Promoting the Quality of Medicines Plus

Guidance on Expedited Regulatory Pathways: New Resources for Therapeutics Emergency Use Authorization (EUA) and Model Dossier

December 12, 2023

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Agenda

- Welcome (2 min)
- Opening Remarks (5 min)
- Introduction and Overview (5 min)
- EUA Guidance for Therapeutics (20 min)
- Model Dossier (20 min)
- Country Experience with EUA (15 min)
- Q&A (15 min)
- Closing Remarks (5 min)

Opening Remarks

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Introduction and Overview

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Emergency Use Authorizations for Therapeutics: Guidance for National Medicines Regulatory Authorities

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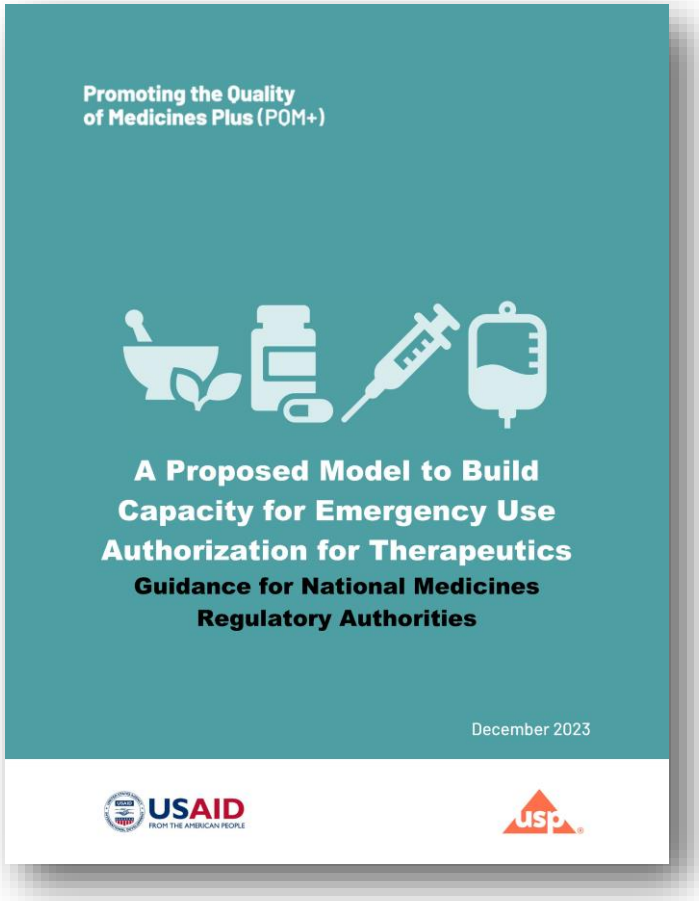


Purpose, Primary Audiences, and Goal

Purpose:

Provide practical guidance to medicines regulatory authorities (MRAs) on adopting, implementing, and managing expedited approval pathways, with a focus on emergency use authorizations

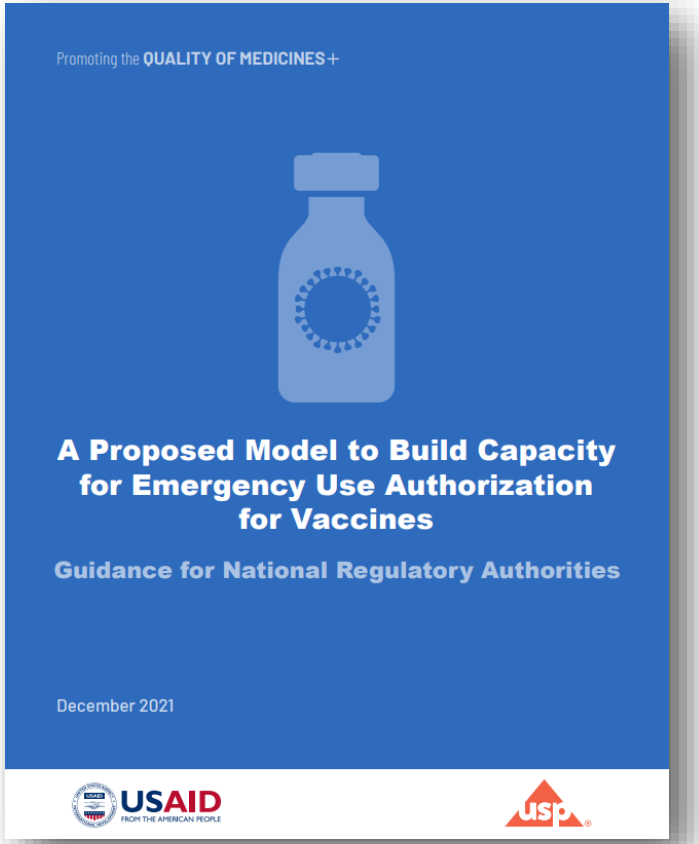
Primary Audiences:

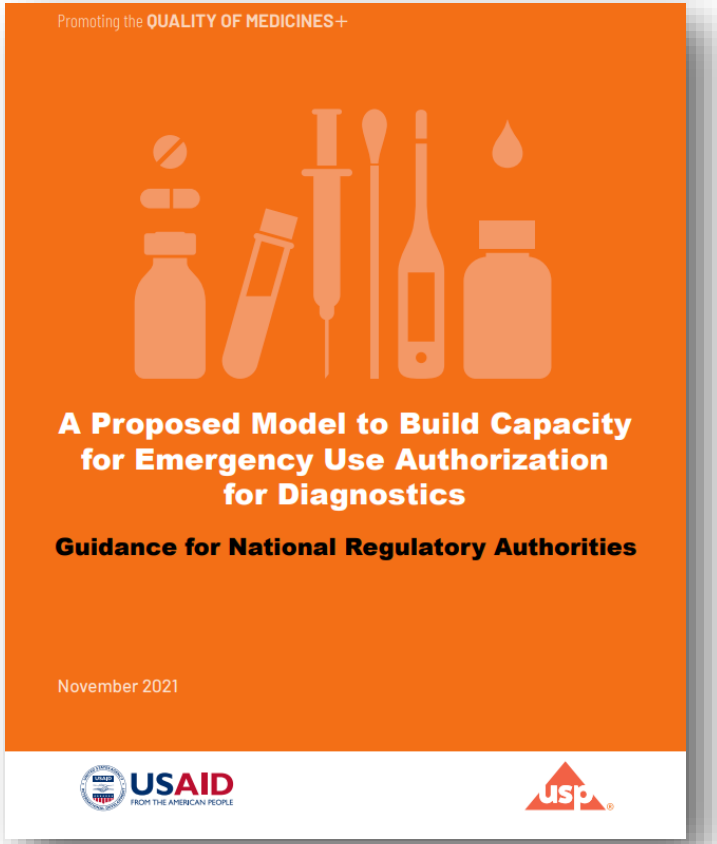
1. MRAs in LMICs that have yet to reach Maturity Level 4 per WHO's Global Benchmarking Tool
2. Countries with EUA process and countries without existing EUA process

Goal:

Facilitate rapid access to safe, effective, and quality therapeutics in response to public health emergencies and facilitate greater international collaboration, harmonization, and data sharing between MRAs

Previous PQM+ Guidance on EUAs for Vaccines & Diagnostics





Considerations for Therapeutic EUAs

More Complex Benefit-Risk Assessments

- Patients receiving therapeutics under an EUA have often already become ill, except in the case of preventive therapeutics
- Risk-benefit analysis differs significantly from that of preventive vaccines, where healthy individuals are the recipients

Wider Range of Manufacturing Processes

- Therapeutics can be chemical or biological based with a range of manufacturing processes, from relatively simple to very complex

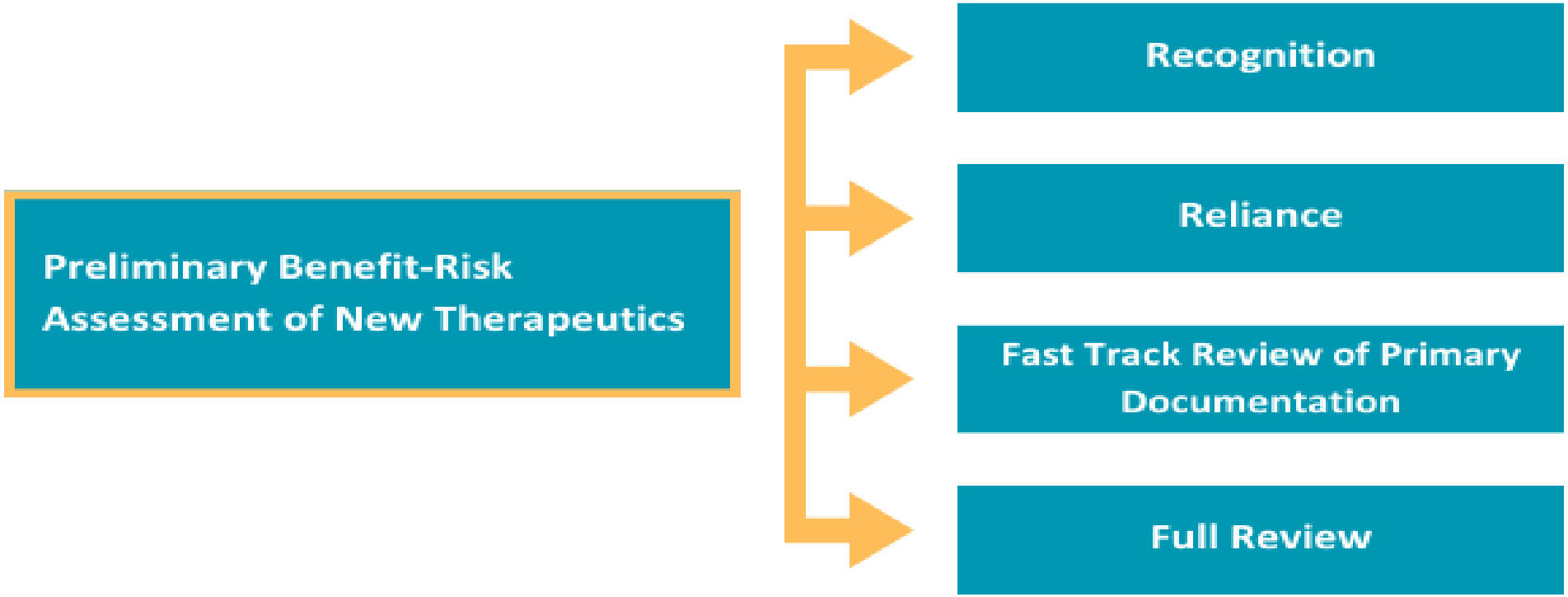
Wider Range of Compositions and Safety Considerations

- Therapeutics can take a variety of forms, including chemotherapeutics, manufactured biologicals, and convalescent plasmas
- May focus on different body systems
- May have very different indications
- May have different drug interactions or contraindications

Methods

- Desk review of medicines regulatory laws and policies from 42 countries (27 LMICs and 15 high-income countries); identified EUA laws/policies from 21 countries/regions
- Rapid assessment of EUA policies and laws in countries participating in PQM+ (15 countries completed and returned the survey)
- Review of WHO and other international guidance
- Synthesized into practical considerations guidance, tools, and checklists

Therapeutic EUA Assignment Pathways Framework



12 Practical Recommendations for Therapeutics EUAs (1-6)

1. Define criteria for granting therapeutics EUAs in the legal and regulatory framework
2. Formalize collaborative review structures and processes
3. Standardize expedited review pathways, including reliance and recognition pathways
4. Assign therapeutics to review pathways based on preliminary benefit-risk assessment
5. Impose conditions on approvals to ensure ongoing evaluation of quality, safety, and effectiveness
6. Monitor condition compliance closely to facilitate conversion to full approval, withdrawal, or revocation of EUAs

12 Practical Recommendations for Therapeutics EUAs (7-12)

7. Require risk management plans and periodic safety update reports
8. Monitor availability of therapeutics to guide EUA decisions and ensure equitable distribution
9. Manage modification requests for therapeutics EUA decisions
10. Embrace transparent communication and community engagement to build trust in regulatory reviews
11. Use a phased planning approach to prioritize finite resources
12. Update operational policies and procedures to find efficiencies and facilitate collaborative review

Tools & Checklists

- Appendix A. Checklist for Strengthening Management of Therapeutic EUAs
- Appendix B. Illustrative Workflows for Processing EUA Applications
- Appendix C. Illustrative Application Checklist for Therapeutic EUAs
- Appendix D. Preliminary Benefit-Risk Assessment Tool to Inform Pathway Assignment
- Appendix E. Communication Product Guidance
- Appendix F. Template Therapeutics EUA Review Memorandum/Assessment Report

Model Dossier: Facilitated Regulatory Pathways for Medicinal Products in Public Health Emergencies and Unmet Medical Needs

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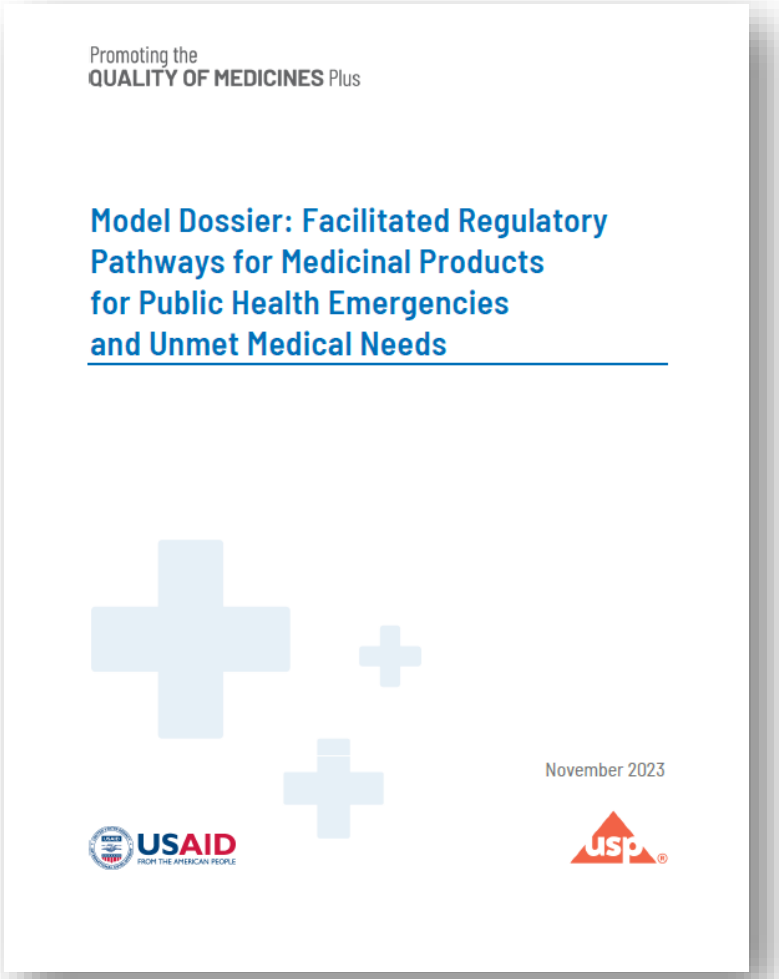
USAID's Promoting the Quality of Medicines Plus (PQM+) Program
U.S. Pharmacopeial Convention (USP)



Introduction

During public health emergencies and for unmet medical needs, it is critical that patients have access to lifesaving medicines as soon as possible.

Barriers to access have included:

- Long review timelines
- Lack of expedited review pathways
- Limited data available to make benefit-risk determinations

Introduction

Stringent regulatory authorities (SRAs) have developed various ***facilitated regulatory pathways (FRPs).***

- Developed to expedite review and approval of products
- Facilitate review based on limited data or as data becomes available
- Products are still expected to meet acceptable standards of quality, safety, and efficacy
- Authorization conditions may be subject to change

However, FRPs used by SRAs still require a **full review** of a medicinal product dossier.

Introduction

As an alternative, *reliance FRPs* have been developed as an efficient way for regulatory authorities in low- and middle-income countries (LMICs) to maximize their available resources and avoid redundant review processes.

Reliance

The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision.

These review pathways do not require a full review, instead the **capacity of SRAs and agencies with maturity level 3/4 is leveraged.**

https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/inspections/grelp-annex-10-trs-1033/trs1033_annex10-good-reliance-practices.pdf?sfvrsn=dd5502cb_17&download=true

Introduction

Redundant reviews or arbitrary additional requirements further exacerbate inequities in access to medicines products by:

1. Restricting or delaying access to essential lifesaving medicinal products.
2. Redirecting resources (financial, human, and technical) that could otherwise be spent on process and procedures specific to the country of context that ensure the quality of products available.

Reliance FRPs will bring efficiency to the regulatory processes to expedite the availability of and access to medicinal products.

Purpose

As a model dossier applicable to various approval pathways that national MRAs can adapt for use and implementation during a health emergency or for an unmet medical need.

As a guidance for manufacturers to navigate different approval pathways to facilitate dossier compilation and submission.

To provide an adaptive common technical document (CTD) format that would be acceptable in a health emergency or for an unmet need for a majority of national MRAs in LMICs.

To provide alternatives to redundant and noncritical review requirements when using reliance pathways that hinge on reviews conducted by SRAs.

Model Dossier Content

1. Legal and regulatory considerations
2. Recommendations for harmonizing dossier submission formats
3. Description of each facilitated regulatory pathway
4. Priority review areas for LMICs
5. Guidance for the selection of an approval pathway
6. Guidance for differences in labeling and package inserts

Facilitated Regulatory Pathways

Emergency Use Authorizations

- Full
- Abridged
- Reliance

Full Approval Pathways

- Accelerated approval
- Breakthrough therapy designation (BTD)
- Fast track
- Priority review

Reliance Pathways

- Abridged review
- Collaborative registration procedures (CRP)
- Reliance and regional regulatory harmonization
- Recognition

Annexures

Annex 1: Model Dossier Requirements by Reliance Pathway
Annex 2: Decision Tree for Approval Pathways
Annex 3: Description of ICH CTD organization
Annex 4: Description of ASEAN CTD Organization
Annex 5: Proposed Module 1 (ICH CTD) or Part 1 (ACTD)
Annex 6: Comparison between ICH CTD and ACTD
Annex 7: EUA timelines and mechanisms for transition to full approval
Annex 8: Summary of Breakthrough Therapy Designation Criteria and Requirements
Annex 9: Summary of the World Health Organization Standard Structured Product Labeling Requirements for Medicines
Annex 10: Overview of World Health Organization Recommended Patient Information Leaflet
Annex 11: Provisions and Procedures for Emergency Use Medicines Sent to LMICs
Annex 12: Modifying Label of Medicines for Export to LMICs - Pros and Cons

A series of annexures provide additional resources.

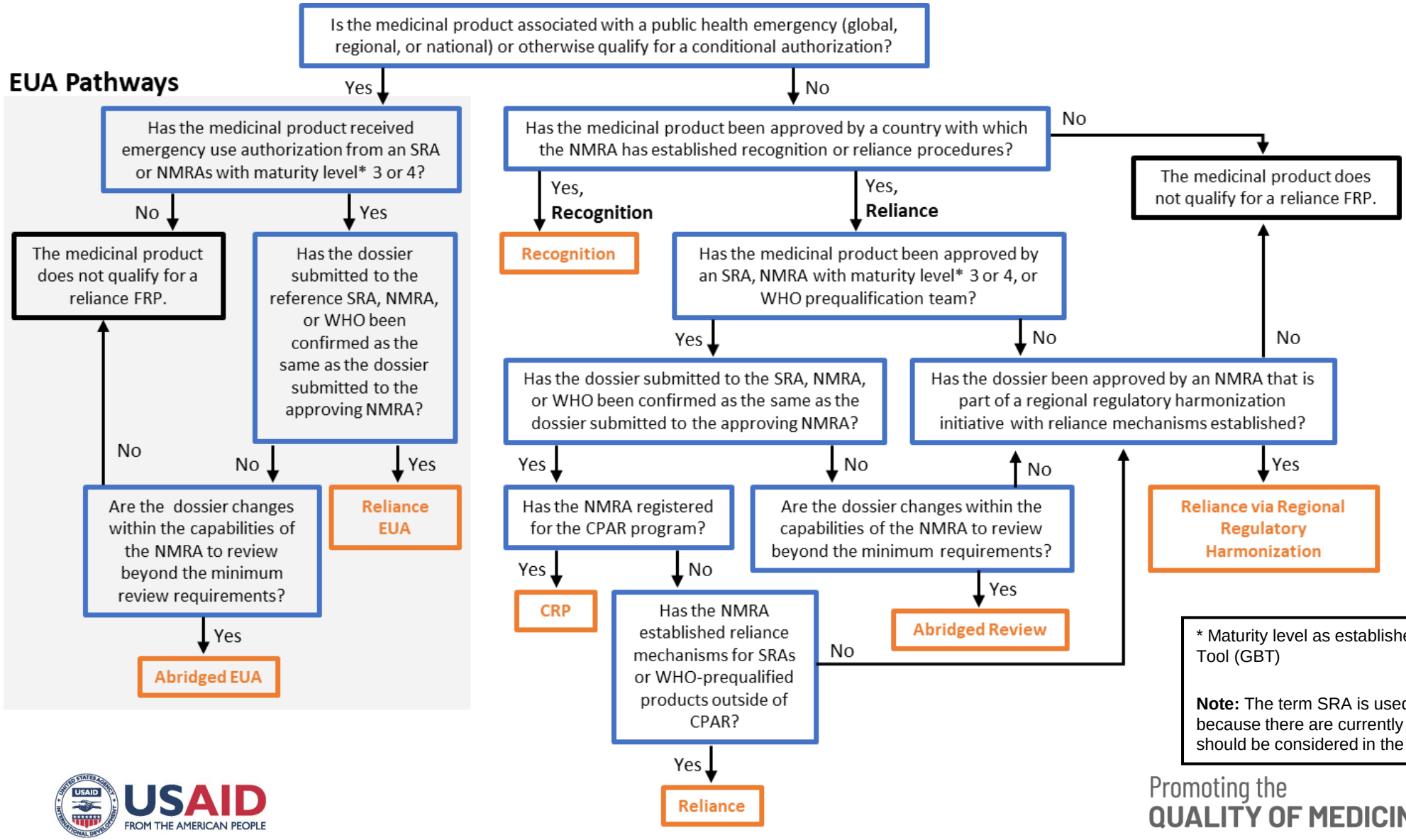
Useful resources specific to **structured product labeling** and **summary of product characteristics** package inserts

Annex 1: Model Dossier Requirements by Reliance FRP

Application Package Contents	Reliance FRPs					
	Reliance EUA	Abridged EUA	Recognition	Reliance	CRP	Abridged Review
Module 1 (ICH CTD) / part 1 (ACTD); application form	Yes	Yes	Yes	Yes	Yes	Yes
SRA- or WHO-approved package insert	Yes	Yes	Yes	Yes	No †	Yes
SRA- or WHO-approved label *or* fact sheet for product recipients and caregivers and fact sheet for health care providers (as applicable)	Yes	Yes	Yes	Yes	Yes	Yes
Proposed risk management and post-marketing surveillance plans	Yes	Yes	Yes	Yes	No †	Yes
Assurance of sameness	Yes	Yes	Yes	Yes	No †	Yes
Certificate of the responsible SRA's or WHO's decision	Yes	Yes	Yes	Yes	No †	Yes
Assessment reports of the responsible SRA(s) or WHO	Yes	Yes	Yes	Yes	No †	Yes
Evidence of quality and good manufacturing practices compliance (GMP certificate)	No*	Yes	No	No*	No †	Yes
CTD quality, nonclinical, and clinical overviews (module 2 of ICH CTD or parts II–IV of ACTD)	No*	Yes	No	No*	No	Yes
Full dossier as required by national law and/or regulations (e.g., CTD modules 2–5)	No	No	No	No	Yes (same as submitted to SRA or WHO)	No ‡
Minutes from presubmission meeting(s) as applicable	Yes	Yes	No	No	No	No

* These components may be required depending on the level of reliance
† These are made available by the SRA or WHO via CRP procedures
‡ Specific components may be necessary if there have been changes to the dossier

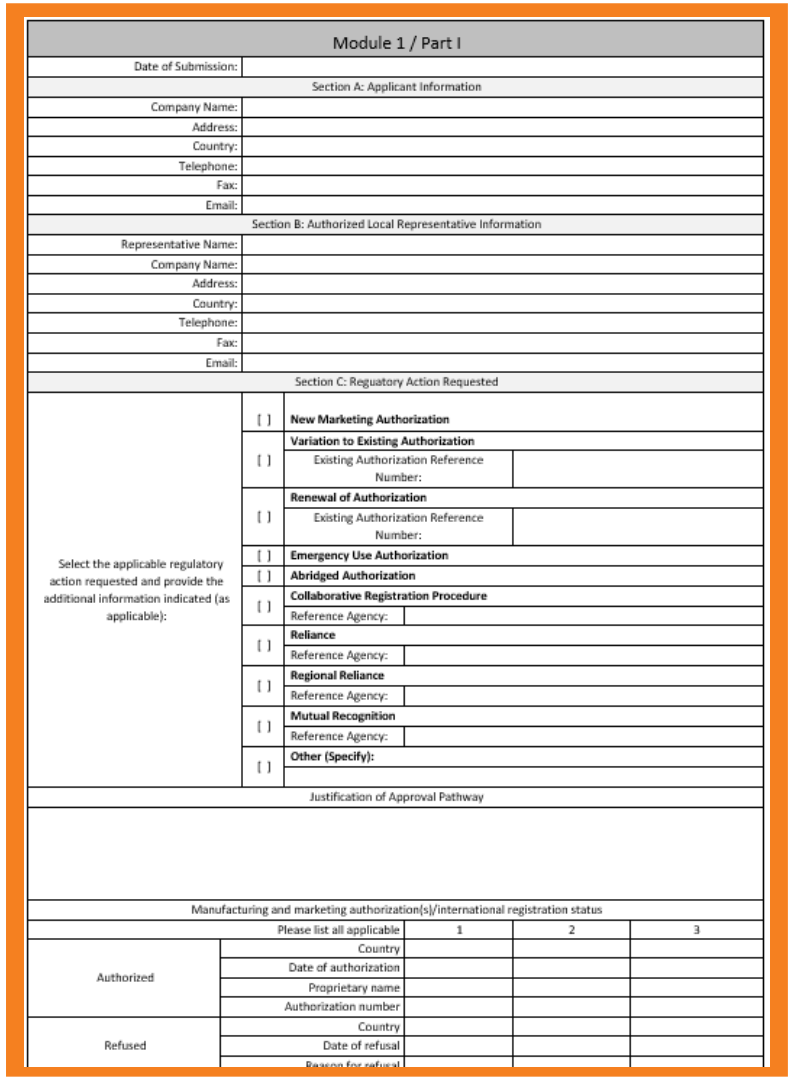
Annex 2: Decision Tree for Approval Pathways



* Maturity level as established by the WHO Global Benchmarking Tool (GBT)

Note: The term SRA is used instead of WHO-Listed Authority because there are currently only 3 WHO-listed authorities. They should be considered in the same way as SRAs.

Annex 5: Proposed Module 1 (ICH-CTD) or Part 1 (ACTD)



Module 1 / Part I				
Date of Submission:				
Section A: Applicant Information				
Company Name:				
Address:				
Country:				
Telephone:				
Fax:				
Email:				
Section B: Authorized Local Representative Information				
Representative Name:				
Company Name:				
Address:				
Country:				
Telephone:				
Fax:				
Email:				
Section C: Reguatory Action Requested				
Select the applicable regulatory action requested and provide the additional information indicated (as applicable):	[ ]	**New Marketing Authorization**		
	[ ]	**Variation to Existing Authorization**		
		Existing Authorization Reference Number:		
	[ ]	**Renewal of Authorization**		
		Existing Authorization Reference Number:		
	[ ]	**Emergency Use Authorization**		
	[ ]	**Abridged Authorization**		
	[ ]	**Collaborative Registration Procedure**		
		Reference Agency:		
	[ ]	**Reliance**		
		Reference Agency:		
	[ ]	**Regional Reliance**		
		Reference Agency:		
	[ ]	**Mutual Recognition**		
		Reference Agency:		
	[ ]	**Other (Specify):**		
Justification of Approval Pathway				
Manufacturing and marketing authorization(s)/international registration status				
		Please list all applicable	1	2	3
Authorized		Country			
		Date of authorization			
		Proprietary name			
		Authorization number			
Refused		Country			
		Date of refusal			
		Reason for refusal			

Designed with critical application information

Can be adopted by regulatory agencies without specified Module 1 requirements or adapted for harmonization initiatives

Section A: Applicant Information
Section B: Authorized Local Representative Information
Section C: Regulatory Action Requested
Section D: Product Information
Section E: Stability
Section F: Attachments
Section G: Declaration

Ethiopia's Experience with Emergency Use Authorizations

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Lead Executive Officer
Medicine Evaluation and Market Authorization
Ethiopian Food and Drug Authority (EFDA)

Topics

- Background
- Strategies to expedite marketing authorization (MA)
- Pre-implementation of EUA in Ethiopia
- Post-implementation of EUA in Ethiopia
- Challenges and lesson learned in Ethiopia

Legal Basis

- EFDA Proclamation 1112/2019 (Article 20 (1)) indicated that any medicine shall not be manufactured, imported, exported, stored, distributed, transported, sold, held, or used without marketing authorization.
- **Marketing authorization (MA)** is a **crucial** regulatory requirement to **ensure quality, safety,** and **efficacy/effectiveness** of a medicine or medical device.

Strategies to Expedite Marketing Authorization

Marketing authorization requires three processes:

- Dossier assessment, which ensures quality, safety, and efficacy or effectiveness to grant MA
- Site inspection of facility/good manufacturing practices (GMP) waiver, showing the manufacturing facility is in compliance with GMP
- Quality control testing: as appropriate, shifted from pre-market testing to consignment testing.

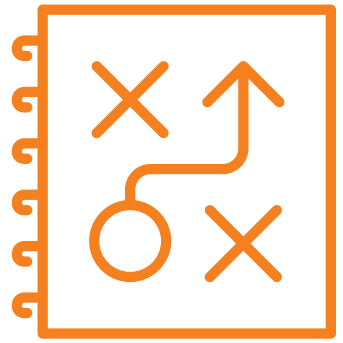
Strategies to Expedite Marketing Authorization

- Per Article 19(1) of Food and Medicine Administration Proclamation No. 1112/2019, the rigor of the regulatory assessment of a medicine shall be commensurate with the product's type, nature, and potential risk to human health.
- It is good to know the pathways that the authority follows to register medicines (grant MA).

Strategies to Expedite Marketing Authorization

Pathways to grant MA:

- Regular pathway
- Low-Risk pathway
- Fast-track procedure for priority products
- Reliance pathway

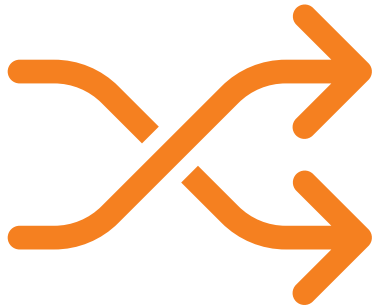


Reliance Pathway

An alternative, nonroutine approval pathway used by the authority in its regulatory decisions regarding marketing authorization of a product based on assessment outcomes of one or more recognized regulatory authority.

Reliance Pathways: Conditions for Reliance

Medicinal products that have been approved via:

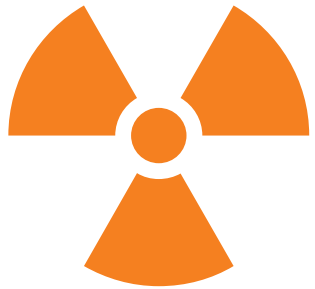


- WHO PQ collaborative registration procedure (CRP)
- WHO collaborative registration pilot for SRA
- Stringent regulatory authorities, as recognized by EFDA.
- Intergovernmental Agency for Development (IGAD) through a joint assessment scheme
- African Medicines Regulatory Harmonization (AMRH) initiatives, such as the African Medicines Agency (AMA)
- WHO-listed agencies may be considered through reliance pathways on a case-by-case basis
- WHO CRP: Vaccines and in vitro diagnostics (IVDs)

Reliance Under Emergency Situations

Conditional approval:

- An alternative approval pathway is devised to provide access to certain medicines for an unmet medical need of the public.



EUA/Emergency Use Listing Procedure (EUL):

- During COVID-19 vaccine EUL with WHO
- Ethiopia among African countries (South Africa, Ghana, Rwanda, and Ethiopia)

Pre-Implementation of EUA – Ethiopia

- National Disaster Prevention and Preparedness Strategy for Ethiopia - led by Ethiopian Public Health Institute (EPHI).
- Expediting Medicine Marketing Authorization Strategy, October 2017.
- Guideline for Conditional Approval of Medicines, January 2021.

Conditional Approval of Medicines

- Alternative approval pathway is devised to provide access to certain medicines for unmet medical need of the public.
- Benefit – risk balance of medicine is positive.
- It is likely that the applicant will provide comprehensive data.
- Unmet medical needs will be fulfilled.
- Immediate availability of the medicine on the market outweighs any risks that result from the need for additional data.

Emergency Use Authorization (EUA)

- In response to the COVID-19 pandemic, Ethiopia developed its Guideline for Emergency Use Authorization (EUA) of COVID-19 Vaccine.
- Ethiopia was one of four African countries (with South Africa, Ghana, and Rwanda) selected by WHO to review COVID-19 vaccine dossiers for EUL of COVID-19 vaccines to facilitate the COVAX platform.

Emergency Use Authorization (EUA)

- Ethiopia sent four experts to participate in reviewing sections of COVID-19 vaccine dossiers: nonclinical; clinical; chemistry, manufacturing, and controls (CMC); and risk management plan (RMP).
- The authority (MA head) granted EUA for Pfizer, AstraZeneca, SinoPharm (BIBP), and Janssen COVID-19 vaccines following EUL by WHO.
- Ethiopia signed a declaration of interest and confidentiality agreement and an information-sharing agreement with WHO.

Post-Implementation of EUA

- Revised the **risk management plan guideline** to address COVID-19 issues – pharmacovigilance (PV) department.
- Provided **training of trainers (TOT),** capacitating trainees to teach other health professionals how to handle COVID-19 vaccines and administration.
- **PV focal persons** provided mass training to health professionals, spreading adequate information on side effects/adverse drug reactions (ADRs) and contraindications of COVID-19 treatments.
- Prepared a form containing detailed information on individuals who receive vaccines.

Challenges and Lesson Learned

- **Cost** of testing for COVID-19 created challenges to administer the vaccine after testing.
- **Availability** issues.
- **Adherence** to receive the COVID-19 vaccine and fear of vaccination.
- **Follow-up** issues
- Unwilling to take **booster dose** (complaints about side effects from the first dose).

Lessons Learned from COVID-19

Lessons learned from the COVID-19 pandemic underscore the importance of implementing **effective policies** that enhance food conditions, promote physical activity, and protect families' health and well-being.

Questions & Answers

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Associate Dean, School of Pharmacy
Director, Global Medicines Program
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Closing Remarks

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Links to Resources

Proposed Model to Build Capacity for Emergency Use Authorization for Therapeutics: Guidance for National Medicine Regulatory Authorities | Promoting the Quality of Medicines Plus (usp-pqmplus.org)

Facilitated Regulatory Pathways Model Dossier | Promoting the Quality of Medicines Plus (usp-pqmplus.org)

A proposed Model to Build Capacity for Emergency Use Authorization for Vaccines

A Proposed Model to Build Capacity for Emergency Use Authorization for Diagnostics

Thank you!