Joint UNICEF–UNFPA–WHO Meeting for Manufacturers and Suppliers
Session 5.3: WHO Vaccines & Immunization Prequalification Track – 29 November 2022

WHO PQ: Risk benefit assessment procedures - updates on EUL

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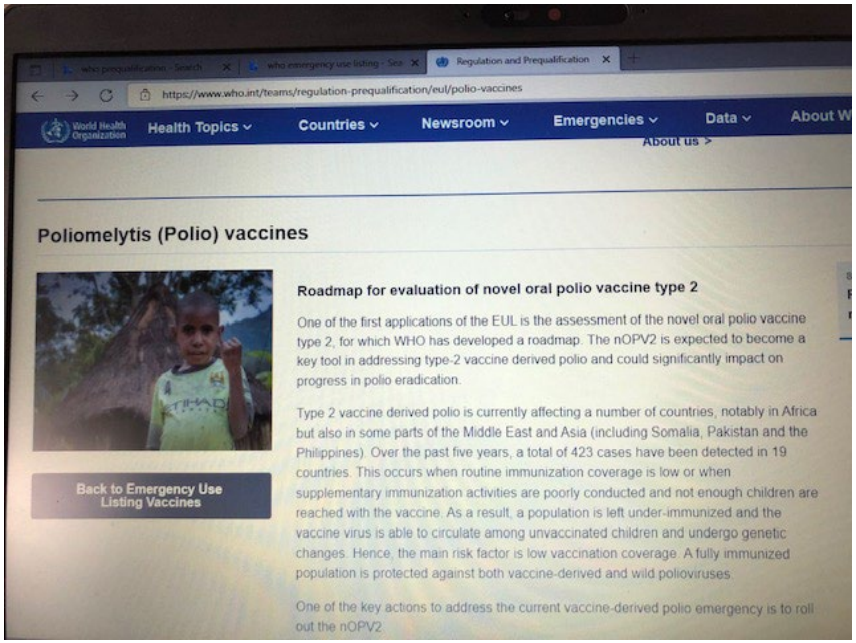
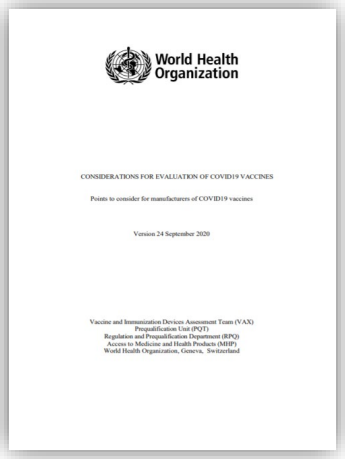
Novel oral polio vaccine type 2 (Nov. 2020)



WHO regulatory preparedness for COVID-19 vaccines

WHO released “Considerations for the assessment of COVID-19 vaccines” (Nov2020) and addendum March 2021


World Health Organization

CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

Points to consider for manufacturers of COVID19 vaccines

Version 24 September 2020

Vaccine and Immunization Devices Assessment Team (VAX)
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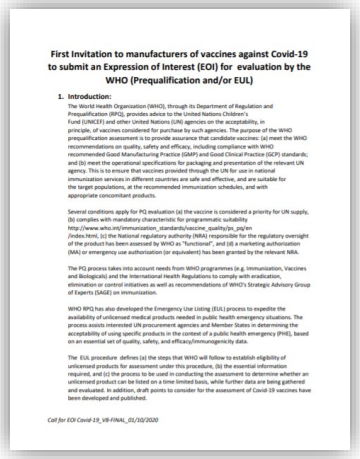
WHO issued a call for Expressions of Interest for Emergency Use Listing of COVID-19 Vaccines (2020)


First Invitation to manufacturers of vaccines against Covid-19 to submit an Expression of Interest (EOI) for evaluation by the WHO (Prequalification and/or EUL)

1. Introduction:

The World Health Organization (WHO), through its Department of Regulation and Prequalification (RPQ), provides advice to the United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies. The purpose of the WHO prequalification assessment is to provide assurance that candidate vaccines: (a) meet the WHO recommendations on quality, safety and efficacy, including compliance with WHO recommended Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards; and (b) meet the operational specifications for packaging and presentation of the relevant UN agency. This is to ensure that vaccines provided through the UN for use in national immunization services in different countries are safe and effective, and are suitable for the target populations, at the recommended immunization schedules, and with appropriate concomitant products.

Several conditions apply for PQ evaluation (a) the vaccine is considered a priority for UN supply, (b) complies with mandatory characteristic for programmatic suitability http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en /index.html, (c) the National regulatory authority (NRA) responsible for the regulatory oversight of the product has been assessed by WHO as "functional", and (d) a marketing authorization (MA) or emergency use authorization (or equivalent) has been granted by the relevant NRA.

The PQ process takes into account needs from WHO programmes (e.g. Immunization, Vaccines and Biologicals) and the International Health Regulations to comply with eradication, elimination or control initiatives as well as recommendations of WHO's Strategic Advisory Group of Experts (SAGE) on immunization.

WHO RPQ has also developed the Emergency Use Listing (EUL) process to expedite the availability of unlicensed medical products needed in public health emergency situations. The process assists interested UN procurement agencies and Member States in determining the acceptability of using specific products in the context of a public health emergency (PHE), based on an essential set of quality, safety, and efficacy/immunogenicity data.

The EUL procedure defines (a) the steps that WHO will follow to establish eligibility of unlicensed products for assessment under this procedure, (b) the essential information required, and (c) the process to be used in conducting the assessment to determine whether an unlicensed product can be listed on a time limited basis, while further data are being gathered and evaluated. In addition, draft points to consider for the assessment of Covid-19 vaccines have been developed and published.

Call for EOI Covid-19_ VB-FINAL_01/10/2020

... Revised guidelines 30 March 2022 and 2nd call for EOI in 2022

Source: https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf?ua=1

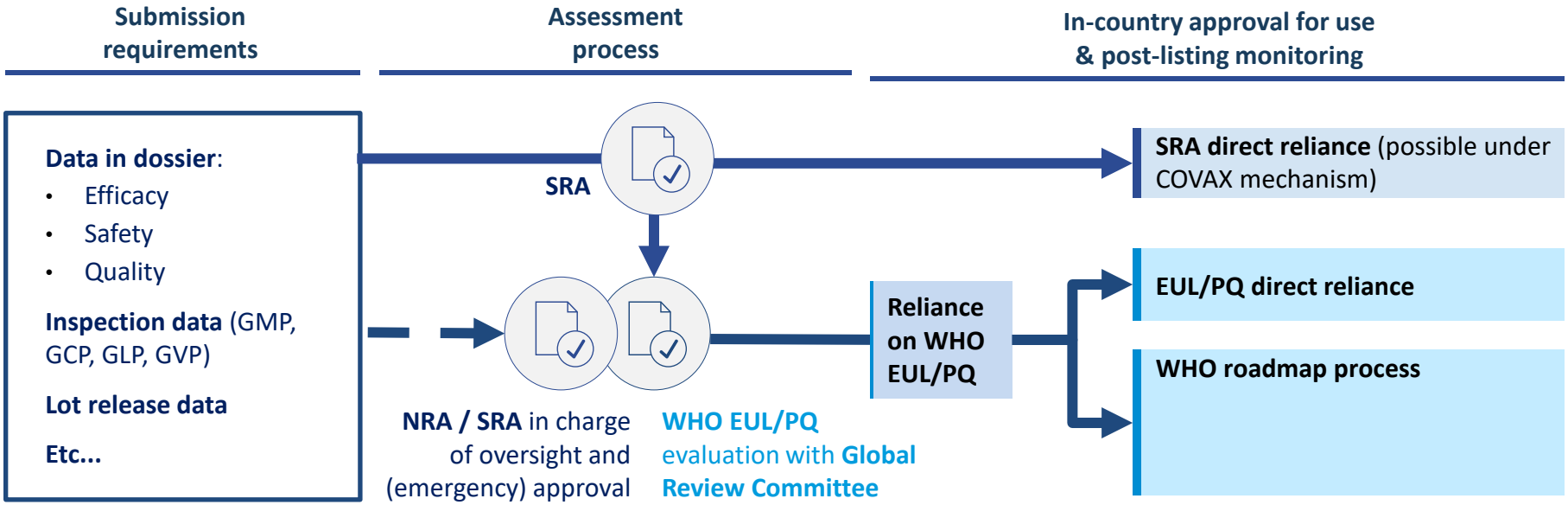
WHO alignment activities for COVID-19 vaccines ongoing since Feb 2020

Development criteria	Submission requirements	Assessment process	In-country approval for use & post approval monitoring
✓ **Target Product Profiles** ✓ **Expert Committee on Biological Standards** guidance ✓ **Regulatory guidelines**	✓ **EUL and PQ guidance** and **Questions & Answers** ✓ **EUL/PQ Expressions of Interest** (conditions & evaluation criteria) • **Labelling & packaging**	• **Evaluation of candidates** for EUL/PQ (incl. inspection, lot release process & post-listing commitment) • **Interactions & agreements** with NRAs/SRAs* • **Global assessment process*** with region-designated national authority reps	• **Country regulatory reliance** on EUL/PQ* • Support for **safety monitoring** (based on safety preparedness manual) • Tools for **risk communication** and strengthening **response capabilities**

- **Roadmap*** to enable product specific regulatory alignment (assessment process, in-country approval & post-listing monitoring)
- **Alignment ongoing** (Regulatory Advisory Group, ICMRA, regional regulatory networks, Vaccine cluster etc.)
- Regulatory **updates and webinars**
- Best practice principles for **regulatory "agility"**

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

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 • **Technical Advisory Group** convened (post-listing commitment) • **WHO EUL 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 | NRA reliance on EUL

Facilitated access to countries

- **Sharing of assessment/ inspection reports / lot release** with regional-designated country reps
- WHO-facilitated **national approval process**

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

Highlights of Covid 19 vaccines under EUL

Main features

11 vaccines with different manufacturing platforms
- mRNA (2)
- Viral vector (4)
- Inactivated (3)
- Protein subunit (2)

- Expanding regulatory oversight and manufacturing sites
- 19 NRAs of reference (mainly EMA)
- over 70 manufacturing sites

A range of age indications, shelf life and storage conditions

Covid 19 adapted vaccines → Approval by authority of reference → WHO EUL recommendation

WHO COVID-19 advisory groups develop recommendations on boosters, variants and variant vaccines along a comprehensive pathway

Aim: Monitor & assess SARS-CoV-2 variants and evaluate their impact on countermeasures, including vaccines, therapeutics, diagnostics or effectiveness of public health and social measures.

Virus → **Monitoring & surveillance**

TAG-Virus Evolution (VE)

- determines where variants are circulating
- advises on VOI or VOC determination based on alteration in
  - transmission or disease characteristics or
  - impact vaccines, therapeutics, diagnostics or
  - effectiveness of public health and social measures

Vaccine → **Research, evidence & assessment**

TAG-CO-VAC

determines if changes to vaccine composition needed through evidence-based assessment

Vax Research Expert Group

methods for vaccine development & assessment

Vax Effectiveness WG

assesses & supports VE and impact studies

Regulatory TAG

advises on EUL of vaccines through evidence-based assessment

Vaccine impact → **Policy**

SAGE

- recommends policies & strategies on vaccine use and immunization programmes through evidence-based assessment

WHO revised its guidance on applications for EUL based on immuno-bridging

30 March 2022

Guidance revised based on discussions with regulators and the WHO R&D Blueprint Team

- Acknowledges applications for **EUL based on immuno-bridging**
- Indicates a **careful choice of comparators** is important
- Indicates additional non-clinical and immunogenicity data may be required
- Indicates that as a **post-listing commitment** either of the following is needed:
  - **Demonstration of efficacy by in-deployment clinical trials,** or
  - **Effectiveness by post-deployment observational studies** (more likely to happen in practice)
- **Avoids being too prescriptive –** Is aligned with:
  - Revised WHO Target Product Profiles (TPP) for COVID-19 vaccines
  - Draft R&D Blueprint Team "Framework" document

* **Considerations for evaluation of COVID-19 vaccines: Points to consider for manufacturers of COVID-19 vaccines. Revised version, 30 March 2022 (**https://extranet.who.int/pqweb/sites/default/files/documents/Considerations_Assessment_Covid-19_Vaccines_v30March2022.pdf)

Countries with access

Dossier	No. access
Tozinameran	63
AZD1222 (AZ/SK)	81
COVISHIELD SII	58
Janssen	67
Moderna	53
BIBP	61
Sinovac	47
Bharat	20
Novavax	22
Covovax SII	11
CanSino	14
Total number of countries with access	**101**

Total number of dossiers shared: 497

COVID-19 vaccines Age and Booster status

Vaccine	Age group submitted	EUL recommendation	Monovalent Booster	Bivalent booster submitted BA.1	Bivalent booster submitted BA.4/5
Comirnaty Pfizer/BioNTech	18 years and above	+	+	+	+
	12 -17 years	+	-	-	-
	5 – 11 years	+	-	-	-
Vaxzevria AZ	18 years and above	+	+	-	-
Covishield SIIPL	18 years and above	+	+	-	-
Janssen	18 years and above	+	+	-	-
Spikevax Moderna	18 years and above	+	Under review	Under review	-
	12 -17 years	RMP not sufficient	-	-	-
	6-11 years	RMP not sufficient	-	-	-
BIBP/Sinopharm	18 to 59 years of age	+	-	-	-
	60+	Under review	-		
	3 years and above	Under review	-	-	-
Convidecia Sinovac	18 to 59 years of age	+	-	-	-
	60+	Under review	-		
	3 years and above	Under review	-	-	-
Covovax SIIPL	18 years and above	+	Under review	-	-
	12 -17 years	Under review	-	-	-
Nuvaxovid Novavax	18 years and above	+	Under review	-	-
	12 -17 years	Under review	-	-	-
SKYCovione CanSino	18 years and above	+	-	-	-

EOIs received and platform

Manufacturer	Name of Vaccine	NRA of Record	Platform
WestVac Biopharma	Recombinant COVID-19 Vaccine	NMPA China	Recombinant SARS-CoV-2 S-RBD protein
Nanogen	Nanocovax	Drug Administration of Vietnam	Recombinant Spike protein
Livzon Mabpharm Inc.	Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	NMPA China	Recombinant Protein
Cinnagen	SpikoGen	Iran Food Drug Administration (IFDA)	Recombinant Protein
R-PHARM	Vaccine R-COVI	Russian NRA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
Arcturus Therapeutics	ARCT-154	Drug Administration of Vietnam	RNA Vaccine
Bio-Manguinhos/Fiocruz	AZD1222	ANVISA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
Vaxxinity	UB-612	FDA	Protein-peptide vaccine
Sinocelltech, Ltd	SCTV01C	NMPA China	Recombinant Protein
Razi Vaccine & Serum Research Institute	Razi Cov Pars Vaccine	Iran Food Drug Administration (IFDA)	Recombinant Protein
Valneva	VLA2001	EMA	Inactivated
Medigen	MVC-COV1901	TGA	CHO cell derived spike protein (Subunit)
HIPRA	BIMERVAX	EMA	Recombinant Protein
Stelis Biopharma Limited	AKS-452 Vaccine (AmbiVax -CTM)	DCGI India	Protein subunit
PT Biofarma	SARS CoV-2 RBD	Badan Pom Indonesia	Recombinant Protein Vaccine

Triggers & Considerations

Moving from EUL to PQ could potentially be triggered by:

- Availability of data – EUL commitments + PQ requirements.
- Declaration of end of PHEIC, graded emergency.
- NRA of record granting full MA (no restrictions in place) for several vaccines.
- A transition period of 6 months will be needed following the triggers.

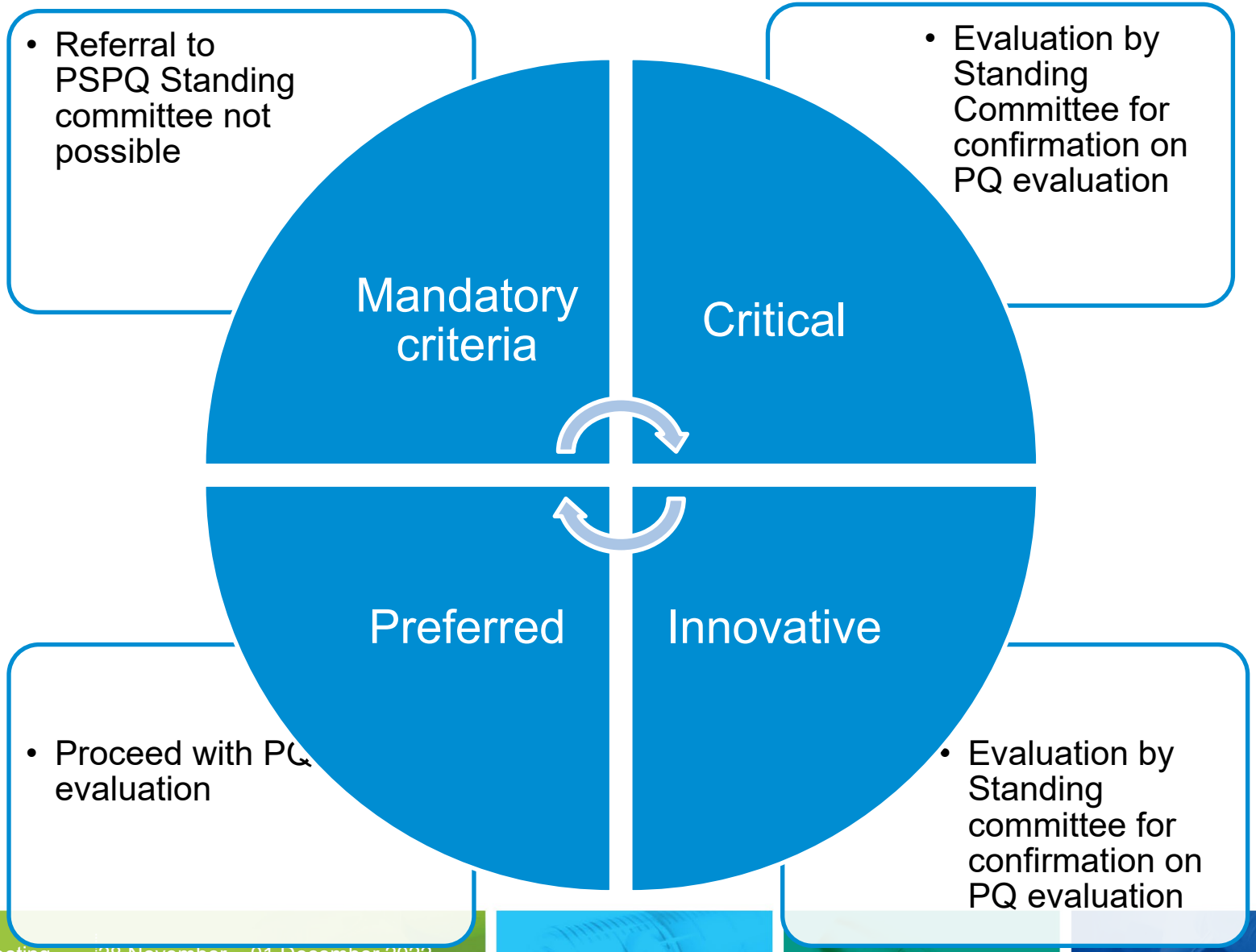
Consider implication on applicability of EUL and supply if one vaccine progressed to PQ ahead of others:

- Continued eligibility for EUL.
- Indications or populations not covered.
- Vaccines targeting new variants and/or boosting.
- Geographical access and supply security.
- Accepting only one vaccine as eligible or wait until more vaccines are eligible?
- That for most vaccines still restrictive authorizations in place.
- Indemnification & liability.

Steps for transition Covid-19 vaccines from EUL to PQ

Available Data	• Availability of data to fulfill EUL listing commitments and PQ requirements.
NRA of Record	• Full authorization by the NRA of reference.
Submission to PQ	• Submission to WHO for PQ – consolidated updated dossier.
PQ Review	• WHO PQ review: ✓Programmatic suitability. ✓Additional data.
PQ Listing	• PQ Listing.
National Authorization	• Facilitation of national authorization.

Deviation of Programmatic suitability criteria



Covid 19 vaccines recommended under EUL Deviation Programmatic suitability criteria for PQ

Criteria	Applicable to	Solutions & implications
Mandatory: Storage conditions less than – 20 C	mRNA Pfizer vaccine	Ultra Cold chain equipment at central level Training Health care workers **Implications:** Wastages
Mandatory: Antimicrobial preservative more than 2 doses	All Covid 19 vaccines	Training HCW to discard vaccines at the end of the session once vial is opened **Implication:** Wastages
Critical: Storage at 2-8 for more than 6 months	mRNA Moderna	Training HCW **Implication:** Wastages
Critical VVM	All Covid 19 vaccines	Maintenance cold chain **Implication:** Wastages

Additional information PQ&EUL:

PQT/VXA procedure [TRS 978, Annex 6 (2013]
http://www.who.int/entity/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf

Programmatic Suitability for Prequalification
http://www.who.int/immunization_standards/vaccine_quality/pspq2_v140512.pdf

EUL Procedure and Questions and Answers
https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

Target product profile
https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true

Additional information PQ&EUL:

Evaluation criteria and EOI.
https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1

Roadmap
https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19

Contact: EUL@who.int

World Health Organization

WORKING TOGETHER

Department of Regulation and Prequalification, WHO

BACK UP SLIDES

Vaccines PQ in 2020

World Health Organization

PQ vaccines 2020 11 vaccines (13 presentations)				
PQ date	Vaccine	No. Doses	Manufacturer	Country
21/01/2020	Hepatitis B (paediatric)	1	Lg Chem Ltd	Republic of Korea
28/01/2020	Rotavirus (live attenuated)	1 & 2	Serum Institute of India Pvt. Ltd.	India
07/02/2020	Influenza seasonal (Trivalent)	10	Seqirus Limited	Australia
09/03/2020	Diphteria-Tetanus (reduced antigen content)	20	Biological E. Limited	India
25/03/2020	Dengue	5	Sanofi Pasteur	France
21/04/2020	Polio Vaccine - Inactivated (IPV)	5	AJ Vaccines A/S	Denmark
31/08/2020	Polio Vaccine - Oral (OPV) Trivalent	20	PT Bio Farma (Persero)	India
15/10/2020	Influenza, seasonal (Quadrivalent)	10	Sanofi Pasteur	France
04/12/2020	Typhoid (conjugate)	1 & 5	Biological E. Limited	India
18/12/2020	Influenza Pandemic H5N1	1	AstraZeneca Pharmaceuticals LP.	UK
21/12/2020	Polio Vaccine - Inactivated Sabin (sIPV)	5	LG Chem Ltd	Republic of Korea

https://extranet.who.int/pqweb/vaccines/prequalified-vaccines

Vaccines PQ in 2021

6 vaccines (7 presentations)

World Health Organization

PQ date	Vaccine	No. Doses	Manufacturer	Country
18/02/2021	Rotavirus (live, attenuated)	1	Serum Institute of India Pvt. Ltd	India
26/04/2021	Influenza, seasonal (Trivalent)	10	Instituto Butantan	Brazil
27/04/2021	Ebola vaccine (MVA-BN-Filo [recombinant]) Ebola vaccine (Ad26.ZEBOV-GP [recombinant])	1	Janssen Vaccines, Branch of Cilag GmbH International	Switzerland
18/06/2021	Rotavirus (live attenuated)	1 & 5	Bharat Biotech International Limited	India
01/06/2021	Polio Vaccine - Inactivated Sabin (sIPV)	1	LG Chem Ltd	Republic of Korea
14/10/2021	Human Papillomavirus (Bivalent)	1	Xiamen Innovax Biotech Co. Ltd.	People's Republic of China

https://extranet.who.int/pqweb/vaccines/prequalified-vaccines

Vaccines for emergency response: WHO stockpiles

World Health Organization

Routine and emergency response

Yellow Fever, cholera, meningococcal

Licensed and PQ. Risk mitigation strategies: secure access

Emergency response

mOPV2 and Ebola

Licensed and PQed.

Special conditions under PHE

Emergency response when PHEIC is declared

Pandemic flu

smallpox

License for emergency use pathways

Secure availability

Development of new vaccines

Technology transfer

Partnerships/ Collaboration

Prequalification of vaccines and Immunization equipment

Each year, UNICEF supplies over two billion doses of vaccines, to reach approximately 45 per cent of the world's children under five years of age. This annual investment, totaling $1.656 billion in 2019, supports routine immunization programmes, preventive campaigns and outbreak response around the world. GAVI claims 14 million deaths averted.

UN agencies only procures WHO specified, verified and prequalified immunization equipment and devices.

2

doses per year[1]

14

million

lives saved[2]

70

countries

supplied[2]

Achievements (2020-2022) - Vaccines

World Health Organization

PQ

- 21 vaccines PQed
- Support UN agencies
- Support member states briefings on malaria and Ebola.
- Support suitability of vaccine applications during tender process.
- Assessment of 246 variations

EUL

- 11 vaccines (19) Covid 19 vaccines
- 1 nOPV2 vaccine
- Support member states through reliance
- Briefing workshops
- One on one support (meetings, emails)
- Assessment of changes, 454 Post EUL submissions
- Variants of concern

Other

- Snake antivenoms risk benefit
- Monkeypox, 2 vaccines
- Release of polio vaccines into WHO stockpiles,
- 169 lots of mOPV vaccines 462 MD
- 201 lots of tOPV vaccines, 315 MD
- 181 lots of nOPV2, 749 MD

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

World Health Organization

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COVAX | EUL | NRA reliance on EUL → **Facilitated access to countries**

- **Sharing of assessment/ inspection reports / lot release** with regional-designated country reps
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* *Roadmap for WHO Assessment of* vaccine x *during the COVID-19 Public Health Emergency*

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World Health Organization

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Total number of dossiers shared: 497

Risk-benefit assessment of snake antivenoms

World Health Organization

- Expanded programme supported by $3 million in funding from Wellcome Trust
- Global burden of snakebite affects 4.5-5.5 million people/yr and claims 80,000-140,000 lives annually
- Focus on assessing products from Africa, Middle East and Asia aims to reduce the mortality and morbidity in the worst-affected regions of the world by up to 50%.
- Goal is identify products that can be recommended for procurement on the basis of comprehensive dossier review, laboratory evaluation and GMP compliance.
- 7 sub-Saharan African products already evaluated. 1 reapplication received and a second one pending submission.
- 8 product applications under assessment that are marketed in South Asia and 9 more for products marketed in North Africa & the Middle East.

World Health Organization

Benefits

- Procedure has already resulted in substantial new investment by manufacturers aimed at attaining GMP compliance, improving the design and efficacy of antivenoms, and introducing new production technologies.
- Provides procurement agencies with greater confidence in products that NRAs may not have the capacity to adequately assess themselves.
- Supports decision-making on product registration by regulatory agencies
- Stimulated interest in development of new products by manufacturers who see the procedure as a precursor to possible future prequalification of antivenoms.
- Recommended products are likely to be taken up for use in regional antivenom stockpiles to increase access to safe and effective products.