risk to enable earlier access to novel vaccines
- CMC
 - > Accelerated scale-up and early commitment to expand stockpiles are inherently risky approaches
 - > Developers/procurement groups understand that product may be sacrificed if subsequent data is not supportive for use
- Post-deployment Monitoring
 - Systems may be weaker in some LMIC. Risk is that ability to monitor vaccine safety and effectiveness may be compromised during a pandemic.

QUESTIONS & ACKNOWLEDGEMENTS

EUL Best Practices Project Members:

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Thank You