

Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19)

Purpose and Context

This document provides guidance to national regulatory authorities (NRAs) and regulatory systems on practical ways to implement reliance for emergency use of medicines and other health technologies in and around a pandemic.¹ Note that countries use different terminologies for emergency use and the Pan American Health Organization (PAHO) will use the term “Emergency Use Authorization” (EUA). For the purposes of this document, medicines and other health technologies are defined to include pharmaceuticals, vaccines, and in Vitro Diagnostics (IVDs).

Countries are encouraged to develop plans for regulatory preparedness and response in a pandemic including related to EUA of medicines and health technologies. This will afford an orderly and legal process to expedite the incorporation of these products into health systems. According to WHO guidance⁽¹⁾, **country regulatory frameworks should include laws and/or policies that permit EUA for medicines and other health technologies, a pandemic preparedness plan that acknowledges EUA, technical procedures that use reliance and recognition on trusted/reference authorities for the EUA, and a system to monitor EUA products in the market.** This document focuses on technical procedures for reliance to issue an EUA.

Definitions and Principles of Reliance and Recognition

PAHO’s “Regulatory Reliance Principles: Concept Note and Recommendations”⁽²⁾, cites WHO’s definition of reliance as “the act whereby the NRA in one jurisdiction may consider and give significant weight to—i.e. totally or partially rely upon—evaluations performed by another NRA 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”. PAHO’s document goes on to say that recognition is considered a form of reliance. The WHO defines recognition as “the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or other trusted institution”. The use of reliance should incorporate the following principles: 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.

When Should NRAs Consider Applying an EUA?

Requests for an EUA are often submitted to the NRA by government sponsors, such as a national procurer or public health program, however, industry may also submit such requests. Countries usually declare that parameters for emergencies are met before an EUA can be issued. They also typically ensure that certain criteria are satisfied before an EUA can be issued, such as: there is a serious or life-threatening disease; there is evidence a given product “may be effective” to prevent, diagnose, or treat the disease; there is a positive risk-benefit balance; and there are not adequate, approved and available alternatives.^(3,4) WHO’s equivalent procedure is called Emergency Use Listing (EUL) and is often used when WHO declares a Public Health Emergency of International Concern (PHEIC). The procedure applies to medicines (including vaccines) and IVDs. The EUL factors in the morbidity and/or mortality of the disease,

¹ WHO defines different phases of a pandemic for influenza, including: the alert phase; pandemic phase; transition phase; and interpandemic phase. The alert phase is when a new strain of influenza is identified in humans. The pandemic phase is the period of global spread of the new strain. The transition phase is the de-escalation of global actions to address the pandemic. The interpandemic phase is the period between pandemics.⁽¹⁾

as well as lack of treatment or prevention options and applies a risk-based approach to decision-making.⁽⁵⁾ The extraordinary nature of emergency situations frequently means that countries abbreviate their requirements for the product application^(6,7,8), and thus, risk assessment is key.

Risk Assessment

A critical component of any EUA is the risk assessment of the product. In most cases, there will be less evidence of efficacy and safety when the procedure is initiated than that required in a non-emergency situation. When WHO carries out its assessment under these circumstances, for example, it considers all available scientific data, including non-clinical and clinical information. For example, pharmacodynamic data, as well as data on efficacy and safety in animal models or *in vitro* systems under well-controlled and documented conditions. In addition, existing information on similar products or platform technologies (e.g. viral vectors, DNA etc.) which have been already used in clinical trials could be used to reduce the need for additional studies. WHO advises that evaluators responsible for conducting the assessment examine which published guidelines/recommendations may be applicable and where there is evidence of scientific consensus to make a recommendation to WHO on the risk/benefit assessment regarding the use of the product. All information should justify the need for the product before additional data is provided and/or development advances.⁽⁵⁾ A caveat is that an EUA is only valid during the time of declared emergency and should be monitored on a daily basis for changing circumstances.

However, many NRAs do not necessarily have the staff or expertise to evaluate clinical data supporting the safety and effectiveness of the product in an EUA scenario. In these cases, they can rely on the scientific consensus published as WHO standard treatment guidelines. Randomized controlled trials are the gold standard for evidence of efficacy and safety, including in a pandemic situation, and they are increasingly being designed to produce results more rapidly in emergencies. If evidence in favor of the use of a product emerges, WHO's expert committees will advise a change in standard treatment guidelines accordingly.

Another way to address the scientific and regulatory challenges when conducting a risk-benefit assessment related to the use of a specific product is for NRAs to monitor whether other trusted/reference authorities are issuing EUAs to particular medicines and other health technologies. Some health authorities may decide to wait until multiple trusted/reference authorities issue an EUA to avoid circumstances that may uniquely influence individual trusted/reference authority decisions, and this is a prudent approach.

Applying Emergency Use Authorization

Adaptation of WHO's guidelines, which have been developed to support the approval of influenza vaccines under pandemic situations^(1,9), can provide a framework for executing the technical and regulatory actions required for approving an EUA for a specific product to treat or diagnose COVID-19 under pandemic situation. In these situations, WHO acknowledges that NRAs have different options: conduct a full or abridged review of the quality, nonclinical and clinical information, or apply reliance, and recognition approaches to support approval.

PAHO/WHO recommends that NRAs expedite their reviews in EUA situations and put in place procedures for reliance and recognition, rather than conduct full or abridged reviews which must be conducted by trained personnel. Using reliance and recognition procedures acknowledges the risk-based assessment conducted by a trusted/reference authority for a given product under an emergency situation. It is important to note that manufacturers sometimes produce the same product using different standards which are distributed to different markets, including "for export only".⁽¹⁰⁾ Therefore, it is critical that NRAs focus their resources in ensuring that the same product is being authorized in both the NRA and the trusted/reference authority.

Selecting Trusted/ Reference Authorities

It is ultimately up to the individual NRA and their government to make the determination on who constitutes a trusted/reference authority. However, the decision needs to be informed by data rather than reputation or historical international alignments. WHO has designated a list of trusted regulatory authorities based on their documented capacity to implement a regulatory oversight of different health technologies; not all authorities are listed for the same technologies. In addition, WHO has a specific list for IVDs² (see annex 1). Historically, WHO has relied on a group of “Stringent Regulatory Authorities”³ constituted by the founding members of the International Council on Harmonization (ICH), however, this terminology is no longer in use. Currently, WHO is working on a framework to designate NRAs based on the outcome of an evaluation using a set of indicators outlined in the “Global Benchmarking Tool (GBT)”. NRAs that meet a certain high percentage of indicators on the GBT are going to be listed as “WHO Listed Authorities”. This list should provide a good start for those NRAs willing to implement a reliance process in their country. In the Region of the Americas, PAHO/WHO has designated some regulatory bodies as “National Regulatory Authorities of Regional Reference”⁴(NRAR) using a very similar indicator- based methodology. The NRAR designation applies to NRAs which have demonstrated strong regulatory oversight of pharmaceuticals, and in some cases of biologicals. Many authorities in the region have instituted reliance practices based on NRAR decisions.

Although not a regulatory authority, PAHO/WHO recommends that NRAs consider WHO a trusted/reference authority for the purposes of reliance on prequalified products and/or WHO EUL products.

Suggested Technical Requirements for Medicines and IVDs for EUA

In general, PAHO/WHO recommends an approach that uses reliance on the product EUA from the trusted/reference authorities, and verification of the supporting documentation in the national official language of the NRA. This information includes product-specific characteristics, manufacturing, and labeling. Supplemental documentation regarding nonclinical, clinical and quality information can be requested in a summary format depending on the NRA capacity, but is not required or recommended under emergency situations.

Suppliers should provide the following, but countries can modify the documentation according to their situations:

- *Product Category*
 - Different types of products (e.g. medicines vs. vaccines vs. IVDs) have different requirements. The information included below are general criteria that can be applied to each of these product categories. The Matrix in Annex 2 provides a more specific breakdown of differences in requirements.
- *Assurance of sameness*
 - A formal declaration (cover letter (see Annex 3)) confirming the product / presentations offered to the NRA correspond in all respects (e.g. qualitative/quantitative formula, manufacturing of finished pharmaceutical product (FPP) and active pharmaceutical ingredient (API) facilities, stability, summary product characteristics and labeling, etc.) to the product approved by the trusted/reference authority or WHO Prequalification.
 - The product EUA or marketing authorization certificate issued by the trusted/reference authority.
 - The corresponding web-link to the registration database.

² WHO uses Australia, Canada, Japan, Singapore, United States as trusted/reference authorities for IVDs.

³ Australia, Canada, European Union, Iceland, Japan, Liechtenstein, Norway, Switzerland, United Kingdom, United States.

⁴ Argentina, Brazil, Canada Chile, Colombia, Cuba, Mexico, United States.

- *Product description*
 - Product description including the Summary of Product Characteristics (SPC/SMPC), Product monograph, or equivalent, and Package insert/prescribing information approved by the trusted/reference authority for pharmaceuticals and biologics (e.g. vaccines) and variants (configurations) and accessories if an IVD.
 - Note: the information must include the product name, overview and intended use, as well as the shelf life and storage conditions approved. If an IVD, a general description of the principle of the assay method or instrument principles of operation should be provided.
 - Finished product release specifications.
- *Manufacturing information*
 - List of all sites involved, including FPP and API, accepted by the trusted/reference authority in the manufacturing process, including name, current address and manufacturing responsibilities/activities of each site.
 - Certificate of GMP of the finished product or equivalent accepted by the trusted/reference authority (ISO 13485 certificate if IVD).
- *Product labeling*
 - The supplier must provide a complete set of PDF artworks in the national official language of the NRA country including labelling, primary/secondary packaging, and any informational inserts. If an IVD, this should include instructions for use as well as instrument manual and any other instructional materials provided to the user.
 - Note: labels must include product name, manufacturer contact information, reagent/ingredient name, expiry date, any special storage and/or handling conditions, warning and precautions, lot/batch/serial number, particular product conditions (e.g. sterility), names of all included reagents in each box on the outer package label, as applicable.
 - The instruction for use should, where possible, comply with the principles of labelling for medical devices and IVD medical devices of IMDRF/GRRP WG/N52 FINAL: 2019.
 - If the product requires associated instrumentation, an electronic version of the instrument manual and/or associated operator manuals must be available in case countries request it.
- *Post Market Surveillance*
 - For designated higher risk products, the supplier must commit to provide a copy of the Risk Management Plan and Vigilance Report approved by the trusted/reference authority (e.g. Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report) when they become available. The plan must be in alignment with the WHO guidance “WHO guidance on post-market surveillance of in vitro diagnostics”.⁽¹¹⁾ The NRA should have a post market surveillance system that includes a reporting system for adverse events and substandard/falsified medicines so that health system stakeholders (patients, providers, industry, etc. can report if there are issues with the EUA product).

Supplemental Documentation for Pharmaceuticals and Vaccines (Not Recommended)

Some NRAs may want to request additional documentation for pharmaceutical products or vaccines. Although under normal circumstances quality, nonclinical and clinical information could be provided using the summaries of Module 2 of the ICH Common Technical Document⁽¹²⁾, this is not recommended under an emergency situation because the preparation of this information. The preparation of this information, including translation, requires time and resources which can cause unnecessary delays in submission of these documents, which ultimately will impact the access to such important products.

Decision making

A template to document the approval process of EUA products needs to be developed by each NRA and be accompanied by an evaluation report. Annex 4 provides guidance on the minimum considerations to be included in the approval letter. This is based on available WHO recommendations “Guidelines on regulatory preparedness for human pandemic influenza vaccines (Adopted 2007)”.⁽⁹⁾

Post Market Surveillance Considerations

As per WHO recommendations, local authorities should do the following: keep records of the product’s lot deployment, implement the national post-marketing surveillance plan, continue to update the EUA as additional information is received from manufacturers concerning the full-product life-cycle (e.g. PSUR, variations, etc.) which should be approved by the trusted/reference authority, and continue to monitor the status of the EUA in the trusted/reference authority.

Concluding Remarks

This document provides a conceptual and technical framework to help NRAs navigate the complex dynamics of product approvals in an emergency situation using reliance in and around the pandemic phase of a disease when the need to act quickly must be carefully balanced taking into account the benefits and risks. It is not intended to replace marketing authorization processes under regular circumstances. Any NRA, regardless of the level of resources available can use and/or modify the concepts and technical standards put forward in this document.

Annexes

Annex 1: WHO reference authorities for IVDs

Regulatory Authority	Country	Website
Food and Drug Administration (FDA)	United States	https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd
Health Canada	Canada	https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/covid-19/diagnostic-devices-authorized.html
Therapeutic Goods Administration	Australia	https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia
Ministry of Health, Labour and Welfare	Japan	https://www.mhlw.go.jp/english/ https://www.who.int/diagnostics_laboratory/200402_imdrf_collated_table_2_april_2020.pdf?ua=1
Health Sciences Authority	Singapore	https://www.hsa.gov.sg/announcements/regulatory-updates/hsa-expedites-approval-of-covid-19-diagnostic-tests-in-singapore-via-provisional-authorisation

* Although EU Member States are considered WHO reference authorities for IVDs, in Europe all COVID-19 IVDs currently available are based on a self-declaration by the manufacturer and no NRA or other authority is involved in the review of such products, thus WHO EUL processes applied on COVID-19 response are not relying on EU Member States to date.

Annex 2: Summary of Requirements for Different Product Category

	Pharmaceutical	Vaccine	IVD
Assurance of Sameness	*Cover letter; *EUA or marketing authorization certificate	*Cover letter; *EUA or marketing authorization certificate	*Cover letter; *EUA or marketing authorization certificate
Product Description	* Summary of Product Characteristics (SPC/SMPC), Product monograph, or equivalent, and Package insert/prescribing information approved by trusted/reference authority * Finished product release specifications	* Summary of Product Characteristics (SPC/SMPC), Product monograph, or equivalent, and Package insert/prescribing information approved by trusted/reference authority * Finished product release specifications	*Variants and configurations
Manufacturing Information	*List of all sites involved in manufacturing process; *Certification of FPP GMP accepted by trusted/reference authority	*List of all sites involved in manufacturing process; *Certification of FPP GMP accepted by trusted/reference authority	*List of all sites involved in manufacturing process; *ISO 13485 certificate if IVDs
Product Labeling	*PDF artworks including labelling, primary/secondary packaging, and product leaflet	*PDF artworks including labelling, primary/secondary packaging, and any product leaflet	*PDF artworks including labelling, primary/secondary packaging, and any informational inserts
Post Market Surveillance	*A copy of the Risk Management Plan and Vigilance Report approved by the trusted/reference authority (e.g. Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report) when they become available *Report to PV/SF surveillance system if problems	*A copy of the Risk Management Plan and Vigilance Report approved by the trusted/reference authority (e.g. Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report) when they become available *Report to PV/SF surveillance system if problems	*Report to PV/SF surveillance system if problems

Annex 3: Sample Cover Letter to NRA

[COMPANY LETTERHEAD – Name, address, phone number, email]

DATE: <Insert Date>

TO: NRA
Address

Dear Sir/Miss,

SUBJECT: Application for Emergency Use Authorization (EUA) <Insert Trade Name > (<Insert International Nonproprietary Name of the Active Pharmaceutical Ingredient(s) (API), strength, dosage form or In Vitro Diagnostic device name>)

<Insert NAME OF APPLICANT> of <Insert ADDRESS OF APPLICANT> has submitted this application for EUA of the aforementioned product. The details of the product are included in the submitted application.

<Insert TRADE NAME> has an EUA or marketing authorization in <Insert TRUSTED/REFERENCE AUTHORITY (TA) COUNTRY NAME>. The current EUA/marketing authorization was issued by <Insert TA NAME> on <Insert DATE OF ISSUANCE> and will expire on <Insert DATE OF EXPIRY, if applicable>.

We confirm that the product, including but not limited to composition/formulation, strength, manufacturing of finished product and active pharmaceutical ingredients, specifications, packaging, product information, etc.- will, at the time of submission and after EUA, be the same in all respects as the product given EUA or marketing authorization with the TA <Insert TA NAME>. Note, there is an exception for different languages on labeling and packaging, if applicable.

We confirm that all the information in the accompanying documentation concerning this application is true and correct.

We confirm that we have read and understood the <Insert NRA NAME> guidance document on applications for EUA.

We therefore kindly request that <Insert NRA NAME> consider the submitted application for this product in order to grant an EUA.

Yours faithfully,

[Insert signature]

[Insert Full Name of Signee]

[Insert Company Position]

[Insert Signee's Email and Phone number (if different from that stated otherwise)]

Annex 4: Minimum Information Suggested to be Included in the NRA Letter / Issuance of EUA

A template for approval of the EUA product should be developed by each NRA, and evaluation report must be completed.

This annex provides a short guidance on minimum suggested information for development of an approval letter/publication of results.

It is expected that EUA approval include date of approval, product name, manufacturer including sites, and artworks approved (primary and secondary packaging, as well as informational leaflet).

The letter / publication of outcomes of the EUA may need to be based upon minimal and incomplete documentation, and this should be acknowledged.

The approval may include one or more special conditions for use. These can include post-marketing safety reporting requirements, and limitations such as:

- use only during the pandemic period
- use only by certain agencies
- use only in certain listed groups at high risk
- special conditions for post-marketing safety reporting.

The approval must include the approving NRA contact information in case additional questions/concerns need to be reported.

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