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Crisis Management During an Epidemic: General guidelines for efficient response coordination by national regulatory authorities

I. Introduction

Considering the advance of the COVID-19 (novel coronavirus SARS-CoV-2) pandemic and the resulting declarations of health emergencies in the countries of the Region of the Americas, it is necessary to clarify the role and responsibility of each country's National Regulatory Authority (NRA) regarding medicines and to establish appropriate channels for its participation in a coordinated strategy at the country level to provide an agile response in the pandemic.

To ensure timely access to essential medicines and health technologies during the pandemic, countries will almost certainly need to develop, update, or even relax their regulatory frameworks, processes, and procedures. These actions may be necessary, for example, to use registered products for off-label uses, ensure the quality of donated products, deal with shortages of health products, etc. The actions that the NRA will implement must be effective and timesaving, which means that the country should create a coordinating group or committee with clear functions.

The objective of this document is to provide guidance to NRAs on how to establish/review/implement regulatory committees for crisis management, how to coordinate with other health authorities, and how to promote improvements in communication with other government entities, civil society, and other relevant actors, in the framework of the regulatory response to the COVID-19 pandemic.

This guide is a tool to facilitate operational implementation of a rapid response to regulatory challenges in a crisis situation, with a view to avoiding duplication or complication of existing oversight systems.

Each country should have up-to-date frameworks for dealing with emergencies, particularly pandemics (e.g., operational emergency plan) *(1-7)*. Recognizing that there are specific constraints, different national contexts, and scenarios beyond those included here, this document proposes guidelines to serve as a basis for addressing the regulatory challenges in the pandemic response phase.

The World Health Organization (WHO) guidelines on the COVID-19 pandemic preparedness and response plan include a situation analysis (risk assessment), selection of response strategy, determination of resource requirements, and monitoring of implemented actions *(1)*. These guidelines propose strategic actions that can guide the development of operational plans specific to each country and region, where they do not yet exist.

II. Potential crisis scenarios in relation to NRA activities

In April 2019, the International Coalition of Medicines Regulatory Authorities (ICMRA) agreed on an operational framework for management of global health crises *(8)*. This framework presents the importance, tasks, and responsibilities of NRAs during crisis management and identifies opportunities for collaboration among drug regulatory authorities.

This document, addressed to NRAs, presents elements that were considered when developing the three scenarios presented below, in which regulatory committees for crisis management are expected to

coordinate with other health authorities and promote improvements in communication within the framework of a regulatory response to the COVID-19 pandemic.

Scenario 1: Incidents related to quality or safety issues for products on the market that may have an impact on public health

While most incidents related to product quality or safety issues are likely to be ordinary ones that can be addressed with existing resources and protocols, there may be events that require broader involvement and collaboration, both from national actors and, potentially, other NRAs. In particular, multi-stakeholder action may be needed when there is a risk of a possible global health crisis.

A concrete example of this is the off-label use of products, for example, chloroquine for treatment of COVID-19. This "unapproved" use may: a) cause serious adverse events; and b) lead to shortages of the product for meeting the needs of patients in treatment for approved indications.

It is up to each NRA to assess and decide whether an incident requires or would benefit from broader international involvement, for example, with other NRAs. Such involvement may be through existing networks, such as the Pan American Network for Drug Regulatory Harmonization (PANDRH), bilateral liaison, or contacts with national public health organizations or national or international experts.

Scenario 2: Unavailability of products due to a crisis, where already registered products are in short supply or unavailable due to increased demand

As the ICMRA *(8)* document points out, examples in this category may include a viral pandemic where antiviral medications or vaccines are in short supply or unavailable. In these circumstances, NRAs should play an important role to minimize the negative impact on patients, healthcare facilities, and clinicians.

In this scenario, promoting the exchange of regulatory information at the international level is a very useful way to overcome constraints such as a lack of timely supplies (restrictions on condition of sale, health registration of new products, licensing for other manufacturing purposes, etc.). The regular exchange of regulatory information is part of the implementation of good regulatory practices.

Scenario 3: Urgent need for new medical treatments or vaccines in the face of an emerging health threat

It is up to each country's NRA to identify and implement rapid assessment procedures to grant registration and marketing authorization for new products or new indications, and to participate in collaborative initiatives in the regulatory field with other NRAs and international organizations.

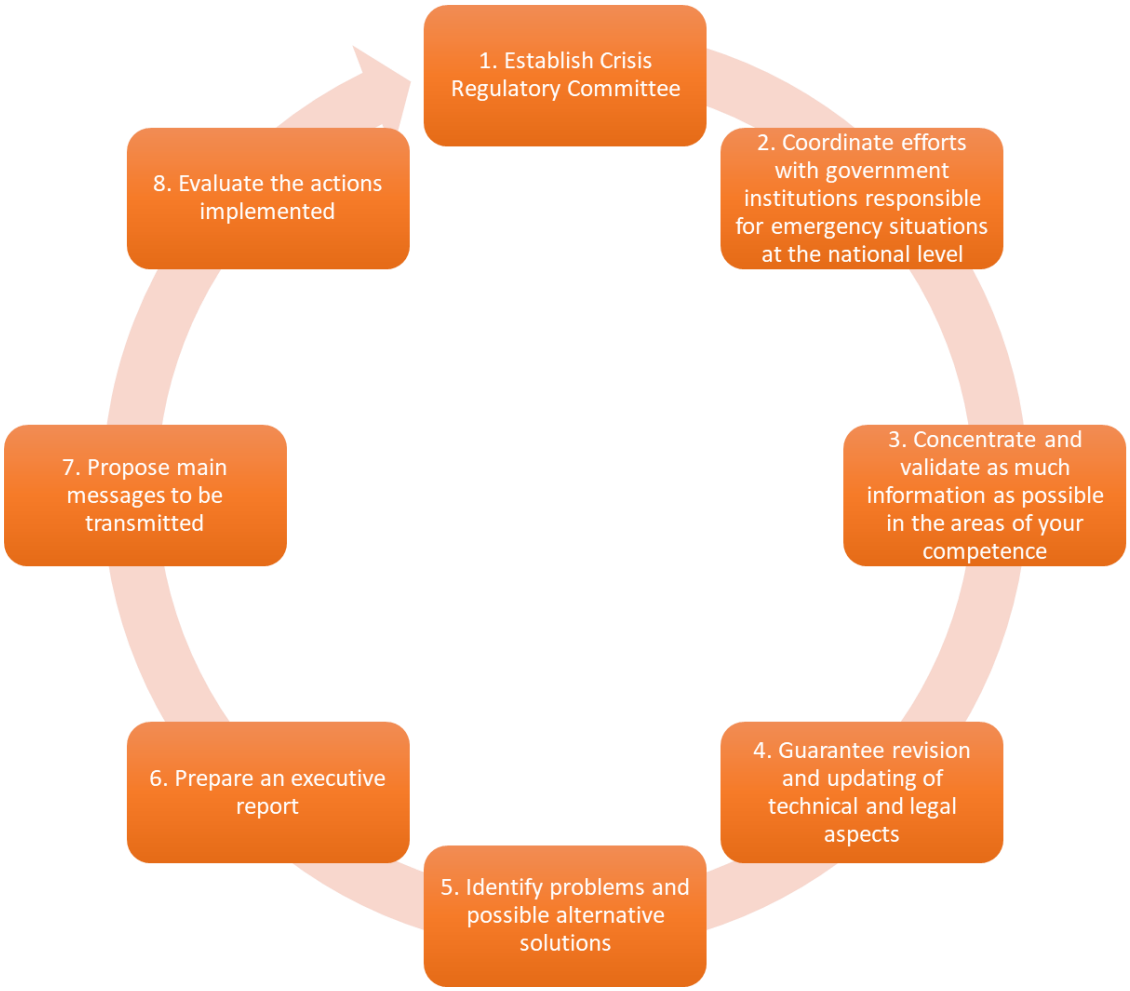
Each country's NRA and health ministry can utilize mechanisms for mutual recognition, convergence, and/or previously established regulatory reliance, as they deem appropriate. These mechanisms are mentioned in multiple international references, but for practical reasons, only two of them are referenced here *(5, 9)*.

The regulatory committee for the crisis can facilitate the steps necessary for efficient implementation of these procedures, which it should list in its emergency portfolio.

III. Steps to follow when addressing a crisis

Figure 1, below, proposes 8 steps to addressing a crisis, followed by their implementation. This proposal has been adapted from the document (in Spanish), *"Guide to managing crises that affect patient safety in hospitals" (10)*. All these stages/steps should be considered part of the response, and all the actions carried out in each one must be evaluated. This is why these steps are presented as a cycle that requires periodic review.

Figure 1: Steps to addressing a crisis



Step 1: Establish a regulatory committee for the pandemic crisis

Objective: Form a special crisis group within the regulatory entity. This group will be responsible for defining legal, technical, and communication issues.

In the first phase, the committee identifies the priority challenges related to the management and treatment of the pandemic (present or potential) and either refers them to the corresponding areas or finds information to address them.

As far as regulatory aspects are concerned, the respective areas will be given specific deadlines to address potential or imminent activities related to authorizations or procedures required for the evaluation and/or

incorporation of new products/indications, medical devices, in vitro diagnostic tests, equipment, and in general any other medical product associated with the pandemic.

Moreover, potential areas of improvement in the regulatory response should be identified, through:

1. Review, updating, and/or implementation of changes in policy frameworks, procedures, rules, or regulations to improve the efficiency of the response required during the pandemic *(11, 12),* for example: authorizations for emergency use, updating conditions of sale and/or use of circulating products, market control and oversight, strategies for monitoring adverse events, as well as identification of illicit products, and authorization of clinical trials and compliance with their conditions, among others, and/or
2. Preparation and implementation of new procedures or guidelines based on risk analysis and mitigation, to address particular circumstances, or new ones that arise as part of the pandemic.

The regulatory emergency committee will be made up of a delegate of NRA management, a delegate of the Ministry of Health and, whenever possible, according to each NRA's structure, the heads of regulatory functions and cross-cutting areas mentioned below:

- Health authorization (registration, import permits, or exceptional approvals in response to public health or emergency needs)
- Health surveillance
- Pharmacovigilance
- Clinical trial authorization and control
- Quality control laboratory
- Regulatory inspections (control of good manufacturing practices, good distribution practices, and good storage practices)
- Communications area
- Legal advisory services
- International/interinstitutional relations area

A point of contact, coordinator, or designated official for each area should actively participate in the committee.

It is important to ensure that the committee also has the regular involvement of internal experts on subjects directly related to the cause of the crisis; e.g., specialists in infections and/or vaccines in the case of COVID-19. In their absence, the participation of independent ad hoc experts could be considered (following declaration and management of possible conflicts of interest).

In accordance with the need and actions foreseen by the committee and under well-defined terms of responsibility, ad hoc representatives may be invited from professional schools, medical societies, as well as outside experts (e.g., infectious disease, pharmacology, and epidemiology societies, etc.).

Step 2: Coordinate efforts (identify focal point and determine functions)

Objective: Ensure that efforts are not duplicated and calculate the country's installed capacity, maintaining close collaboration with the Ministry of Health and other institutions related to the emergency (national crisis and disaster room).

The committee will develop a work and communication plan that indicates the needs and priorities that have been set, expected outputs, risks, and required resources, as well as a way to evaluate the actions under each regulatory area.

The committee will designate a spokesperson (possibly the communications delegate) who will communicate actions or recommendations when the committee deems it necessary.

The NRA management delegate is responsible for updating the proposals produced by the committee and, when needed, requesting that the respective spokesperson communicate them. The delegate is also responsible for ongoing contact with support areas on priority issues that the NRA should resolve and for requesting reports to be presented to the committee.

A flow of communication must be established among agencies, the country's health-sector institutions, governmental institutions, and relevant actors, such as:

- Pharmaceutical industry associations
- Health product distributors
- Customs
- Civil society
- Professional institutions
- Reference laboratories
- International organizations (PAHO/WHO,)
- Others (drug regulatory authorities of other countries)

Step 3: Collect as much relevant information as possible

Objective: Identify and integrate experiences and tools from other countries/institutions that have contributed to good management of the crisis, as well as privileged information regarding registered products and their therapeutic indications, suppliers, inventory of drugs and medical devices, etc. Information should be collected about the following:

- Prior experiences in ministries of health and NRAs in general (compile good practices and success stories).
- Existing regulatory mechanisms for product authorization during the emergency.
- Available scientific evidence.
- International organizations and regulatory authorities of international reference.
- Available products, their origin, type, and approval status.
- Active clinical trials and applications in the pipeline.
- Authorization of off-label uses.
- Chain of supply and distribution of essential medicines and supplies.[1]
- Monitoring of reagent supply (diagnostic tests) and of the strategic reserve of medical devices, vaccines, medicines, including antivirals (when available) to serve strategic and vulnerable groups, as well as personal protective equipment, among others.

Step 4: Review and update technical and legal aspects

Objective: Within the framework of the pandemic and a health emergency declaration and/or state of constitutional exception (where applicable) it may be necessary to prepare, repeal, or amend a number

[1] In an emergency, where there are restrictions on movement, or social isolation or quarantine measures, the supply chain and distribution of essential medicines may be affected. Therefore, the NRA and the committee should propose viable alternatives to overcome these problems, for example: home delivery, exceptional prescription renewal, etc.

of standards, regulations, or procedures. This means it is essential to have legal certainty about the required regulatory actions.

- Designate a legal team exclusively dedicated to this contingency.
- Check the current legal framework related to the health emergency declaration (legal basis and its application in each country).
- Survey all standard operating procedures that need to be prepared and/or modified, including:
    1. Registry of new products, through abbreviated mechanisms.
    2. Standard operating procedures, inclusion of new off-label uses for registered products, including compassionate use.
    3. Requirements for timely donation of medicines and other health technologies to manage the emergency.
    4. Monitoring of active clinical trials, including uncommon modalities during the emergency.
    5. Rapid approval of clinical trials for medicines related to the pandemic.
    6. Authorization of facilities to manufacture health products required to treat the health emergency (to respond to shortages).
    7. Changes in the conditions of sale for medicines and other health technologies.

Step 5: Analyze available information and identify problems and possible alternative solutions

In a crisis, information cycles will likely be very dynamic and should be adapted as needs change with the evolving situation and its consequences. The health situation of the community will be changing, and the NRA should have the capacity to detect these changes to recommend the corresponding interventions.

It is necessary to identify possible alternative solutions that can be implemented immediately, viable alternative solutions, and the person in charge of their implementation. The objective of these alternatives and the tasks to be carried out must be clearly defined.

In contrast to Step 1, the committee's work here is aimed at concrete actions in situations that have already been identified and prioritized. The committee's expected role in this step is to carry out a critical analysis of the proposed alternatives and the plan for managing the situation.

Step 6: Prepare executive reports

Based on the available information and an established format, the committee will prepare a report. It should be concrete, objective, and clear, and should contain information related to the problem, its causes, proposed solution, actions implemented to date, and any necessary additional resources and support.

Step 7: Propose the main messages to be conveyed

Objective: Promote timely access to information in a transparent manner, validated by the NRA, to prevent situations that could worsen the crisis. This aspect is key to crisis management; institutions and civil society deserve and need to have access to information.

- As mentioned above, the committee's designated spokesperson will be the person in charge of communicating coordinated actions. On some occasions, when public addresses are needed, it is suggested that members of the institution's management participate as well, to convey that the authorities are not indifferent to the events and to provide clarification when necessary.

- Establish a partnership with the mass media and not only with specialized health media outlets. To this end, information on health problems and products should be provided regularly to the media. It is useful to have up-to-date reports on side effects and/or precautions on the incorrect use of medicines and other health products.
- Prepare press releases and briefings, as well as questions and answers about adverse events.
- Use all media: social media, press, radio, television, billboards, posters, flyers, and broadcasting by sound truck to disseminate the messages approved by the committee in the most relevant format for the target audience, for example: interviews, press conferences, email, etc.

Step 8: Evaluate implemented actions

Before implementing a plan, those in charge of this task should determine its strengths and weaknesses (internal forces), and opportunities and threats (external forces). Strengths and opportunities are positive elements that should be used to execute the plan efficiently. Weaknesses and threats are obstacles that can get in the way of the plan's implementation and must be overcome.

Oversight is important in the implementation phase of the plan to ensure that it is done correctly. This is an ongoing process that the committee should define before implementation of the plan begins. Oversight activities should be included in the work plan and involve all stakeholders. If activities are not progressing well, arrangements should be made to acknowledge the problem so that it can be corrected.

The progress made with implementation of alternative solutions must be evaluated daily, or more frequently if the problem warrants it. It is important to be flexible in order to change actions, depending on the response. However, these changes should be made with care and only when suggested by careful analysis of the situation, to avoid situations involving erratic counterproductive changes.

Together with the rest of the crisis management team, the NRA should identify points where flaws occurred and propose alternative solutions.

Conclusions

1. NRAs should act under the premise of ongoing cooperation, both national and international, to respond to any of the scenarios posed by emergency situations.
2. NRAs need to consider and/or implement operational modalities to respond to new scenarios that may arise (regulatory flexibility, periodic review of regulatory frameworks, etc.).
3. Contingency regulatory measures should be anticipated and updated regularly for use in crises.
4. Considering the dynamic with which new scientific evidence is produced, a responsible, critical, and flexible spirit should be maintained to adequately address crises.
5. Regulatory emergency management committees that can coordinate with other health authorities should be quickly established.

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