WHO Prequalification and EUL updates

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At the Division of Access to Medicines and Health Products
Outline of presentation

- PQ of Vaccines and Immunization equipment team
- WHO assessment: processes and achievement
- Programmatic Suitability for PQ
- WHO post recommendation monitoring activities and achievements
- PQ of immunization equipment
- Covid 19 vaccines under EUL
- Transition from EUL to PQ
WHO Vaccines PQ Team

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- Recel S. Office Assistant
- Rana G. Office Assistant
- Deusedit M. PQ Head

- Clinical assessment
- CMC assessment
- Immunization Devices
- Post-PQ activities
- Administrative staff

- Vaccines PQT staff for all vaccines and processes
**WHO PQ assessment**

**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
- 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
- Post-deployment monitoring
- Time limited recommendation
- Development should continue for MA/PQ

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- Risk benefit i.e. Monkeypox
- Stockpiles
- Risk benefit snake antivenoms
Principles

Reliance on NRA

Meeting WHO requirements and tender specifications

Consistency of final product characteristics

Clinical data

GMP
Pre-conditions for PQ evaluation

Reliance on the National Regulatory Authority (NRA) of the exporting country

- NRA must be assessed as functional or Maturity Level 3 (ML3) 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
Pre-conditions for PQ evaluation

- Vaccine is licensed/registered by the responsible NRA (Scientific opinion by EMA accepted)
- 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)

(Prioritization 2024-2025 under finalization)
Prequalification process

- Scientific review of quality dossier
- Scientific review of clinical data
- Testing of samples
- Consultation with responsible NRA
- Site audit to manufacturing facilities
Vaccine Prequalification workflow

Dossier submission (CTD format)

Screening

ML3 NRA
Programmatic suitability

Assessment
Inspection

Follow-up inspection

Prequalification decision
Ensure that vaccines used in low and middle income countries can be used safely and effectively, given the constraints and conditions of their immunization systems.

Nicaragua, rotavirus delivery. Photo: Gates Foundation

Mali, polio campaign. Photos: WHO/Olivier Ronveaux
Objectives of PSPQ:

✓ Judge the programmatic suitability against defined mandatory, critical and preferred characteristics

Benefits of PSPQ:

✓ Give clear directions to vaccine industry before PQ submission
✓ Reduce decision making time

PSPQ:
https://apps.who.int/iris/bitstream/handle/10665/148168/WHO_IVB_14.10_eng.pdf
Prequalification process: timelines (excluding applicant response times)

- Submission of application for PQ
- Screening (30 days + 90 days if there is critical PSPQ non compliance)
- 270 days internal time
- Streamlined based on SRA approval and sharing of NRA reports
- 90 days internal time
- Submission of variation
- Screening
- 90 days internal time
Number of vaccines PQed and EUL from 2014 to 2023

- **PQ non-DCVMN**
- **PQ DCVMN**
- **Ongoing PQ**
- **EUL listed**
- **Ongoing EUL**

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Vaccines Post monitoring activities

- Continuous monitoring of the quality, safety, efficacy and programmatic of vaccines under PQ and EUL
- Variations
- Annual Report evaluation
- Reassessment
- Targeted testing program
- Monitoring/Investigation of vaccine quality and cold chain complaints
- Monitoring/investigation of Adverse Events following immunization (AEFI)

Other activities.
- Facilitation of National authorization
- Technical Review of tenders for UNICEF
- Technical support to member states
Product Lifecycle Management

Drug Discovery | Preclinical | Clinical Trials | Scale-Up to Mfg. | Post-Marketing Surveillance

- VPQD Rev
- Conditions/Commitments
- Variations
- PQVARs
- Complaints/AEFI
- Testing
- Reassessment
- Others

Post Approval changes
NRA Approval

WHO PQed vaccine

3 – 6 YEARS

~ 5,000 - 10,000 COMPOUNDS

250

NUMBER OF VOLUNTEERS

20 - 100

100 - 500

1,000 - 5,000

IND SUBMITTED

IND SUBMITTED

NDA SUBMITTED

0.5 – 2 YEARS

INDEFINITE
Post-PQ and Post EUL activities from 2014 to 2023

![Chart showing PQ variations, PQ annual reports (PQVAR), EUL variations, and EUL annual reports from 2014 to 2023.](chart.png)

- PQ variations
- PQ annual reports (PQVAR)
- EUL variations
- EUL annual reports
Achievements (2020-2023) - Vaccines

**PQ**
- 23 vaccines PQed
- Support UN agencies
- Support member states briefings on malaria and Ebola.
- Support suitability of vaccine applications during tender process.
- Assessment of 385 variations

**EUL**
- 12 vaccines Covid 19 vaccines
- 1 nOPV2 vaccine
- Support member states through reliance
- Briefing workshops
- One on one support (meetings, emails)
- Assessment of changes, 562 Post EUL submissions

**Other**
- Snake antivenoms risk benefit
- Release of polio vaccines into WHO stockpiles (2022)
- 169 lots of mOPV vaccines 462 MD
- 201 lots of tOPV vaccines, 315 MD
- 181 lots of nOPV2, 749 MD
Why WHO IMD PQ?

WHO Immunization Devices (IMD) Prequalification:

- ensures the **access, availability and quality** of prequalified products to safeguard vaccines & other immunization supplies.

- support WHO’s **disease elimination & eradication** efforts, as well as countries’ **preparedness & resilience** for health emergencies.
What WHO IMD does

The WHO VAX IMD PQ programme **sets the standards** for equipment and devices that:

- are used for the **safe storage, transport, monitoring and administration** of life-saving vaccines
- **protect the significant investment** in resources required to develop, procure and deliver potent vaccines.

PATH/Gabe Bienczycki
WHO-IMD overview

- PQS STANDARDS: > 100
- PRODUCTS PREQUALIFIED: 425
- PRODUCT CATEGORIES: 10
- Which includes...
  - PRODUCT SPECIFICATIONS
  - VERIFICATION PROTOCOLS
  - MANUFACTURER GUIDES & MORE
  - MANUFACTURERS: 66
Progression of PQS of products since 2008
WHO Immunization Devices (IMD):

- ensures the availability and quality of prequalified products to safeguard vaccines & other immunization supplies.

- supports WHO’s disease elimination & eradication efforts, as well as countries’ preparedness & resilience for health emergencies.
The WHO Shipping guidelines & Bar codes

2005 (5th edition)
2020 (6th edition)
2023 6th edition rev1 (in process)
The WHO Shipping guidelines

- This document was first published in 1990. It then went through several revisions, in 1995, 1998, 2001 (WHO/V&B/01.05), and 2005 (5th edition).
- It went through and extensive revision in 2020 (6th edition)
- The 6th edition has been revised (6th edition revision 1) to incorporate requirements for ultralow temperature shipments, following the COVID pandemic. It is currently undergoing executive clearance for publication
Risk Benefit assessment  Emergency use listing
Novel oral polio vaccine type 2

**Polio**{\textit{myelitis}} (Polio) vaccines

**Roadmap for evaluation of novel oral polio vaccine type 2**

One of the first applications of the EUA is the assessment of the novel oral polio vaccine type 2, for which WHO has developed a roadmap. This rOPV2 is expected to become a key tool in addressing type 2 vaccine-derived polio and could significantly impact on progress in polio eradication.

Type 2 vaccine-derived polio is currently affecting a number of countries, notably in Africa but also in some parts of the Middle East and Asia (including Somalia, Pakistan and the Philippines). Over the past five years, a total of 423 cases have been detected in 19 countries. The decline in routine immunization coverage is one of the factors leading to supplementary immunization activities being poorly conducted and not enough children are reached with the vaccine. As a result, a proportion of the unvaccinated population is left under-vaccinated and the vaccine virus is able to circulate among unvaccinated children and undergo genetic changes. Hence, the main risk factor is the vaccination coverage. A fully immunized population is protected against both vaccine-derived and wild polioviruses.

One of the key actions to address the current vaccine-derived polio emerging is to roll out the rOPV2.
Main features

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

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

1. Preliminary activities
   - Global regulatory cooperation
   - Establishment of strategies for expedited approval in participants & post-listing monitoring

2. Launching of EOIIs
   - Manufacturers EOIIs (Phase IIb/III & approval by NRA/SRA in charge of oversight within 6 months & compliance with criteria for assessment)
   - Discussions on rolling submission procedure

3. Submissions & assessment
   - 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)

4. Recommendation for listing
   - Approval granted by NRA/SRA in charge of oversight
   - Advisory committee convened (post-listing commitment)
   - WHO EUL/ PQ recommendation with conditions

5. Post-listing monitoring
   - Implementation of strategies for safety, quality & effectiveness monitoring
   - Validity of listing based on new data generated
   - Possible conversion of EUL to PQ

Facilitated access to countries

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

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**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

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**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

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**Vaccine impact**

**Policy**

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

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Path forward

- **Statement webpage**
  - EUL vaccines transition to PQ
  - Ongoing EUL (2)
  - New applications: PQ submission

- **Ongoing discussion**
  - Submission to PQ process
  - Stopping manufacturing but EUL maintenance
  - Adaptation to New variants

- **Index strain Vs new Variants**
  - Post EUL Vs PQ

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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
Additional information EUL:

Covid 19 vaccines: Guidance documents and EUL submissions

https://extranet.who.int/pqweb/vaccines/covid-19-vaccines

Target product profile


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

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