Questions and answers (Q&A) on regulatory matters related to the introduction and pharmacovigilance of vaccines against COVID-19

19 January 2021

1. What criteria will the COVAX Facility use to determine vaccine eligibility?

For the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO) to procure a vaccine through the Facility for global access to the COVID-19 vaccine (COVAX), the vaccine must be prequalified by the World Health Organization (WHO) or assessed by WHO and included in the Emergency Use Listing (EUL).

Exceptionally, UNICEF AND PAHO can procure a vaccine through the COVAX Facility that has received marketing authorization from a stringent regulatory authority (SRI), provided that the receiving country consents to the procurement and the established requirements have been met.

For current information on the status of vaccines being evaluated for the EUL, see: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_Dec2020.pdf

2. What role does the WHO prequalification program play in the COVAX Facility?

The vaccines to be procured under the COVAX Facility will be assessed by the WHO vaccine prequalification program. This assessment is among the eligibility criteria adopted by the COVAX Facility for product procurement and distribution. To proceed with this assessment, the prequalification program enlists the participation of international experts from national regulatory authorities (NRAs) of regional reference. The relevant information and reports issued as part of this assessment will be shared with the NRAs of the vaccine-receiving countries through PAHO mechanisms such as the Revolving Fund for Vaccine Procurement (Revolving Fund).

Furthermore, the prequalification program and PAHO will provide support for monitoring the quality, safety, and efficacy of the vaccines listed for procurement through United Nations agencies, as well as support for the verification of any post-authorization changes.

3. What action will the prequalification program take with respect to a product submitted for inclusion in the EUL if a stringent regulatory authority has assessed and approved it for use?

When a product submitted for inclusion in the EUL has been assessed through other emergency mechanisms by a stringent authority that shares its information with the prequalification program, WHO has no intention of duplicating the work. It will, however, assess the suitability of the product from a global health public standpoint and may assess aspects of the quality, safety, efficacy, and performance of products on a case-by-case basis.

4. How do the Emergency Use Listing (EUL) and the prequalification program differ?

The EUL is a procedure for assessing unregistered vaccines, therapeutics, and in vitro diagnostics during public health emergencies with the ultimate goal of expediting the availability of these products to people who need them. Prequalification takes a relatively long time and involves an extensive review of the quality, safety, efficacy, and programmatic suitability of a vaccine. The EUL procedure differs from the WHO prequalification procedure. As mentioned, the EUL is a special procedure for unregistered products used in emergencies, when the community or the authorities may be willing to tolerate less certainty about efficacy or safety, given the morbidity or mortality of the disease and the lack or scarcity of treatment, diagnosis/detection, or prevention options.

The differences between the WHO prequalification program and the EUL are summarized in Table 1.

Prequalification (1987)	Emergency Use Listing of products (2015)
Extensive review of the quality, safety, efficacy, and programmatic suitability of vaccines for international supply	**Risk-benefit assessment of an essential set of quality, safety, and efficacy data for use during public health emergencies**
Initial extensive review	**Rolling review of data**
Assessment performed by WHO independent experts	Assessments performed by WHO independent experts in collaboration with national regulatory authorities

Utilization of decisions of stringent regulatory authorities for abbreviated procedures and exhaustive review of programmatic aspects by WHO	Utilization of decisions of stringent regulatory authorities for abbreviated procedures and exhaustive review of programmatic aspects by WHO
Meetings encouraged prior to submission of the request and required information	Meetings encouraged prior to submission of the request and required information
Post-prequalification monitoring	**Post-deployment monitoring of the vaccine**
Reassessment/requalification	**Time-limited recommendation**
	Process should continue for marketing authorization/prequalification

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5. Will PAHO purchase COVID-19 vaccines approved by national regulatory authorities of regional reference (NRAr)?

PAHO will not purchase vaccines authorized by national regulatory authorities (NRAs) of regional reference if they have not been assessed by WHO and included in the EUL. PAHO, through its Revolving Fund, is supporting the COVAX Facility and will follow the criteria it sets. Under the COVAX Facility, vaccine eligibility is restricted to products that have been approved through the WHO prequalification process or EUL procedure, and in exceptional cases, those approved by an SRA.

6. How can national regulatory authorities verify that the vaccines they authorize for use in their national territory meet quality, safety, and efficacy standards?

The national regulatory authorities are responsible for establishing the requirements, procedures, and times when vaccine manufacturers request authorization for the introduction and use of their products at the national level.

These authorities are responsible for ensuring that both the vaccines and the facilities where they are manufactured meet the standards set for their clinical study, manufacture, distribution, and control.

PAHO/WHO recommends that the requirements follow the international recommendations established in the vaccine standards of the World Health Organization's Expert Committee on Biological Standards (ECBS) and international agencies such as the International Council for Harmonisation (ICH). These standards serve as a model for manufacturers to submit documentation to the regulatory authorities for vaccine authorization. The information is submitted on a standard form—the Common Technical Document (CTD)—that must include information on quality and manufacturing, clinical and non-clinical information, and risk management plans. This information will serve as the basis for informed decision-making by NRAs to ensure the quality, safety, and efficacy of authorized vaccines.

These same recommendations are emphasized in the considerations for the assessment of COVID-19 vaccines in the Emergency Use Listing (EUL) procedure. **The CTD must include information on all phases of clinical research. Completion of phases 1, 2, and 3 of clinical trials is essential to ensure vaccine effectiveness and safety. Even under emergency use authorization, a product must complete these three phases of clinical development and meet quality criteria in the production process.**

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7. What happens when a national regulatory authority authorizes the use of a COVID-19 vaccine?

During an emergency such as a pandemic, a regulatory authority can grant temporary authorization for an unlicensed medical product such as a vaccine for use and sale in a particular market for a stipulated time period to diagnose, treat, or prevent a specific disease. This type of authorization constitutes a legal measure and a sovereign decision that is normally granted if the known and potential benefits of a product outweigh any known and potential risks and if no alternative product is available.

Some of the PAHO Member States have signed bilateral agreements with different manufacturers to procure COVID-19 vaccines. The NRAs—not PAHO/WHO—are responsible for issuing authorizations prior to the use of any vaccines employed in their national territory and for auditing and monitoring their safety, quality, and efficacy once deployed in the country. PAHO can support the Member States in the adoption of appropriate regulatory frameworks to ensure that these procedures are implemented according to international standards.

In emergencies such as the COVID-19 pandemic, NRAs must define the regulatory frameworks, procedures, requirements, and timeframes for the authorization, importation, batch release, and post-authorization surveillance of the vaccines to be used. Different regulatory mechanisms are currently being used for this purpose, namely:

- Registration and marketing authorization (procedures used in normal situations);
- Emergency use authorization;
- Licensing exemption at the request of the ministries of health during pandemics, stock-outs, or the absence of national manufacturing of a needed product;

In all these cases, the vaccine provider has sole responsibility for submitting the information that the NRA has deemed necessary for this purpose.

SRAs have regulatory frameworks for these three mechanisms. In the case of emergency use authorizations, authorization can be granted on the basis of limited quality, safety, and efficacy data, allowing the manufacturer to submit the data as it is generated, based on a risk-benefit assessment and risk management plans governing emergency use authorizations. However, procedures and decision-making of this kind entail important considerations and responsibilities for NRAs, namely:

1. Emergency approval can include one or more special conditions for vaccine use: authorization only during the emergency, use of a product only by certain institutions, use of a product only for certain high-risk groups, and special conditions for post-authorization safety reporting.
2. When this approval is based on the decision of other regulatory entities, we suggest that the principles promoted by WHO and PAHO concerning good regulatory practices be applied, as well as the general principles for recognition of the regulatory decisions of other jurisdictions. Consideration should be given to establishing systems to monitor the use of products approved in this manner.

References:

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8. What support will PAHO provide to national regulatory authorities for the regulation and control of COVID-19 vaccines?

PAHO will provide countries with ample support to guarantee the quality, safety, and efficacy of COVID-19 vaccines. For products procured through COVAX and the PAHO Revolving Fund, PAHO intends to:

- Facilitate mechanisms for the exchange of information about the products included in the prequalification program and EUL.
- Assure quality, based on the documentation submitted by producers as part of the tender process.
- Support the investigation of reports of deviations in quality, temperature, and the safety and efficacy of vaccines procured through the COVAX Facility and issue the pertinent recommendations.
- Support post-deployment surveillance activities for COVID-19 vaccines (pharmacovigilance).
- Support market surveillance and control, especially for the prevention, detection, and response to unregulated, substandard, or falsified products.
- Promote the sharing of experiences among NRAs at the regional level.

In the case of products procured bilaterally by the countries, PAHO can provide support for the establishment of stringent expeditious procedures to the enable countries to assess the quality, safety, and efficacy of vaccines.

9. What are the role and commitments of national regulatory authorities in post-marketing surveillance and pharmacovigilance of COVID-19 vaccines, particularly if they use the COVAX Facility?

Under the COVAX initiative and the EUL and prequalification procedures, manufacturers must submit vaccine safety monitoring and risk management plans and keep the NRAs apprised of these aspects. In any case, NRAs must have structures, procedures, and trained human resources, coordinating with the Expanded Program on Immunization to implement the pharmacovigilance plan; this will enable them to update the risk-benefit ratio and adopt the appropriate regulatory measures to optimize it.

As mentioned, to perform this function, it is important to receive current information from the manufacturer and other regulatory authorities, and to have procedures and strategies for assessing adverse events following immunization (AEFI) or other problems occurring with the vaccine.

According to WHO recommendations, local authorities should keep a record of the distribution of product lots, implement the national post-marketing surveillance plan, update the emergency use authorization as more information is received from manufacturers on the complete product life cycle (for example, reports with periodic updates on safety and variations), and continue reviewing the status of the authority's emergency use authorization. The WHO *COVID-19 Vaccines: Safety Surveillance Manual* includes recommended activities for AEFI surveillance, regardless of capacities. Moreover, PAHO has developed guidelines for post-authorization surveillance of medical products during a pandemic emergency.

With regard to the detection, prevention, and response to the appearance of substandard or falsified vaccines on the market, strategies and measures will be proposed for each component, with risk-based prioritization based on local and international experiences.

Regional networks of focal points for pharmacovigilance and falsified medical products, as well as the WHO Rapid Alert System, are tools that support the exchange of dynamic information and facilitate country decision-making in these domains.

References:

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10. What impact do regulatory readiness and import authorization and importation procedures have on the availability of vaccines through COVAX?

Regulatory readiness is key to a rapid response when an emergency is declared. Readiness activities are essential for minimizing the time it takes to reach a final decision on the potential inclusion of products and the consequent importation and national deployment procedures. Delays in regulatory readiness will affect a product's availability. COVAX requires the existence of a national readiness plan. Local procedures should guarantee an accelerated approval process, the granting of import permits within 5 days, and the prevention of duplication in batch releases, applying general principles for recognition of the regulatory decisions of other jurisdictions. In addition, post-deployment activities should ensure adequate pharmacovigilance based on risk management plans.

References:

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11. How does PAHO intend to support the introduction of vaccines in countries with limited regulatory capacity?

PAHO supports countries that may lack the ability to develop stringent streamlined procedures for exhaustive regulatory assessment of the records so that they can adopt procedures based on WHO (EUL /prequalification) or SRA decisions. In conjunction with the WHO vaccine prequalification program, PAHO will facilitate access to the assessment reports published as part of EUL/prequalification procedures.

Based on the risk management plans provided by the manufacturers and taking the national context and national plans into account, PAHO will support monitoring following approval and the safety and efficacy assessment.

12. How important are subregional regulatory coordination mechanisms for COVID-19 vaccines?

Subregional mechanisms offer a single point of entry to streamline the granting of emergency use authorizations that can be utilized in several countries. These mechanisms are therefore essential for minimizing the time it takes for a product to be authorized for emergency use or procurement. These mechanisms can also help to boost the efficiency of national staff by reorganizing functions and substituting regular tasks with other emergency response activities.

Subregional regulatory mechanisms can also provide support for pharmacovigilance and of post-authorization surveillance activities through the exchange of information on suspected adverse drug reactions and substandard and/or falsified products in all countries.

13. What are the provisions regarding COVAX Facility responsibility and compensation and how is PAHO involved?

PAHO is not a party to agreements on responsibility and compensation that the countries sign under the COVAX initiative but can provide technical cooperation and assistance in the procedures for signing such agreements.

PAHO/IMS/HSS/MT/COVID-19/21-0001