Promoting the Quality of Medicines Plus (PQM+)

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

Guidance for National Medicines Regulatory Authorities

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A Proposed Model to Build Capacity for Emergency Use Authorization for Therapeutics: Guidance for National Medicines Regulatory Authorities

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About PQM+

PQM+ is a six-year cooperative agreement between USAID and USP and its consortium of partners to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases and other infection diseases, as well as improve maternal, newborn, and child health.

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Acronyms

COVID-19	Coronavirus Disease 2019, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CTD	Common Technical Document
EMA	European Medicines Agency
EUA	emergency use authorization
EUL	emergency use listing
FAQ	frequently asked questions
FDA	Food and Drug Administration
GMP	good manufacturing practice
HHS	Health and Human Services
LMIC	low- and middle-income countries
ML	maturity level (WHO Global Benchmarking Tool)
MRA	medicines regulatory authority
PMS	post-marketing surveillance
PQM+	Promoting the Quality of Medicines Plus
TWG	technical working group
USAID	U.S. Agency for International Development
WHO	World Health Organization

Executive Summary

During the COVID-19 pandemic, many medicines regulatory authorities (MRAs) implemented various forms of expedited approval pathways such as conditional market authorizations and emergency use authorizations (EUA) to review and accelerate the availability of acceptable vaccines, therapeutics, and diagnostics to respond to the pandemic. EUA frameworks are a critical part of preparing for and responding to outbreaks and pandemic emergencies that allow regulators and policymakers to balance the benefits and risks of new products. Many of these expedited review frameworks can be built on to review vaccines, therapeutics, and medical devices beyond the COVID-19 pandemic. However, reviewing and managing EUAs for therapeutics presents some unique considerations for MRAs, particularly those in low- and middle-income countries (LMICs).

In 2021, USAID's Promoting the Quality of Medicines Plus (PQM+) program published two practical guidance documents for MRAs on managing EUAs: one for vaccines, titled *A Proposed Model to Build Capacity for Emergency Use Authorization for Vaccines – Guidance for National Regulatory Authorities,* and one for diagnostics, titled *A Proposed Model to Build Capacity for Emergency Use Authorization for Diagnostics: Guidance for National Regulatory Authorities*. The present guidance builds on that work by providing practical guidance to MRAs on adopting, implementing, and managing expedited approval pathways for **therapeutics**—that is, for drugs and non-vaccine biological products. Preparation of this guidance included a desk review of therapeutics EUA laws, policies, and processes in 27 LMICs and 15 high-income countries. In addition, this guidance is informed by a rapid assessment through a survey completed and returned by MRAs in 15 LMICs to evaluate emergency regulatory processes and procedures for therapeutics that PQM+ countries use.

This document presents practical recommendations for strengthening operational policies and procedures for therapeutics EUAs, establishing clear review timelines, allowing for rolling submissions, using standardized application forms and checklists, and investing in electronic regulatory information systems. The guidance includes the following appendices, which are practical tools, checklists, and resources for MRAs to facilitate efficient management of therapeutics EUAs during public health emergencies:

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

This guidance emphasizes the importance of the following recommendations for therapeutics EUAs and provides examples of approaches MRAs have taken to address them:

a) Define criteria for granting therapeutics EUAs in the legal and regulatory framework.
b) Formalize collaborative review structures and processes.
c) Standardize expedited review pathways, including reliance and recognition pathways.
d) Assign therapeutics to review pathways based on preliminary benefit-risk assessment.

e) Impose conditions on approvals to ensure ongoing evaluation of quality, safety, and effectiveness.
f) Monitor condition compliance closely to facilitate conversion to full approval, withdrawal, or revocation of EUAs.
g) Require risk management plans and periodic safety update reports.
h) Monitor availability of therapeutics to guide EUA decisions and ensure equitable distribution.
i) Manage modification requests for therapeutics EUA decisions.
j) Embrace transparent communication and community engagement to build trust in regulatory reviews.
k) Use a phased planning approach to prioritize finite resources.
l) Update operational policies and procedures to find efficiencies and facilitate collaborative review.

Introduction

Many countries have established legal and regulatory frameworks allowing for emergency use authorizations (EUA) or similar expedited pathways to facilitate access to medicines when certain criteria are met, including during public health emergencies. EUA frameworks are a critical part of preparing for and responding to outbreaks and pandemic emergencies while allowing regulators and policymakers to balance the benefits and risks of new products. These frameworks can often be used for a variety of medical products, including therapeutics, vaccines, diagnostics, and other types of medical devices and supplies, as well as in situations that warrant the need for accelerated approval processes.

Countries have issued EUAs in response to a range of public health emergencies.[1] For example, the U.S. Food and Drug Administration (FDA) issued EUAs relating to COVID-19, enterovirus D68, Zika virus, Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), H1N1, H7N9, anthrax, freeze-dried plasma for treatment of hemorrhage or coagulopathy, nerve agents, and Mpox virus.[2] Managing EUA reviews and decisions during public health emergencies presents a number of challenges for medicines regulatory authorities (MRAs), especially MRAs in low- and middle-income countries (LMICs). Some of the challenges include trying to balance access with safety, making decisions based on limited data, and intense scrutiny and pressure to expedite decisions in times of crisis.

Purpose and Scope

This guidance aims to provide practical guidance to MRAs on adopting, implementing, and managing expedited approval pathways for therapeutics. The primary audiences for this guidance are MRAs and other stakeholders in countries that have yet to reach Maturity Level 4 (ML4) based on the WHO Global Benchmarking Tool.[7] This guidance should be useful to MRAs without a current EUA pathway and to those looking to strengthen their existing EUA framework.

The goal of this guidance is to facilitate greater international collaboration, harmonization, and data sharing between MRAs to reduce duplication and facilitate rapid access to safe, effective, and quality therapeutics in response to public health emergencies. This guidance also seeks to improve communication and transparency to the public to maintain trust in the rigor of the regulatory review process and confidence in the safety, effectiveness, and quality of therapeutics.

In 2021, USAID's Promoting Quality of Medicines Plus (PQM+) program published *A Proposed Model to Build Capacity for Emergency Use Authorization for Vaccines: Guidance for National Regulatory Authorities*.[3] Similar guidance, also published in 2021, focused on diagnostics: *A*

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[1] The Petrie-Flom Center Staff, From 9/11 to COVID-19: A Brief History of FDA Emergency Use Authorization, January 28, 2021, https://blog.petrieflom.law.harvard.edu/2021/01/28/fda-emergency-use-authorization-history/#:~:text=The%20enactment%20and%20early%20years,Project%20Bioshield%20Act%20of%202004 (last visited July 7, 2023).

[2] U.S. FDA, Emergency Use Authorization--Archived Information, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information (last visited July 7, 2023)

[3] PQM+. 2021. Promoting the Quality of Medicines Plus (PQM+) A proposed model to build capacity for emergency use authorization for vaccines: Guidance for national regulatory authorities. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.

Proposed Model to Build Capacity for Emergency Use Authorization for Diagnostics Guidance for National Regulatory Authorities.[4] This document builds on these publications and focuses on the unique aspects of implementing and managing EUA processes for therapeutics during public health emergencies. **In this guidance, we use the term *therapeutics* to refer to drugs and non-vaccine biological products**.

The terminology used for expedited and conditional medicine approvals during public health emergencies varies by country. For example, the European Medicines Agency (EMA) uses the term "conditional market authorization" to refer to its fast-track approval pathways of medicines that fulfill an unmet medical need (regardless of whether a public health emergency exists).[5] The U.K. uses the term "temporary authorization."[6] The U.S. uses "emergency use authorization" to refer to those issued under a public health emergency declaration. This guidance uses the term **emergency use authorization (EUA)** to refer to all types of expedited medicine regulatory approvals issued in response to a public health emergency, regardless of whether a formal emergency declaration is required.

EUAs for therapeutics present unique considerations that may affect how MRAs approach their reviews as compared to EUAs for diagnostics or vaccines. **First,** patients receiving therapeutics under an EUA often already have become ill with the contagion and/or developed the disease (except for preventative therapeutics). Therefore, the risk-benefit analysis differs significantly from that of preventive vaccines, where healthy individuals are the recipients. **Second,** many therapeutics are chemical-based, rather than biologic-based, leading to potentially simpler manufacturing processes compared to biologic-based vaccines. **Third,** reviewing EUA applications for therapeutics can require a wider range of expertise. For example, therapeutics can take a variety of forms, including chemotherapeutics, manufactured biologicals, and convalescent plasmas. In addition, medicines under review for a potential EUA can focus on different body systems and their indications can vary significantly. For example, during the COVID-19 public health emergency, the U.S. FDA issued EUAs for antivirals and monoclonal antibodies for the treatment of COVID-19, but also issued EUAs for medicines to support sedation of patients on ventilators and renal replacement therapies due to increased incidence of kidney failure and dialysis during the pandemic. Approving new therapeutics or existing therapeutics for new indications also raises concerns about potential drug interactions, necessitating thorough evaluation during the review process. As a result, evaluating therapeutics for EUAs can require a more diverse range of expertise within MRAs compared to other types of products seeking an EUA.

Future public health emergencies could lead to an increased need for EUAs for therapeutics to respond to a variety of types of public health emergencies. Developing robust systems to review and manage EUAs will be critical for MRAs preparing to respond to public health emergencies.

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[4] PQM+. 2021. Promoting the Quality of Medicines Plus (PQM+) A proposed model to build capacity for emergency use authorization for diagnostics: Guidance for national regulatory authorities. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.
[5] European Medicines Agency, Conditional marketing authorization, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (last visited on 7 July 2023).
[6] U.K. Government, Decision ARCHIVE: Conditions of Authorisation for COVID-19 Vaccine Pfizer/BioNTech (Regulation 174) Updated 5 June 2023, https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine (last visited on July 7, 2023).

This guidance should be viewed as presenting considerations and illustrative procedures and a step-by-step framework for operationalizing therapeutics EUAs. Each therapeutic candidate and country context may require modifications to the procedures and tools presented in this guidance. Every country will also have its own policy and legal framework, which should be reviewed to ensure alignment between EUA procedures and national policy and legal requirements. Therefore, this guidance should be reviewed critically by policymakers, subject matter experts, civil society representatives, and other key stakeholders in each country and adapted as appropriate for the national context.

Methods and Findings

This guidance builds on the previously published guidance titled *A Proposed Model to Build Capacity for Emergency Use Authorization for Vaccines: Guidance for National Regulatory Authorities* (2021)[7] and is based on a landscape analysis conducted in 2023 of therapeutic EUA laws, policies, processes, and decisions. To inform the analysis, we first developed a questionnaire on EUAs for therapeutics and sent it to PQM+ points of contact in countries participating in the PQM+ program. We received completed questionnaires from 15 countries.[8]

We conducted a desk review of therapeutics EUA laws, policies, and decisions. We reviewed publicly available laws and policies and the MRA websites from 27 LMICs and 15 high-income countries to identify EUA laws and policies, and we identified EUA frameworks in 21 countries and regions (seven LMICs and 14 high-income countries and/or regions). The countries included in the review were those participating in PQM+ and/or participating in the International Coalition of Medicines Regulatory Authorities (ICMRA) and MRAs operating at Maturity Level 3 (ML3) and Maturity Level 4 (ML4) pursuant to the World Health Organization (WHO) Global Benchmarking Tool. We also included the relevant guidance documents from the WHO and other international organizations on managing EUAs for therapeutics.

Our desk review identified laws and policies governing EUAs for therapeutics for 21 countries and regions: Australia, Brazil, Canada, China, European Union, France, Germany, Ghana, Egypt, Ireland, Italy, Kenya, Japan, Netherlands, Singapore, Sweden, Switzerland, Tanzania, U.K., U.S., and Vietnam. Table 1 provides an illustrative list of EUA laws and policies governing therapeutics.

[7] PQM+. 2021. Promoting the Quality of Medicines Plus (PQM+) A proposed model to build capacity for emergency use authorization for vaccines: Guidance for national regulatory authorities. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention.
[8] We received questionnaires from the following countries: Bangladesh, Benin, Burkina Faso, Democratic Republic of Congo, Ethiopia, Ghana, Guinea, Kazakhstan, Kenya, Liberia, Madagascar, Mali, Mozambique, Nepal, Nigeria, Pakistan, Rwanda, Senegal, and Uzbekistan.

Table 1. Illustrative List of Therapeutics EUA Guidance

Country	Title of Guidance
Australia	Therapeutic Goods Act 1989, Section 22C(2)
Brazil	Resolução Da Diretoria Colegiada (RDC) no. 475 of 10 March 2021
Burkina Faso	Decree No. 2003-382/PRES/PM/MCPEA/MFB/MS of July 31, 2003, on the national nomenclature of pharmaceutical specialties and generic drugs authorized in Burkina Faso
Canada	Interim Order Respecting the Importation, Sale, and Advertising of Drugs for Use in Relation to COVID-19 under subsection 30.1(1) of the Food and Drugs Act
Ethiopia	Sub-article 5 of article 20(1) of Food and Medicine Administration proclamation number 1112/2019.
European Union	Regulation (EU) 2022/123 of the European Parliament and of the Council of January 25, 2022, on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices
Ghana	1. Public Health Act 2012, Act 851, sections 169-173 2. Ghana Food and Drug Administration, Guidelines For Emergency Use Authorization of Medical Products, Issued: February 5, 2021
Kazakhstan	Clause 17 of the order of the Minister of Health of the RoK dated January 27, 2021, No. KR DSM-10 "On approval of the rules for conducting the examination of medicines or medical devices"
Kenya	1. Republic of Kenya, Ministry of Health, Pharmacy, and Poisons Board, Guidelines on submission of documentation for emergency use and compassionate use authorization (EUA/CUA) of health products and technologies (January 2022) 2. Kenya, Pharmacy and Poisons Act, Cap 244, Section 3B(2)(e), as amended by the Health Laws (Amendment) Act, 2019
Madagascar	Order No. 30803-2010-MSANP of August 6, 2010, relating to the registration of medicinal products
Nepal	Code on emergency use authorization of medicines and devices 2077 (2021), Effective January 12, 2021
Singapore	Health Product (Therapeutic Products) Regulations, subregulations 60A(4) and (5)(b)
Tanzania	Medicines and Medical Devices Act, Cap 219, Section 51 (1)(a) and 57 (1)
U.K.	Human Medicines Regulations, Regulations 174 and 345
U.S.	Food, Drug, and Cosmetics Act (21 U.S.C. 360bbb-3), Section 564

We identified multiple MRAs that recently issued EUAs for therapeutics. For example, during the COVID-19 pandemic, the U.S. FDA issued EUAs for 19 therapeutics relating to COVID-19, including three antivirals (nirmatrelvir and ritonavir; molnupiravir; and remdesivir); 10 monoclonal antibodies; convalescent plasma; two renal replacement therapies; two sedation therapeutics; and chloroquine phosphate/hydroxychloroquine sulfate.[9] The EMA issued conditional market authorizations for nine therapeutics each year in 2021[10] and 2022,[11] however, most of the conditional market authorizations the EMA issued during these years were not directly related to COVID-19. Among LMICs, Egypt, Ghana, Tanzania, and Vietnam have EUA guidelines for medicinal and pharmaceutical products developed during the COVID-19

[9] U.S. FDA, Coronavirus Disease 2019 (COVID-19) EUA Information, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#convplasma (last visited on July 7, 2023)
[10] European Medicines Agency, ANNUAL REPORT 2021.
[11] European Medicines Agency, ANNUAL REPORT 2022.

pandemic. Identifying EUAs for therapeutics issued by MRAs in LMICs was generally more challenging, possibly because MRAs in LMICs do not have such guidelines for therapeutics and/or are less likely to publish their EUA guidelines on their websites.

We also reviewed the WHO's emergency use listing (EUL) program, which can be used for vaccines, diagnostics, and therapeutics. However, the WHO appears to not have used its emergency use listing procedure for any therapeutics.[12] Instead, the WHO used its full or abridged prequalification procedure to prequalify multiple therapeutics relating to COVID-19. The WHO uses its abridged prequalification process when assessing products that have already been stringently assessed and approved. Abridged reviews primarily question whether the product has undergone stringent assessment and, if so, whether the version of the product submitted is the one that received approval.[13,14] From 2020 to June 2023, the WHO prequalified therapeutics containing dexamethasone, remdesivir, tocilizumab, molnupiravir, and nirmatrelvir/ritonavir.[15] WHO prequalified three versions of nirmatrelvir/ritonavir, including one produced by Pfizer and two generic versions manufactured under a voluntary licensing and sublicensing agreement framework between Pfizer and the Medicines Patent Pool.[16]

After reviewing the identified laws and policies, we synthesized the components of these various guidance documents and policies into this guidance with an emphasis on practical recommendations, especially for MRAs that have yet to reach WHO ML4.

Practical Recommendations for Managing EUAs for Therapeutics During Public Health Emergencies

This section summarizes practical recommendations for MRAs when developing and implementing EUA procedures for therapeutics during public health emergencies. Many of the recommendations in this section may be applicable to the review of medicines in nonemergency settings. Guidance on vaccines EUAs is more prevalent, especially for COVID-19 vaccines, than therapeutics EUAs. As a result, we have referenced some models and guidance for vaccine EUAs, which may also be useful frameworks to manage therapeutics EUAs.

The recommendations in this section are combined into the Checklist for Strengthening Management of Therapeutics EUAs, **Appendix A**. An illustrative workflow for processing initial EUA applications and modifications to EUA decisions is in **Appendix B**.

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[12] WHO, Emergency Use Listing, https://www.who.int/teams/regulation-prequalification/eul#:~:text=The%20WHO%20Emergency%20Use%20Listing,by%20a%20public%20health%20emergency (accessed July 14, 2023).
[13] WHO, WHO Medicines Prequalification Guidance, https://extranet.who.int/pqweb/medicines/who-medicines-prequalification-guidance (accessed 27 September 2023).
[14] WHO, Eligibility for Abridged Assessment, https://extranet.who.int/pqweb/vitro-diagnostics/eligibility-abridged-assessment#:~:text=An%20abridged%20assessment%20takes%20into,of%20its%20stringent%20regulatory%20approvals (accessed August 29, 2023).
[15] WHO, Medicines (Finished Pharmaceutical Products/Biotherapeutic products) – Prequalification, https://extranet.who.int/pqweb/medicines/finished-pharmaceutical-products/prequalified (accessed July 14, 2023).
[16] Medicines Patent Pool, 35 generic manufacturers sign agreements with MPP to produce low-cost, generic versions of Pfizer's oral COVID-19 treatment nirmatrelvir in combination with ritonavir for supply in 95 low- and middle-income countries, 17 March 2022, https://medicinespatentpool.org/news-publications-post/35-generic-manufacturers-sign-agreements-with-mpp-to-produce-low-cost-generic-versions-of-pfizers-oral-covid-19-treatment-nirmatrelvir-in-combination-with-ritonavir-for-supply-in-95-low-and.

1. Define Criteria for Granting Therapeutics EUAs in the Legal and Regulatory Framework

The first step in operationalizing an EUA process is ensuring that a legal framework exists to grant the national MRA the legal authority to deviate from required medical product registration and marketing authorization requirements during public health emergencies, such as a local or regional outbreak of an infectious disease or a pandemic. Ghana adopted its EUA statutory framework within its Public Health Act,[17] and Kenya adopted its EUA framework within its Pharmacy and Poisons Act.[18] Countries should have statutes and regulations in place that regulate the marketing of medicines. EUAs should be a legally recognized exception to this requirement. Countries will need to carefully assess how much detail on EUAs to include in statutes, versus delegating authority to other entities within appropriate government agencies. For example, the criteria for issuing an EUA in the United States is defined in U.S. statutory law, but the secretary of the Department of Health and Human Services (HHS) is also granted discretion under the statute to adopt implementing regulations for EUAs.[19]

Statutory provisions provide a strong legal foundation for EUAs, but statutes can also be the most time-consuming to amend in the future. In many settings, adopting regulations can also be a multi-month process due to notice and comment requirements. In contrast, policies, guidelines, and circulars are often the quickest to adopt and amend. A country's statutory environment will influence whether a statute or regulation may be required. For example, if an EUA process would conflict with an existing statute, a country may be forced to revise the statute prior to operationalizing an EUA framework. Often a combination of a statute with implementing regulations and/or policies can be useful framework for establishing a strong legal foundation for EUAs, while granting the MRA flexibility to adopt and amend regulations or policy guidance that lay out the criteria and specific requirements for EUAs.

EUA legal and policy frameworks can apply to single or multiple categories of products. During the COVID-19 pandemic, some countries issued EUA policy guidance focused specifically on COVID-19 vaccines.[20] Other legal and policy frameworks apply to EUAs for vaccines, therapeutics, medical devices, and other medical products. For example, Kenya's *Guidelines on Submission of Documentation for Emergency Use and Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies* allows for EUAs for medicines (therapeutics), blood and blood products, biotherapeutics products, chemical products, vaccines, and medical devices and in vitro diagnostics.[21] Ghana's *Guidelines for Emergency Use Authorizations of Medical Products* (2021) allows EUAs for a range of "medical products," including drugs,

[17] Ghana, Public Health Act 2012, Act 851 (sections 169-173).
[18] Kenya, Pharmacy and Poisons Act, Cap 244, Section 3B(2)(e), as amended by the Health Laws (Amendment) Act, 2019.
[19] 21 USC 360bbb-3 - Authorization for medical products for use in emergencies.
[20] PQM+. 2021. Promoting the Quality of Medicines Plus (PQM+) A proposed model to build capacity for emergency use authorization for vaccines: Guidance for national regulatory authorities. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention. (Table 1).
[21] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines on Submission of Documentation for Emergency Use & Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies (January 2022).

vaccines, medical devices, and biological products.[22] Pakistan's EUA legal framework also covers "drugs and vaccines."[23]

Laws, regulations, and policies for EUAs should clearly establish the criteria for issuing EUAs. For example, the law in Europe allows conditional marketing authorizations only when all following criteria have been met:

- The benefit-risk balance of the medicine is positive.
- It is likely that the applicant will be able to provide comprehensive data post-authorization.
- The medicine fulfills an unmet medical need.
- The benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.[24]

U.S. law prescribes similar criteria for the issuance of an EUA. A summary of these criteria follows:

- An agent referred to in an emergency declaration can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, it is reasonable to believe that (a) the product may be effective in diagnosing, treating, or preventing such disease or condition; and (b) the known and potential benefits of the product outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition.[25]

Note that this last issuance criterion above requires that there not be an alternative product that is adequate, approved, and available. Therefore, a therapeutic may still be eligible for an EUA even after multiple other therapeutics have been approved for the same agent (e.g., COVID-19), if the previously approved therapeutics are not adequate and sufficiently available to meet the public health emergency. In addition, a new therapeutic that has significantly superior attributes compared to approved therapeutics may be eligible for an EUA if approved therapeutics are not "adequate" to respond to the agent.

Ghana has adopted criteria for issuing EUAs that align closely with the criteria adopted under U.S. law.[26] Kenya has also adopted specific criteria for issuing EUAs[27] as follows:

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[22] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (5 Feb 2021).
[23] Drug Regulatory Authority of Pakistan, EUA for Drugs & Vaccines, https://www.dra.gov.pk/therapeutic-goods/emergency-use-authorizations/eua-for-drugs/ (accessed July 14, 2023).
[24] EMA, Conditional marketing authorization, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (accessed July 13, 2023).
[25] 21 USC 360bbb-3 - Authorization for medical products for use in emergencies.
[26] Ghana Food and Drug Administration, Guidelines for Emergency Use Authorization of Medical Products, Issued: February 5, 2021.
[27] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines on Submission of Documentation for Emergency Use & Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies (January 2022).

- The disease for which the product is intended is serious, immediately life-threatening, or has the potential of causing an outbreak, an epidemic, or pandemic and there are no registered products for the indication or for a critical subpopulation.
- Existing products have not been successful in eradicating the disease or preventing outbreaks. The potential EUA/CUA product may also be an antidote that could mitigate a disease or condition caused by use of an already registered product.
- The potential benefits of the product must outweigh potential risks.
- The product is manufactured in compliance with good manufacturing practices (medicines and vaccines) and under a functional quality management system (ISO standards) in the case of in vitro diagnostics (IVDs) and medical devices.
- Where relevant, the applicant undertakes complete development of the product (clinical trials in the case of medicines and vaccines; validation and verification in the case of IVDs) and subsequently applies for registration of the product.

Harmonizing issuance criteria between countries can be important to facilitate reliance and recognition pathways for EUAs. Significant differences between issuance or review criteria can undermine a MRA's ability to rely on or recognize the decision of other competent authorities if review or issuance criteria between countries conflict. Therefore, countries should strongly consider aligning EUA issuance criteria to that of MRAs with which they plan to establish reliance or recognition relationships; this will facilitate rapid reliance and recognition reviews during public health emergencies.

National laws vary depending on whether a formal emergency must be declared before issuing an EUA. Some national laws require an emergency declaration by a governmental authority to issue an EUA. For example, the U.S. FDA guidance on EUAs for medical products states the EUA will stay in effect only until the end of the emergency declaration, and "When an EUA declaration is terminated, then any EUA(s) issued based on that declaration will no longer remain in effect."[28] The EUA frameworks in Kenya[29] and Ghana[30] also require a formal emergency declaration. In contrast, the EMA,[31] U.K.,[32] and South Africa[33] use a conditional market authorization or similar approach that does not require a formal emergency declaration. Countries should strongly consider adopting EUA frameworks that provide flexibility for EUAs to continue beyond the end of formal emergency declarations to facilitate ongoing treatment and/or applications to transition therapeutics to full approval. See consideration 6 below for additional guidance on facilitating a conversion from EUA to full approval.

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[28] U.S. FDA, Emergency Use Authorization of Medical Products and Related Authorities, Guidance for Industry and Other Stakeholders, January 2017, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities.

[29] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines on Submission of Documentation for Emergency Use & Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies (January 2022).

[30] Ghana Food and Drug Administration, Guidelines for Emergency Use Authorization of Medical Products, Issued: February 5, 2021.

[31] EMA, Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

[32] U.K. Medicines and Healthcare products Regulatory Agency, Decision Regulatory approval of Paxlovid, https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid (accessed July 12, 2023).

[33] South African Health Products Regulatory Authority. Information and Guidance on Application for Registration of Candidate COVID-19 Vaccine Communication to Industry (November 1, 2020).

Separating EUA Emergency Declarations from Other Types of Public Health Emergency Declarations

The grounds for declaring and rescinding an emergency declaration relating to EUAs can differ from the basis for declaring and rescinding other types of public health emergency declarations.

Establishing emergency declarations specifically for issuing EUAs can allow the governmental authority overseeing EUAs more discretion on when to declare and end the EUA emergency declaration.

For legal frameworks that require a formal emergency declaration, consultation with other governmental authorities is sometimes required prior to issuance of the emergency declaration. The emergency declaration that opens an EUA pathway can differ from emergency declarations issued by other governmental authorities. For example, in the United States, the secretary of HHS must declare an emergency to open the EUA pathway. Yet, the emergency declaration issued by the HHS secretary that activates the EUA pathway for COVID-19 vaccines and therapeutics was distinct from emergency declarations issued by the U.S. president relating to COVID-19. This is an important distinction, because the grounds for declaring and rescinding an emergency declaration relating to EUAs can differ from the basis for declaring and rescinding other types of public health emergency declarations; this allows the governmental authority overseeing EUAs more discretion on when to declare and end the EUA emergency declaration.

2. Formalize Collaborative Review Structures and Processes

MRAs in countries that plan to import therapeutics should carefully consider reliance on evaluation decisions that other MRAs and review authorities, such as WHO, have made. They should establish formal structures to facilitate collaborative reviews during public health emergencies. Ongoing relationships and data-sharing agreements with other MRAs can help facilitate access to information and reports about therapeutics, including post-approval safety data. Collaborating with other MRAs for joint regional reviews of medicines can be another mechanism that can reduce duplication between MRAs.[34] For example, the South Africa Health Products Regulatory Authority and the Egyptian Drug Authority signed a memorandum of understanding in July 2023 to allow "collaboration and engagement on mutual reliance for pharmaceuticals, biological products, and medical devices."[35] In the Region of the Americas, the Pan American Health Organization (PAHO)/WHO have supported the designation of National Regulatory Authorities of Regional Reference, which have facilitated regional reliance mechanisms.[36] WHO has supported regional collaboration registration mechanisms in the East African Community, the Southern African Development Community, the Economic Community of West African States, the Caribbean Community and Common Market, and the Association of Southeast Asian Nations.[37]

[34] WHO Technical Report Series, No. 1019, 2019, TRS 1019 - Annex 6: Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products.
[35] South African Health Products Regulatory Authority, SAHPRA Signs MOU With Egyptian Drug Authority, July 11, 2023, https://www.sahpra.org.za/news-and-updates/sahpra-signs-mou-with-egyptian-drug-authority/ (accessed July 13, 2023).
[36] Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference. Washington, D.C.: Pan American Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO.
[37] WHO Technical Report Series, No. 1019, 2019, TRS 1019 – Annex 6: Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products.

WHO has established a collaborative procedure for accelerated registration of prequalified pharmaceutical products.[38] This framework can provide a useful structure to facilitate collaborative review of WHO-prequalified therapeutics. WHO has also established a collaborative review structure to facilitate review of finished pharmaceutical products approved by designated regulatory authorities[39] More than 50 LMICs and regions are participating in this collaborative review structure for finished pharmaceutical products approved by designated regulatory authorities.[40] In 2020, PAHO/WHO published guidance titled *Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19)* for regulatory authorities on implementing reliance structures for EUAs in a pandemic.[41]

The landscape of pharmaceutical manufacturing has been globalizing for years and may be accelerating due to concerns about the inequitable distribution of vaccines and therapeutics during the COVID-19 pandemic. For example, under a license agreement between Pfizer and the Medicines Patent Pool, 35 generic medicine manufacturers located in at least 12 countries signed sublicense agreements to manufacture generic versions of Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets).[42] While reliance and recognition pathways can be important methods to expedite reviews, the globalization of pharmaceutical manufacturing may complicate the ability to use these mechanisms as manufacturing scales up in countries that have not achieved WHO ML3 or ML4 designation. In these cases, MRAs in import countries may be less willing to rely on the decision of the MRA in the manufacturing country. As the pharmaceutical manufacturing diversifies, MRAs will have to critically assess the rigor of local MRAs and determine what level of additional review may be required before relying on the local MRA approval. In these cases, obtaining WHO prequalification or EUL may be especially important to facilitate export and MRA approval outside the manufacturing country. PAHO's 2020 guidance even states: "Although not a regulatory authority, PAHO/WHO recommends that [MRAs] consider WHO a trusted/reference authority for the purposes of reliance on prequalified products and/or WHO EUL products."[43] In 2022, WHO published a list of MRAs designated as Transitional WHO Listed Authorities as part of establishing a "transparent and evidence-based pathway for regulatory authorities operating at an advanced level of performance to be globally recognized."[44] This new designation replaces the previous "stringent regulatory authority" designation. The transitional list will remain in effect until 2027, at which time the transitional qualifier will be

[38] WHO, Accelerated Registration of Prequalified FPPs, https://extranet.who.int/pqweb/medicines/collaborative-registration-faster-registration (accessed July 13, 2023).
[39] WHO, Accelerated Registration of FPPs Approved by SRAs, https://extranet.who.int/pqweb/medicines/faster-registration-fpps-approved-sras (accessed July 13, 2023).
[40] WHO, Accelerated Registration of FPPs Approved by SRAs, https://extranet.who.int/pqweb/medicines/faster-registration-fpps-approved-sras (accessed July 13, 2023).
[41] Pan American Health Organization, Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g., COVID-19) (2020).
[42] Medicines Patent Pool, 35 generic manufacturers sign agreements with MPP to produce low-cost, generic versions of Pfizer's oral COVID-19 treatment nirmatrelvir in combination with ritonavir for supply in 95 low- and middle-income countries, March 17, 2022. https://medicinespatentpool.org/news-publications-post/35-generic-manufacturers-sign-agreements-with-mpp-to-produce-low-cost-generic-versions-of-pfizers-oral-covid-19-treatment-nirmatrelvir-in-combination-with-ritonavir-for-supply-in-95-low-and.
[43] Pan American Health Organization, Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g., COVID-19) (2020).
[44] WHO, A Framework for evaluating and publicly designating regulatory authorities as WHO Listed Authorities (WLA), https://www.who.int/initiatives/who-listed-authority-reg-authorities (accessed September 27, 2023).

removed for some MRAs. In the future, MRAs will be able to use the WHO Listed Authorities designation to guide reliance and recognition decisions.

3. Standardize Expedited Review Pathways, Including Recognition and Reliance Pathways

Countries should establish standardized expedited review pathways to facilitate reviews during public health emergencies. The WHO proposed a regulatory pathway framework for influenza pandemic preparedness that may present a useful framework for considering expedited EUA pathways for therapeutics.[45] Nigeria adopted a similar version of this pathway framework for use for COVID-19 vaccines, with some modifications.[46] A framework for expedited review pathways modeled on the WHO pandemic influenza framework could consist of the following four pathways: 1) recognition; 2) reliance; 3) fast-track review of basic documentation; and 4) full review. Each of these potential pathways is discussed below. **Appendix C** contains an illustrative application checklist for possible use to facilitate reviews of EUA applications based on pathway assignment.

a. Recognition

Recognition is a pathway that heeds the decision of a trusted reference authority (e.g., MRA or WHO prequalification or EUL decision) without further technical evaluation by the MRA. As with reliance, approval through a recognition pathway usually involves accepting the conditions and limitations on the use included in the relied-on decision.

Applications reviewed under a reliance or recognition pathway should include an "assurance of sameness" signed by the manufacturer confirming that the product and packaging correspond in all respects (e.g., qualitative/quantitative formula, manufacturing of finished pharmaceutical product and active pharmaceutical ingredient facilities, stability, summary product characteristics and labeling, etc.) to the product approved by the authority on which the MRA is relying, with any exceptions clearly identified.[47] The Pan American Health Organization issued guidance in 2020 titled *Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g., COVID-19*) that includes a sample "assurance of sameness" letter.[48]

Recognition is the most expedited review pathway and will generally be limited to a review of the following components:

- Certificate of the responsible MRA's decision or WHO assessment report; and
- Assurance of sameness.

[45] WHO Expert Committee on Biological Standardization, Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries, sixty-seventh report. Geneva: World Health Organization. WHO Technical Report Series, No. 1004 (2017).
[46] National Agency for Food & Drug Administration & Control (NAFDAC), Guidance on Regulatory Preparedness for Licensing or Access to COVID-19 Vaccines (October 2020).
[47] WHO Technical Report Series, No. 1019, 2019, TRS 1019 - Annex 6: Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products.
[48] Pan American Health Organization, Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g., COVID-19) (2020).

b. Reliance

Reliance is a pathway that reviews the EUA or marketing authorization report(s) and decisions issued by a trusted reference authority (e.g., WHO EUL or prequalification, or other MRA). The WHO defines reliance as "the act whereby the [MRA] in one jurisdiction may consider and give significant weight to—i.e., totally or partially rely upon—evaluations performed by another [MRA] or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken even when it relies on the decisions and information of others."[49] The Pan American Health Organization/WHO (PAHO) developed the following regulatory reliance principles to facilitate the implementation of this pathway: "a legal basis to carry out reliance; sovereignty in making the decision to use reliance, including the need to document the decision as part of good review practices; transparency in the standards and processes used; consistent application; and staff competencies to implement reliance."[50]

A reliance pathway depends on access to the report issued by the supporting MRA or WHO. It will include a technical review by the MRA, but the technical review will generally be limited to the report issued by the authority being relied on. Any approval through a reliance pathway usually involves accepting the conditions and limitations on the use of the product included in the decision being relied on. Additional information or documentation can be requested of the applicant if deemed necessary by the MRA's technical review committee.

The documentation reviewed under a reliance pathway could include:

- Certificate of the decision by the responsible MRA or WHO.
- Assessment reports of the responsible MRA(s) or WHO.
- Assurance of sameness.

c. Fast-Track Review of Basic Documentation

Fast-track review of basic documentation is an expedited review process based on available information. Often information will be submitted in batches to and reviewed by the MRA on a rolling basis as available. Documentation to be reviewed under this pathway could include:

- If the therapeutic has been approved by the WHO, the evidence/certificate of WHO prequalification or EUL with assessment report.
- Assurance of sameness.
- If the therapeutic has been approved by a WHO Listed MRA, the Common Technical Document (CTD) Module-2 and assessment report by the MRA.
- If the therapeutic has not been approved by WHO or WHO Listed MRA, or the reviewing MRA does not have access to the reports issued by licensing MRAs, the CTD Module-2 quality, nonclinical, and clinical overviews, and full dossier to the extent available.

[49] Pan American Health Organization. Regulatory Reliance Principles: Concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). (San Salvador, October 24-26, 2018). Washington, D.C.: PAHO; 2019.
[50] Pan American Health Organization, Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g., COVID-19) (2020) *citing* Pan American Health Organization. Regulatory Reliance Principles: Concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). (San Salvador, October 24-26, 2018). Washington, D.C.: PAHO; 2019.

- Evidence of quality (certificate of analysis or lot release) and GMP compliance certificate.

d. Full Review

Full review refers to the MRA's regular review process as determined by legal and regulatory requirements and internal policies and procedures. Full review can include optional fast-track procedures that establish shorter review timelines for priority products. WHO's prequalification program for medicines includes guidance on the dossier content for submissions for finished pharmaceutical products and active pharmaceutical ingredients.[51]

4. Assign Therapeutics to Review Pathways Based on Preliminary Benefit-Risk Assessment

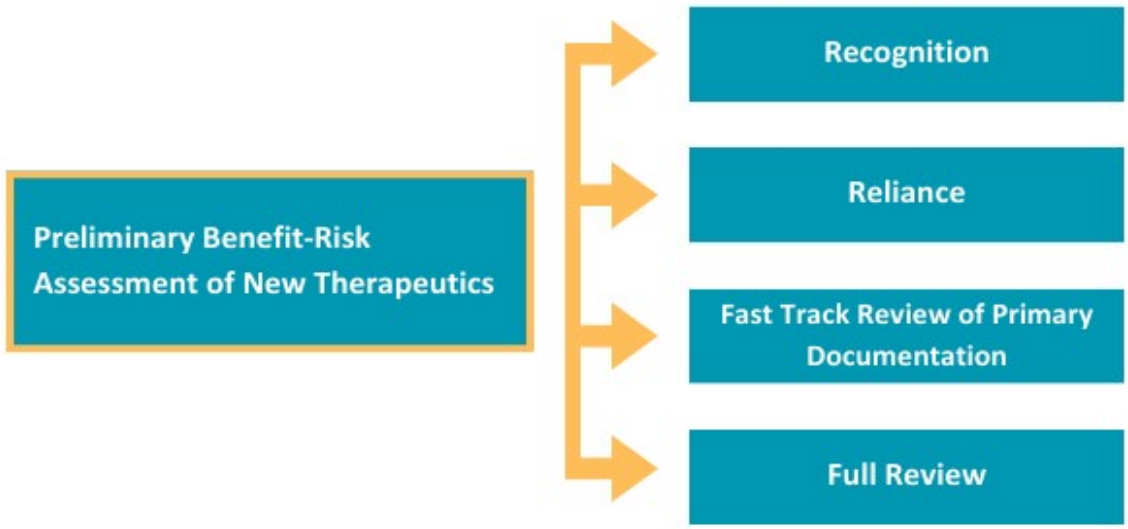
A benefit-risk assessment is an important step in deciding which review pathway to use for a particular therapeutic. MRAs may need to use a multi-criteria benefit-risk assessment approach to determine the appropriate review pathway for each therapeutic. **Appendix D** presents illustrative criteria that an MRA could consider using to inform its decision-making on pathway assignments. The criteria in **Appendix D** are illustrative only and MRAs can adapt these criteria or develop their own based on their review priorities. Establishing explicit benefit-risk criteria prior to the analysis can help ensure consideration of the various categories of benefits and risks. The WHO's influenza guidance also includes a proposed decision-making framework for assignment to various review pathways based on the status of the vaccine and the continuum of pandemic phases, which may also be a useful model for therapeutics.

MRAs can allow applicants to propose an expedited pathway and justify their rationale by providing written responses to questionnaires structured to align with the criteria selected by the MRA. However, MRAs should consider retaining the right to assign an application to the pathway determined most appropriate by the MRA. For example, Ghana's reliance policy allows the Ghana FDA to "activate the reliance pathway to facilitate regulatory decisions either on a case-by-case basis or at the explicit request of the applicant."[52]

Figure 1 illustrates the four pathways that could result from a preliminary benefit-risk assessment of application.

[51] WHO, Prequalification Procedures and Fees: FPPs, APIs & QCLs, https://extranet.who.int/pqweb/medicines/prequalification-procedures-and-fees (accessed July 13, 2023).
[52] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (5 Feb 2021).

Figure 1. Illustrative EUA Assignment Pathways Framework



5. Impose Conditions on Approvals to Ensure Ongoing Evaluation of Quality, Safety, and Effectiveness

Placing conditions on therapeutics EUAs is an important step to mitigate risks associated with EUAs. MRAs have imposed a range of conditions on EUAs for COVID-19 therapeutics approved via expedited pathways to ensure ongoing evaluation of quality, safety, efficacy, and effectiveness. Further, the WHO guideline "Good storage and distribution practices for medical products" should be followed to ensure the quality of medical products is not compromised.[53] These conditions can vary, including the completion of ongoing Phase III clinical trials. For example, the U.S. FDA imposed a range of conditions on Paxlovid relating to instructions for use, manufacturing, reporting adverse events or other quality problems, and distribution and inventory controls to ensure product quality and stability.[54] The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) imposed a range of conditions on the temporary authorization of molnupiravir, including establishing a comprehensive pharmacovigilance system for the product.[55]

Countries should consider placing conditions on therapeutics EUA relating to the following areas:

- Ensuring that health care providers administering the product are aware of the product's emergency use status, its important known benefits and risks, and any alternatives.

[53] Good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025).
[54] U.S. FDA, Emergency Use Authorization 105, May 25, 2023, available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19.
[55] U.K. Medicines and Healthcare products Regulatory Agency, Conditions for authorisation for supply under regulation 174 of the Human Medicines Regulations 2012 for Lagevrio (Molnupiravir), available at https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir

- Ensuring that patients are made aware of its emergency use status, known important benefits and risks, any alternatives, and the option to accept or refuse the product.
- Monitoring, analyzing, and reporting adverse events, i.e., routine pharmacovigilance.
- Manufacturing recordkeeping and reporting.
- Distribution of the product (who may distribute it, means of distribution, and inventory tracking).
- Collecting and analyzing safety data beyond routine pharmacovigilance to fill any evidence gaps relating to use of the product in the local context.
- Assessing product effectiveness in the local context where warranted.
- Advertising the product during the period of emergency use.
- Requiring the applicant to submit an application for full approval once adequate data is available and/or within a certain amount of time after the therapeutic obtains full approval from a trusted MRA or WHO prequalification.

Ghana's Guidelines for Emergency Use Authorization of Medical Products, for example, includes a section on required conditions for medicines receiving an EUA. The conditions include requiring medicines authorized under an EUA to be supplied to the Ministry of Health, which will then distribute to health care facilities information for health care providers and recipients, adverse event reporting, recordkeeping, manufacturing in compliance with GMP, and advertising.[56]

6. Monitor Condition Compliance Closely to Facilitate Conversion to Full Approval, Withdrawal, or Revocation of EUAs

MRAs should establish processes to monitor compliance with conditions placed on EUAs. MRAs should consider the implications of transitioning therapeutics from conditional market approval or EUA to full approval or whether an EUA should be revoked based on new evidence or the results of updated benefit-risk analyses. Some substantial differences between EUAs implicate condition monitoring and regulatory decision-making for EUAs at the end of a public health emergency.

EUAs that link authorization to the duration of a declared public health emergency should establish processes to facilitate regulatory decisions about whether to transition EUAs into full approval, allow continued marketing with conditions, or revoke the EUA. As discussed above, the emergency declaration relating to EUAs can be distinct from other types of emergency declarations issued by other government officials. MRAs should give notice to manufacturers receiving EUAs prior to termination of the emergency declaration. The notice should allow sufficient time for the manufacturer to submit an application to the MRA for full marketing approval. Ghana's EUA guidance includes a framework for terminating EUAs at the end of an emergency declaration and allowing continued use in certain situations.[57] Kenya's January 2022 EUA guidance provides some flexibility to the Kenya Pharmacy and Poisons Board to extend EUAs beyond the end of the emergency declaration under certain conditions, stating: "The

[56] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (Feb. 5, 2021).
[57] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (February 5, 2021).

validity of EUA shall terminate at the end of the emergency or as determined by the Board [Rule 8 of the Pharmacy and Poisons (registration of drugs) rules]."

As noted, MRAs can also consider placing a condition on the EUA that requires the manufacturer to submit an application for full approval when adequate data are available or within a certain amount of time after the therapeutic obtains full marketing approval from a trusted MRA, or to withdraw the EUA application. This condition may help facilitate converting EUAs into full approvals or revoking EUAs on a rolling basis instead of having to process numerous regulatory decisions at the same time at the end of an emergency declaration. The expedited pathways framework adopted by the MRA can also be used to process conversions to full approval, remove conditions on conditional approvals, or revoke an EUA. If a sponsor achieves full approval by a trusted MRA or obtains WHO prequalification, the MRA can process those conversions using the expedited reliance or recognition procedures. Similarly, if a trusted MRA revokes an EUA for a therapeutic, the expedited pathways may be used to recognize or rely on that revocation to terminate an EUA. Transitioning conditional authorizations to regular authorizations or revocations as soon as appropriate will help prevent a backlog in decisions, which could unintentionally allow EUAs to lapse or allow for therapeutics with newly identified concerns to remain subject to an EUA when other trusted MRAs have already revoked the EUA.

EUA legal and regulatory frameworks can also address compassionate use or other types of continued use following the cessation of an EUA. For example, Kenya's EUA policy states, "For cases affecting individuals following a public health emergency, the use of products shall continue under the compassionate use authorization clause."[58] Ghana's EUA guidance contains a similar provision allowing for an authorization to "continue to be effective to provide for continued use in any patient who began treatment before termination (to the extent found necessary by the patient's attending physician)."[59] The statute authorizing EUAs in the United States allows for continued use of a medical product approved with an EUA following the cessation of the public health emergency when the patient received the medical product during the period of the EUA and the patient's attending physician deems continued use necessary.

7. Require Risk Management Plans, Post-Authorization Surveillance Procedures, and Periodic Safety Update Reports

A risk management plan is an important tool to help ensure that the benefits of a medical product exceed its risks by the greatest margin possible.[60] A risk management plan will often include information regarding: 1) a medicine's safety profile; 2) how those risks will be prevented or minimized in patients; 3) plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; and 4) steps to measure the effectiveness of risk-minimization measures.[61]

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[58] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines for Emergency and Compassionate Use Authorization of Health Products and Technologies, PPB/PER/MED/GUD/024, Rev. No. 0 (April 2020).
[59] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (February 5, 2021).
[60] PAHO, Risk Management Plans and Periodic Safety Update Reports, https://www.paho.org/en/topics/health-services/risk-management-plans-and-periodic-safety-update-reports (accessed August 29, 2023).
[61] EMA, Risk Management Plans, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans (accessed August 29, 2023).

EUA guidance requires applicants to submit a risk management plan that includes a process for submitting periodic safety update reports that describe the ongoing results of safety monitoring worldwide. Ghana's EUA guidance, for example, includes a requirement that EUA applications include a risk management plan that complies with the content and format of the EMA risk management plan guidelines or the guideline on good pharmacovigilance practices, Module V: risk management systems.[62]

Post-authorization surveillance procedures should include monitoring of prespecified adverse events of special interest (AESIs), addressing evidence gaps for special populations (e.g., children, pregnant women, lactating women, immunocompromised persons, people with pre-existing health conditions), and the use of appropriate methods to detect, characterize, and communicate potential safety concerns in the local context. These safety surveillance procedures, including those beyond "routine surveillance," can be specified in a pharmacovigilance plan as submitted by the market authorization holder.

8. Monitor Availability of Therapeutics to Guide EUA Decisions and Ensure Equitable Distribution

MRAs can establish availability monitoring systems to help ensure equitable and timely access to therapeutics authorized under EUAs. Facilitating transparency about locations with available medicine can be critically important for therapeutics in particular because some need to be taken quickly after symptom onset and diagnosis to be optimally effective. Others, such as monoclonal antibodies, may require laboratory testing or other medical procedures. Medicine availability systems can vary in complexity. For example, the Drug Regulatory Authority of Pakistan posted on its website a list of locations where COVID-19-related therapeutics were available.[63] The list included the name of the therapeutic, manufacturer, maximum retail price, and contact information of the location. This list allowed health care providers and patients to identify locations that may have COVID-19 therapeutics available.

Another example is the COVID-19 Therapeutics Locator published by the U.S. Administration for Strategic Preparedness and Response. This website displayed a national map of public locations that received shipments of COVID-19 therapeutics under U.S. FDA EUA authority.[64] The map also displayed whether the location had reported doses of the therapeutics available in the last two weeks and the number of doses available. Patients or health care providers can use postal zip code to search for the closest locations with available therapeutics.

Monitoring EUA therapeutics availability can be easier in countries that require EUA therapeutics to be received by the central ministry of health, which then distributes the medicine to health care facilities. In these circumstances, the central ministry of health will have data on which facilities received doses and how many they received, and can request or require health care facilities to report to the ministry how many doses they have remaining.

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[62] Ghana Food and Drugs Authority, Guidelines for Emergency Use Authorizations of Medical Products, FDA/GEN/GL-EUA/2021/04 (February 5, 2021).
[63] Drug Regulatory Authority of Pakistan, COVID-19 Drugs Availability, https://www.dra.gov.pk/covid-19/approved-drugs/ (accessed July 13, 2023).
[64] U.S. Administration for Strategic Preparedness & Response, COVID-19 Therapeutics Locator, https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/ (accessed July 13, 2023).

Monitoring shortages of therapeutics in general will also help inform future EUA decisions. Many countries regularly experience medicine shortages for a variety of reasons. Some MRAs routinely monitor these shortages to inform regulatory decisions to mitigate the harm of these shortages on public health. For example, the EMA regularly monitors medicine shortages in Europe.[65] The U.S. FDA also monitors medicine shortages; in 2022, it identified 49 new drug shortages in the U.S. and worked to prevent 222 additional drug shortages from occurring using regulatory and enforcement flexibilities.[66,67] The South African Health Products Regulatory Authority also reported on its monitoring of medicine shortages.[68] Such shortages can become more frequent during public health emergencies,[69] and EUAs can play an important role in addressing therapeutics shortages during these times. For example, the U.S. issued four EUAs for therapeutics relating to renal replacement therapy and sedation during the COVID-19 pandemic, because the pandemic was leading to shortages of these classes of therapeutics.

9. Manage Modification Requests for Therapeutics EUA Decisions

EUA decisions will be based on the information included in the application submitted. Key aspects of the application will often be identified in the EUA decision letter as conditions. These can include manufacturing location(s), eligibility criteria (e.g., age), manufacturing processes, formulations, education materials, and other key aspects of the approval. Prior to implementation, the MRA should approve material changes to information included in the EUA application, such as changes to manufacturing location(s) or processes, or patient eligibility criteria. For example, the U.S. FDA's letter of authorization for Paxlovid stated, "Pfizer may request changes to this authorization, including to the authorized Fact Sheets for Paxlovid. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation."[70]

Managing these EUA modification requests can require significant MRA resources, especially if multiple therapeutics have received EUAs, such as with COVID-19. MRAs can conduct risk-benefit assessments to determine the appropriate level of review or pathway to process supplemental applications that seek to change or add new manufacturing sites. Depending on the nature of the proposed changes, the appropriate pathway to process the supplemental filing could be the same pathway used to review the original application (e.g., reliance or recognition) or the risk-benefit assessment may indicate that a different pathway is more appropriate. The risk-benefit assessment can help ensure that the appropriate level of review occurs for supplemental filings seeking to make material changes to the EUA decision letter.

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[65] EMA, Public information on medicine shortages, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/public-information-medicine-shortages (accessed August 2, 2023).
[66] US FDA, Drug Shortages, https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages (last visited on July 13, 2023)
[67] U.S. FDA, Report to Congress, Drug Shortages, CY 2022, available at https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.
[68] South African Health Products Regulatory Authority, COVID-19 Information, Communication to Stakeholders, SAHPRA responds to coronavirus (COVID-19): Medicines/medical devices supply challenges, available at https://www.sahpra.org.za/be-prepared-for-covid-19/.
[69] U.S. FDA, Report to Congress, Drug Shortages, CY 2022, available at https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.
[70] U.S. FDA, Emergency Use Authorization 105, May 25, 2023, available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19.

10. Embrace Transparent Communication and Community Engagement to Build Trust in Regulatory Reviews

Open and transparent communication builds public trust in medicine regulatory review processes. MRAs should develop a comprehensive communication strategy that provides information to a wide range of audiences. Some MRAs have developed therapeutic-specific webpages to share information broadly on specific therapeutics.[71] Other MRAs have used social media channels to disseminate EUAs or approval decisions for COVID-19 therapeutics.[72] MRAs should consider developing a standardized communication plan for key regulatory decisions. These plans should consider language and disability access to ensure that materials are accessible to the entire population in the country. Some of the components of a standardized communication package could be:

- Decision memorandum/assessment report explaining rationale for the regulatory decision.
- Letter of authorization.
- Press release.
- Fact sheet for product recipients and caregivers.
- Fact sheet for health care providers.
- Frequently asked questions (FAQ) page/document.[73]

The WHO has issued communication guidelines for outbreak responses and pandemic influenza, which provide helpful principles and approaches for managing communication with all stakeholders about therapeutics review and deployment.[74,75,76]

Appendix E contains more detailed guidance on the content for each of the following communication products:

- MRA product-specific web pages.
- Review or decision memorandum/assessment report.
- Letters of authorization.
- Press releases.
- Fact sheet for health care providers.
- Fact sheets for recipients and caregivers.
- Frequently asked questions.
- Social media content.

[71] U.K. MHRA, Regulatory approval of Paxlovid, https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid (accessed July 13, 2023).
[72] U.S. FDA Twitter post, July 6, 2022, https://twitter.com/FDA_Drug_Info/status/1544737733524049920 (accessed July 13, 2023).
[73] U.S. FDA, Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19
[74] Guidance on development and implementation of a national deployment and vaccination plan for pandemic influenza vaccines. Geneva: World Health Organization; 2012.
[75] WHO outbreak communication guidelines. Geneva: World Health Organization; 2005 (WHO/CDS/2005.28.).
[76] World Health Organization outbreak communication planning guide. 2008 edition. Geneva: World Health Organization; 2008.

11. Use a Phased Planning Approach to Prioritize Finite Resources

Anticipating the needs and opportunities of the phases of public health emergencies can help improve the preparedness and efficiency of EUA reviews. WHO's *Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries* categorizes influenza pandemics into four phases: 1) interpandemic phase, 2) alert phase, 3) pandemic phase, and 4) transition phase. The guidelines present steps to take during these phases and how procedures may need to be modified depending on the phase. WHO's EUL Procedure uses a three-phase approach: pre-emergency, emergency, and post-listing. Kenya's COVID-19 EUA guidance adopts a similar phased framework that includes pre-emergency, emergency, and post-authorization.[77] MRAs can consider adopting a phases framework to optimize allocation of resources during a public health emergency's stages. Table 2 provides an overview of key activities to consider during pre-emergency, emergency, and post-emergency phases for therapeutics.

Table 2. Key EUA Activities for MRAs in the Pre-Emergency, Emergency, and Post-Emergency Phases

Pre-Emergency Phase
Establish legal and regulatory frameworks and clear issuance criteria for EUAs.
Strengthen and streamline MRA application policies and procedures.
Consider adopting electronic regulatory information systems to facilitate remote reviews.
Establish technical working groups (TWGs) with needed technical expertise to facilitate rapid EUA review when emergencies arise.
Establish reliance and recognition arrangement and data-sharing agreements with trusted MRAs, regional MRAs, and WHO.
Emergency Phase
Process EUA applications.
Activate TWGs to provide technical guidance on EUA applications.
Monitor compliance with EUA conditions.
Maintain reliance and recognition arrangements, including data-sharing agreements with other MRAs and WHO.
Post-Emergency Phase
Work with manufacturers to convert EUAs into full marketing authorizations and/or revoke EUAs based on ongoing review of data and evolving benefit-risk assessments.
Conduct after-action review of processes and identify opportunities for improvement.
Continue oversight of post-marketing surveillance (PMS) programs.

[77] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines for Emergency and Compassionate Use Authorization of Health Products and Technologies, PPB/PER/MED/GUD/024, Rev. No. 0 (April 2020).

12. Update Operational Policies and Procedures to Find Efficiencies and Facilitate Collaborative Review

Processing EUAs during a public health emergency can put significant strain on the administrative and operational capacity of MRAs. To streamline EUA reviews, the MRA can review its operational policies and procedures to identify ways to improve the efficiency of reviews and adopt mechanisms that facilitate collaborative reviews.

a. Establish Clear Review Timelines

Some national MRAs have established expedited review timelines for EUA reviews and decisions. Kenya's policy states that abridged reviews and WHO EUL products will be evaluated within seven calendar days.[78] Ghana's policy states that an EUA application will be "acted upon within 15 working days."[79]

b. Allow for Rolling Submissions

Rolling reviews can facilitate expedited product regulatory reviews while late-stage clinical trials are ongoing. The amount of clinical trial data required before submitting an initial application may vary, but EUA policies can lay out categories of required information to facilitate reviews. Encouraging pre-submission meeting(s) with applicants can help clarify expectations for rolling submission applications to ensure alignment between data availability and the needs of MRA reviewers. Minutes of pre-submission meetings should be prepared and agreed on by the MRA and applicant for transparency and recordkeeping purposes. For example, Kenya's EUA framework includes application templates to help standard EUA applications and includes guidance on conducting pre-submission meetings.[80]

c. Use Standardized Application Forms and Checklists

Using standardized application forms and checklists will help ensure that the submitted applications have the information the MRA needs. MRAs dossier requirements can vary based on the risk assessment and the individual MRA's views. However, much of the information in MRA applications is the same across countries. MRAs should consider harmonizing EUA application forms to facilitate a manufacturer's submission to multiple MRAs. The MRAs can still require supplemental forms for information that is not part of the standardized application. For example, the CTD format is accepted for WHO prequalification of therapeutics. An electronic version of the CTD (eCTD) has also been developed.[81] Ghana's EUA policy even states that

[78] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines on Submission of Documentation for Emergency Use & Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies (January 2022).
[79] Ghana Food and Drug Administration, Guidelines for Emergency Use Authorization of Medical Products, Issued: February 5, 2021.
[80] Republic of Kenya, Ministry of Health, Pharmacy and Poisons Board, Guidelines on Submission of Documentation for Emergency Use & Compassionate Use Authorization (EUA/CUA) of Health Products and Technologies (January 2022).
[81] ICH, Multidisciplinary Guidelines, M8 Electronic Common Technical Document (eCTD), available at https://www.ich.org/page/multidisciplinary-guidelines#8-1 [accessed September 9, 2021].

EUA applications "should be in a format that is globally acceptable, (preferably in the Common Technical Document (CTD) format)."[82]

d. Invest in Electronic Regulatory Information Systems

Electronic application systems can facilitate timely review of EUA applications.[83] Paper-based application systems present multiple barriers to expedited reviews, including challenges of sharing key documents with reviewers and processing delays. Electronic application systems can also facilitate remote reviews by parties who are not ind the same location. Facilitating remote review can be especially important when technical experts are located throughout the country or when MRA staff are not able to work in-person or travel to the MRA office due to the public health emergency. Ideally, electronic applications systems would be established and fully implemented in a pre-pandemic phase to facilitate remote access and communication during a public health emergency. Implementing a software system during a pandemic phase may be challenging and divert attention from more urgent priorities.

[82] Ghana Food and Drug Administration, Guidelines for Emergency Use Authorization of Medical Products, Issued: February 5, 2021.
[83] USAID MTaPS and PQM+ programs. Pathway to Digitalize Regulatory Information Management Systems for National Medicines Regulatory Authorities in Low- and Middle-Income Countries. Submitted to the U.S. Agency for International Development by the USAID PQM+ and MTaPS Programs.

Appendix A. Checklist for Strengthening Management of Therapeutics EUAs

- □ Establish clear criteria for issuing EUAs in legal and regulatory framework.
- □ Adopt a EUA application form that facilitates rapid review and pathway assignment of EUA applications containing the following information:
  a. Applicant and manufacturer information.
  b. Basic information about the product and intended population.
  c. Information about submissions to other MRAs or WHO and associated decisions.
  d. Proposed pathway.
  e. Risk assessment justifying pathway assignment.
  f. Proposed risk management and post-marketing surveillance or pharmacovigilance plan.
- □ Adopt standardized pathways for expedited review of therapeutics during public health emergencies and clear review expectations for each pathway.
- □ Require applicants seeking EUA to complete a risk assessment to inform pathway assignment; the EUA application can include a risk assessment tool.
- □ Establish MRA review timeline expectations and monitor performance against these timelines for continuous process improvement.
- □ Establish and maintain a technical review committee with technical expertise needed to review quality, clinical, and nonclinical study data.
- □ Allow for product quality and study data reports to be submitted in the CTD format.
- □ Adopt online application processes for EUA applications to facilitate submission and coordinate MRA staff reviews.
- □ Develop and maintain post-marketing surveillance information monitoring system to aid in monitoring PMS data.
- □ Develop and maintain system to monitor compliance with conditions placed on EUAs (e.g., supplemental data submission requirements).
- □ Ensure that each approved therapeutic has a designated point of contact within MRA responsible for monitoring supplemental submissions, including post-marketing surveillance and safety monitoring data.
- □ Establish and maintain community engagement mechanisms to receive real-time feedback from key stakeholders and affected communities about therapeutics decisions and monitoring.
- □ Establish a publicly available website for each EUA therapeutic with key information about each approved therapeutic (e.g., recipient fact sheet, FAQs, assessment report, decision letter).
- □ Share key decisions and information about approved therapeutics on social media channels to facilitate public awareness and understanding of MRA decisions.

Appendix B. Illustrative Workflow for Processing EUA Applications

Initial EUA Applications

- □ Therapeutics application file opened by MRA.
- □ MRA point of contact for application designated.
- □ Minutes from pre-submission meeting(s) prepared and added to application file.
- □ Therapeutics application received and added to application file.
- □ Written acknowledgment of application receipt sent to applicant.
- □ MRA management team conducts initial review of application to assess whether application contains the information required to conduct pathway assignment analysis.
  - If application is found to lack information needed for pathway assignment, a letter should be sent to applicant requesting missing information.
- □ MRA review team conducts risk-benefit assessment and documents pathway assignment decision.
- □ MRA review team reviews application to determine whether application contains sufficient information for assigned pathway.
  - If application is found to lack information needed for assigned pathway, a letter should be sent to applicant requesting missing information.
- □ Application assigned to application review team with targeted review completion date.
  - Composition of review team determined by MRA pathway framework (e.g., internal MRA staff, external technical review committee).
- □ Application review team reviews application and documents analysis and decision in decision memorandum/report.
- □ MRA prepares decision letter, including any conditions on the authorization.
- □ Decision letter and review memorandum/report added to MRA application file.
- □ Decision letter and review memorandum/report sent to applicant.
- □ Decision letter, review memorandum/report, and key associated documents (e.g., provider fact sheet, patient fact sheet) posted on MRA website.

EUA Modification Requests

- □ Request for modification received by MRA.
- □ Written receipt of request sent to applicant.
- □ MRA team reviews request to determine if information sufficient to conduct risk-benefit analysis to inform pathway assignment.

- If application is found to lack information needed for pathway assignment, a letter should be sent to applicant requesting missing information.

□ MRA review team conducts risk-benefit assessment and documents pathway assignment decision.

□ Application assigned to review team with targeted review completion date.

□ Composition of review team determined by MRA pathway framework (e.g., internal MRA staff, external technical review committee).

□ Review team reviews modification request and documents analysis and decision in the decision memorandum/report.

□ MRA prepares decision letter modifying original decision letter, or explaining rationale for rejecting the modification request.

□ Modified decision letter and review memorandum/report added to MRA application file.

□ Modified decision letter and review memorandum/report sent to applicant.

□ Modified decision letter and review memorandum/report posted to MRA website.

Appendix C. Illustrative Application Checklist for Therapeutics EUAs

Application Package Contents	Required by Pathway*			
	Recognition	Reliance	Fast-Track Abbreviated Review	Full Review
EUA application form	Yes	Yes	Yes	Yes
Minutes from pre-submission meeting	Yes	Yes	Yes	Yes
Proposed package insert	Yes	Yes	Yes	Yes
Proposed fact sheet for product recipients and caregivers	Yes	Yes	Yes	Yes
Proposed fact sheet for health care providers	Yes	Yes	Yes	Yes
Proposed risk management and post-marketing surveillance plan	Yes	Yes	Yes	Yes
Assurance of sameness	Yes	Yes	Yes (if applicable)	Yes (if applicable)
Certificate of decision by the responsible MRA or WHO	Yes	Yes	Yes	Yes
Assessment reports of the responsible MRA(s) or WHO	No	Yes	Yes	Yes
Evidence of quality and good manufacturing practices compliance (GMP certificate)	No	No**	Yes	Yes
CTD Module-2 quality, nonclinical, and clinical overview	No	No**	Yes	Yes
Full dossier as required by national law and/or regulations (e.g., CTD Modules 2-5)	No	No	No	Yes

* If required information is not available, please explain the absence in the cover letter (e.g., if the product has not had any previous reviews by the WHO or another MRA).
** These components may be required depending on the level of reliance.

Appendix D. Preliminary Risk-Benefit Assessment Tool to Inform Pathway Assignment

Applicant Name	
Product Name	
Application No.	
Application Receipt Date	
Preliminary Review Team	
Criteria	**Narrative Discussion of Risks & Benefits**
Prior Review Decisions on Applying Product (e.g., outcomes of reviews conducted by other MRAs and maturity level of those MRAs and/or WHO prequalification or EUL)	
Quality (e.g., whether product manufacturer has other products that have been WHO-prequalified or been approved by WHO Listed MRAs, product design characteristics, stringency of MRA providing lot release certification)	
Safety (e.g., consider important identified or potential risk[s] from the clinical development program or other adverse events of special interest, including uncommon and delayed onset adverse events)	
Need (e.g., ability of approved products to meet near-, medium-, and long-term demand for various populations in the country, reported efficacy of the product relative to other products on the market)	
Access (e.g., the extent to which the country will be able to access the product if approved, which may be influenced by manufacturer's capacity, access channels through international mechanisms, planned donations, cost)	
Deployment Feasibility (e.g., cold chain requirements, number of doses required)	

Appendix E. Communication Product Guidance

a. MRA Therapeutics-Specific Webpages

An MRA's website presents a space for the MRA to share key information with the public regarding a therapeutics regulatory review. Some MRAs publish a specific webpage for each authorized therapeutic to help share information about each product. The webpages can include a document repository that includes all versions of key documents relating to the regulatory process, including safety updates, news, review reports, MRA letters, etc. An example of an MRA webpage for a specific EUA therapeutic is the U.K. MHRA webpage for the Paxlovid.[84] The U.S. FDA has developed therapeutic-specific webpages, but also created a single page listing all Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.[85] A table on that page lists all current EUAs and links to key documents for each therapeutic EUA. The product-specific webpage can have a variety of structures, but below is a list of components that MRAs could consider including on a webpage dedicated to a particular therapeutic:

- Product overview section
- Downloadable package insert
- FAQs
- Fact sheets for caregivers and patients
- Fact sheets for health care providers
- Letters of authorization (and amendments thereto)
- Review memorandum/assessment reports
- Press releases
- Links to webcasts of MRA press conferences and video interviews

b. Review or Decision Memorandum/Assessment Report

The purpose of a review memorandum (also called a decision memorandum or assessment report) is to collect and synthesize the MRA's analysis and rationale underlying its decision. The format of the decision memorandum may vary depending on the level of review (e.g., full review, review of basic documentation, reliance, and recognition). **Appendix F** includes an illustrative template of a review memorandum/assessment report. MRAs can also consider adapting the WHO prequalification public assessment report outline as a template for a MRA review memorandum/assessment report.[86] The U.S. FDA, EMA, and MHRA have published their review memoranda for COVID-19 therapeutics on their websites, which may present useful examples for other MRAs.

c. Letters of Authorization

A letter of authorization is usually written by the MRA to the applicant documenting the decision of the MRA. These letters can be published on MRA website to increase awareness and

[84] U.K. MHRA, Regulatory approval of Paxlovid, https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid (accessed July 13, 2023).
[85] U.S. FDA, Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products, https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products (accessed July 13, 2023).
[86] WHO, WHO Public Assessment Reports (WHOPARs) Medicines, https://extranet.who.int/pqweb/medicines/prequalification-reports/whopars (accessed August 28, 2023).

transparency regarding the scope and conditions of the authorization. An EUA Letter of Authorization could include the following sections:

- Criteria for issuance of authorization.
- Scope of authorization.
- Product description.
- Conditions of authorization.
- Duration of authorization.

d. Press Releases

Publishing press releases can be an important mechanism for communicating with the public and specifically with mass media, such as news websites, TV, and radio. Press releases are generally summaries of key information and will frequently include quotes from key MRA officials, which media reports can then use. The WHO Regional Office for Europe has published guidance titled "*How to prepare a press release"* that includes instruction on the elements of a press release, strategies for media engagement, and model press releases as examples.[87] This guidance specifically focuses on press releases relating to vaccine and immunization programs, but may be a helpful resource for strategizing how to structure a press release for a therapeutics EUA as well.

e. Fact Sheet for Health Care Providers

Fact sheets for health care providers should deliver the most critical information for health care providers about a vaccine. The fact sheet should provide key step-by-step instructions, such as information relating to storage and handling, dosage and scheduling, administration, contraindications, warnings, and adverse reactions. The health care provider fact sheet should also summarize information to provide to vaccine recipients/caregivers. The fact sheet can also list the mandatory requirements/conditions on the vaccine due to its EUA authorization status and include the full prescribing information insert as an attachment to the fact sheet.

f. Fact Sheet for Therapeutics Recipients and Caregivers

Fact sheets for therapeutics recipients and their caregivers are summaries of the most important information for patients and caregivers to inform their decision-making about the product and instructions for patients after receiving the medicine. The fact sheet can be formatted in various ways, but a question and answer (Q&A) format can be useful. The fact sheet should present the risks and benefits of the medicine and instructions regarding communications with health care providers and contraindications. The fact sheet should also provide the recipient and caregiver contact information if the recipient suffers from side effects, including reporting information to any passive surveillance systems. For example, the FDA fact sheet for recipients and caregivers of COVID-19 therapeutics includes the information for reporting adverse reactions to the FDA MedWatch system.[88]

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[87] World Health Organization Regional Office for Europe, How to prepare a press release (2017), available at https://www.euro.who.int/__data/assets/pdf_file/0020/333137/VSS-press-release.pdf [accessed September 14, 2021].

[88] U.S. FDA, Fact Sheet for Patients And Caregivers Emergency Use Authorization (EUA) Of LAGEVRIO™ (molnupiravir) capsules For Coronavirus Disease 2019 (COVID-19), available at https://www.fda.gov/media/155055/download.

g. Frequently Asked Questions (FAQ)

An FAQ page and/or document can be a useful tool to communicate with the public about a vaccine approved under an EUA. The FAQ format delivers information succinctly and can be updated regularly to respond to new concerns or questions. FAQs can also be helpful for responding to concerns or rumors circulating on social media, in part because FAQs can easily be converted into social media messages and shared by the MRA to respond to rumors or misinformation circulating online. You can find an example of an FAQ responding to social media rumors on the U.S. FDA FAQ page for the Pfizer-BioNTech COVID-19 vaccine.[89]

h. Social Media Content

Posting key regulatory documents online is important for building public trust in medicine regulatory decisions, but it is also important to ensure that key information is shared with the public using social media and other channels where many people receive their news and information. MRAs should strongly consider mapping the landscape of the social media interfaces their population uses and sharing key regulatory information from accounts on those platforms. Often this will require converting regulatory decisions into a range of formats (e.g., shorter statements, infographics, photo boards, videos). These abbreviated communications can include links to full documents the MRA has prepared and published. The time investment to publicize key information, especially FAQs, via social media can be well worth the cost to ensure that the public is adequately educated about the scientific evidence underlying medicines regulatory decisions. Community advisory mechanisms, such as community advisory boards, can be helpful for identifying active social media platforms and early identification of rumors that are circulating on social media. Community advisory and engagement boards can also help with designing and providing feedback on social media content that maximizes circulation on social media platforms.

[89] U.S. FDA, Q&A for Comirnaty (COVID-19 Vaccine mRNA), Can Comirnaty cause infertility in women? https://www.fda.gov/vaccines-blood-biologics/qa-comirnaty-covid-19-vaccine-mrna [accessed September 14, 2021].

Appendix F. Template Therapeutics EUA Review Memorandum/Assessment Report

An EUA Review Memorandum/Assessment Report could include the following sections:

A. Executive Summary

B. Background
   a. Public health situation background
   b. Available therapies
   c. Applicable regulatory requirements

C. Therapeutics Overview
   a. Therapeutics composition
   b. Dosing regimen
   c. Proposed use
   d. Stability and storage requirements

D. Review of Clinical Safety and Effectiveness Data
   a. Overview of clinical studies
   b. Analysis of specific studies
      i. Design
      ii. Assessment of follow-up duration
      iii. Subject disposition and inclusion in analysis populations
      iv. Demographics and other baseline characteristics
      v. Efficacy
      vi. Safety

E. Review of Other Information Submitted in Support of Application
   a. Plan for continuing blinded, placebo-controlled follow-up
   b. Pharmacovigilance activities
   c. Nonclinical studies
   d. Chemistry, manufacturing, and control information
   e. Clinical assay information
   f. Inspections of clinical study sites
   g. Prescribing information and fact sheets
   h. Distribution and logistics considerations

F. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA
   a. Known benefits
   b. Unknown benefits and data gaps
   c. Known risks
   d. Unknown risks and data gaps
   e. Risk management and pharmacovigilance plan

G. Review Meeting Summary

H. Overall Summary and Recommendations

I. References