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Post-authorization Surveillance of Medical Products during a Pandemic Emergency

Purpose and context

The purpose of this report is to furnish guidance and recommendations to support regulatory decision-making in pharmacovigilance, technovigilance, and hemovigilance during pandemics in the Region of the Americas. Furthermore, given the heightened importance of improving the detection, prevention, and response to unregistered, substandard, or falsified medical products in this context, it addresses key issues in this regard. This report is designed for national regulatory authorities (NRAs) and other actors (Expanded Program on Immunization, disease-specific and public health programs, health service professionals, etc.) involved in the regulation, selection, indication, and utilization of health technologies.

Although this report discusses both medicines (including vaccines) and medical devices[1], the steps prior to their use and conditions of authorization, as well as post-authorization surveillance, are clearly very different for each of these health technologies. Since post-authorization surveillance is a regulatory function of the health authorities, the report describes common approaches for the different types of technologies, as well as aspects specific to each one. The market surveillance components associated with importation/exportation, distribution, regulation of promotion and advertising, quality control, and inspection are beyond the scope of this report, unless they are related to the main components mentioned.

Challenges in pharmacovigilance, technovigilance, and hemovigilance during pandemics, and challenges in prevention, detection, and response to unregulated, substandard, and falsified medical products

On 11 March 2020, the World Health Organization (WHO) declared the SARS-CoV-2 (COVID-19) outbreak a global pandemic [1]. Given the need for rapid and effective decision-making to manage the pandemic, NRAs must develop strategies to shorten the time between the appearance of the new disease and access to a specific therapy or vaccine, while ensuring its efficacy, safety, and quality [2, 3]. Such strategies should also include medical devices in order to ensure that they perform with proven levels of quality and safety. Hence, it is necessary to review regulatory requirements and post-authorization surveillance mechanisms when authorizations for use are issued during a pandemic [4].

One measure often employed in such situations is the Emergency Use Authorization (EUA). When an emergency such as the current pandemic is declared, an EUA permits the use of a medicine or medical device that is not authorized for use, or the use of any such technology for an indication other than the one authorized through regular mechanisms [5]. The situation or condition that prompts the EUA must have a high public health impact. Furthermore, it is valid only during the emergency and must meet specific criteria in circumstances where no other treatment alternative is available [4]. In this regard, the World Health Organization (WHO) has designed three groups of emergency procedures with special requirements: one to evaluate pharmaceutical products, another specifically for vaccines, and a third one for in vitro diagnostic medical devices (IVDMD) [6]. Different examples of medicines and medical devices illustrate this [7, 8].

When temporary use authorizations for groups of patients are involved, the pharmaceutical laboratory or clinical trial sponsor should commit to promptly reporting any information to the NRA about the safety of the pharmaceutical product that could be important for the authorization of compassionate use, in keeping with local post-authorization surveillance regulations. Compassionate use with unapproved experimental therapies or pharmaceutical products can result in severe unknown adverse reactions [9, 10], which must be reported to the NRA so that it can continuously monitor the risk-benefit ratio and take action commensurate with this evaluation.

These conditions make the post-authorization phase even more important for the protection of users and health professionals. Thus, during the pandemic emergency, the use of new medicines and medical devices, new uses for

[1] This report uses the customary definition of a medicine, which includes vaccines, and the term “medical products” to include medical devices in addition to medicines.

medicines already authorized, and compassionate or expanded use in groups of patients should be accompanied by a post-authorization surveillance plan to prevent, detect, and appropriately and rapidly respond to events and incidents connected with these products. Complementary action to minimize risk may also be required, including changes in the legal requirements for prescribing or dispensing the medicines involved, changes in the conditions of use stipulated in the technical specifications, or additional measures to discourage the use of medicines for unauthorized indications of unproven efficacy. Table 1 describes specific challenges by type of health technology.

Table 1. *Situations with specific challenges for surveillance*

Pharmaceutical Products
• In emergencies, clinical trials for new products tend to be methodologically diverse. Limited evaluation of safety. • Surveillance of a new product under investigation in clinical trials. • Therapeutic repurposing of a previously registered pharmaceutical product to evaluate an indication other than the one that prompted its authorization [4] • Unregistered pharmaceutical product that requires an authorization for use under special conditions.
Vaccines
• During an emergency, there is a tendency to speed up clinical trials and include the minimum number of subjects. Limited evaluation of safety. • Regional coordination between the NRA and the National Immunization Program (see details on this point in specific guidelines for this type of context [11]). • Formulation of new vaccine distribution and use plans. • Adjustments to the passive surveillance system and the planning of observational studies. • Particular conditions and potential associated risks, such as administration of the vaccine to vulnerable groups or potential interference with another vaccination schedule in progress.
Blood
• In a hemovigilance system, the surveillance of events associated with blood, plasma, or cells may be organized differently and have a different structure than that for blood derivatives (e.g., immunoglobulin) customarily grouped under pharmacovigilance [12]. • The use, for example, of convalescent blood or plasma in situations of unproven efficacy (which will make it necessary to have or create a specific surveillance and reporting system to determine the risks associated with its use). • Evaluation of the indicators of overall effectiveness of the measures adopted in donation and transfusion services during a pandemic [12, 13, 14].
Medical devices
• Product scarcities at the national or regional level, both of products that are rapidly developed– for example, in vitro diagnostic medical devices (IVDMD), platforms for their analysis, and the pertinent laboratory materials – and those that already have an NRA-issued authorization for use. • Need to ensure that these devices meet the minimum technical specifications for safe patient care. Verification of compliance with standards that assure their quality, safety, and performance, for those from both international suppliers and donations or local initiatives. • Medical devices with authorization for use for an indication other than the one originally approved by the NRA. • Deficiencies in quality management systems, as manufacturers increase their production lines, produce other medical devices, and new business initiatives emerge. • Small companies or companies that have recently begun manufacturing medical devices, who therefore have little experience with quality control.

As part of regulatory efficiency, the use of regulatory reliance practices has been recommended. However, in the case of post-authorization surveillance, the conditions for marketing should follow the recommendations of the NRAs whose decisions are being used, without neglecting the post-marketing conditions and surveillance plan. Through this procedure, the *risk-based* evaluation by a trusted/reference authority is recognized and this evaluation will be taken into account in the surveillance plan for a given product during an emergency [15].

It is also common, particularly in the context of a pandemic, for countries to see a surge in substandard, falsified, or unregistered medicines or medical devices that should be subject to surveillance and intervention by the NRAs [16].

> **Note:** Due to the need for rapid decision-making, it is recommended that an emergency regulatory committee be created, as described in the report: *Crisis Management during an Epidemic: General guidelines for efficient response coordination by national regulatory authorities* [3]. This committee will promote the coordination of different actors and regulatory areas to provide an efficient response. It is recommended that responsibilities be assigned for each area: vaccine safety monitoring; pharmacovigilance, which can also include coordination with the individuals responsible for hemovigilance; and technovigilance. Even in the absence of a professional for every area (i.e., responsibility is exercised by a single person), a situation analysis should be performed and specific strategies prepared for each area. The individual responsible for pharmaco- and/or technovigilance should be a member of the regulatory decision-making group, preferably the emergency regulatory committee, and should promote information exchange with the health authorities of other countries. There should also be coordination with the specific local or national committees (e.g., vaccine safety committee) to support the analysis of evidence on the safety of products, determine the desirability of keeping them on the market, and prepare the respective management protocols. It is very important during this pandemic for each NRA to upload all the relevant information on COVID-19 to a single page on its website [17].

Pharmacovigilance , technovigilance, and hemovigilance during and after the pandemic

As part of pharmacovigilance and technovigilance activities during this pandemic—as in any crisis—, consideration should be given to preparing plans that prioritize strategies and activities in surveillance *per se* (combining active and passive procedures) and in the management of contingencies, resources, roles and responsibilities, personnel, monitoring mechanisms, feedback, adjustment of activities, and identification of vulnerable or at-risk groups. When identifying management activities, it is important to consider the regulatory scenarios described in this report and the management of risks associated with the medical products to be authorized (prevention, evaluation, and mitigation measures). A theoretical action framework for the planning phase can be found in the report "Expecting the Worst. Anticipating, preventing and managing medicinal product and other healthcare crises" [18].

Spontaneous reporting is an essential and well-developed component of event monitoring in countries. It is usually less expensive/complicated and faster to implement than active strategies for both medicines or medical devices, even in areas with less regulatory development [19].

Spontaneous notification systems can be reoriented as the emergency dictates, deploying strategies to encourage reporting, especially to capture sentinel events associated with medicines or devices associated with the pandemic [20], whether recently authorized or with new indications for use. Operational mechanisms should be strengthened and actors should be informed about the importance of reporting to the health authority. Depending on the case, this will make it possible to identify potential signals that indicate use-related problems that should be investigated. Special attention should be paid to safety monitoring in special populations, such as children, pregnant women, and older adults, especially those with comorbidities.

As one of its key activities during the pandemic, the NRA should evaluate the quality and degree of available evidence for decision-making [21]. In this context, there are some recommendations that could be useful for different scenarios [9]. This evaluation of information from different sources (clinical trials, periodic safety reports [PSRs], other agencies, international alerts, country surveillance systems, etc.) will be necessary for both new and repurposed products, since a new indication can be related to the difference in appearance, frequency, or severity of events. Thus, the plan should define mechanisms, functions, and roles in order to proceed with the necessary

regulatory action, including the suspension or cancellation of the authorization for use of a medicine or medical device if new information and a reassessment of the risk-benefit profile so require to protect public health.

During the pandemic, activities in the pharmacovigilance or technovigilance plan should be prioritized in terms of capacities. Regulatory requirements for pharmaceutical products, vaccines, and medical devices linked to the pandemic can be made more flexible for planning activities that meet the new requirements stemming from the emergency. Examples include requesting simplified PSRs for pharmaceutical products or vaccines to expedite their submission, based on risk assessment [22]; modifying the frequencies/dates for submitting reports; prioritizing inspections based on the risk assessment. This will postpone nonessential in-person pharmacovigilance and technovigilance inspections or replace them with remote evaluations, as the United Kingdom's NRA has proposed[2].

In a broader context, the pandemic can affect the pharmaco- and technovigilance of medical products unrelated to the pandemic itself. Strategies should therefore be developed to ensure the continuity of these non-pandemic activities. The authorities may have to coordinate with the pharmaceutical companies to ensure the sustainability of the most important activities in their risk minimization programs that are unrelated to the pandemic [20]. Furthermore, a strategy should be prepared and teams should be designated for information, updates, regulatory decisions, and crisis management in general; for example, when a vaccine is introduced, a medical device needs to be withdrawn, or the indications for use of a pharmaceutical product has to be restricted.

Databases and other tools for collaboration and for the identification of adverse events or alerts can provide additional support for these actions. Large multinational databases of spontaneous reports are very sensitive, detecting signals better than smaller or national databases [23]. Priority should be given to sending data to the Uppsala Monitoring Centre (UMC), so that it can be rapidly entered in VigiBase and studied by any of the program's member countries (or at least, so that the data can be consolidated in the country's system and exchanged at the regional level).

In the field of medical devices in particular, NRAs in the Region are engaging in activities for collaborative exchange and the search for solutions to regulatory challenges, including the development of synergies to consolidate reports. One example of this is the Report Exchange Program on Medical Devices between National Regulatory Authorities in the Region of the Americas (REDMA) [24], created to promote the exchange of adverse event or incident reports among the NRAs of the Region. Other examples are the Health Technology Assessment Network of the Americas (RedETSA) [25] and the Regional Network of Pharmacovigilance Focal Points of the Americas [26].

Prioritization of surveillance reports and strategies during the pandemic.

Pharmaceutical products

- **Prioritization of reports**

For pharmaceutical products, the health authority should monitor and encourage the reporting of suspected adverse reactions, prioritizing their submission and analysis in the following order (adapted from the original reference) [27]:

1. Submission of individual case safety reports (ICSRs) on serious adverse reactions associated with pharmaceutical products used for treatment or prevention of the infection responsible for a pandemic (e.g., COVID-19);
2. Submission of ICSRs on serious adverse reactions associated with other products;
3. Submission of ICSRs on new, unexpected, or undescribed reactions;
4. Submission of ICSRs on non-serious adverse reactions associated with pharmaceutical products used for treatment or prevention of the infection responsible for the pandemic (e.g., COVID-19);
5. Submission of ICSRs on non-serious adverse reactions related to other products.

- **Strategies**

[2] MHRA announces a risk-based prioritization of on-site Good Practice inspections during COVID-19. Available from: https://www.insideeulifesciences.com/2020/03/25/mhra-announces-a-risk-based-prioritisation-of-on-site-good-practice-inspections-during-covid-19/ [Cited 19 July 2020].

During the pandemic, there should be periodic (weekly or biweekly) evaluations of the event reports received and also managed in other databases or by other agencies, in order to study and weigh the potential risks.

This should be accompanied by the reports received from marketing authorization holders (MAHs), with whom appropriate coordination should be maintained and who must meet the reporting deadlines and provide the basic information that these reports must contain.

In the aforementioned spontaneous reporting strategy, limitations such as underreporting and the absence of denominators and control groups hinder the establishment of causal relationships. However, such reporting may be useful for local decision-making (e.g., generating notes on improper use or signals that subsequently lead to formal investigations).

Another alternative for increasing specificity and efficiency is facilitated reporting. This enables groups of pharmaceutical products and possible events associated with the pandemic to be targeted. Spontaneous reporting is essential, but specific sites, contacts, reminders, and consultations are held periodically with focal points. At sentinel sites, it may be possible to obtain denominators for exposure or treatment.

The development, planning, and implementation of active pharmacovigilance strategies requires considerable human and economic resources. Cohort event monitoring (CEM), whose design is similar to that of cohort studies, makes it possible estimate incidences of events under the right methodological conditions [28] but involves complexities and challenges that will depend on the maturity of the regulatory systems.

Note: The potential for an increase in patient self-medication with both approved and unauthorized products should be considered. Suspected adverse reactions occurring in these situations should also be reported. Documentation of unapproved use can ultimately support measures such as the imposition of dispensing restrictions by the health authority. The MedDRA dictionary makes it possible to code these reports, using terms such as “off-label use,” "therapeutic product ineffective for unapproved indication," and "therapeutic product effective for unapproved indication." Moreover, the observations section can be used to provide more details on treatment indications [29]. The last update of the MedDRA dictionary (version 23.0) includes new terms related to COVID-19, such as “COVID-19 pneumonia,” “Suspected COVID-19,” and “COVID-19 test positive” that can contribute to better characterization of reporting [30].

Vaccines

A risk-benefit assessment, especially for vaccines, should be conducted simultaneously with their mass administration. Mechanisms for obtaining real-time information on their safety, efficacy, and immunogenicity should therefore be in place. NRAs should coordinate with the Expanded Program on Immunization, the National Immunization Technical Advisory Group (NITAG), local committees and offices, or entities that collaborate in the investigation of adverse events following immunization (AEFI). Basic passive surveillance can be targeted to identify potential events, based on evidence from preclinical and clinical vaccine trials, the behavior of the disease, and the type of vaccine or adjuvant used. It will also identify reports of the more frequent program errors, especially at the start of vaccination, as well as reports grouped by geographical area, age, or the presence of underlying pathologies. The main points to consider in this evaluation are detailed further on in this evaluation.

The active surveillance approach should also be considered—for example, through a specific protocol with a network of sentinel hospitals for evaluating the potential association between adverse events and their magnitude and the vaccine [22, 31, 32].

- **Prioritization of reports**

In the case of vaccines, the health authority should also monitor and promote the reporting not only of severe AEFIs, but also of:

1. program events, regardless of their severity,
2. events that affect a group of people,

3. geographically related events or those that involve vulnerable or specific groups of people,
4. new or undescribed events,
5. events with an abnormally high frequency
6. events linked to a concomitant treatment
7. adverse events of special interest (AESI), prioritized by PAHO/WHO.

When a new vaccine is introduced, given high the number of individuals who will receive it, there will very likely be a relatively high frequency of program errors and coincidental events requiring rapid analysis for potential corrective action or to properly communicate the findings in order to avoid false alarms [33].

- **Strategies**

As part of the SPEAC project (Safety Platform for Emergency Vaccines), the Coalition for Epidemic Preparedness Innovations (CEPI) has conducted an evaluation of adverse events of special interest for COVID-19 vaccines and proposed a list of structured definitions [34]. These identified AESIs, combined with emerging AESIs, should be included in the vaccine's risk management plan, using a prospective observational study design to capture these events and other severe adverse reactions associated with the vaccination process. By way of example, in the recommendations of the European Medicines Agency (EMEA) on pharmacovigilance plans for a vaccine to combat the H1N1 influenza pandemic, a series of AESIs were identified and proposed for consideration in surveillance plans [35].

In the stages prior to the introduction of the vaccine, it will be necessary to collect information on potential AEFIs, based on the data from clinical trials, along with local baseline frequencies of these events–especially if they were identified for other vaccines. It will be particularly useful to identify and study adverse events of special interest (AESIs) before and after the introduction of COVID-19 vaccines, identifying them with Brighton and other criteria for standardization and comparison purposes, and to consider them in the design of the monitoring strategy. It will also be necessary to consider the events produced by the disease, including in the development stages of the vaccine. Having baseline rates for these events will make it possible to compare and assess a potential increase in these rates with the introduction of the COVID-19 vaccine.

As is customary, the AEFI evaluation committee and the Expanded Program on Immunization (EPI) in general should help lead the development of the plan and its subsequent implementation.

The identification of AESIs will depend on each vaccine, and while there is limited information on the risk factors for COVID-19, the identification of events should consider those that are higher in older population groups with serious comorbidities and polymedication [36] or other factors related to a higher risk of complications from COVID-19.

As part of the safety monitoring strategy, it will also be a priority to conduct periodic evaluations of reports (weekly or as often as necessary) and new developments to identify program errors, potential serious AEFIs, signals, or any problem related to the coadministration of other vaccines or treatments.

When a new vaccine is introduced, passive AEFI surveillance is essential for identifying and investigating events, evaluating them, and proceeding with possible corrective action or communication. The identification of events is particularly related to reporting priorities and evaluation of background information on the vaccines.

Mild local systemic reactions, such as fever or swelling at the injection site, are quite common with the administration of inactivated vaccines, but they also tend to be self-limiting. These reactions can have less priority in a pandemic. In any case, their rates can usually be estimated from previous studies, and with these data, deviations in local frequencies can be evaluated. However, given the different production technologies—whether traditional ones, such as for inactivated viruses, or more complex ones, such as those for viral vectors and recombinant DNA—the surveillance strategy should consider them a potential factor in the generation of serious AEFIs.

In the case of vaccines, it will be useful to develop safety monitoring mechanisms, through observational studies, as a complement to passive pharmacovigilance. Considering the speed of change in the availability of evidence for other interventions, the prioritization of outcomes to be evaluated in any observational safety study or pharmacovigilance study of vaccines should follow the recommendations of the Global Advisory Committee on

Vaccine Safety (GACVS), the Strategic Advisory Group of Experts on Immunization (SAGE) (published on the WHO website), and PAHO technical groups [37, 38].

Concerning safety and the identification of events potentially associated with the vaccine, it is important to know whether this association is real and, ultimately, the extent of the risk. Observational studies can vary in their design (self-controlled case series method, case and control method, etc.) depending on the available time, type of event, etc.

It is important to harmonize the generation of safety data with the national plan for introducing the new COVID-19 vaccine. Joint efforts with national immunization programs are essential when planning any initiative and evaluating information needs, research, actions, and joint reporting.

The evaluation of vaccine efficacy will depend, *inter alia*, on data on epidemiological behavior and information on national coverage. Many countries have nominal vaccination information systems with detailed registries of the products administered, which can facilitate research (knowing the exposure component).

At the regional level, efforts to measure the efficacy of the vaccine (which will be used to contribute to the risk-benefit ratio of any candidate) will rely on the capacities of the Influenza Vaccine Effectiveness Evaluation Network for Latin America and the Caribbean (REVELAC-i) [39]. Any national initiative can therefore channel the available resources more effectively by linking with this initiative.

In Latin America, previous studies have been conducted to examine a specific event through the use of self-controlled case series in hospitals [31, 40]. In addition, based on cases identified in hospitals, hospital case-control or case-population studies could be conducted. Prospective pharmacoepidemiologic registries could also be constructed. This type of registry can consist of cohorts of subjects exposed to the medicines of interest, drug registries, or disease-specific patient registries that include data on all treatments used in customary clinical practice. The latter are preferable, as they permit comparisons between potential treatment alternatives. Developing a registry requires considerable human and economic resources in relation to the modest samples of patients that they are capable of recruiting. While they can obtain very accurate or interesting data (such as patient-centered results), their potential is limited to the study of the most evident effects—i.e., those of greatest magnitude or frequency [41]. Partnerships with universities, hospitals, or other research institutions will be very useful in the implementation of such studies[3].

Blood

Hemovigilance (HV) systems include the entire transfusion chain, beginning with donor selection and continuing through blood extraction, complications of donation, processing and analysis of blood components, and, finally, transfusion itself and any unexpected adverse events (reactions) that recipients may experience, whether immediately or later on. The objective is to investigate causes and outcomes and prevent their recurrence.

The system should have an HV procedure consistent with the current legislation in each country that describes the procedures for the detection, recording, reporting, management, and study of serious adverse reactions and events associated with the transfusion process (from donor to recipient or to the final destination of each component) and the monitoring of these events.

- **Reporting priorities**

When reporting any adverse event linked with blood donation or transfusion, the severity and degree of imputability should be considered, i.e., the risk to the health of the donor or patient and the extent to which this event is associated with the donation or transfusion process. Moreover, the process should be completely traceable, including for blood components [16].

In the case of convalescent donor plasma, any serious adverse reaction or event during apheresis donation, such as citrate toxicity, should be reported, following the protocol established for this purpose.

[3] Applications for research funding through competitive grants can be considered.

For the plasma recipient, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) are the two leading causes of mortality associated with this type of transfusion and should be reported immediately to the treating physician, transfusion committee, and competent authority, following the protocol established by the hemovigilance system. Other reactions, such as fever, allergic reactions, and possible exacerbation of symptoms in seriously ill patients should be also reported to the hemovigilance system. In both cases, in addition to immediate intervention for events experienced by the donor or recipient, an investigation should be launched to determine the possible cause of these adverse reactions or events.

Case reporting should provide a brief description of the event and the case definition. The sources of information will be the clinical history, data from the transfusion service and reporting form, and interventions subsequent to the analysis, which will make it possible to issue the pertinent recommendations and monitor the system.

These interventions should be conducted at both the individual/institutional level (patient care, analysis and reporting, and follow-up) and the collective level through transfusion audits and reviews by the transfusion committee and, in some cases, by the quality committee. Finally, monitoring should be based on indicators such as the number of adverse events in the period analyzed, considering the number of transfusions in the same period [42].

- **Strategies**

All events should receive the necessary medical attention and should be investigated by the treating physician and the transfusion service and reported to the institutional transfusion committee, which will study the report and forward it to the regional and national authority. The transfusion committees will study and take the necessary action to mitigate or prevent another such event.

Immediate reporting: The treating physician should immediately report all cases of serious adverse reactions that could put the patient's life at risk to the transfusion service and transfusion committee for investigation, monitoring, and immediate reporting to the regional and national authority. Examples: TRALI and TACO, suspected cases of transfusion-transmitted infections.

Passive surveillance: Moderate and mild cases can be reported in the routine report that the health authority has established for this purpose [42]. These reports should be submitted at least monthly.

Medical devices

- **Reporting priorities**

Priority should be given to reporting events and incidents associated with the use of priority medical devices in the emergency, when the following criteria are met [43, 44]:

1. An event that leads to the death of a patient, user, or other person directly or indirectly involved.
2. An event that leads to serious harm or a deterioration in the health of a patient, user, or other person directly or indirectly involved (for example, hospitalization or prolonged stay, medical-surgical intervention, harm to a bodily function or structure, etc.).
3. An event that did not cause death or serious injury to a patient, user, or other person directly or indirectly involve but could do so if it recurs.
4. An event due to a medical decision or action taken or not taken due to the interpretation of the results obtained from an IVDMD (usually: a diagnostic error; delayed diagnosis; delayed treatment; or inappropriate treatment).
5. When the case description states that the event occurred during the care of a patient diagnosed with the virus responsible for the pandemic.

NRAs with well-developed technovigilance systems should improve statistical and comparative analysis of the frequency of reporting by type of technology in a specific time period (e.g., weekly, biweekly, monthly).
The NRA will set the deadlines for case reporting, since adverse events that lead to death or a serious deterioration in the health of the patient, user, or operator and those that pose a serious threat to public health should be reported immediately to the NRA by the manufacturer, its authorized representative, or the importer [43] through the established system. In addition, these reports can be prepared by hospitals, clinics, health centers, ministries of health (provinces, states), etc. in cases where the NRA includes this obligation in its post-authorization regulations.

In the case of COVID-19, the receipt and analysis of reports on certain medical devices should be a priority. Examples of these include:

1. Ventilators designed and manufactured exclusively to mitigate the scarcity of ventilation equipment during the pandemic, since the requirements for their design and manufacture were lower than those for conventional ventilators. This equipment is therefore expected to have technical limitations that could translate into safety risks for patients and users (e.g., alarm control [visual and audio], autonomous battery operation, ventilation parameter control, etc.).

2. PPE such as Class 1 (low risk) face masks or surgical masks, since they can create significant problems that should be reported (e.g., breathing problems, splash resistance, skin allergies, etc.). Another example is N95 respirators – in the class II category (moderate risk) – which can present problems such as adjustment issues, fluid resistance, incompatibility with the skin, failure to meet the required percentage of particle filtrate, or unauthorized reuse [45].

3. IVDMDs are used for the diagnosis of disease–for example, when the number of false positives increases with the use of specific reagents.

- **Strategies**

It is important to conduct effective joint post-authorization surveillance activities in sustained coordination with the authorization of priority devices in the NRA market. To minimize post-authorization events, especially when on-site inspections to verify good manufacturing practices (GMP) are impossible, ISO 13485 certification can be requested [11, 46, 47]. This strategy, however, will depend on each country's regulatory requirements for the manufacture and importation of priority devices (e.g., if they were simplified in order to authorize their marketing with a view to increasing supply).

Countries that already possess well-developed technovigilance systems should base their action during the emergency on the level of risk posed by the priority medical devices and the indications in the previous section.

For countries that do not have technovigilance systems or if such systems are in the initial stages of development, during the emergency they can refer to the pharmacovigilance system and adapt the process for receiving, analyzing, and making decisions on notifications. When the country lacks a pharmacovigilance system, one alternative is to appoint an ad hoc committee, a procurement team, and/or a team from other institutional areas of the Ministry of Health.

In any case, the basic procedures that should be implemented are [48]:

- A system to receive complaints about medical devices in the jurisdiction, and for the manufacturer or its authorized representative to receive adverse event reports – for example, through an online reporting system or a designated email address.
- A procedure to evaluate adverse event reports with a view to introducing critical measures, such as the suspension of temporary use or the withdrawal of specific lots or entire units from the market.
- A system to receive information on any field safety corrective action (FSCA) that the manufacturer or its authorized representative takes in the country.
- A procedure to withdraw unsafe medical devices from the market when they endanger public health.
- A procedure or mechanism (e.g., a website) to directly notify the users of medical devices about adverse events and FSCAs through alerts and safety notifications.
- Monitoring of the domestic market to supervise medical devices.
- A reporting system facilitated by the use of a reporting form that includes the basic information necessary for evaluation (case description, traceability of the priority device, and the reporting party's contact information) and establishment of specific sites and contacts, issuing of reminders, and periodic consultations with focal points.
- A procedure to monitor technovigilance alerts issued by other NRAs inside and outside the Region, in addition to measures based on the findings.

As part of the surveillance process, based on the issues reported, regulators can adopt any of the following common measures: advertising bans, rejections, suspensions, cancellations, changes in conditions of use, or withdrawal of the products involved, as established in the current legislation. Where possible, the respective information will be provided on the NRA website.

It should be pointed out that manufacturers or their authorized representatives are responsible for the quality, safety, and performance of their products, regardless of the products' regulatory status. Furthermore, manufacturers, their authorized representatives, importers, and distributors must ensure that when an adverse event associated with a product is reported to the NRA, the records associated with the report, as well as the action taken, are available on request during NRA inspections or verifications.

Periodic Safety Reports and Risk Management Plans

With regard to the medicines authorized in the pandemic, the NRA should consider the study of adverse reactions, early detection and evaluation of signals, risk communication, and—as key instruments to support safety monitoring—periodic safety reports (PSRs) and risk management plans (RMPs), which should accompany the application to register a new pharmaceutical product or vaccine.

The request for an RMP, especially for new pharmaceutical products and vaccines, is especially important [49], because the authorization may occur in a scenario where evidence is limited and the risk-benefit ratio cannot be accurately stated in the conditions of use.

The NRA can allow shortened evaluation times for the authorization for use, as well as long-term monitoring of the product, based on the PSR, if the RMP's conditions of authorization allow it. As mentioned earlier, to accelerate these steps, regulatory reliance practices from other jurisdictions can be adopted. [11].

Monitoring activities related to the safety profile, type, and method of adverse event reporting, as well as additional measures that require further intervention will be considered in the RMP. The latter may include additional studies, monitoring of specific adverse events or populations, implementation of communication mechanisms, interaction with health professionals, and other risk minimization measures. The standardization of data, activities, and agreements on submission dates will be especially important, particularly when a new vaccine is involved [35]. Surveillance will focus on characteristics detected during clinical development. For example, in the influenza pandemic, it was especially important to monitor people with compromised immune systems, pregnant women, and cases of Guillain-Barré syndrome in particular.

In an emergency authorization scenario, the following are particularly important: the reporting periods established or imposed on registration holders, continuous updating of evidence from ongoing studies (including the request for a PSR and the reporting and evaluation of suspected unexpected serious adverse reactions [SUSAR]), and relevant changes in the conditions of authorization and technical specifications as evidence is made available.

In the case of medical devices, the NRA can postpone or suspend periodic reporting or can simplify the requirements, considering the risk class of the device.

Risk management reports are especially important for the authorization of devices manufactured to alleviate the scarcity of conventional equipment in emergencies. These reports should include the analysis, assessment, and control of risks in all phases of the life cycle of the medical device, ensuring that the manufacturer takes steps to guarantee the maximum possible safety. The reports may be modified as information about the product is obtained during its use in the post-marketing stage; this information can come from reports through the technovigilance system. The NRA can establish shorter evaluation times and, if necessary, request additional information. The risk management system should be based on the ISO 14971 international standard or equivalent national standards.

A dynamic risk assessment should planned and documented, relying on the aforementioned local and international information sources so that the necessary adjustments can be made in plans and regulations to preserve the maximum benefits.

Monitoring of safety data: Information and communication

In the three months since the publication of the first article on COVID-19, approximately 7,000 scientific articles have been indexed in PubMed in one of the greatest bursts in scientific literature ever described [50]. Beyond the extent of the evidence generated, the exceptional nature of the pandemic, together with the need to generate evidence in the short term, has led many investigators to focus on the study of the same topics. Together with the publication of articles as un-peer-reviewed preprints, this can sow doubts about the quality of the work and in some cases, generate potential redundancy or overlapping of research [51]. In this scenario, the use of meta-research methods based on a systematic review that make it possible to identify, evaluate, and distill the findings of all relevant individual studies on health topics becomes especially important [52]. The use of systematic reviews and meta-analysis is considered a third-generation pharmacovigilance method [53]. The distillation of evidence through continuous rapid reviews is occurring largely in academic institutions such as the Oxford CEBM COVID-19 Evidence Service [54], Cochrane Collaboration [55], agencies working for health authorities such as the United Kingdom's National Institute for Health and Care Excellence (NICE) [56], and the Pan American Health Organization (PAHO/WHO) [57]. These sources can support NRAs in the continuous monitoring of evidence.

To avoid disinformation or the spread of rumors, any information about the safety of medical products that emerges should be continuously monitored and swift action taken when necessary, in keeping the current communication and crisis management strategy in the surveillance plan. To this end, information bulletins with the available evidence can be published, with clear messages containing public health recommendations [58] (e.g., discouraging self-medication and off-label use). These bulletins should be periodically reviewed and updated as new studies are published.

Considering the need for global coordination and management of different information sources, it should be kept in mind that during the pandemic of 2009, the European Medicines Agency (EMA) issued weekly public reports in the EudraVigilance database summarizing the adverse reactions to the pandemic vaccines and antivirals used in the treatment of influenza H1N1 [59]. Currently, the UMC is also publishing periodic reports on suspected adverse drug reactions (ADR) associated with treatments used in the COVID-19 pandemic and reported to VigiBase [60].

Since vaccines are interventions for healthy populations at risk, mass communication strategies will be incorporated in the regional plan for the introduction of COVID-19 vaccines as part of a structured plan that includes an ongoing communication strategy on the evolution of the vaccine risk-benefit ratio and preparedness in the face of emerging crises [13, 61]. This coordinated response by the National Immunization Program and the national regulatory authorities is vitally important for preventing adverse events related to SARS-CoV-2 vaccines, which could reduce acceptance of the rest of the vaccines in the program. The participation of regional or global vaccine safety monitoring initiatives will be indispensable not only to identify potential signals but for discussion of incidents and to support more effective communication with professionals and the community.

Additional control measures for pharmaceutical products and other health technologies used in the treatment of COVID-19

The health authority can impose measures for the prescription or dispensing of a pharmaceutical product under investigation in order to minimize exposure to known risks in its safety profile and unapproved or contraindicated use. These measures will also warn the public about the need for close monitoring and supervision of a drug's use in a hospital setting or clinical trial; for example, when an emergency use authorization is issued (as occurred in the United States in the case of hydroxychloroquine and chloroquine). Analogously, restrictions can be placed on the dispensing of a pharmaceutical product that could normally be obtained without a prescription (e.g., making it prescription-restricted) if it is suspected that it will be abused or subject to irrational use. These measures should be considered, based on the regulatory framework of each country.

Actions for the prevention, detection, and response to unregistered, substandard, and falsified medical products

WHO has determined that the three main factors facilitating the proliferation of substandard, falsified, and unregistered medical products in the countries are related to: i) limited access to health technologies, ii) weak technical capacity of regulators; and iii) poor governance [62]. Nevertheless, other variables contribute to these problems in pandemics, namely: the urgent need to find effective alternative therapies, uncertainty about the effectiveness of new or old molecules, unfounded media assertions, pressure from the public and the media, and

scarcities of strategic products—all of which help create a business opportunity for unscrupulous actors who seek to exploit the situation for monetary gain.

Several countries in the Region have national plans of action coordinated with key actors in the prevention, detection, and response to unregistered, substandard, and falsified medical products. Nevertheless, given the particular threat posed by these types of products in the context of a pandemic, WHO is requesting heightened monitoring at critical points in country supply chains. It has been documented that supply chain vulnerability increases as products move toward the patient, largely because there is regulatory emphasis on investigators, developers, and producers, but limited control over distributors, wholesalers, retailers, and health services [62].

In the first four months of 2020, several countries in the Region, including Canada, Chile, Colombia, and Costa Rica, discovered and confiscated medical products that were falsely advertised as treatments for COVID-19 [63, 64, 65, 66]. WHO has also issued international alerts for similar products, including IVDMDs [67], the majority of which do not have health registration or valid authorizations for use and are illegally marketed by unscrupulous individuals or companies. Therefore, sharing information among countries is essential when such incidents are discovered, as is reporting them to the Regional Network for Substandard and Falsified Medical Products and the WHO Global Surveillance and Monitoring System (GSMS). In addition, communication channels among NRAs should be strengthened for adequate dissemination of the information and good decision-making, regardless of their functional capacity [3].

Although the authorities involved in the aforementioned incidents have issued alerts, conducted inspections, and withdrawn products from the market, many such products are marketed through the internet and social networks, which facilitate direct access. The use of unregistered medical products is usually related to public ignorance or lack of awareness about their risks. Public awareness campaigns and communication materials for the general public can help reduce the demand for these products.

Falsified medicines and medical devices can be manufactured locally or imported. NRAs should use the available legal framework to make risk-based decisions to prevent, detect, and respond to this threat during the pandemic.

If priorities are properly strategized, inspections of manufacturers or distributors can be scheduled when irregularities are suspected, when there has been recent non-compliance, or when critical or high-risk supplies for the treatment of COVID-19 are produced/distributed (e.g. class IIb and III medical devices).

It will be also necessary for the health authority to create an emergency coordination mechanism with focal points among the different actors/entities involved (e.g., customs, police, distributors, judicial authority, professional associations, and patient groups) to promote preventive and corrective action in coordination with the emergency regulatory committee, if one exists [3].

Table 2 presents the framework of action suggested by WHO to tackle these problems [62]. Each NRA should prioritize the activities it considers critical in its particular situation. Activities that can be considered a priority during the emergency are presented in boldface and shaded.

Rapid access to quality control laboratories is vitally important, ideally at the national level or through international outsourcing (e.g., in the English-speaking Caribbean) in order to determine the composition of unregistered or falsified products and the extent of the quality deviations of substandard products. When a falsified product is suspected, the first suggested step is to contact the supplier, authentic manufacturer, or authorized representative, who will determine whether it made/distributed the product in question.

Table 2. *Framework of action suggested by WHO to deal with falsified medical products*

Action for prevention	Action for detection	Action for the response
Guarantee of a comprehensive regulatory framework	Access to laboratories and technologies for analysis and detection	Product alert and withdrawal mechanisms
Participation by all actors involved (police, customs, distributors, health authority, judicial authority, professional associations, patient groups, etc.)	Risk-based inspections	Strengthening of regulatory capacity
Education and information for users	Strengthening of reporting systems	Transparent judicial processes
Strengthening the integrity of the supply chain	International border control	Evidence-based policies and procedures

Finally, the NRA should maintain a system that ensures that medical products are imported in compliance with standards that guarantee their authenticity. The documents generally verified for this purpose are:

- Certificates of good manufacturing practices
- Pharmaceutical product certificates
- Letter of legal representation for importation or licensing of use or distribution
- Certificate of lot conformance for the imported medicine
- Batch release certificate
- Purchase invoices

Conclusions and recommendations

In a context of changing evidence, NRAs should anticipate potential scenarios to prepare for the potential authorization of new treatments. Despite the urgency of having a treatment, vaccine, or medical device in the shortest possible time, NRAs should ensure that every authorization for use is based on criteria grounded in the best evidence of efficacy, safety, quality and, in the case of medical devices, performance.

Authorizations for use of these medical products should include a pharmaco-, techno- or hemosurveillance plan indicating the resources, strategies, and actions to ensure an iterative balance between access to the best evidence and information on safety, both in internal and external systems, and data on the benefits of the treatments or interventions adopted. NRAs must make the necessary regulatory and communication decisions to ensure a positive risk-benefit ratio.

Collaboration among countries is a key tool that adds great value to national capacities.

Member States can respond to emergencies in many ways, depending on their capacities and regulatory structure. In contexts where regulatory functions are more restricted, strategies can be developed that are more limited in scope and consume fewer resources but still guarantee adequate regulation and supervision [68]. The design and operationalization of the use of regulatory reliance practices can support certain procedures related to authorization and clinical trials, as well as the management of safety information.

Classifying regulatory capabilities as proposed in Table 3 could help in self-identifying the development of these capabilities to manage different degrees of complexity in pharmaco- and technovigilance during the emergency.

Special precautions should be taken regarding pressure from advertising and unfounded opinions expressed in the media and social networks, in order to produce communications positively and non-reactively.

Table 3. *Guidelines for identifying approaches and activities that can be implemented during a pandemic, based on the level of regulatory development and the organizational structure of Member States*

	Surveillance, approaches, and activities	Level of regulatory development and organizational structure [68]				
		A	B	C	D	Note
1	Mechanism for use of regulatory reliance practices	✓	✓	✓	✓	See mechanism for authorization of the emergency use of medicines and other health technologies in a pandemic (for example, COVID-19) [11].
2	Risk management plan (RMP)	✓	✓	?	?	The risk minimization approach through an RMP or an equivalent method could be employed to monitor patient and user exposure to unsafe or defective products during emergencies.
3	Active surveillance/ sentinel surveillance	✓	✓	?	?	A system used when high-quality data on a particular problem or disease are needed that cannot be obtained through a passive system. Selected reporting units with a high probability of seeing cases of the disease in question [69, 70].
4	Spontaneous reporting system (passive system)	✓	✓	✓	✓	Any quality, safety, or performance problem identified for medical devices could be reported
5	Health professionals of reference	✓	✓	✓	✓	A local or regionally distributed support group of health professionals identified, guided, and encouraged to report serious problems observed during in practice.
6	Development of a sentinel reporting network	✓	✓	?	?	Selected health institutions that commit to monitoring and reporting to representative national institutions on the safety, quality, and performance of medical devices in use[71].
7	International collaboration (participation in specialized international networks (for example, IMDRF, MDSAP, PARF, ARC)	✓	✓	✓	✓	Evaluation of lessons learned about the global or regional situation. Mechanisms for receiving and providing collaboration [72, 73, 74].

Legend:

✓ Potential existing capacity

? Unknown or nonexistent capacity

A - States that have a national regulatory authority with the highest level of development
B - States that have legal foundations and organizational structures for a comprehensive regulatory system
C - States that have some legal foundations and organizational structures for a regulatory system
D - States that currently do not have legal foundations and/or organizational structures for a regulatory system

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