Use of decisions of other regulatory authorities to authorize the emergency use of medicines and other health technologies in a pandemic (for example, COVID-19)

Purpose and context

This document provides guidance to national regulatory authorities (NRAs) and regulatory systems on some practical ways to use decisions by authorities in other jurisdictions to authorize the emergency use of medicines and other health technologies in a pandemic and just before or after.

[1] It should be noted that countries use different terms to refer to emergency use, but the Pan American Health Organization (PAHO) uses the phrase “emergency use authorization”. For the purposes of this document, medicines and other health technologies encompass pharmaceuticals, vaccines, and *in vitro diagnostics.*

Countries are urged to develop plans for pandemic preparedness and regulatory response, including authorizing emergency use of medicines and health technologies. In this way there will be a legal and orderly process to accelerate the incorporation of these products in health systems. According to the WHO (1), **the regulatory framework of the countries must contain laws or policies that allow the authorization of the emergency use of medicines and other health technologies, a plan of preparation for a pandemic in which the emergency use is authorized, procedures technicians who resort to the decisions of regulatory authorities of other jurisdictions and the recognition of reliable or reference authorities for the authorization of emergency use, and a tracking system for products whose sale has been authorized for emergency use.** This document focuses on the technical procedures to authorize emergency use based on the decisions of regulatory authorities in other jurisdictions.

Definitions and principles of the recognition and use of the decisions of regulatory authorities of other jurisdictions

In the document entitled *Principles Regarding the Use of Decisions of Other Regulatory Authorities: Concept Note and Recommendations* (2), PAHO cites the WHO definition of use of the decisions of regulatory authorities of other jurisdictions: “the act by which the NRA of a jurisdiction may take into account and give great weight (ie, resort in whole or in part) to the evaluations carried out by another NRA or credible institution in making its own decision. The authority that resorts to the decisions of another remains responsible for the decisions adopted and must account for them, even if it resorts to the decisions and information of others”.

In that document, PAHO states that recognition is considered a form of utilization of the decisions of regulatory authorities of other jurisdictions. According to the WHO, recognition is “the systematic acceptance by the NRA of one jurisdiction of the regulatory decisions of another NRA or other reliable institution”. The use of the decisions of regulatory authorities of other jurisdictions must follow the following principles: presence of a legal basis for this act; sovereignty of the decision to go this route and documentation of this decision as part of good review practice; transparency of the rules and processes used; uniformity of its application, and competence of the personnel to resort to the decisions of regulatory authorities of other jurisdictions.

In which cases should NRAs consider the possibility of authorizing emergency use?

Applications for emergency use authorization received by the NRA typically come from public sector sponsors, such as a national buyer or a public health program, although industry can also submit

[1] According to the WHO, an influenza pandemic encompasses the following phases: alert, pandemic, transition and interpandemic. The alert phase begins with the detection of a new strain of influenza in humans. The pandemic phase is the period of global spread of the new strain. The transition phase covers the period of easing of global measures to deal with the pandemic. The interpandemic phase is the period between pandemics (1).

requests of this type. In general, to authorize emergency use, countries require that certain parameters and criteria be met, such as the presence of serious or life-threatening disease, evidence
that a product "could be effective" in preventing, diagnosing, or treating the disease, a positive risk-benefit ratio, and the absence of other suitable, approved, and available alternatives *(3,* 4). The WHO equivalent procedure is called "listing for emergency use" and is typically used when the WHO declares a public health emergency of international concern. The procedure applies to medicines (including vaccines) and *in vitro diagnostic media.* Listing for emergency use takes into account the morbidity and mortality of the disease and the lack of options for treatment or prevention, and applies a risk-based decision-making approach (5). Due to the extraordinary nature of emergency situations, countries often shorten the requirements for product use *(6, 7,* 8), so risk assessment is essential.

Risks evaluation

A critical component of any emergency use authorization is the product risk assessment. In most cases there will be less evidence of efficacy and safety when the procedure is first used in a non-emergency situation. When making an assessment in these circumstances, WHO considers all available scientific data, including clinical and other information, such as pharmacokinetic data and data on the efficacy and safety of models obtained in experimental animals or *in vitro* systems under well conditions . controlled and documented. In addition, information about similar products or platform technologies (such as viral vectors and DNA) that has already been used in clinical studies could be used in such a way that no further study is necessary. The WHO advises that the evaluators responsible for conducting the analysis determine what published guidelines or recommendations could be applied and on what evidence there is scientific consensus to formulate a recommendation on the risks and benefits of the use of the product. All the information must justify the need for the product before more data is provided or its development is advanced (5). One caveat that is important to note is that the emergency use authorization is valid only for the duration of the declared emergency and must be monitored daily in case circumstances change.

However, many NRAs do not necessarily have the staff or expertise to evaluate clinical data to support the safety and efficacy of the product being authorized for use in an emergency situation.
In such cases, they can rely on published scientific consensus in the form of WHO standard guidelines for treatment. Randomized controlled trials are the gold standard for evidence of efficacy and safety, even in a pandemic, and are increasingly being structured in ways that allow faster results in emergency situations. If evidence emerges to support the use of a product, WHO expert committees will advise a corresponding change in standard treatment guidelines.

Another way to address the scientific and regulatory challenges in assessing the risks and benefits of a product's use is that NRAs could also determine whether other trusted or reference authorities are authorizing the emergency use of certain medicines and other health technologies. In order to avoid circumstances that may influence the decisions of a trusted or reference authority in a particular way, some health authorities may wait until several trusted or reference authorities
authorize emergency use, which is a prudent approach.

Emergency Use Authorization in Practice

The adaptation of the WHO guidelines that were developed to facilitate the approval of influenza vaccines in pandemic situations *(1,* 9) could offer a framework for the adoption of the necessary technical and regulatory measures in order to authorize the emergency use of a given product for the diagnosis or treatment of COVID-19 in a pandemic . In these cases, the WHO recognizes that the NRAs have different options: to make a complete or abbreviated analysis of the information on quality, as well as of the information

clinical and other, or resort to the recognition or decisions of regulatory authorities of other jurisdictions to support approval.

PAHO/WHO recommends that NRAs accelerate their analyzes to authorize use in emergency situations and establish procedures to recognize and use the decisions of the regulatory authorities of other jurisdictions, instead of making complete or abbreviated analyses, which should be in charge of trained personnel. By acknowledging or using the decisions of regulatory authorities in other jurisdictions, you accept the risk assessment made by a trusted or reference authority in relation to a given product in an emergency situation. It is important to note that manufacturers sometimes apply different standards in the production of a product that is distributed in different markets or is "for export only" (10). Therefore, it is essential that the NRAs focus their resources on verifying that the product has been authorized both by the NRA and by the reliable or reference authority.

Selection of reliable or reference authorities

Ultimately it is up to each national regulatory authority and government to make the determination of what constitutes a trusted or reference authority. However, that decision must be based on data and not on reputation or the alignment between countries observed throughout history. The WHO has designated a list of credible regulatory authorities based on their documented ability to exercise regulatory oversight of various health technologies. Not all authorities are in a position to control the same technologies.
In addition, the WHO has a list specifically for in vitro diagnostic *methods2* (see Annex 1). The WHO has routinely relied on a group of "strict regulatory authorities" [3] made up of the founding members of the International Council on the Harmonization of Technical Requirements for Pharmaceutical Substances for Human Use. However, this terminology is no longer used. WHO is currently developing a framework for designating NRAs based on the results of an assessment using a set of indicators set out in the "global benchmarking tool". NRAs that meet a high percentage of these indicators are included in the WHO list of authorities, which is a good starting point for NRAs
who are willing to use the decisions of regulatory authorities of other jurisdictions in their country. In the Region of the Americas, PAHO/WHO has designated some regulatory bodies as "Regional Reference NRAs" [4] (rRNA) using a very similar reporter-based methodology. The rRNA designation applies to NRAs that have shown that they exercise strong regulatory oversight of pharmaceutical products and, in some cases, of biological products. Many authorities in the Region have instituted practices to use the decisions of regulatory authorities of other jurisdictions on the basis of the decisions of the NRAs.

Although not a regulatory authority, PAHO/WHO recommends that NRAs consider WHO as a reliable or reference authority for the purposes of using the decisions of regulatory authorities of other jurisdictions in regard to products prequalified or included in the list for emergency use.

Recommended technical requirements for the authorization of the emergency use of medicines and *in vitro* diagnostic means

In general, PAHO/WHO recommends acknowledging the authorization of the emergency use of a product by reliable or reference authorities and verifying the documentation in the official language of the country of the NRA. This information covers the characteristics of the product, its manufacture and its labelling. Supplemental summary documentation of quality information, as well as clinical and other information, may be requested depending on the capacity of the ARN, but is not required or recommended in emergency situations.

2 WHO considers Australia, Canada, Japan, Singapore and the United States to be reliable or reference authorities for *in vitro diagnostics.*

[3] Australia, Canada, the United States, Iceland, Japan, Liechtenstein, Norway, the United Kingdom, Switzerland and the European Union.

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

Suppliers must provide the following, but countries may modify the documentation based on their situation:

- *Product category*
  - o Different types of products (for example, drugs, vaccines, or *in vitro diagnostics)* have different requirements. The information below is the general criteria that may apply to each product category. A breakdown of the different requirements is presented in the matrix in Annex 2.

- *Guarantee of similarity*
  - o Formal declaration (referral letter; see Annex 3) confirming that the product or pharmaceutical forms offered to the ARN correspond in every way (for example, the formula qualitative and quantitative, facilities where finished pharmaceutical products are manufactured and active pharmaceutical ingredients, stability, summary of product characteristics and labeling) to the product approved by the reliable or reference authority or prequalified by WHO.

  - o Authorization for the emergency use of the product or marketing authorization certificate issued by the trusted or reference authority.
  - o Link to the web page of the registry database.

- *Product description*
  - o Description of the product, with a summary of its characteristics, a monograph or its equivalent, and a package insert or prescribing information approved by the reliable or reference authority for pharmaceutical and biological products (for example, vaccines), their variants (configurations) or its accessories in the case of an *in vitro* diagnostic medium .

    - ÿ Note: Information should include product name, overview and intended use, as well as product shelf life and approved storage conditions. If it is an *in vitro* diagnostic medium , a general description of the method of analysis or the principles governing the operation of the instrument should be provided.

  - o Specifications for the release of the finished product.
- *Manufacturing information*
  - o List of all facilities involved in the manufacturing process of finished pharmaceutical products and active pharmaceutical ingredients accepted by the trustworthy or reference authority, with the name, current address and the responsibilities and activities related to manufacturing corresponding to each site .

  - o Certificate of good manufacturing practices of the finished product or the equivalent accepted by the reliable or reference authority (ISO 13485 certificate if it is an *in vitro diagnostic tool).*

- *Product labeling*
  - o The supplier must provide a complete set of illustrations in PDF format, in the official language of the country of the NRA, of the labels, the primary and secondary packaging and any information leaflets. If it is an *in vitro* diagnostic medium , instructions for use, an instrument manual and any other instructional material provided to the user must be included.

    - ÿ Note: The label of the outer container must contain the name of the product, the information to contact the manufacturer, the name of the reagents or ingredients, the expiration date, special conditions for storage or handling, warnings and precautions, lot or serial number, particular conditions of the product (for example, sterility) and the name of all reagents included in each box, as appropriate.

    - ÿ To the extent possible, the instructions for use must adhere to the principles of labeling of medical devices and *in vitro* diagnostic media established in the document IMDRF/GRRP WG/N52 FINAL: 2019.

- If instruments are needed to use the product, the instrument manual or user manual in electronic format should be available if requested by countries.

• *Post-market surveillance*

- For products designated as higher risk, the supplier must agree to provide a copy of the risk management plan and surveillance report approved by the trusted or reference authority (for example, the periodic update report of safety report or periodic benefit-risk assessment report) when they are ready. The plan should be in line with the WHO guidelines for post-marketing surveillance of *in vitro* diagnostics *(11).* The ARN must have a post-marketing surveillance system with a mechanism to report adverse events and substandard or falsified medicines, so that stakeholders in the health system (such as patients, providers and industry) can report if there are problems with the product whose use has been authorized for emergency use.

Complementary documentation of pharmaceutical products and vaccines (not recommended)

Some NRAs may want more documentation on pharmaceuticals or vaccines. Although under normal circumstances information on quality, as well as clinical and other information, could be provided through the summaries of module 2 of the common technical document of the International Council on the Harmonization of Technical Requirements for Pharmaceutical Substances for Human Use *(12),* this is not recommended in an emergency situation because preparing this information and translating it takes time and resources, which could cause unnecessary delays in the submission of these documents and ultimately undermine access to these important documents. products.

Decision making

Each national regulatory authority must develop a template to document the process of authorizing products for use in an emergency, accompanied by an assessment report. Annex 4 provides guidance on the minimum considerations to be taken into account in the approval letter, according to the guidelines adopted by the WHO in 2007 on regulatory preparation for human pandemic influenza vaccines (9).

Post-Marketing Surveillance Considerations

In accordance with WHO recommendations, local authorities should maintain a record of the distribution of batches of the product, implement the national post-marketing surveillance plan, update the emergency use authorization as more information is received from the manufacturers over the entire product life cycle (eg periodic safety update report and variations) approved by the trusted or reference authority, and continue to monitor the status of emergency use authorization by that authority.

Conclusions

This document presents a conceptual and technical framework to guide NRAs on the complex dynamics of product approval in an emergency situation based on the decisions of regulatory authorities of other jurisdictions in the pandemic phase of a disease and just sooner or later, during which a balance must be struck between the need to act quickly and weigh the risks and benefits. It is not intended to replace marketing authorization processes under normal circumstances. Any national regulatory authority, regardless of its resources, may use or modify the concepts and technical standards proposed in this document.

Organización Panamericana de la Salud
Organización Mundial de la Salud
OFICINA REGIONAL PARA LAS Américas

Attachments

Annex 1. WHO Reference Authorities for *In Vitro* Diagnostics

regulatory authority	Country	Website
Food and Drug Administration (FDA)	U.S	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, Employment and Welfare	Japan	https://www.mhlw.go.jp/english/ https://www.who.int/diagnostics_laboratory/200402_imdrf_colla ted_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 the Member States of the European Union are considered as the WHO reference authorities for *in vitro diagnostics,* in Europe all COVID-19 *in vitro* diagnostics currently in use are based on a manufacturer's declaration, and no national regulatory authority or
otherwise in the examination of these products. Consequently, WHO's emergency use listing processes applied to the response to COVID-19 have not used Member States of the European Union to date.

Annex 2. Summary of the requirements for different categories of products

	pharmaceutical product	**Vaccine**	***In vitro* diagnostic medium**
Similarity Guarantee	• Referral letter • Authorization of the use of emergency or sale authorization certificate	• Referral letter • Authorization of the use of emergency or sale authorization certificate	• Referral letter • Authorization of the use of emergency or sale authorization certificate
Product description	• Summary of product characteristics, monograph or its equivalent, and package insert or prescribing information approved by the reference or trusted authority • Specifications for the release of the finished product	• Summary of product characteristics, monograph or its equivalent, and package insert or prescribing information approved by the reference or trusted authority • Specifications for the release of the finished product	• Variants and configurations
Manufacturing Information	• List of all facilities involved in the manufacturing process • Internship Certificate suitable for manufacturing finished product accepted by trusted or reference authority	• List of all facilities involved in the manufacturing process • Internship Certificate suitable for manufacturing finished product accepted by the trusted or reference authority	• List of all facilities involved in the manufacturing process • ISO 13485 certificate in the case of means of *in vitro* diagnostics
Product labeling	Illustrations in PDF format of the labels, the primary and secondary packaging, and any information leaflets	Illustrations in PDF format of the labels, the primary and secondary packaging, and any information leaflets	Illustrations in PDF format of the labels, the primary and secondary packaging, and any information leaflets
Post marketing surveillance	• Copy of the risk management plan and surveillance report approved by the trusted or reference authority (for example, the periodic security update report and the periodic report of the evaluation of risks and benefits) when they are ready. • Report any problem that arises to the pharmacovigilance and surveillance system for substandard or falsified medicines.	• Copy of the risk management plan and surveillance report approved by the trusted or reference authority (for example, the periodic security update report and the periodic report of the evaluation of risks and benefits) when they are ready. • Report any problem that arises to the pharmacovigilance and surveillance system for substandard or falsified medicines.	Report any problem that arises to the pharmacovigilance and surveillance system for substandard or falsified medicines

Annex 3. Sample letter of referral to a national regulatory authority

[BUSINESS LETTERHEAD: name, address, phone number, email]

DATE: <Date>

TO: <National Regulatory Authority>
<Address>

SUBJECT: Request for authorization of the emergency use of ***<trade name> (<international nonproprietary name of the active pharmaceutical ingredients, strength, pharmaceutical form or name of the in vitro diagnostic device>)***

Of my highest consideration:

<APPLICANT'S NAME>, residing at **<APPLICANT'S ADDRESS>,** hereby requests that the above product be authorized for emergency use. The application contains detailed product information.

<TRUSTWORTHY OR REFERENCE AUTHORITY> of **<COUNTRY>** authorized the emergency use or marketing of **<COMMERCIAL NAME>** on **<DATE OF AUTHORIZATION>.** This authorization will expire on **<EXPIRATION DATE, if applicable>.**

We confirm that, at the time of the submission of this application and after the emergency use authorization, the product, as well as its composition, formula and strength, the manufacture of the finished product and active pharmaceutical ingredients, the specifications, the packaging and the information about the product, will be identical in every way to the product whose emergency use or commercialization has been authorized by **<RELIABLE OR REFERENCE AUTHORITY>.** Note that languages used on labels and packaging, if applicable, are excepted.

We confirm that all information contained in the documents accompanying this application is true and correct.

We confirm that we have read and understand the **<NATIONAL REGULATORY AUTHORITY>** guidance document on emergency use authorization requests.

Therefore, we request that **<NATIONAL REGULATORY AUTHORITY>** consider the application submitted in relation to this product and authorize its emergency use.

Sincerely,

_[Company]_____
[Full name of signatory]
[Position]
[Signer's email and phone number (if different from letterhead)]

Annex 4. Minimum information that is recommended to be included in the ARN letter of authorization for emergency use

Each national regulatory authority must develop a template to authorize the emergency use of the product and prepare an evaluation report.

This annex provides brief guidance on the recommended minimum information to be used to write an approval letter and publish the results.

The emergency use authorization must contain the date of approval, the name of the product, the manufacturer and manufacturing facility, and the approved illustrations (primary and secondary packaging and information leaflet).

The letter and publication of the results of the emergency use authorization request may must be based on minimal and incomplete documentation, which must be indicated.

Approval may include special conditions for use, including safety reporting requirements and limitations such as:

- ÿ use only during the pandemic period;
- ÿ use only by certain organisms;
- ÿ use only in certain high-risk groups indicated on a list;
- ÿ special conditions for post-marketing safety reports.

The approval must contain contact information for the national regulatory authority should questions or concerns arise.

REFERENCES

[1] Organización Mundial de la Salud. *Annex 7: Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries. WHO Technical Report Series, No. 1004, 2017.* Ginebra: OMS; 2017. Se encuentra en https://apps.who.int/medicinedocs/documents/s23326en/s23326en.pdf.

[2] Pan American Health Organization. *Principles related to the use of decisions of other regulatory authorities: concept note and recommendations.* IX Conference of the Pan American Network for Pharmaceutical Regulatory Harmonization (PANDRH). San Salvador, from October 24 to 26, 2018). Washington, DC: PAHO; 2019. Found at https://iris.paho.org/bitstream/handle/10665.2/51550/OPSHSS1903_spa.pdf?sequence=1&isAllowed=y.

[3] Office of Counterterrorism and Emerging Threats. *Emergency Use Authorization of Medical Products and Related Authorities Guidance for Industry and Other Stakeholders.* Silver Spring, MD: FDA; 2017. Se encuentra en https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical products-and-related-authorities.

[4] European Medicines Agency. *Conditional marketing authorization. Report on ten years of experience at the European Medicines Agency.* London: European Medicines Agency; 2017. Found at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation.

[5] World Health Organization. *Emergency Use Listing Procedure.* Geneva: WHO; 2020. Found at https://www.who.int/docs/default-source/medicines/eulprocedure.pdf?sfvrsn=55fe3ab8_2.

[6] Ministry of Health. National Health Surveillance Agency. *ANVISA RDC 203/2017.* Brasilia: Ministry of Health; 2018 Can be found at http://www.in.gov.br/web/guest/materia/-/asset_publisher/Kujrw0TZC2Mb/ content/id/31718805/do1-2018-07-17-resolucao-rdc-n-203- de-26-de-26-de-2017--31718795].

[7] Ministry of Health. National Health Surveillance Agency. *ANVISA RDC 348/2020.* Brasilia: Ministry of Health; 2020. It can be found at http://www.in.gov.br/en/web/dou/-/resolucao-rdc-n-348-de-17-de-marco-de-2020-248564332.

[8] Ministry of Health and Social Protection. *Decree 476/2020.* Bogotá: Ministry of Health and Social Protection; 2020. Available at https://dapre.presidencia.gov.co/normativa/normativa/DECRETO%20476%20DEL%2025%20DE%20MARZO%20DE% 202020.pdf (9).

[9] World Health Organization. *Annex 2: Guidelines on regulatory preparedness for human pandemic influenza vaccines (Adopted 2007) WHO Technical Report Series No. 963, 2011.* Geneva: WHO; 2011. Found at https://www.who.int/biologicals/vaccines/Annex_2_WHO_TRS_963-3.pdf?ua=1 (12).

[10] Caudron JM, Ford N, Henkens M, Macé C, Kiddle-Monroe R, Pinel J. *Substandard medicines in resource-poor settings: a problem that can no longer be ignored.* Tropical Medicine and International Health. Volume 13 No 8 PP 1062-1072: agosto del 2008.

[11] World Health Organization. *In Vitro diagnostics and laboratory technology. Post-market surveillance or in vitro diagnostics (IVDs).* Geneva: WHO; without date. It is located at https://www.who.int/diagnostics_laboratory/postmarket/en/.

[12] International Council on the Harmonization of Technical Requirements for Pharmaceutical Substances for Human use. *M4: The Common Technical Document.* Geneva: ICH; without date. It is located at https://www.ich.org/page/ctd.

HSS/MT/COVID-19/20-0006