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COVID-19 and the medicines regulation challenges in times of pandemic

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Abstract *The SARS-CoV-2 pandemic has brought challenges related to prevention, protection and care. Coping strategies, such as social distancing, individual protection for the population and workers, increase in the number of intensive care beds, provision of human resources and equipment are necessary actions. However, there are yet no specific effective and safe medicines that justify their use. The challenge imposed on the regulatory framework for medicines is aimed at providing timely access to medicines capable of modifying the course of the disease and leading to better treatment outcomes, with health safety. Regulatory agencies must protect the health by assessing the actual benefits and harms of the medicines under these specific conditions. The article discusses the main regulatory challenges and response of regulatory agencies to the demands imposed by the COVID-19 pandemic, especially, drug development strategies and regulatory strategies related to off-label use. Emergency drug use authorization and alternatives for extended/compassionate use are addressed, as well as clinical trials, safety assessment and monitoring of adverse events.*

Key words *COVID-19, Pharmaceutical Preparations, Pandemics, Health Surveillance*

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Introduction

A new type of coronavirus, SARS-CoV-2, was detected in China in 2019, being responsible for COVID-19. In January 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC), and in March 2020, a pandemic was declared[1]. Until May 14, 2021, 160,813,869 cases of the disease and 3,339,002 deaths were confirmed worldwide. In Brazil, there were 15,359,397 cases and 428,034 deaths[2].

Approximately 80% of those affected are asymptomatic, and half of the symptomatic individuals progress to the severe form of the disease, requiring hospitalization or intensive treatment[3]. Health systems have faced and still face major difficulties in tracking and caring for mild cases and especially the hospitalized ones, with structural and human resources often being below the needs of the country and use of ephemeral care protocols. Strategies such as social distancing, individual protection for the population and workers, assistance flows, intensive care beds, specialized human resources and medical equipment remain a growing challenge, as the epidemic progresses in waves, with different intensity and temporal distribution in different countries[4].

Some of the virus characteristics are already known, but uncertainties remain about the natural history of the disease, its forms in each individual and the outcome of immunization[5]. The main pharmacological measures, such as the use of corticosteroids and anticoagulants, still comprise the adjuvant treatments that have shown some degree of efficacy at certain stages of the disease[6]. Others, although authorized by medical entities within the scope of the service provision relationship between professionals and patients[7], are characterized by empiricism and off-label use[4,8]. Such use is encouraged by strong pressure to disseminate the use of drugs already known for other indications (repositioned), with concerns about their safety, as they may be associated with severe adverse events when used at the same doses of some off-label recommendations[6,8].

It is the responsibility of the regulatory agencies to protect health from a collective perspective and, regarding medications, they have an important role to assess the actual benefits and harms of treatment. They seek to provide timely access to necessary medications, and at the same time prevent medications with possible severe adverse events from being misused, so as not to subject patients to health risks. The evaluation of the benefits and risks of new medicines and new therapeutic indications remains necessary even for many years after the medicine registration, aiming to support innovation and, concomitantly, preserve Public Health[9,10]. Regulatory agencies, therefore, were often considered bureaucratic and having very well-established clinical evidence requirements, leading to longer responses, which would hinder the incorporation of potentially effective new technologies in health systems.

The regulatory framework for medicines has undergone an important change worldwide after 2012. The development of biological medicines, especially for rare and severe diseases, has led to the relaxation of regulatory requirements[11]. It is increasingly necessary to generate safety information after the drug marketing to corroborate the suitability of the decision to approve an early registration[12].

Health emergencies, especially those related to infectious diseases, bring new and important challenges for regulatory agencies. In these contexts, access to vaccines and medicines that can respond to the disease is urgent, with scarce time between regulation and use. At these times, the health system is at the limit of its capabilities, the community is fearful and health professionals themselves are at risk. It is based on these facts that it becomes important to critically discuss, based on selected examples, the difficulties faced by regulatory agencies.

The aim herein is to introduce the measures taken by regulatory agencies and discuss the challenges regarding the implementation of the medicine regulatory policy in light of the requirements imposed by the COVID-19 pandemic, especially in Brazil. Examples selected from the literature are used as the basis to organize and make sense of the evidence, considering the profusion, the great methodological variability, the adverse conditions for carrying out clinical studies, as well as the pressure on health services and the difficulties in the organization of clinical care.

Access to medicines and regulation: traditional and accelerated forms of registration, and use without registration

Drug development is a long, expensive task that is full of uncertainties[13]. Clinical research is required to establish evidence of efficacy and safety. In phase IV studies, after registration, the clinical benefits are confirmed (or not), thus more appropriately establishing the therapeutic value of the drug. The benefit and risk of new

medicines or new therapeutic indications only become evident when used by many individuals and for a long period[9,10].

Regulatory agencies such as the North American Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Brazilian National Health Surveillance Agency (ANVISA) already offered ways to anticipate access, speeding up the time to registration[14], even before the pandemic. The FDA allows: (i) using surrogate outcomes (accelerated approval); (ii) reducing the time of the analysis in case of severe diseases, or when there is no available alternative (priority review); (iii) greater interaction between the FDA and the company, allowing registration requests at any time (fast track); (iv) special medical use, when the drug is considered revolutionary, proposed for a potentially fatal condition or with preliminary evidence of benefit, compared to existing therapeutic alternatives (breakthrough therapy)[15].

The European Medicines Agency (EMA) has similar modalities. In March 2016, it instituted the PRIME (PRIority MEdicines) program, aiming to support the development of medicines to treat needs for which there are no alternative (unmet need), optimizing development plans, collecting more robust data collection and submission of registration requests with higher quality[16].

ANVISA admits the prioritization of registration, with prior consent for clinical research being criteria for prioritizing, among others, medicines used for rare, neglected, emerging or re-emerging diseases[17].

Alternative ways have been used to have access to medicines prior to health registration. In rare diseases and cancer, where time is crucial, the possibility of access to medicines in Phase III or II studies is made possible through expanded access (or expanded use – the nomenclature varies according to the regulatory agency), whether individual or in groups[15,18]. The "Right to Try" Act, since 2018, allows the FDA to offer critically-ill patients access to drugs of which Phase I study has already been completed[15].

In Brazil, expanded access for groups of patients takes place during or after phase-III studies. There is also compassionate use, for individuals with severe debilitating and/or life-threatening diseases, for whom there is no therapeutic alternative in the country. In this case, it can be used in the earlier phases of the clinical research[19].

How long does time have? Medicine registration in times of pandemic

Under normal conditions, the ethical precept of research with health technologies is that there is a time for the investigation, which has to be respected. The time must be that necessary to carry out the research and to develop the analysis of the results, avoiding potential harm to patients[20].

The World Health Organization (WHO)[21] considers it a moral obligation to produce knowledge as quickly as possible in response to epidemics, with clinical research being conducted in an ethical manner. During the Ebola epidemic, clinical trials were carried out in reduced time, despite the logistical difficulties when facing the epidemic spread, under very adverse sanitary, economic and social conditions[22].

An assertion that arises from the Ebola epidemic, which addresses the issue of medicines use in emergencies, is the perception that the patient is the center of the matter: the research, which would indicate the effectiveness and safety of interventions, would depend on the patient's pressing needs. In other words, an unproven intervention could be used in emergencies, given the urgent need to save lives[23]. This use is close to that of expanded access/compassionate use programs, where there must be close monitoring of results.

The debate around prioritizing the use of medicines in the context of clinical trials during an epidemic has been improved[22,24,25]. Baden et al.[24] acknowledge the difficulty of conducting randomized clinical trials during emergencies. It is important to differentiate clinical care and research. The research subject should be informed that the study contemplates the potential benefit for other people in the future and not necessarily for their individual clinical care. Finally, the information must be disseminated quickly and equitable access to the benefits of research must be guaranteed[21,25].

International organizations indicate the need, in the periods between epidemics, to develop a reference framework aiming to provide a prompt and effective response to an upcoming event[24]. The WHO[21] recommends that the study methodology should be appropriate, avoiding exposing the research subject to risks. Dodd et al.[26], in a meta-analysis of trials carried out during the Ebola epidemic, identified considerable heterogeneity between the studies. The control groups were very different, suggesting that nonrandomized studies are not reliable as a valid reference for ef-

ficacy evidence. Therefore, the recommendation that access to unregistered medicines or with new indications for use during epidemics should be primarily recommended in the context of clinical research is emphasized[27].

The Emergency Use Authorization (EUA) has been predominantly used in the epidemic as an alternative form of access to technologies, or to unregistered indications. The EMA, since 2009, when the H1N1 epidemic appeared, instituted the Emergency Authorization Procedure. In the United States, the EUA, according to the FDA, facilitates the availability and use of technologies necessary to face health emergencies and helps to protect Public Health against chemical, biological, radioactive and nuclear threats[8]. The WHO proposes some criteria for accessing treatment through emergency use: lack of effective treatment; impossibility of starting a clinical trial immediately; available preliminary data to support the efficacy and safety of the intervention; approval from local Ethics Committee authorities; available resources to ensure that the risk of use is minimized; patient informed consent; monitoring of use with results being quickly shared with the scientific community[21].

Medicine regulation in COVID-19 time: the response time to the pandemic and scientific or "factual" evidence

The evolution of knowledge about the natural history of the disease showed distinct phases - viremia, inflammatory phase, hypercoagulation state and respiratory failure and, in case of worsening, hyperinflammation and renal failure[5]. The use of medicines reflects this evolution. In addition to antivirals, support drugs, such as corticosteroids, heparins, anesthetics, vasopressors and antibiotics, emerged as relevant.

Three approaches have been used for drug discovery for coronavirus epidemics: (i) use of existing broad-spectrum antivirals; (ii) drug repositioning from chemical libraries of synthesized compounds, where molecules with possible therapeutic effects are screened; (iii) drug development based on genomic information and the characteristics of SARS-CoV-2, which follows the usual procedures for drug development, which may take many years, and running the risks that are inherent to the process[28].

Throughout the epidemic, many studies have been carried out in several countries. The characteristics of the pandemic were different in each region, whether in the most affected population subgroups, whether in temporal progress, or in the most severe forms of the disease. And the trials reflected these specificities[28].

In the absence of specific antiviral treatment, some drugs with proven antiviral action in other clinical conditions were included in clinical and observational studies. Most of them have already been marketed for other indications, which is why they are called 'repositioned': chloroquine/hydroxychloroquine, azithromycin, nitazoxanide, ivermectin, lopinavir-ritonavir, olsetamivir, darunavir, remdesivir.

The International Coalition of Medicines Regulatory Authorities (ICMRA), bringing together 28 representatives of regulatory agencies, has held regular meetings to discuss regulatory actions in the face of COVID-19[29]. One concern is the number of low-power trials and observational studies competing for resources and eligible patients without generating robust evidence. Rome and Avorn[30] highlight the importance of regulatory agencies to quickly assess the results of clinical trials, given the fact that studies are being performed while using inadequate methodology and the widespread use of medicines without established efficacy or safety. This would prevent the legacy of mistrust about the medicine evaluation process in pandemic situations[20]. The ICMRA reinforces the need for multicenter trials, with master protocols and multiple arms, including a control one[31]. One example is the SOLIDARITY trial by the WHO, which involves hospitalized patients with the participation of more than 100 countries[32].

The multiplicity of studies incapable of generating robust evidence does not contribute to decision-making by regulatory agencies, nor does it help clinical decisions in health services, which are under high pressure[33].

The FDA created the COVID-19 Treatment Acceleration Program to facilitate the development and access to potential treatments for the disease, with strategies to ensure good clinical practice, as well as to minimize risk. As it is expected that in emergency situations the study protocol can be modified, any eventual changes must be documented and informed to the participants. Information on the drug efficacy and safety needs to be evaluated, even if through alternative strategies, when there are difficulties following the protocol[34]. The FDA implemented a Sentinel System for COVID-19, aiming to monitor the course of the disease, the use of medicines and the impact of treatments, whereas using real-world data[35].

The European Medicines Agency (EMA) has organized two task forces to respond to the pandemic: The COVID-19 EMA pandemic Task Force aims to assist in rapid decision-making and coordinate regulatory actions related to the development, registration and safety monitoring of treatments and vaccines[36]. The COVID-19 Task Force seeks to respond to challenges for scientific and regulatory actions, including the alignment with European and international partners. Among the measures taken by the task forces, the EMA envisioned a series of fast-track procedures for vaccines and drugs. An accelerated registration procedure has been projected for technologies of interest for Public Health, as well as the compassionate use of technologies that are not yet registered in the European Community[36,37]. It also provides for the use of medicines that are already registered, which are undergoing clinical trials.

The rapid "turn over" of evidence and regulatory agencies

Chloroquine and hydroxychloroquine were globally tested under different conditions. Its prophylactic use, after exposure, did not show greater protection than the placebo[6,32,38]. The WHO, given the lack of evidence of efficacy from several trials with preliminary published results, removed chloroquine and hydroxychloroquine from the Solidarity[32] trial. Subsequently, Mehra et al.[39] retracted themselves due to the study that supported the use of these substances, as they used non-validated data on hospital use. The WHO, after the publication of the results of the Recovery[40] trials, removed the drugs from the Solidarity trial. Several studies carried out with these drugs have shown results that do not support their efficacy and even show adverse events[6,32,38,41].

Both drugs, chloroquine and hydroxychloroquine, have been approved for FDA Emergency Use Authorization. Some conditions would be necessary for the EUA, among them the request that health systems maintain information on the medication distribution and be capable of monitoring and report adverse events and medication errors[42]. On June 15, the FDA revoked the Emergency Use Authorization, having as justification the fact that three large trials found no gains in survival or clinical benefits[43].

The EMA, on the other hand, did not approve the use of these drugs, leaving the decision in the scope of clinical studies or protocols for each country of the European Community[44]. Moreover, it warned health professionals about the need to monitor adverse events and report them to health authorities in their respective countries[45].

At the FDA, remdesivir obtained authorization for the investigation of a new drug and had been approved for expanded use. The Adaptive COVID-19 Treatment Trial (ACTT), a multicenter study evaluating the treatment of hospitalized adult patients in approximately 60 locations worldwide, showed, in its preliminary results, that the compassionate use of remdesivir resulted in a shorter hospital length of stay[46]. In May Remdesivir obtained the EUA for the treatment of hospitalized adults and children with severe disease. In addition to remdesivir, in late 2020 and in 2021, the FDA granted EUA for: baracitinib[e], casirivimab and imdevimab, bamlanivimab and etesevimab[47].

The EMA allowed the compassionate use of remdesivir for COVID-19 in hospitalized patients, older than 12 years, with severe acute respiratory syndrome[48], and in July 2020 granted a conditional registration, valid for one year[49].

As in the rest of the world, the coronavirus pandemic, since it was decreed a Public Health Emergency in Brazil[50], has generated a large amount of information and clinical research. As the possible effects of hydroxychloroquine and chloroquine came to light, there was a rush of the population to retail aimed at stocking on these medicines, with harmful consequences for patients with lupus, users of hydroxychloroquine. ANVISA acted quickly, including both drugs in the list of drugs under dispensing control[51]. The Agency's first concern was related to shortages, arising from purchases by off-label use indication, whether under medical prescription or by self-medication, with important personalities in the country clearly in favor of its use. Ivermectin, nitazoxanide, interferon and other medicines with potential antiviral action were then included in RDC 405/2020, in the list of drugs under special prescription[52]. ANVISA has not acknowledged the efficacy of hydroxychloroquine, chloroquine or ivermectin in the treatment of COVID-19[53,54].

ANVISA has also issued extraordinary standards to streamline the registration of diagnostic tests (*in vitro*), medicines and biologicals for the prevention and treatment of COVID-19. Brazil has admitted the use of chloroquine and hydroxychloroquine in its services, at the physicians' discretion, supported by an informative

note by the Ministry of Health[55,56], differently from the FDA and contrary to the WHO, outside the environment of clinical trials or EUA, which configures a non-rational use. The use of medicines for COVID-19 has followed, so far, an off-label regimen, without emergency use protocols. Although it has been concerned about not confirming the use of medicines without robust evidence of efficacy and safety, ANVISA did not employ adverse event monitoring strategies.

In 2021, ANVISA granted conditional registration to remdesivir for inpatient treatment of COVID-19 and the EUA for the combination in fixed doses of intravenous administration of monoclonal antibodies casirivimab and imdevimab, for the treatment of outpatients with COVID-19, without need for oxygen supplementation and at risk for progression to the severe form of the disease[57,58]. Although they have been registered, the use of these medicines has not been recommended by the Commission for the Incorporation of Technologies (Conitec - *Comissão de Incorporação de Tecnologias*) of the Ministry of Health, for the treatment of patients hospitalized due to COVID-19[59]. To date there is no Conitec guideline for the outpatient or preventive treatment.

The evolution of the COVID-19 pandemic has brought lessons and challenges. Thomson and Nachlis[60] have proposed strategies based on what happened at the FDA with chloroquine/hydroxychloroquine, including: analysis of emergency authorization/registration by an Advisory Committee in which different actors are involved; transparency in the process with the participation of the population; prioritize the establishment of robust post-marketing monitoring that includes strict and comprehensive Phase 4 studies; consider a Nationwide Vaccine Harm Compensation Program; increase communication for the population; involve experts and the medical community; review and communicate information about adverse events to the population; establish different standards for granting EUAs: stricter for medicines and vaccines and more flexible for diagnostic tests and products that will be used for specific populations; establish and communicate the evidence that will inform the granting and withdrawal of the EUA.

One of the challenges concerns the difficulties to follow the guidelines for Emergency Use Authorization, such as the application of the Free and Informed Consent Form, approval by the National Ethics Committee and the generation of information with the use of technology[61,62].

Final considerations

The COVID-19 epidemic brought with it the need to know the natural history of the disease, its main characteristics, and also to seek specific and appropriate treatments for each stage of the disease. Drugs and medicines that are candidates to effectiveness against COVID-19, each with its particularities: medicines already used in other diseases – under emergency use or in other forms of off-label use – and new medicines, in the expanded access/compassionate use modality.

The alternative way to regulate the use of interventions in emergencies, and especially the "emergency" use, is a possible meeting between the urgency of the epidemic and the need for approval, surveillance or scrutiny by the regulatory authority. The FDA and EMA use this strategy, with very well-defined assumptions, continuous monitoring and reporting of adverse events. All over the world, decision-making regarding the use of medicines has proved to be unstable and, at times, responsive to external and internal pressures in countries, influenced by the scientific seesaw, which involves the intense performance of studies of several types, often of questionable quality, sometimes generating conflicting or inconclusive results.

In addition to the pressure from regulatory agencies for registration in an accelerated situation, there are also pressures on managers, health professionals and even the population, under the most diverse strategies, for the use of new drugs and their use under unregistered indications. Large international companies in Brazil have also resorted to the legislative system to guarantee their interests, even when there is technical recommendation against them by the regulatory agency. This aspect is of the utmost importance, since in the post-pandemic period, these actors will eventually feel strengthened to increasingly pressure for deregulation and, therefore, weaken the constitutional principle of health protection.

The experience with other epidemics and with COVID-19 has advocated the importance of using medicines under clinical, collaborative, multicenter research, with a precise question and a well-designed study, aiming to produce more robust evidence as earlier as possible. These measures also contribute to establishing a more stable and evidence-based regulatory framework in the context of the pandemic.

Collaborations

VLE Pepe, HMD Novaes and CGS Osorio-de-Castro contributed equally to the research concept, development, analysis, and the writing and final review of the manuscript.

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