Regulatory, safety and monitoring, including pharmacovigilance – EUL experiences from COVID

World Health Organization

Global Vaccine/Medicine Procurement Practitioners Exchange Forum (eV-MPPEF) 2021

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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
- 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**

WHO regulatory preparedness for COVID-19 vaccines

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


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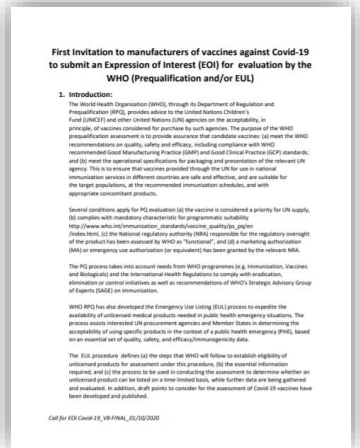
CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

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

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

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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

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*

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 > 400 reports > 100 countries LMIC and HIC
2. Discussion on outcome of review: Facilitated workshops

   One on one discussions with countries.
3. Additional guidance for decision making on expedited authorization

   Support to RO and agencies providing relevant docs for actual shipments
4. Post listing changes: > 152 changes clinical, CMC and labelling/packaging changes

>100 countries granted EUAs within 15 days post EUL
Over 500 regulatory approvals based on reliance

WHO listed Covid-19 vaccines

Platform	Manufacturer / EUL holder / name	NRA of Record	Post-EUL commitments
mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	BioNTech Manufacturing GmbH BNT162b2 / COMIRNATY: Tozinameran (INN)	EMA, US FDA	• CMC updates • Clinical • Updated data on the efficacy/effectiveness • Updated RMP • Monthly safety reports, and Periodic Benefit Risk Evaluation Reports (PBRER) every 6 months • Updated labelling, shipping validation (if applicable) and data for VVM • Others:
	Moderna Biotech, mRNA-1273: elasomeran (INN)	EMA, US FDA	
Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	AstraZeneca, AB: AZD1222 Vaxzevria	EMA, Health Canada, MFDS, MHLW-PMDA, TGA	
	Serum Institute of India Pvt. Ltd: Covishield (ChAdOx1_nCoV-19)	DCGI	
Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the SARS-CoV-2 Spike (S) protein	Janssen–Cilag International NV: Ad26.COV2.S	EMA	
Inactivated, produced in Vero cells	Sinopharm / Beijing Institute of Biological Products Co., Ltd. (BIBP)	NMPA	
	Sinovac Life Sciences Co., Ltd.: Coronavac™	NMPA	

Post-EUL commitments (details)

- CMC updates: stability, trends and others
- Clinical: ongoing efficacy/effectiveness data in different target population/comorbidities
- Updated data on the efficacy/effectiveness of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351, P.1, B.1.617.2 and others).
- Updated RMP based on assessment vaccine safety profile
- Monthly safety reports, and Periodic Benefit Risk Evaluation Reports (PBRER) every 6 months
- Updated labelling, shipping validation (if applicable) and data for VVM

Post-EUL commitments (details)

- Others:

a) report serious adverse events following immunization (within 15 days of receipt of the report);

b) report quality complaints from the field for batches supplied;

c) report any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA of reference (NMPA);

- Expansion capacity: New sites
- New storage conditions
- New indications
- New presentations
- Shelf life updates

d) report any problems/constraints in production or quality control which might affect the emergency use condition granted to this product.

Case example

WHO considerations for evaluation of Covid 19 vaccines*.

Main outcome	Submission requirements	Assessment process	Programmatic suitability & post approval monitoring
Storage conditions and shelf-life, (in-use storage conditions and shelf-life).	**Stability data for the vaccine produced at the scale intended for distribution**	• **scientific risk-based approach** to determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches • **Consideration of** platform stability data, prior knowledge from early clinical batches or statistical modelling may also be applied to forecast expiry of product.	• **storage at less than -20°C:** • **if storage below +2°C, period, a minimum period of storage between +2°C and +8°C is required** **Assistance with regards to infrastructure for vaccine storage and distribution at required temperatures.**

- **The summary should include results, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.**
- **Information on the analytical procedures used to generate the data and validation of these procedures should be included**

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

Path forward

Challenge	Requirements	Solution
International Transportation		• ultra-low shipment supplement to the WHO shipping guidelines will be developed published in Q1 2021) • Shipping validation to show evidence that the amount of dry ice used is able to maintain the temperature inside the shipping container at between - 80 degrees to – 60 degrees for 48 hrs.
Containers		• Passive Insulated polystyrene boxes can be used with dry ice as the coolant. • Dry ice sublimates at about 3-5 kg per 24 hrs. so the weight of dry ice needs to be factored-in • For a 48 hr. trip for example it would be safe to have about 6-10 kg of dry ice

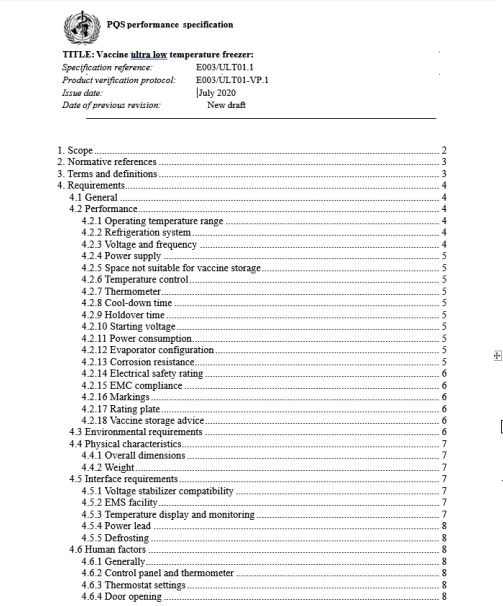
Path forward

Challenge	Requirements	Solution
Dataloggers		• Current WHO prequalified data loggers cannot perform at temperatures below -30 degrees. • WHO has been in touch with manufacturers of devices which can perform down to -80 degrees. • Specifications for ultralow data loggers being developed
Vaccine vial monitor		• WHO has been in touch the VVM manufacturer and they are ready to develop VVMs of appropriate categories to suit the stability of ultralow temperature vaccines as needed

Path forward: Country preparedness

- **Ultra-low temperature freezers:**
- WHO specifications for ULT freezers and associated power requirements, and transport cold boxes

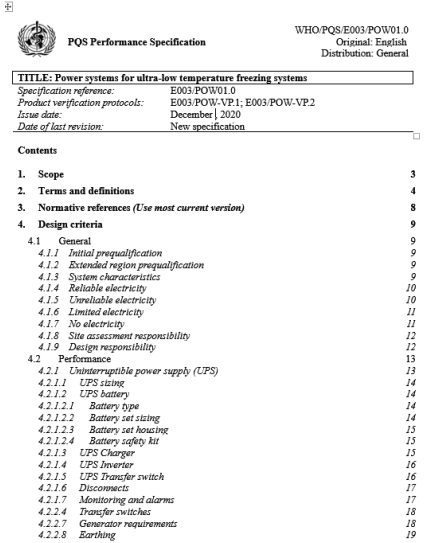
- **Training**
- Appropriate cold chain and vaccine management training package tailored to ultralow temperature vaccines for health workers will be needed, including training on safety and the provision of safety equipment such as gloves



PQS performance specification

TITLE: Vaccine ultra low temperature freezer:

Specification reference: E003/ULT01.1
Product verification protocol: E003/ULT01-VP.1
Issue date: July 2020
Date of previous revision: New draft



PQS Performance Specification

WHO/PQS/E003/POW01.0
Original: English
Distribution: General

TITLE: Power systems for ultra-low temperature freezing systems

Specification reference: E003/POW01.0
Product verification protocols: E003/POW-VP.1; E003/POW-VP.2
Issue date: December 2020
Date of last revision: New specification

Contents

Additional information 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

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

Additional information EUL:

Covid 19 vaccines: Guidance documents and EUL submissions

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

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

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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WORKING TOGETHER

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