COVID-19

Risk Management Plans and Periodic Safety Reports for COVID-19 Vaccines

Recommendations for Their Request, Preparation, Management, and Assessment

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Situation analysis

The continuous assessment of benefits and risks, as well as effective communication among stakeholders, is key for protecting and promoting public health, and for strengthening public trust in vaccines and the authorities that oversee the vaccination process (*1*).

During the current COVID-19 pandemic, the private sector has played a critical role in the rapid development of vaccines. Furthermore, primary responsibility for vaccine safety and efficacy monitoring rests with use authorization holders. The national regulatory authorities (NRAs) have to make decisions based on limited safety and efficacy data at the time of authorization. Thus, constant monitoring is necessary as soon as the vaccine is authorized, in order to detect and assess possible safety problems associated with the approved vaccines (*1*).

All efforts should focus on timely and effective monitoring of the safety profile of the COVID-19 vaccines used during this emergency, with the participation of all responsible actors. A basic element of vaccine safety monitoring is to request and assess risk management plans (RMPs), as part of the set of documents required for vaccine approvals. The following should also be considered: requesting a common RMP for the Region of the Americas, including the review of periodic safety reports (PSRs) on vaccines; and the development of strategies for the reporting and assessment of adverse events following immunization (AEFI) as part of the surveillance plan.

Objectives and reach

This document establishes recommendations and considerations to guide the development of strategies to assess the RMPs and PSRs requested as regulatory requirements for use authorization of COVID-19 vaccines and for safety monitoring once their use is authorized.

This document is intended mainly for NRAs in the Region of the Americas and may be considered by COVID-19 vaccine use authorization holders when preparing PSRs and RMPs for submitting to health authorities.

Background

On 30 January 2020, the World Health Organization (WHO) declared a public health emergency of international concern due to the COVID-19 outbreak, which corresponds to the highest level of the WHO grading of emergencies. On 11 March, the Organization's assessment determined that COVID-19 could be characterized as a pandemic (*2*).

At the global level, several private and governmental entities are collaborating in different areas to mitigate the spread of diseases through case-finding mechanisms, development of critical interventions, distribution of vital medical supplies, and support for the development of treatments and vaccines.

Coronaviruses are a large family of viruses that can cause diseases in animals and humans. In humans, several coronaviruses are known to cause respiratory infections with symptoms that range from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), discovered more recently, causes coronavirus disease (COVID-19). SARS-CoV-2 was unknown until the outbreak in Wuhan (China) in December 2019. It has now caused a pandemic that affects most countries around the world. Understanding of COVID-19 epidemiology continues to rapidly evolve and change (*3*).

During the development phase of any drug, a limited number of participants are selected for clinical trials and monitored for a relatively short period under controlled conditions. Under such conditions, certain side effects – particularly those that are rare or unusual – only emerge during "real life" use of the drug by different populations. Therefore, it is fundamental to strengthen monitoring of the safety and efficacy of any drug once its use is authorized.

It is anticipated that, following regulatory authority approval of COVID-19 vaccines, their use will be highly widespread. This can lead to a high volume of reports of suspected adverse events and other safety-related issues. Thus, prompt identification and assessment of new information on the benefit-risk balance of these vaccines, timely communication, and strong transparency will be key for protecting public health and ensuring public trust in the vaccines and the regulatory system (*4*).

Requesting and assessing risk management plans

This section lists special considerations for each section of the RMP that need to be considered when assessing COVID-19 vaccines, excerpted from the European Medicines Agency (EMA) guidelines (*5-7*) and the WHO manual on safety surveillance of COVID-19 vaccines (*8*):

Safety specifications

- **Epidemiology of the disease and the target population groups**: This section should present updated information on COVID-19 while recognizing uncertainties. The sponsor should include specific information from the country or region where the vaccine will be used.
- **Characteristics of the vaccine:**
  - Production and formulation platform; degradation of the active substance or antigen; and potential related impacts on safety (for example, mRNA, protein subunit, or vaccine vector) (*9, 10*).
  - Presence of an adjuvant (*11*).
  - Risks that may be specific to COVID-19 vaccination, such as exacerbated respiratory disease.
- **Reactogenicity:**
  - If the vaccine group presented greater reactogenicity than the control group during clinical trials (pain, redness, swelling, induration at the injection site, and systemic symptoms like fever, myalgia, or headache) (*12*), the RMP should include a discussion of this risk and how it may influence the safety profile.

- Review of information on the following should be considered: population groups in conditions of vulnerability, such as older people or patients with chronic inflammatory diseases; and differences in reactogenicity between the first and second or subsequent vaccine doses.
- Aspects of vaccine formulation and preparation should be discussed in the analysis of reactogenicity when an increase in associated adverse reactions is suspected. One example is local reactions or abscesses that may be related to effects on the sterility of the product when reconstituting the vaccine.

- **Preclinical information about specifications:** This section may be available even if the presentation of the RMP has not been completed. The sponsor should present new information from non-clinical studies in future revisions of the RMP.
- **Information from clinical trials:** General information on the protocols of the trials in progress should be presented in the RMP as part of the application for approval. This includes the number of subjects exposed as of the application date and whether any problems related to vaccine safety have been observed.
- **Post-authorization experience:** If the vaccine has been authorized in other countries, the RMP should include any reference information about post-authorization exposures.
- **Identified and potential risks:** In applications made through the progressive review mechanism, as is the case with the emergency use authorization (EUA) for COVID-19 vaccines, it is recognized that only limited information from the first stages of the presentation of the RMP will be available. It is to be expected that the safety specifications will be completed after the results of the preliminary clinical trials are available, vaccine efficacy is determined, and there is experience with post-authorization use.
- **Missing information:** Populations not studied in the clinical trials, for example, pregnant women, children, older people, or patients with severe comorbidities.

Pharmacovigilance plan

- **Basic elements and routine actions:**
  - *Signal detection* (*13*) *and review or analysis of individual case safety reports (ICSRs)* (*14*): In addition to the information presented by manufacturers in the RMPs, it is advisable to use other databases to integrate the information –such as national databases or VigiLyze, a system that can use national, regional, or global data – as a starting point for the quantitative identification and assessment of signals. The Uppsala Monitoring Centre (UMC) has published instructions on how to find ICSRs associated with COVID-19 treatments (*15*).
  - *Analysis of adverse events of special interest (AESI) associated with COVID-19:* It is advisable to consult the priority list of these events prepared by the Brighton Collaboration (*16*), among others.
  - *Specific questionnaires, for example, for monitoring pregnant women who have been vaccinated* (*9*)*:* It is expected that a summary and analysis of safety considerations will be included in the PSRs.

- *Observations about the background of the following elements:* Administration of the vaccine in the pediatric population, vaccination in people with COVID-19, and people that received another vaccine at the same time.
- *PSRs, including simplified reports:* These should include the preliminary and final results of safety-related considerations from the studies in progress. They should also discuss whether there were any early signals during the clinical trials. For more information on the PSRs, see the following section.
- *Strategies for vaccine traceability:* For example, the use of stickers or cards, or electronic methods such as bar codes or QR codes, with the vaccine name and lot numbers.

- **Additional activities:**
  - As priority, carry out monitoring of the clinical trials in progress.
  - Review the safety information reported in the post-authorization studies if there are any in progress.
  - Review the safety information reported in medical records, for example, of pregnant women, children, or immunocompromised people who have received the vaccine.

Measures to minimize risk

- In principle, complete and appropriate product labeling is a key element for minimizing the risks of COVID-19 vaccines.
- Nevertheless, the RMP should also include training and communication strategies to inform health professionals and patients or guardians about the type of vaccine, the risks, and how to prevent or minimize risks.
- Vaccination services should implement measures to adequately manage known events, whether they are potentially serious (for example, anaphylaxis) or non-serious but frequent, since that may discourage patients from being vaccinated.

Regional risk management plan

A regional RMP, considered as an annex to the standard RMP (*7, 8*), may provide important additional details for the countries of the Region of the Americas since it documents differences in the frequency, severity, or nature of the safety problems resulting from ethnic or epidemiologic differences that are specific to the Region (*17*). A regional RMP for the Americas could contain the following elements:

Safety specifications

- Epidemiology of COVID-19 and the target population group, considering the available information on disease incidence, prevalence, and presentation by age, sex, and ethnic characteristics; risk factors; mortality; and treatment options.
- Description of vaccine use in the Region, for example, vaccination in autochthonous populations or populations with different vulnerabilities.
- Risk of errors in the distribution, conservation, and administration of vaccines given local contexts.

Pharmacovigilance plan

- Manufacturers should describe the communication strategy and the analysis of ICSRs for the Region.

- The NRAs should include the search in VigiLyze.
- In the additional pharmacovigilance activities (for example, post-authorization studies or clinical records), assess the periodic or final reports and carry out monitoring of possible signal detections or early identification of safety problems.
- Plan for monitoring programmatic errors or errors in vaccine use.
- Plan for monitoring and action when facing deviations in vaccine quality identified by the individuals in charge of their use. Technical assistance activities that will be implemented for investigation purposes and analysis of adverse events that involve reported suspected deviation from the quality standard should be specified.

Measures to minimize risk

- Complete and standardized labeling for the countries of the Region, in the language of the destination country.
- Consider risk communication strategies for populations that cannot read or do not speak the population's main language, for example, that speak indigenous languages.
- Specific strategies should be included for complete and accurate communication about vaccine use and prevention of errors related to vaccine manipulation and use. The target audience is national immunization programs, based on the local conditions that can generate or increase the presence of these risks.

Requesting and assessing periodic safety reports

PSRs are documents requested by regulatory authorities from use authorization holders, in which the holders summarize and consolidate the updated global information on the safety of a drug, vaccine, or biotechnology product. In normal situations, the presentation of PSRs is established in semiannual, annual, three-year, or five-year periods, depending on the marketing or use period and the safety profile (*18*).

In the case of COVID-19 vaccines, given the need to generate and strengthen safety data, a semiannual period may be too long for assessing safety since high exposure levels are expected in a short period and there is greater uncertainty than usual concerning the occurrence of events. For this reason, the NRAs could establish shorter PSR presentation periods in the requirements for emergency authorizations or marketing authorizations, in order to expedite their submission and ensure more timely assessments (*19*).

According to the international guidelines published by the EMA and other entities, it is expected that use authorization holders will submit simplified monthly PSRs to regulatory authorities. The PSRs will include information on suspected adverse reactions reported, including adverse events of special interest (AESI), and data of the doses administered, among others. The presentation of abbreviated monthly PSRs complements but does not replace the presentation of regular PSRs. Regulatory authorities can reevaluate the need for and periodicity of the presentation of these reports based on the evidence

available during each vaccine's post-authorization period. The periodicity of the simplified and regular PSRs can follow related international recommendations (*7*).

The content of the simplified PSRs should be agreed upon by each NRA and the authorization use holders in accordance with each country's legislative framework. However, they should include, at a minimum (*7*):

- Interval and cumulative number of spontaneous reports, overall, by age groups, and in special populations (for example, pregnant women).
- Interval and cumulative number of ICSRs.
- Consolidated ICSRs by country or geographic region, and by causal classification, for example, Latin America or the Caribbean.
- Exposure data stratified by country and age groups.
- Changes in the reference safety information during the report interval or period.
- Signals that are ongoing and under evaluation during the report interval or period.
- Reports of AESI, with relevant numbers and cases, including analyses of observed or expected cases.
- Reports of fatal cases, with relevant numbers and cases, including the respective analyses.
- Considerations related to risks and benefits.

Considerations for the assessment of RMPs and PSRs in the Latin American and Caribbean context

Within the framework of the Regional Network of Pharmacovigilance Focal Points of the Americas, several members have indicated the following as feasible strategies for assessing RMPs and PSRs (in addition to independent assessment by each NRA): the establishment of agreements to exchange assessments with other NRAs and the establishment of agreements to adopt these assessments.

Given the different levels of development and technical and human resource capabilities, the NRAs in Latin America and the Caribbean should establish the work approaches or combination of strategies that work best for each authority. For example, they could establish reliance mechanisms for the use of regulatory decisions of other jurisdictions, through which the NRAs could consider measures issued by reference NRAs. Other NRAs could opt for recognition mechanisms. This strategy requires formal or legal agreements because it involves the NRA's acceptance of the reference NRA's regulatory assessments, in order to obviate the need for the NRA's own assessment (*8, 20, 21*).

In addition, both mechanisms (reliance and recognition) can be applied either unilaterally or mutually, or modified by the types of approved vaccines. Coalitions between different countries can also be created according to the vaccines approved in each participating NRA and their technical and information exchange capabilities (*8, 20, 21*).

In general, the establishment of pharmacovigilance mechanisms —and specifically, the assessment of RMPs and simplified and regular PSRs — requires an iterative process with decisions that are made and modified as more data about the approved vaccines becomes available. The process also requires communication and transparency mechanisms to obtain timely information about safety and efficacy.

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