JOINT UNICEF – UNFPA – WHO meeting

WHO PQ: Risk benefit assessment procedures

Elisabeth Pluut, DrPH, MPH

Vaccine Prequalification (PQ VAX)
Prequalification Team (PQT)
Regulation & Prequalification Dept. (RPQ)
Medicines and other Health Technologies (MHP)
World Health Organization
Geneva, Switzerland
E-mail: vaccprequalification@who.int

Outline of presentation

- Goal and objectives
- WHO regulatory alignment roadmap
- Examples
- Post EUL submission
- Transition EUL to PQ

Goal and objectives

Goal

- to optimize access & availability to safe, efficacious, quality-assured COVID-19 products by further aligning regulatory processes

Objectives :

- Explain and update on **WHO's roadmap** for aligning regulatory processes impacting access to vaccines during public health emergencies (nOPV2, Covid-19, Mpox)
- Explain the activities of the evaluation of vaccines under the EUL

WHO PQ assessment

Prequalification (PQ) 1987	Emergency Use Listing (EUL) 2015*
• Review of extensive quality, safety and efficacy and PSPQ for international supply	• **Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs**
• Assessment performed by WHO independent experts	• **Rolling review of data**
• Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)	• 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	• Pre-submission meetings
• Post-PQ monitoring	• **Post- deployment monitoring**
• Reassessment/requalification	• **Time limited recommendation**
	• **Development should continue for MA/PQ**

*** Updated in 2019 – published January 2020**

Risk benefit i.e Monkeypox → **Stockpiles** → **Risk benefit snake antivenoms**

Pre-conditions for EUL/PQ evaluation

- Reliance on the National Regulatory Authority (NRA) of the exporting country
  - ✓ NRA must be assessed as functional or Maturity Level 3 (ML3) for vaccine producing country, as a result of successful evaluation using the WHO NRA assessment tool
  - ✓ NRA's functional status needs to be sustained over time
  - ✓ Continued regulatory oversight by NRA is required as well as communication with WHO about potential problems with the vaccine
  - ✓ Agreements are established with the NRAs for information exchange when a vaccine is about to be prequalified
- WHO guidelines/recommendations approved by the ECBS are available (published in the WHO Technical Report Series)
- Listed in the vaccine priority list for PQ (low priority vaccines may be postponed depending on workload and no priority vaccines will not be reviewed)

Emergency Use Listing principles

1. A pre-emergency phase for assessment and allow a rapid decision when the emergency is declared and a post deployment monitoring phase
2. Involvement of NRAs responsible for oversight of the products and NRAs of potentially affected countries at different stages of the procedure
3. The applicant undertakes to complete the development of the product and apply for WHO prequalification once the product is licensed.

Establishment of an assessment platform

- Agreements with NRAs of record for information sharing
- Framework for interaction with NRAs and Expert committees of potentially affected countries
- Roster of experts
- Establishment of Committees:
- Product Evaluation Group (PEG)
- Technical advisory group (TAG)

WHO alignment activities for PHE vaccines

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"**

WHO regulatory preparedness for COVID-19 vaccines

WHO released “Considerations for the assessment of COVID-19 vaccines” (2020, 2022)


World Health Organization

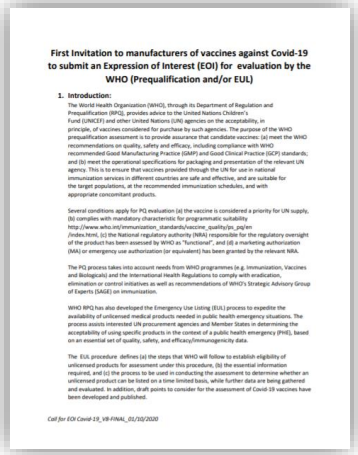
CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

Points to consider for manufacturers of COVID19 vaccines

Version 24 September 2020

Vaccine and Immunization Devices Assessment Team (VAX)
Prequalification Unit (PQT)
Regulation and Prequalification Department (RPQ)
Access to Medicine and Health Products (MHP)
World Health Organization, Geneva, Switzerland

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/pv_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.

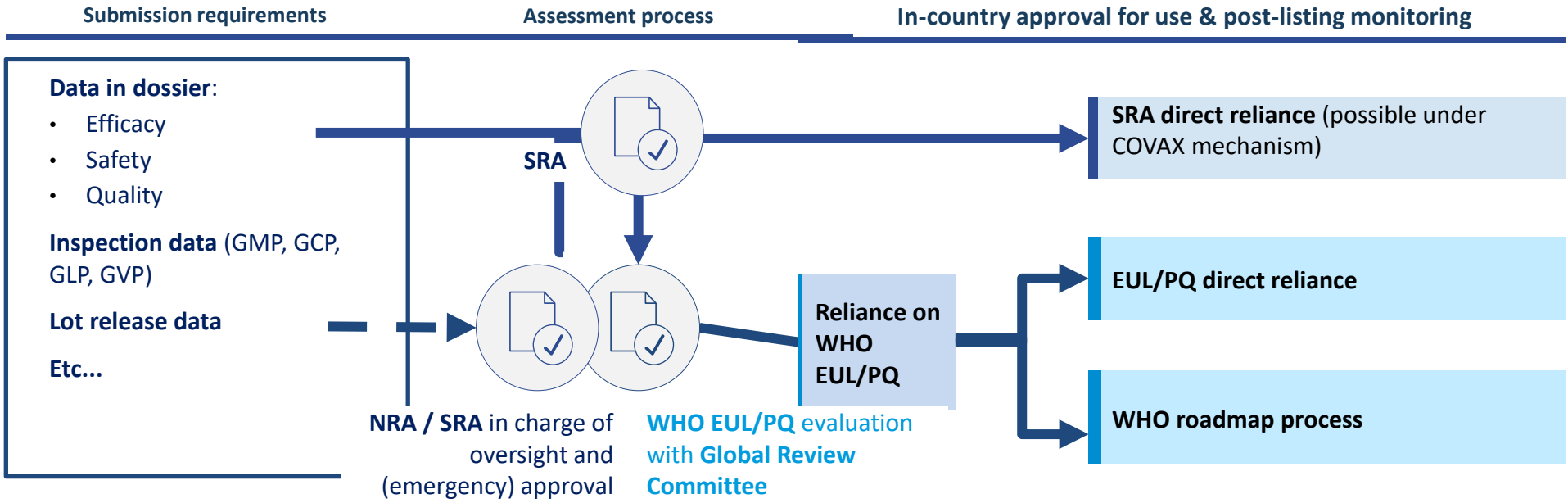
The EUL procedure defines (a) the steps that WHO will follow to establish eligibility of unlicensed products for assessment under this procedure, (b) the essential information required, and (c) the process to be used in conducting the assessment to determine whether an unlicensed product can be listed 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_V8-FINAL_01/10/2020

... aiming for timely regulatory process while maintaining high evaluation stds for EUL/PQ

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

WHO regulatory alignment roadmap for PHE 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)

Support to regions & countries

Designate lead NRAs in the region: WHO EUL assessment

Facilitation expedited national approval

Product Evaluation group PEG: Roster of experts, Regulatory experts all regions.

Technical Advisory group EUL (TAG-EUL): Risk benefit assessment

https://extranet.who.int/pqweb/vaccines/TAG-EUL

Collaboration agreement with NRAs of references and others on regulatory oversight

1. Sharing dossier and EUL reports with 105 countries
2. Discussion on outcome of review
3. Additional guidance for decision making on expedited authorization
   - One on one discussion with countries
   - Support to RO and agencies providing relevant docs
4. Post listing changes: Sharing assessment reports

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**

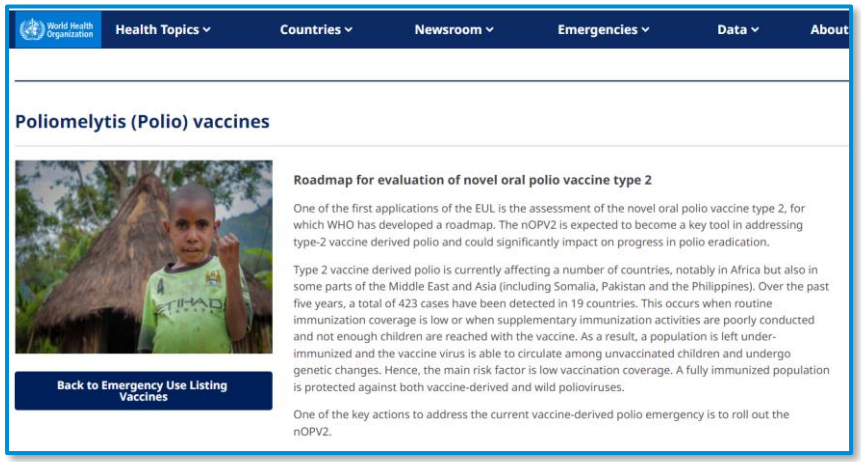
UN agencies | EUL/PQ | NRA reliance on EUL/PQ → **Facilitated access to countries**

nOPV2: 51 authorizations/access to dossier
Covid-19: 105 countries access to dossiers

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

Examples

Novel oral polio vaccine type 2



First vaccine with EUL recommendation that transitioned to prequalification in 2024

Highlights of Covid 19 vaccines under EUL

Main features

13 vaccines with different manufacturing platforms - mRNA - Viral vector - Inactivated - Protein subunit	- 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

Mpox vaccines

WHO prequalifies the first vaccine against mpox

WHO adds LC16m8 mpox vaccine to Emergency Use Listing

Post EUL variations

Post EUL Submissions

1. Variations

The vaccine applicant/EUL holder must promptly inform WHO of all changes to the vaccine regarding formulation, manufacturing process, testing methods, specifications, update on the labelling information, facilities and any other aspects that might (a) result in a change of the safety and/or efficacy and/or performance of the product or (b) change the basis for the listing recommendation.

2. Post EUL commitments

Variations can be classified in 2 groups

1. **Update of EUL recommendation:** major variations that require WHO approval before vaccines can be made available via UN supply and/or COVAX. These include changes in the manufacturing and/or control sites that are necessary to prevent/mitigate shortages of supplies, additions of manufacturing sites for manufacturing antigen or finished EUL vaccine, changes in suppliers of starting materials, reagents, intermediates or active substances (DS), changes to the summary of product characteristics or WHO Product Information (SmPC/product insert-product leaflet). Manufacturers are requested to submit these variations once (and as soon as) the corresponding WHO regulatory authority of record approved the variation
2. **For notification purposes:** The WHO EUL Secretariat must be notified within one month of approval by the WHO regulatory authority of record of the vaccine under EUL recommendation on minor and moderate variations.

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

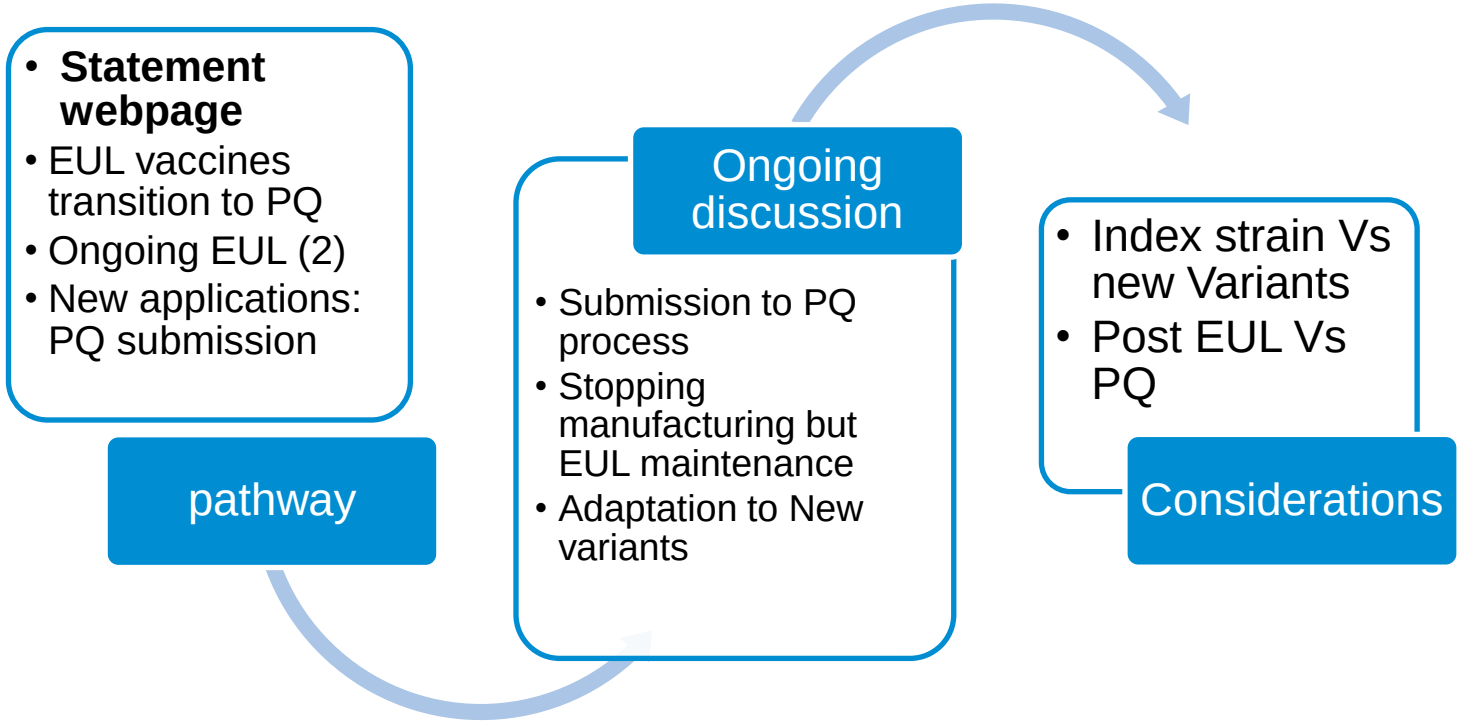
Policy

SAGE

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




Path forward



PHEIC_web_31May2023.pdf (who.int)

Considerations

PQ related

- Fees
- Dossier submission
- PSPQ

Critical key changes

- Complexities of key changes introduced as post EUL and impact on timelines for transition to EUL
- Clear timelines to be set on potential critical changes that may be submitted post EUL (ie VOC), during the PQ assessment and Post PQ.

SAGE policy recommendations

TAG COVAC

Staff Resources

Transition EUL to PQ

Implications of the use of EUL/PQ if PHEIC is terminated

	PHE vaccines
EUL listed	EUL status is maintained for a limited period while the product transitions to PQ and if the product continues to be supplied to LMICs
Under EUL assessment	EUL applications to be closed except for those close to EUL listing
New	Submission and acceptance for PQ assessment is made on a case-by-case basis based on public health benefits and prioritization criteria defined in collaboration with other WHO departments

Steps for transition 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	• Programmatic suitability • Additional data
PQ listing	• PQ listing
National Authorization	• Facilitation of national authorization.

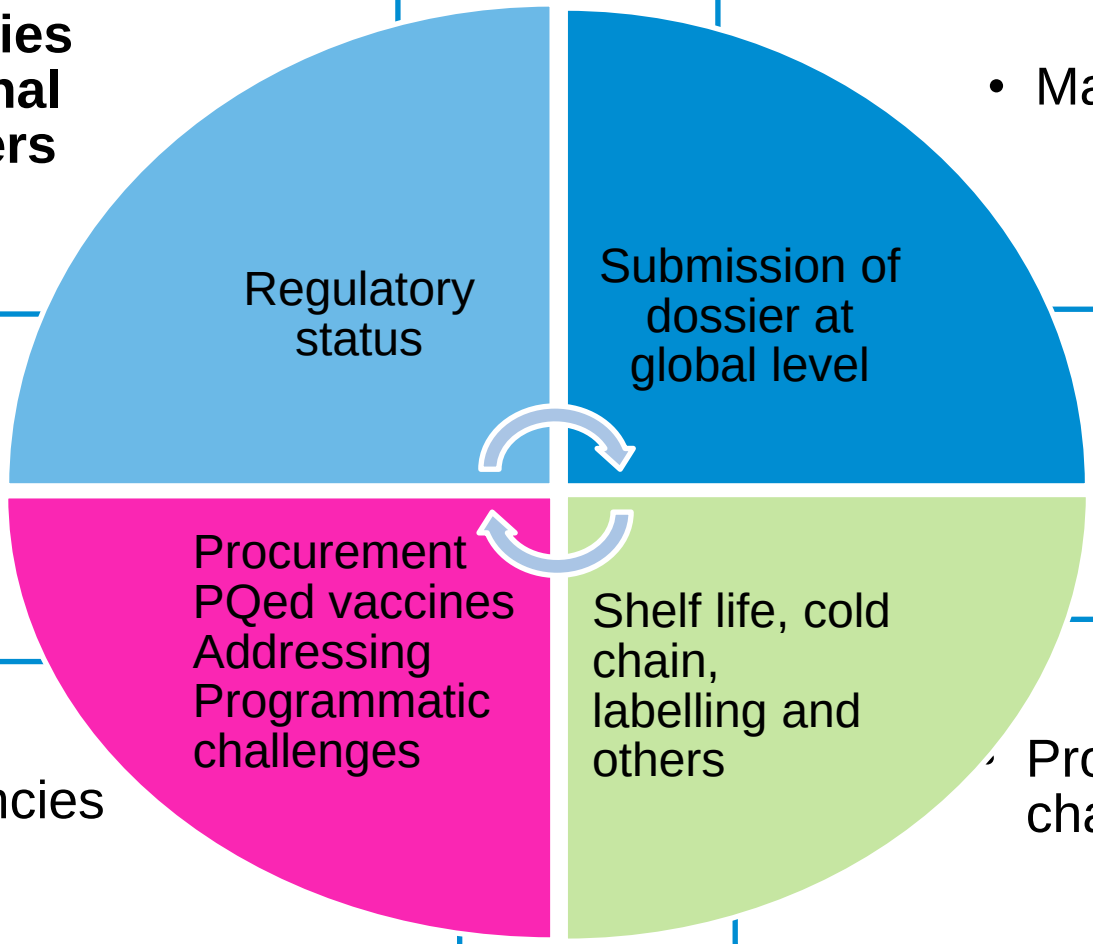
Covid 19 vaccines recommended under EUL
Deviation Programmatic suitability criteria for PQ

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

Support to member states

- **Countries**
- **Regional advisers**

- Manufacturers



- UN agencies COVAX

- Programmatic challenges

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: WHOEUL@who.int

THANK YOU