

## Health policy and regulatory authorities: challenges of technology regulation in Public Health Emergencies

1

THEMATIC ARTICLE

Catia Veronica dos Santos Oliveira (<https://orcid.org/0000-0002-0464-1476>)<sup>1,2</sup>  
Vera Lúcia Edais Pepe (<https://orcid.org/0000-0003-0606-1544>)<sup>1,2</sup>

**Abstract** *Public Health Emergencies (PHE) have had repercussions on health systems on a global scale, and timely access to new health technologies is a challenge for health policy. The national regulatory authorities (NRA) play a key role in the evaluation and regulation of these technologies. The present study aims to analyze the main strategies and regulatory instruments used to deal with the challenges of regulating new technologies necessary for the health system's effective response during a PHE. This research, based on WHO and Brazilian NRA norms and documents, considered dimensions related to strategies for strengthening regulatory activities and regulatory instruments used to accelerate access to technologies, especially during PHEs. International cooperation between the NRA and the WHO were important strategies for strengthening the NRA, with emphasis on the use of reliance, regionalization, accelerated assessments, and work/information sharing, as well as the processes of regulatory harmonization and convergence. In addition to the use of existing regulatory instruments, efforts were also identified in order to implement new ones.*

**Key words** *Emergencies, Health policy, International cooperation, Health surveillance, Brazilian Health Surveillance Agency*

<sup>1</sup> Programa de Pós-Graduação em Saúde Pública, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz. R. Leopoldo Bulhões 1480, Manguinhos. 21041-210 Rio de Janeiro RJ Brasil. [catia.oliveira@fiocruz.br](mailto:catia.oliveira@fiocruz.br)

<sup>2</sup> Departamento de Administração e Planejamento em Saúde, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz. Rio de Janeiro RJ Brasil.

## Introduction

Public Health Emergencies (PHEs), especially those of International Concern (PHEIC), have had an impact on health systems on a global scale, posing challenges to countries in responding to health events. The World Health Organization (WHO), through the International Health Regulations (IHR), recommends actions to prepare healthcare systems to face health emergencies<sup>1,2</sup>. Among the basic capabilities of Member States is the coordinated effort of sectors and institutions, including National Regulatory Authorities (NRA), which can take more direct or indirect action regarding the health risks involved in each event.

NRAs aim to regulate health goods, striving to protect the population's health.<sup>3</sup> The international activity of NRAs stands out, especially in the evaluation and regulation of technologies as well as their globalized circulation<sup>4-7</sup>.

In PHEIC, healthcare systems are challenged to use existing technologies and services, as well as emerging technologies whose research, development, and use need to be conducted in a limited time. Prompt access to new diagnostic or therapeutic technologies (or new therapeutic indications) is a challenge for healthcare policies at these times. The regulation and evaluation of the safety, efficacy, or effectiveness of technologies, especially when it has not yet been possible to produce robust evidence about them, as well as their long-term monitoring, are important challenges for the NRA<sup>8</sup>. The COVID-19 pandemic has dramatically reinforced the need for international cooperation and the strengthening of national regulatory systems<sup>6,9</sup>. This is a critical challenge not only for regulatory policies, but also for healthcare policies since the balance between access to technologies and the assessment of evidence concerning safety and efficacy is decisive for the effectiveness of healthcare policies in these critical times for society.

The present study aims to discuss the main strategies applied by NRAs to deal with the challenges of regulating new technologies and the main regulatory instruments used to accelerate access to them, especially in times of PHEs.

## Method

This exploratory study entailed normative and documentary analysis, using the WHO (<https://www.who.int/>)<sup>10</sup>, the Brazilian NRA, and the Bra-

zilian National Health Surveillance Agency's (Anvisa) (<https://www.gov.br/anvisa/pt-br>)<sup>11</sup> websites as secondary data sources. The period of analysis ran from January 2013 to December 2019 and considered the three years before and after the Zika virus epidemic. Data was collected from September 2021 to January 2022.

In the first stage, the search was conducted using a combination of the keywords, in Portuguese and English, "regulatory authorities;" "international cooperation"; "public health emergency"; and "Zika virus." Legislation and documents, including news that addressed aspects of health regulation, were considered. By reading the titles, the following were excluded: 1) documents and legal framework on epidemiological monitoring, case definition, laboratory surveillance, diagnostic and treatment guidance, or genomic identification; 2) specific legislation for granting registration or emergency use of diagnostic and therapeutic technologies, and 3) repeat records.

In the second stage, by reading the summary or syllabus, documents and legal norms directly related to two topics were selected: 1) strategies to strengthen regulatory activities; and 2) instruments to evaluate and regulate technologies by NRAs, especially during PHEIC. A total of 48 documents were found on the WHO website, and after removing those that met exclusion criteria and repeat entries, six documents remained for analysis. On Anvisa's website, of a total of 186 documents, 27 were analyzed.

In the third stage, the 33 selected documents and legislation were read in full, and a thematic analysis of their content was conducted. These were recorded in an *Excel* spreadsheet containing the month and year of the document, document type, origin, topic, documents/legislation, and strategies/instruments. The same document can refer to both topics.

The first topic lists the main NRA strategies to strengthen regulatory decisions, which can be used in PHEs. The second topic discusses the main regulatory instruments used to provide faster access to new technologies or therapeutic indications, especially when evidence of efficacy, effectiveness, and safety is being defined. In the latter, document analysis was conducted by evaluating health technologies, considering the development of new tools, standards, and frameworks to evaluate the safety, effectiveness, quality, and performance of goods and products, which are applied to support regulatory and healthcare policies.

## Results and discussion

A total of 33 items, including 29 documents and four legal norms, were selected for analysis, six of which came from the WHO and 27 from Anvisa. Nineteen of the documents referred to topic 1 and 10 to topic 2, while 4 addressed both topics. The majority (14/41%) were published in 2016, during the Zika virus PHEIC. The following strategies were found: cooperation, collaboration, information sharing, regionalization, transparency, participation in technical forums, regulatory convergence, harmonization, reliance, and work sharing, as well as the following instruments: accelerated regulatory pathways, registration priority, priority review, prior submission, expanded access, compassionate use, post-trial access to treatment, and Emergency Use Assessment and Listing (EUAL), which will be discussed below (Chart 1).

## Strategies used by National Regulatory Authorities to strengthen regulatory activities

The complexity of the national and international activities of NRAs requires these institutions to be strong in the face of regulatory challenges, as they deal with numerous technologies, uncertainties, and different interests, as well as the need to act considering multilateral organizations and harmonization processes with other regulatory authorities<sup>9</sup>.

Among the strategies found in the selected documents and legislation, international cooperation between the NRAs and the WHO stands out as an important part of the activities of these authorities<sup>4,7,12</sup>. *Cooperation* is a strategy used to mitigate differences between regulatory authorities<sup>4</sup> in order to provide a favorable environment in which to discuss regulatory requirements, share experiences and mutual qualification, and strengthen NRAs<sup>13</sup>. New forms of cooperation

**Chart 1.** List of documents and legal norms selected, considering the strategies used to strengthen regulatory activities (topic 1) and the instruments for the evaluation and regulation of technologies by National Regulatory Authorities (NRAs) (topic 2), 2013-2019.

Month/year	Type	Origin	Topic	Documents/Legal norms	Strategies/Instruments
Aug/13	Standard	Anvisa	2	Resolution of the Collegiate Board - RDC no. 38, of August 12, 2013. Official Gazette of the Federal Government, section 1, p. 48, Aug 18.	Expanded access, compassionate use, and provision of post-trial access to treatment
May/14	Document	WHO	1	Regulatory system fortification for medical products. Sixty-Seventh World Health Assembly WHA 67.20. p. 41-15.	Cooperation, collaboration, regionalization, regulatory convergence; harmonization, transparency in decision-making.
Jul/15	Document	WHO	2	Emergency Use Assessment and Listing Procedure (EUAL) for candidate in vitro diagnostics (IVDs) for use in the context of a public health emergency. 2015.	Emergency Use Assessment and Listing (EUAL).
Jul/15	Document	WHO	2	Norms and legal norms: assessing new medical products in health emergencies: the EUAL procedures. Drug Information, v. 29, n. 3, 2015.	Emergency Use Assessment and Listing (EUAL).
xx/16	Document	Anvisa	1	Anvisa's 2015 Activity Report. Brasília. 2016.	Information sharing.
Jan/16	Document	Anvisa	2	Products regulated by Anvisa for detection of Dengue, Chikungunya and Zika viruses. Communications Office, Brasília, 2016.	Registration prioritization, priority review.

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**Chart 1.** List of documents and legal norms selected, considering the strategies used to strengthen regulatory activities (topic 1) and the instruments for the evaluation and regulation of technologies by National Regulatory Authorities (NRAs) (topic 2), 2013-2019.

Month/year	Type	Origin	Topic	Documents/Legal norms	Strategies/Instruments
Jan/16	Document	Anvisa	2	Anvisa prioritizes analysis of commercial kits to diagnose Zika, Chikungunya and Dengue. Communications Office, Brasília, 2016.	Registration prioritization.
Feb/16	Document	WHO	1 and 2	WHO to fast-track availability of diagnostics for Zika virus. Feb. 15, 2016.	Cooperation, collaboration. Registration prioritization, priority review.
Feb/16	Document	Anvisa	1	International regulatory authorities are committed to combating Zika. Communications Office, Brasília, 2016.	Cooperation, collaboration.
Mar/16	Document	WHO	1 and 2	WHO and experts prioritize vaccines, diagnostics, and innovative vector control tools for Zika R&D. 2016.	Cooperation, regulatory convergence. Accelerated regulatory pathways.
Mar/16	Document	Anvisa	1	Management report for the fiscal year 2015. Brasília, 2016.	Cooperation, regulatory convergence, information sharing.
Apr/16	Document	Anvisa	1	Anvisa joins other regulatory agencies for common actions against the Zika virus. Communications Office, Brasília, 2016.	Information sharing.
Apr/16	Document	Anvisa	1	Anvisa and FDA sign Continuous Cooperation Agreement to combat the Zika Virus. Communications Office, Brasília, 2016.	Cooperation, information sharing.
May/16	Document	Anvisa	1	Anvisa signs a confidentiality agreement with the WHO Department of Essential Medicines. Communications Office, Brasília, 2016.	Cooperation, information sharing, reliance.
Jun/16	Document	Anvisa	2	Anvisa registers new rapid test for Zika. Communications Office, Brasília, 2016.	Registration prioritization, priority review.
Jul/16	Document	Anvisa	1	Anvisa helps combat the Zika epidemic in Peru. Communications Office, Brasília, 2016.	Cooperation, collaboration, information sharing, work sharing.
Oct/16	Document	Anvisa	1	Workshop debates public health emergency scenarios. Communications Office, Brasília, 2016.	Cooperation, collaboration, information sharing.
Dec/16	Document	Anvisa	1	CEO takes stock of 2016. Communications Office, Brasília, 2016.	Cooperation, regulatory convergence, harmonization, participation in technical forums.
May/17	Document	Anvisa	1	Anvisa moderates an event at the WHO on regulatory agencies. Communications Office, Brasília, 2017.	Cooperation, information sharing, participation in technical forums.
Jun/17	Document	Anvisa	1 and 2	CEO highlights mutual support during crises. Communications Office, Brasília, 2017.	International collaboration. Accelerated regulatory pathways.
Jun/17	Document	Anvisa	1	Barbosa debates international regulatory convergence. Communications Office, Brasília, 2017.	International collaboration, regulatory convergence.
Aug/17	Document	Anvisa	2	2016 activity report. Brasília: Anvisa, 2017.	Analysis prioritization

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Month/year	Type	Origin	Topic	Documents/Legal norms	Strategies/Instruments
Dec/17	Standard	Anvisa	2	Resolution of the Collegiate Board - RDC no. 204, of December 26, 2017. Official Gazette of the Federal Government, ed. 248, section 1, p. 32-89, Dec 28.	Accelerated regulatory pathways, submission prior to registration.
Dec/17	Standard	Anvisa	2	Resolution of the Collegiate Board - RDC no. 205, of December 28, 2017. Official Gazette of the Federal Government, ed. 249, v. 249, section 1, p. 28-114, Dec 29.	Accelerated regulatory pathways, submission prior to registration.
Aug/18	Document	Anvisa	1 and 2	2017 activity report Brasília. 2018.	Regulatory convergence, harmonization, participation in technical forums. Registration prioritization.
Aug/18	Document	Anvisa	1	Management report for the fiscal year 2017. Brasília: Aplan/Anvisa, 2018.	Registration prioritization, accelerated regulatory pathways
Aug/18	Document	WHO	2	WHO Emergency use assessment and listing procedures for medical products during public health emergencies. 2018.	Cooperation, collaboration, information sharing.
Aug/18	Document	Anvisa	1	First International Simulated Exercise among Regulatory Authorities. Communications Office, Brasília, 2018.	Cooperation, collaboration, information sharing.
Sep/18	Document	Anvisa	1	Medtrop: Anvisa debates public health emergencies. Communications Office, Brasília, 2018.	Registration prioritization, accelerated regulatory pathways.
Oct/18	Document	Anvisa	1	Anvisa presents Brazil's harmonization with ICH. Communications Office, Brasília, 2018.	Cooperation, harmonization, participation in technical forums, information sharing.
Apr/19	Document	Anvisa	1	Management report for the fiscal year 2018. Brasília: Aplan/Anvisa, 2019.	Cooperation, participation in technical forums.
Sep/19	Standard	Anvisa	1	RDC no. 307, of September 27, 2019. Official Gazette of the Federal Government, section 1, p. 801, Oct 02.	Information sharing, regionalization.
Nov/19	Document	Anvisa	1	Anvisa gets a seat on the ICH Management Committee. Communications Office, Brasília, 2019.	Harmonization, participation in technical forums.

Source: Author.

between regulatory authorities are necessary, with the formation of global and regional networks that promote mutual fortification, recognizing regulations as an essential part of the development of national healthcare systems<sup>12</sup>.

*Information sharing* was another strategy highlighted in the documents, in which information concerning several regulatory activities is shared publicly or confidentially. A significant and particularly useful example is the sharing of

post-market surveillance information between countries that have common products in their markets<sup>14</sup>.

*Regionalization* was another strategy found in the documents, which occurs when countries or organizations with similar characteristics, such as cultural values, languages, among others, establish collaborations to fulfill regulatory functions, generally through economic integration mechanisms<sup>14</sup>, such as the Southern Common Market (MERCOSUR). In the Americas, the Pan American Health Organization (PAHO/WHO) provides support to regulatory health authorities<sup>12</sup>, mainly to develop standards, technical guidance, and training, seeking to implement global guidelines to meet regulatory needs. However, national governments are responsible for establishing strong regulatory authorities with technical, scientific, and political competence that allow them to act independently and following the most recent international regulatory frameworks<sup>5,6,9</sup>. PAHO/WHO, based on assessments conducted up to 2018, considered the regulatory authorities of eight countries as regional references in the Americas, namely: Argentina, Brazil, Canada, Chile, Colombia, Cuba, the United States, and Mexico<sup>15</sup>.

*Transparency* was another important strategy found in the analyzed documents. Some authors have highlighted the efforts of South American countries to improve their regulatory systems, especially to provide greater transparency in their decision-making processes and social accountability<sup>16,17</sup>.

The participation of NRAs in international *technical forums* was also another key strategy, as these forums work to bring together knowledge, data, and experts from different countries to build international technical and scientific references that can be used by regulators for their decision-making<sup>4,7,12-14,18</sup>. Technical forums guide the global regulation of health technologies, mainly with international cooperation and regulatory convergence activities.

*Regulatory convergence* was another important strategy found in the analyzed documents. This is considered a way to strengthen regulatory capabilities and improve coherence between regulatory systems, as it enables information sharing and other collaborative approaches, considering local specificities.<sup>19</sup> Thus, even if the NRA adapts the international reference to its national needs, structures, and capabilities, the objective and foundation of the regulation in question tend to converge<sup>12,13</sup>.

Another strategy found was regulatory harmonization, where NRA rules and procedures must be identical in content and meaning, acting as an important means of achieving regulatory convergence over time<sup>13,19</sup>. However, reservations about this strategy have been raised, especially the increased pressure on countries that do not have strong NRAs, as it can result in constraints, mainly due to the difference in the level of maturity of the countries' regulatory authorities<sup>7,12</sup>.

Anvisa participates in several international forums (bilateral, regional, and multinational), with emphasis on: International Coalition of Medicines Regulatory Authorities (ICMRA); International Conference of Drug Regulatory Authorities (ICDRA); International Pharmaceutical Regulators Programme (IPRP); Global Coalition for Regulatory Science Research (GCRSR); and International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)<sup>20</sup>.

Furthermore, Anvisa coordinates the Network of National Regulatory Authorities in the Region of the Americas and is an effective member of ICH<sup>15</sup>. The ICH is made up of representatives from national regulatory authorities and from the pharmaceutical industry. However, the approximation between regulatory authorities and the pharmaceutical industry must be cautious to minimize the risk of being "captured" by the industrial lobby, thus prioritizing the industry's economic interests rather than those of the population<sup>21,22</sup>.

Another important strategy highlighted in the documents relied on regulatory authorities to bring efficiency to regulatory systems<sup>5,7,8,19,23</sup>. Some authors consider that reliance allows consideration, with relative weight, of the evaluations conducted by NRAs selected for the quality of their evaluation, allowing more efficient use of available resources, while maintaining independence and responsibility for the decision made<sup>8,15</sup>.

*Work sharing*, which was also found in the documents, is a strategy that is often used in the context of reliance. For the cases in which regulatory systems collaborate with regulatory activities, such as evaluating applications for marketing authorization, joint work on post-marketing surveillance, and the safety of therapeutic products, among others.

However, the use of total reliance to approve a new technology can cause some problems, especially when the trusted regulatory authority has assessed the evidence in a misguided or accelerated manner, which can lead to a lack of trans-

parency in the approval paths, inducing the loss of national control over approvals of new technologies and promoting rapid approvals without the national regulatory authority having the capacity to monitor or remove the technology from the market<sup>15</sup>. Three conditions are highlighted for the use of reliance to be considered good regulatory practice: (i) assessments made critically and based on the highest quality evidence; (ii) adaptation to the local reality; and (iii) strong NRA teams capable of dealing with new contrasting evidence, which may emerge and change the initial assessment of technology<sup>15,19</sup>.

The American continent has relied more frequently on the American (Food and Drug Administration – FDA), European (European Medicines Agency – EMA), and Canadian (Health Canada) regulatory authorities.<sup>15</sup> Reliance is more common when there is already a degree of transparency and convergence between the regulatory authorities involved<sup>7,8</sup>.

The successful use of these strategies, to guarantee the safety, effectiveness, and quality of health technologies, is directly related to the implementation and straightening, of regulatory systems<sup>4,7,24</sup>.

In Brazil, Anvisa received technical recognition from the WHO in the Vaccine Pre-Qualification and Medicine Laboratory Control System Qualification programs<sup>15,18</sup>. These programs are strategies developed by the WHO to facilitate access to technologies that meet unified standards of quality, safety, and effectiveness/performance, and that can be used as part of a PHEIC response. Prequalification directs international purchasing agencies and countries, especially those of low and middle income, to make bulk purchases of vaccines, medicines, *in vitro* diagnostics, and other products at lower prices.

Therapeutic and diagnostic technologies are in great demand, especially in times of PHEIC. The next topic addresses the main regulatory instruments used by NRAs to accelerate access to these necessary technologies for healthcare policies.

#### **Instruments for the assessment and regulation of technologies by National Regulatory Agencies during Public Health Emergencies**

Among the regulatory instruments found in the selected legal norms and documents, the use by the main NRAs of *accelerated regulatory pathways* stands out, which makes it possible

to accelerate the development and approval of technology, especially for medicines for serious diseases and which have a greater therapeutic advantage<sup>25,26</sup>.

These instruments aim to meet not only the expectations of technology manufacturers and developers, but also those of patients. Generally, the pharmaceutical industry aims to quickly launch new technologies on the market so as to maximize their return on investment, while patients aim to have access, as quickly as possible, to potentially innovative technologies and, in particular, for diseases for which there is no therapeutic alternative<sup>26</sup>.

Other regulatory instruments highlighted by the documents and legal norms were *registration prioritization*, *priority review*, and *submission prior to registration*, which also make it possible to speed up the regulatory process.

In Brazil, since 2007, Anvisa has been implementing mechanisms to prioritize the analysis of registration petitions, post-registration, and prior approval in clinical drug research. The Resolution of the Collegiate Board of Anvisa, RDC no. 204, of December 27, 2017, defined as priority medicines intended for neglected, rare, emerging, re-emerging diseases, public health emergencies, or seriously debilitating conditions. Another provision published by Anvisa, to encourage the development of new medicines for rare diseases, RDC no. 205, of December 28, 2017, established a special procedure for the approval of clinical trials to be conducted in Brazil; certification of good manufacturing practices; and the registration of new medicines for rare diseases. In general terms, the time for evaluating requests was reduced and greater interaction between interested parties and the Agency, before submitting the required documents, was enabled. In addition to these, RDCs no. 505 and no. 506, of May 27, 2021, address the rules concerning how to conduct clinical trials and the prioritization of the registration of advanced therapy technologies, which can also be used in times of PHE<sup>27,28</sup>.

However, Darrow et al.<sup>26</sup> highlighted that these accelerated programs reduce the quantity and quality of evidence needed to meet health standards, as they allow for the approval of new medicines based on less robust clinical trials, for example, smaller trials, in the early stages. These cannot be randomized, controlled, and blinded, and are based on surrogate endpoints, which cannot predict the actual benefit-risk ratio for the patient. The main challenge faced by NRAs in implementing these accelerated regulatory

pathways is to balance the demands for timely access to technologies, especially medicines, and the generation of sufficient evidence about their benefits and risks, as there is much uncertainty arising due to the lack of robust clinical data<sup>25,26</sup>.

Furthermore, obtaining the information to be generated in post-marketing commitments is not easy for NRAs. In general, the data received is incomplete, and the studies are conducted inappropriately by the developers<sup>26,29</sup>.

Some strategies are used by regulatory authorities to deal with the ambiguities and uncertainties related to accelerated approval, with emphasis on requests for additional data from ongoing studies, provisional results, and post-hoc analyses of trials<sup>25,30</sup>. However, there is a significant chance that medicines approved through priority review will receive a serious safety warning during post-marketing when compared to medicines that have undergone a standard review<sup>31</sup>.

The analysis of documents and legislation revealed that, in addition to programs to accelerate the registration of medicines, regulatory authorities also use other strategies to expedite access to promising technologies that are not yet registered in the country, such as *Compassionate Use*, which is individual, and *Expanded Access*, for groups of patients.

These programs allow access to medicines and new experimental technologies before registration is granted, even during clinical studies, for individual patients or groups of patients not participating in clinical trials. The programs are intended for patients with debilitating, life-threatening illnesses and no alternative treatment. However, its grant cannot delay clinical trials, as the safety data collected during these programs do not replace the clinical trials required to register the technology.

The regulation of these programs by Anvisa in 2013 was accompanied by the founding of the *Post-trial access to treatment program*, which defines the study sponsor's responsibility to supply participants who benefited from the medicine in clinical studies.

These programs are also used in times of public health emergencies<sup>32,33</sup>. However, there are some regulatory instruments created specifically for these contexts, thus demonstrating the commitment of regulatory authorities to take quick measures to respond to the challenges posed by health emergencies<sup>34</sup>. In these situations, the testing and regulation of preventive or therapeutic products, such as diagnostic tests, vaccines, and medicines, become more complex.

The WHO, upon the emergence of the Ebola virus in 2014, created a set of procedures to assess the performance, quality, and safety of health technologies in order to accelerate their use during the epidemic, offering essential guidance to purchasing agencies from the United Nations and to the National Regulatory Authorities of Member States<sup>35</sup>. The Emergency Use Assessment and Listing procedures (EUAL) provision was the first global instrument created by the WHO to be used in PHEIC<sup>33</sup>.

In the Zika virus (ZIKV) PHEIC, the WHO published the EUAL procedure for the following candidate technologies: medicines, vaccines, and *in vitro* diagnostics. Using this instrument, the WHO assesses whether the evidence presented is sufficient to demonstrate that the potential benefits of using the technology outweigh the foreseeable risks and uncertainties in the context of PHEIC. EUAL evaluates technologies based on a minimum set of available quality, safety, and efficacy/performance data, in addition to monitoring and evaluating the course and completion of clinical trials. However, it was the prerogative of Member States to accept or not the emergency use of a candidate technology in each country.

Based on the Ebola and ZIKV PHEIC experiences, vaccine developers and national regulatory authorities have identified the need to review and simplify the EAUL procedure. As a result, in 2020, the WHO replaced the EAUL with the Emergency Use Listing Procedure (EUL) instrument to improve clarity on procedural aspects and avoid overlaps or gaps in their respective functions<sup>36</sup>. The EUL instrument now includes the participation of regulatory authorities in assessing eligible technologies. This is a risk-based procedure to evaluate and list unregistered vaccines, medicines, and *in vitro* diagnostics, which aims to expedite the availability of these technologies to people affected by a PHEIC<sup>33,36</sup>.

Furthermore, the WHO created a framework for the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI). This structure allows a panel of experts to be convened so that Member States, including a suitably qualified ethics committee, can assess whether to make the medicine available under "compassionate use" or "expanded access" in their country<sup>32,33</sup>. The tools developed by the WHO help register vaccines, medicines, and *in vitro* diagnostics around the world during PHEIC times.

Similarly, the FDA can authorize the commercialization of new technologies or new uses



of already registered technologies (repositioning) for the duration of a PHEIC declaration, through the regulatory instrument Emergency Use Authorization (EUA)<sup>37,38</sup>. This initiative reinforced the FDA's role in supporting emergency preparedness and response and in promoting the development and availability of health technologies, such as medicines, vaccines, *in vitro* diagnostics, and personal protective equipment, thus enabling the diagnosis, treatment, or prevention of serious diseases while there are no approved alternatives available<sup>37</sup>.

The use of expanded access/compassionate use programs for medicines in emergencies would be justified by the “perception that the patient is the center of the issue: research, which would indicate the effectiveness and safety of interventions, would be dependent on the patient's pressing needs”<sup>39</sup> (p.4695). However, the authors emphasize the importance of monitoring the results of using these technologies.

The COVID-19 pandemic has caused countries to extensively use some of these instruments, to obtain faster responses to it<sup>23</sup>. In Brazil, Anvisa used the EUA for vaccines and medicines for the first time and granted registration for the emergency use of diagnostic tests with a lower validity than the standard registration<sup>40</sup>. Furthermore, the Agency adopted a simplified procedure to authorize the exceptional import of medicines, vaccines, and other health products to combat COVID-19<sup>41</sup>.

In addition to the programs above, in the context of PHEIC, extra-label use, also referred to as off-label use, has been employed with medicines already registered by regulatory authorities for other therapeutic indications. This use, which is part of clinical practice, does not have the approval of the regulatory authority nor does it produce scientific evidence to support the regulatory process of a medicine<sup>39</sup>. Its use must first consider patient safety<sup>42</sup>.

During the COVID-19 pandemic, the WHO did not recommend the off-label use of medicines, as treatments that are not scientifically proven hinder clinical research, which could generate more robust evidence. Moreover, they may not be safe. Hence, Kalil<sup>43</sup> highlighted the importance of conducting controlled clinical studies, even during PHEIC, as they are more suitable for discovering new treatments when compared to the use of medicines without evidence or control. It is possible that access to experimental treatments without robust evaluation is unsafe and does not produce the intended benefits<sup>39</sup>.

Casas et al.<sup>44</sup> (p.83) emphasize that, in the context of the pandemic, the use of the EUA regulatory instrument of “technologies still without sufficient evidence has called into question the methodological bases of already established assessment processes”. This is because the methods used to evaluate health technologies are stressed to adapt and become flexible in emergencies.

Kurani, Theel, and Greenberg-Worisek<sup>45</sup> highlighted three lessons learned from the FDA's use of EUA for diagnostic testing during ZIKV PHEIC, namely: (i) that sufficient resources need to be available in case of emergency to ensure rapid, timely, and safe approval of a product needed by the general population; (ii) that it is crucial to ensure that all key stakeholders, including funding sources and politicians, support the rapid and efficient development and delivery of necessary tests during an emergency; and (iii) that more attention should be paid to developing infrastructure that can support the demand generated by a global outbreak.

Furthermore, the authors pointed out that it is necessary to have effective communication between public and private laboratories, collaboration between test manufacturers and regulatory authorities, and adherence to clinical, diagnostic, and treatment guidelines for patient care<sup>45</sup>.

During the COVID-19 pandemic, Bolisliis et al.<sup>34</sup> highlighted the agility of regulatory authorities in three circumstances, namely: (i) in facilitating product management throughout the life cycle, notably in accelerating the use of medical products for COVID-19, ensuring the continuity of clinical trials, and addressing supply chain issues; (ii) in strengthening international cooperation; and (iii) in addressing the regulatory burden with the adoption of electronic and digital tools.

## Final considerations

NRAs play a fundamental role, joining efforts with healthcare systems and the WHO in tackling PHEIC, as they can expedite access to new diagnostic means and other technologies, including therapeutics, as well as evaluate and monitor its quality, performance, safety, efficacy, and effectiveness.

Regulatory decision-making during a PHEIC is complex, often requiring additional information to confirm or modify it. Recovering scientific evidence is one of the greatest challenges for health technology evaluation, especially in times

of uncertainty when evidence about health benefits and risks is not very robust.

NRAs must expand their efforts, establishing partnerships with academia and research centers, government organizations, companies, and society. This movement would enable the development of scientific bases that can be used to evaluate new technologies, as well as to define appropriate regulatory mechanisms and practices to quickly respond to the challenges posed by health emergencies.

The COVID-19 pandemic, as an event of greater scope and impact on all continents, meant that NRA actions and regulatory instruments, designed by the WHO and the main NRAs, improved in relation to previous emergencies.

This study detected the efforts of the WHO and the NRAs to create new regulatory instruments, in addition to using some existing ones, to promptly speed up access to health technologies. The EUA strategy stood out internationally in addition to the accelerated access programs, compassionate use and expanded access. Furthermore, instruments were identified to enable, accelerate, and prioritize technology development and evaluation during emergencies, especially diagnostic and therapeutic tests, with interaction between the industry, WHO, and NRAs.

Another important strategy identified here was the international cooperation between NRAs, especially to boost the collaborative generation of evidence to improve the scientific quality of assessments.

The enormous challenge that the performance of NRAs represents, in times of PHEIC, is associated with national challenges, whose health regulation needs to be carried out considering their local and international contexts. It is important to keep a technical team up-to-date and in touch with other NRAs in order to take ownership of the new issues being discussed internationally, while also adapting to what is being built for Brazil.

Anvisa's participation in international forums and in joint decision-making, as well as its ability to establish communication and cooperation mechanisms with national and international organizations, thus participating in the construction of decisions that matter to all nations, is important to improving its national response capacity. However, this also brings the challenge of translating to Brazil what matters most in the specific response to our context and of appropriating advances to be applied in future scenarios.

## Collaborations

CVS Oliveira participated in the conception and design of the article, data collection, analysis and interpretation, initial write-up, critical review, and approval of the version to be published. VLE Pepe participated in the conception and design of the article, critical review, and approval of the version to be published.

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