

Regulatory Pathways part II

E training

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Hints on the WHO

Emergency Use Listing procedure

By Dr Nora Dellepiane, Regulatory Convergence Initiative



Emergency use listing

What it is

- EUL is a special procedure for medicines, vaccines and IVDs in the case of a public health emergency established to expedite the availability of vaccines needed in such situations.
- Intended to assist interested UN procurement agencies and Member States on the acceptability for use of a specific product (i.e.vaccine) in the context of a PHE, based on a minimum set of available quality, safety, and efficacy data.
- Based on review of available quality, safety and efficacy data and on Risk/benefit analysis



What it is not

- It is not prequalification and should not be considered as such
- It is not a replacement of the PQ process
- Not intended to interfere with ongoing clinical development

PQ and EUL

Prequalification (PQ)

Quality, safety and efficacy and PSPQ for international supply

CMC, clinical and programmatic 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

Emergency Use Listing (EUL)

Assessment of limited data for use during PHEs

Assessment performed by WHO independent experts in collaboration with Mature 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

EUL process similar for all product streams, plus review of [programmatic suitability](#) for vaccines

Post- deployment monitoring. RMP in dossier and data collection in countries.

EUL in a nutshell

Purpose

Define the steps followed by WHO to establish eligibility of unlicensed products for assessment under this procedure, the information required, and the assessment process followed to determine whether an unlicensed product can be listed on a time limited basis, while further data is being gathered and evaluated.

Phases

- Pre-emergency
- Emergency
- Post- listing phase

Pre-emergency

1. Establishment of assessment platform
2. Eligibility and assessment of products
3. Roster of experts

Emergency

1. Ad hoc committees
2. WHO decision on EUL
3. Policy recommendations
4. Publication of review outcomes and communications

Post- listing/ deployment

1. Monitoring
2. Post listing changes

Conditions for use of EUL

- ✓ The disease for which the vaccine is intended is serious or life threatening and has been declared by the WHO Director- General to be a Public Health Emergency of International Concern (PHEIC). The Director-General may authorize use of this procedure for a public health emergency that does not meet the criteria of a PHEIC if he determines that this is in the best interest of public health.
- ✓ Depending on the specific public health emergency, a vaccine EUL assessment applies when there is no licensed vaccine for the indication or for a critical subpopulation.
- ✓ The vaccine is manufactured in compliance with current Good Manufacturing Practices (GMP).
- ✓ The vaccine applicant attests that it intends to complete the development of the product and apply for WHO prequalification.

Note: WHO may consider and justify the review of a product that does not meet all of the above requirements

Pre-emergency phase

Pre-emergency

1. Establishment of assessment platform: establishing a collaboration platform between WHO, external experts, NRA of record for the product and NRAs in potential user countries
2. Eligibility and assessment of products: Interaction with manufacturers, i.e pre-submission meetings, selection of products for assessment according to the eligibility criteria assignment of an evaluation pathway and assessment of submitted data (initial data and updates), with reports thereon. Uses the resources of the assessment platform
3. Roster of experts: Select experts to be called upon to set up the necessary advisory committees to support the different stages of the process, including oversight systems and procedures for implementation

Note. For vaccines, an agreement for information sharing is required between WHO and the NRA of record

Elements of assessment platform

1. Agreement with NRA of record for information sharing and framework for interaction with NRA and Ethics Committees
2. Establishment of a roster of experts
3. Consensus on essential requirements on quality, safety, efficacy/immunogenicity/ performance and lot release
4. Pre-submission activities/ meetings
5. Submission of applications
6. Assignment of assessment pathway
7. Assessment of initial information received
8. Submission of updates

Elements of assessment platform (2)

1. Agreement with NRA of record
Establishment of a roster of experts
2. Consensus on essential requirements (PEC)
3. Pre-submission activities/ meetings
4. Submission of applications
5. Assignment of assessment pathway
6. Assessment of initial information received
7. Submission of updates

2. WHO and/or NRA guidelines may not be available.
Generic WHO guidelines would be applicable
Relevant international guidelines and specific scientific literature

3. Meetings with manufacturers as early as possible may be useful.
Discuss availability of essential, expected timelines for submission and updates, monitoring of safety and effectiveness after deployment, and other relevant information.

4. Application letter: Info about product and country of manufacture + authorization for use in CoO granted or not
Review for eligibility by WHO and acceptance by email, rejection through official letter
If accepted, dossier submission can proceed

5. Possibility of abridged review if criteria are met

Roster of experts

Product Evaluation Committee (PEC)

- Defines the set of requirements and guidelines to be used
- Evaluates the applications
- Risk based analysis on quality, safety, efficacy, performance and programmatic aspects
- Reporting



Advisory Committee on emergency use listing (ACEUL)

(active during emergency phase)

- Review of reports of products evaluated
- Can request additional info from applicants
- Issues a recommendation to WHO for listing (or not)

- ***Both committees are coordinated by the relevant Group Lead for Prequalification***
- ***If a product submitted has undergone authorization by NRA of record, WHO will avoid duplicative work if the emergency procedure in place at the NRA is deemed of acceptable standard***
- ***Ideally, the applications should be submitted during the pre-emergency phase, although sometimes this may not be possible***

Assessment

- **Assessment of initial information**

- Designation of focal point
- Screening of information
- Submission to PEC
- Desk review by inspection team to replace inspection
- Report issued by PEC and handed to WHO
- WHO hands report to ACEUL when PHE is declared for recommendation on listing

Updates

Expected timelines for submission of additional information

Updates should follow same numbering as initial evaluation

Essential data requirements (Annex 5)



Manufacturing and QC data

Characterization of cell banks and bacterial or viral seeds

Process validation

Justified specifications for starting materials, intermediates and final product

Stability data on lots of vaccine produced at scale to be supplied

Programmatic suitability characteristics can be waived

Inspection reports from NRA of record or from WHO

Non-clinical and clinical data

Non-clinical data if available in the most appropriate animal model

Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the PHE

Preliminary efficacy data if available, if not WHO will consider whether immunogenicity data can be considered a surrogate

Plan for monitoring and reporting Aes

WHO encourages applicants to discuss proposals for active data collection and follow-up mechanisms to capture adverse event information under the EUL during the pre-submission meetings.

Environmental risk assessment (ERA)

If produced from genetically modified organisms, a complete ERAR should be submitted

Labelling

SPC. patient information leaflet, Container Labelling, other instructional materials and a plan to assure that recipients and healthcare providers are informed about the uncertainties regarding potential benefits and risks.

*NOTE: If there are missing data at time of submission, applicant must justify and provide timeframe for submission of update*¹¹

Emergency phase

emergency

1. Establishment of ACEUL
2. Handing of report from PEC to ACEUL. ACEUL can request additional information to the applicant if deemed necessary.
3. WHO decision on emergency listing by ACEUL
4. Publication of outcomes and communication- WHO will publish outcome whether positive or negative and will reserve confidential information
5. Full reports may be shared upon request by any interested Member State

Post-listing activities

Post- listing

Post-listing monitoring:

- reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the listing status.
- Sources are existing surveillance mechanisms + commitments for surveillance from manufacturers
- WHO reserves the right to withdraw the listing in case of non-compliance with commitments or if a quality or safety issue cannot be resolved to WHO's satisfaction

Post-listing changes:

- inform WHO of all changes regarding formulation, manufacturing process, testing methods, specifications, 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.
- Changes to products listed based on an abridged procedure must be accepted for emergency use by the original NRA responsible for the oversight of the product, and WHO must be notified of the accepted changes.

EUL flowchart

Public Health emergency
declared

Pre-emergency	Submission	Submission updates	Emergency	Post-listing
Roster of experts	PEC established	PEC reviews new data	ACEUL established	Safety/ efficacy data collection
Pre-submission meeting	List of guidelines	Updated report and recommendations to WHO	PEC report review and deliberations	PEC and ACEUL review new data
Eligibility	Initial review		Recommendations	Listing maintained or product delisted
Essential data requirements	List of questions		Public report published	
	Report to WHO with recommendations		Possible listing including post-listing requirements	

Regulatory options for global access to COVID 19 vaccines



Registered by NRA of record

Not registered
Granted authorization for EU

Not registered nor
authorized for EU

SRA (WLA L4)	WLA L3	SRA (WLA L4)	WLA L3	NA
PQ Agreement with NRA in place	PQ	EUL ⁽¹⁾ Agreement with NRA in place	EUL ⁽¹⁾	EUL ⁽¹⁾
Abridged procedure w/ reliance on SRA	Full procedure Collaboration w/NRA possible	Abridged procedure w/ reliance on SRA	Full procedure Collaboration w/NRA possible	Full procedure

(1) If eligibility criteria are met

NOTE: Having prequalified vaccines already may impact the characteristics of the procedure, i.e. inspections

THANK YOU