Promoting the **Quality** of **Medicines** Plus

Emergency Use Authorization for timely and safe access to medical products in LMICs during health emergencies

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April 2021

Learning objectives – understand

1. What emergency use authorization (EUA)/ emergency use listing (EUL) is and when it's needed

2. How the EUA/EUL process differs from the regular approval process

3. How country regulatory authorities can prepare to grant EUA and strengthen regulatory preparedness for health emergencies

4. Case study - Pakistan

In an emergency

- Regulators need to make timely decisions, often based on incomplete data.

- Regulators need to keep collecting/reviewing data and pivot as necessary.

- Situations are fluid and regulators have to respond quickly to new issues.

EUA/EUL is a process for authorizing use of medical products on an emergency basis

- EUA - U.S. Food and Drug Administration (FDA):

  EUA is a mechanism to facilitate the availability and use of medical countermeasures, including vaccines, during public health emergencies such as the current COVID-19 pandemic.

- EUL - World Health Organization (WHO):

  Emergency Use Listing (EUL) procedure is a risk-based approach for assessment and listing of unlicensed vaccines, therapeutics, and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a public health emergency

EUA/EUL is part of facilitated regulatory pathways to ensure early access to medical products for serious or life-threatening conditions.

EUA/EUL must strike a balance

Timely availability of medical products to address a public health emergency (speed)

vs.

The need to safeguard public health (safety)

Criteria for EUA/EUL

1. Serious or life-threatening condition/disease intended for declared public health emergency of international concern
2. Evidence of effectiveness
3. Risk-benefit analysis
4. No alternatives/no licensed product.

Sponsor should commit to complete development until product approval.

Example: WHO EUL Procedure

WHO'S EMERGENCY USE LISTING PROCEDURE

World Health Organization

WHO's Emergency Use Listing (EUL) procedure involves careful and rigorous assessment of available quality, safety and efficacy data to enable early, targeted use of yet to be licensed vaccines, treatments or diagnostics for response to a Public Health Emergency of International Concern.*

PREPAREDNESS PHASE

- **Establish assessment platform** for WHO, external experts and regulatory authorities to collaborate and assess a product
- **Agree on essential requirements** that a product must meet on quality, safety, and efficacy
- **Determine if product is eligible** for assessment under EUL

EMERGENCY PHASE

- **Conduct rigorous assessment** of available data for the product to determine quality, safety and efficacy
- **Review inspection reports** for manufacturing and clinical trial sites, and as appropriate, carry out on-site inspections to ensure highest standards are met
- **Issue recommendation** on whether the product should be used for emergency response under EUL**

POST-LISTING PHASE

- **Continue to collect and assess safety and efficacy/effectiveness data** on the product's use under EUL
- **Actively monitor** product usage for adverse events and ensure that high quality standards are met
- **Reassess validity of listing** based on new data generated

*   This simplified graphic highlights three sets of key actions that make up the EUL process. Depending on the emergency, there may be overlap between phase activities.

** For vaccines, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization endorses policies and strategies for use.

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All medical products must be approved or authorized before use

- **Regular approval process** – Regulatory authorities review full application to determine that a product is safe and effective for intended use and manufactured according to quality standards. Approval allows for commercial marketing of a product.

- **Emergency process** - Provides authorization to use a product where there are no adequate, approved, and available options
  - Not part of the regular drug approval process
  - Allows health authorities to make medical products available based on totality of available scientific evidence

Product quality: differences between EUA & standard approval

	EUA	Standard approval
API/FPP	Characterization, composition, specification, impurities, etc., intended changes on scale-up	Complete data on drug substance and drug product manufacturing quality and specifications.
Manufacturing	Company scales up production during clinical trials	Commercial production starts after approval
Stability	Short-term stability data available	Both short-term and long-term stability data considered
Inspection	May rely on previous GMP inspection report	Remote or onsite inspection
Post authorization commitments	Variations in manufacturing and storage conditions	Variation requests streamlined

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Which product quality data are required, waived or submitted later?

- Data required by regulators are mainly similar

- PQM+ team is reviewing emerging trends on data waived or submitted later

- Compare minimum data requirements for EUA across agencies

Module 3 Quality Headings and Hierarchy			Required for EUA?
3.2 Body of data			
3.2.S Drug substance [name, manufacturer]			
	3.2.S Drug substance [name, manufacturer]		
	3.2.S.1 General information		
		3.2.S.1.1 Nomenclature	
		3.2.S.1.2 Structure	
		3.2.S.1.3 General properties	
	3.2.S.2 Manufacture		
		3.2.S.2.1 Manufacturer(s)	
		3.2.S.2.2 Description of Manufacturing Process and Controls	
		3.2.S.2.3 Control of Materials	
		3.2.S.2.4 Controls of Critical Steps and Intermediates	
		3.2.S.2.5 Process Validation and/or Evaluation	
		3.2.S.2.6 Manufacturing Process Development	
	3.2.S.3 Characterization		
		3.2.S.3.1 Elucidation of Structure	
		3.2.S.3.2 Impurities	
	3.2.S.4 Control of drug substance		
		3.2.S.4.1 Specification	
		3.2.S.4.2 Analytical Procedures	
		3.2.S.4.3 Validation of Analytical Procedures	
		3.2.S.4.4 Batch Analyses	
		3.2.S.4.5 Justification of Specification	
	3.2.S.5 Reference standards or materials		

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What does national regulatory authority need to do **NOW** for EUA of COVID products?

✓ Define simple steps for granting
- Local authorization
- Import permit
- Lot release for vaccines

✓ Access the manufacturer's EUA application dossier submitted to the initial/host regulatory authority (i.e., the reference agency)

✓ Develop a key information package to support appropriate use of the product to drive people's trust in the product

✓ Develop a system for ongoing quality & safety surveillance & complaint handling procedures

Example: COVID-19 Vaccine National Deployment and Vaccination Plan (NDVP) Regulatory Readiness Requirements

CATEGORY	ACTIVITIES
C. REGULATORY	C.1 Confirm the existence of any expedited regulatory pathway for approval of COVID-19 vaccines (i.e. emergency use authorization, exceptional approval/approval mechanism based on reliance/recognition, abbreviated procedure, fast track, etc.). Timelines and maximum number of days should be mentioned.
	C.2 Ensure the national regulatory authority or other concerned authority has clarified the regulatory requirements, and documents needed for regulatory approvals of COVID-19 vaccines and related supplies.
	C.3 Ensure that regulatory procedures are in place for import permit of COVID-19 vaccines and related supplies, and identify the requirements and documents needed to import COVID-19 vaccines and related supplies, including for taxes and tariffs.
	C.4 Confirm to WHO the existence of an expedited import approval from appropriate authorities. Timelines and maximum number of days should be mentioned. (expected timeline: maximum 5 working days).
	C.5 Ensure COVID-19 vaccines can be released (lot release) in less than two days by reviewing the summary lot protocol only (testing is not required). Identify the requirements and documents needed for NRA lot release for COVID-19 vaccines. Timelines and maximum number of days for lot release/waiver process should be mentioned.

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Example: NDVP COVID-19 Vaccine Surveillance Readiness

Excerpts:

1.1. Ensure that guidelines, procedures & tools for conducting vaccine safety surveillance have been disseminated to surveillance sites

1.4. Identify provisions that require manufacturers to implement risk management plans & report vaccine safety data

1.5. Plan active surveillance of specific COVID-19 vaccine related adverse events

	...ools for planning and conducting ...g, investigation, causality assessment, ...d and disseminated to surveillance
	...ailable to conduct surveillance of
	...Rs and training the AEFI committee ...ssessment of serious AEFI, clusters of

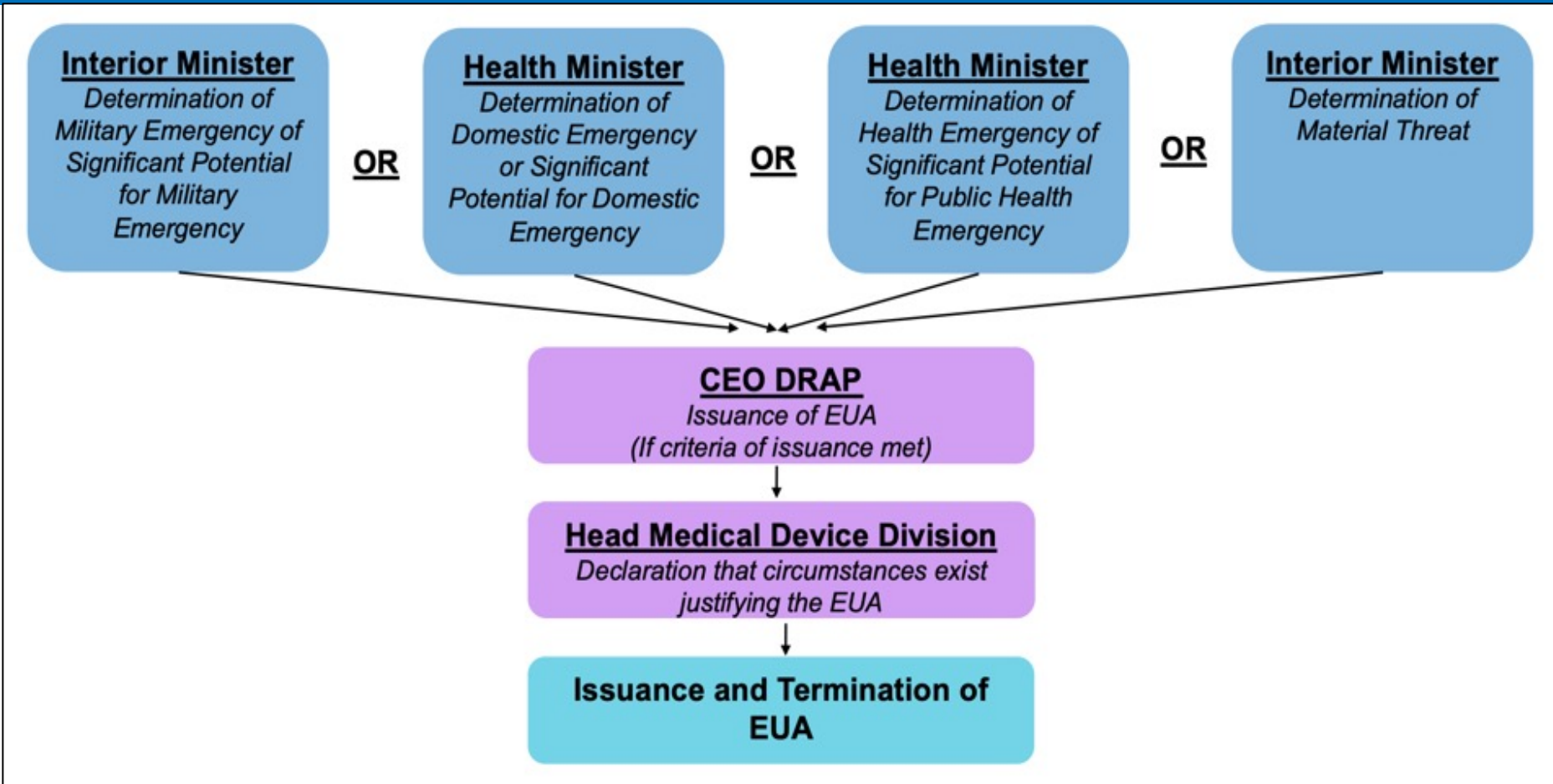| I. SAFETY SURVEILLANCE	
	I.4 Identify provisions that require manufacturers to implement risk management plans and collect and report COVID-19 vaccine safety data to the NRA.
	I.5 Plan active surveillance of specific COVID-19 vaccine related adverse events. If this is not possible, develop provisions that allow reliance on active surveillance data, decisions, and information from other countries or regional or international bodies.
	I.6 Define roles and responsibilities and establish a coordination mechanism between relevant stakeholders (NRA, EPI, MAH, MOH, WHO and others) for exchange of COVID-19 Vaccine safety information.
	I.7 Identify and secure channels of data sharing mechanisms to share COVID-19 vaccine safety data and findings with relevant regional and international partners.
	I.8 Establish compensation schemes in the event that there are unintended health consequences as result of vaccines, including no-fault liability funds, and ensure that associated policies are in place.

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How can national regulatory authority prepare for the NEXT health emergency?

- ✓ Establish emergency regulatory procedures for
  - ▪ Expedited regulatory approvals
  - ▪ Risk-based assessment of product quality

- ✓ Develop reliance procedures for emergencies

- ✓ Develop guidance for industry on requirements for EUA
  - ▪ Can be adapted from stringent agencies (e.g., USFDA, EMA, WHO)
  - ▪ Include post-authorization requirements

- ✓ Develop manual and procedures for review during emergencies

- ✓ Develop guidelines/systems for safety surveillance of medical products introduced in an emergency

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Process for issuance or termination of an EUA in Pakistan

Interior Minister
Determination of Military Emergency of Significant Potential for Military Emergency

OR

Health Minister
Determination of Domestic Emergency or Significant Potential for Domestic Emergency

OR

Health Minister
Determination of Health Emergency of Significant Potential for Public Health Emergency

OR

Interior Minister
Determination of Material Threat

CEO DRAP
*Issuance of EUA
(If criteria of issuance met)*

Head Medical Device Division
Declaration that circumstances exist justifying the EUA

Issuance and Termination of EUA

Authorization criteria

	Possible Situations	Notification Criteria
1	• For medical products approved/registered by recognized countries: (US, EU, Japan, Australia, Canada) • For medical products prequalified by WHO	Route - normal expedited
2	• For medical products approved/registered by foreign regulatory authorities or through emergency requirements	Route A
3	• Medical products manufactured locally • Not approved by reference countries or WHO	Route B

Post handling requirements for medical products under EUA in Pakistan

Reporter	What to Report	To Whom	When
Manufac-turers	30-day reports of deaths, serious injuries and malfunctions	DRAP	Within 30 calendar days of becoming aware of an event
Manufac-turers	5-day reports for an event designated by DRAP or an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health	DRAP	Within 5 work-days of becoming aware of an event
Importers	Reports of deaths and serious injuries	DRAP and the manufacturer	Within 30 calendar days of becoming aware of an event
Importers	Reports of malfunctions	Manufacturer	Within 30 calendar days of becoming aware of an event

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Major challenges faced by DRAP in authorizing COVID–19 products to date

- Need to re-engineer regulatory processes

- Limited data

- Need to build capacity

- Need to converge specialized expertise (e.g., engineering, biostatistics)

- Need to create follow up mechanisms to monitor & address any safety risks

EUAs granted by DRAP for COVID-19

- 4 vaccines

- Ventilators & other medical devices

- Hand sanitizer

- Therapeutics, including now exporting quality-assured medicines for COVID-19

EUA success story for DRAP

- DRAP is now more confident, stronger, and more transparent

- The people of Pakistan and in export markets for Pakistani medical products are benefiting from DRAP's success with EUA

Resources

- WHO Emergency Use Listing Procedure
https://cdn.who.int/media/docs/default-source/medicines/eulprocedure_a63b659c-1cdc-4cee-aa2d-ef5dd9d94f0b.pdf?sfvrsn=55fe3ab8_7&download=true

- WHO Regulatory updates on COVID-19
https://www.who.int/teams/regulation-prequalification/covid-19

- World Bank - Assessing country readiness for COVID-19 vaccines – First insights from the Assessment Rollout
http://documents1.worldbank.org/curated/en/467291615997445437/pdf/Assessing-Country-Readiness-for-COVID-19-Vaccines-First-Insights-from-the-Assessment-Rollout.pdf

- WHO glossary of quality assurance terms
https://www.who.int/medicines/services/expertcommittees/pharmprep/20111208_QASterminologyDB.pdf

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Contact PQM+ with questions

- Email: PQMplus@usp.org

- Visit: https://www.usp.org/our-impact/promoting-quality-of-medicines