ActaBiomedicaScientia

e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X

www.mcmed.us/journal/abs

Research Article

STUDY OF VARIOUS PATHWAYS OF EMERGENCY AUTHORIZATION OF CORONA MEDICATIONS BY VARIOUS REGULATORY AGENCIES AROUND IN THE WORLD

Peethala Harshini[1], Avinash Kumar G[2]*, Manasa E[2], Divya E[1]

[1]Department of Pharmaceutics, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore-524346, Andhra Pradesh, India
[2]Department of Pharmacognosy & Phytochemistry, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore-524346, Andhra Pradesh, India

ABSTRACT

The World Health Organization (WHO) has been leading the global response to COVID-19 by monitoring the virus's spread, facilitating international information exchange, and providing technical support to countries. As of April 30, 2020, COVID-19 had reached 212 countries, causing over 3 million cases and 211,028 deaths. Effective public health measures and surveillance are crucial for managing such health crises. WHO is analyzing COVID-19 data in relation to country readiness to identify gaps in the current public health system. The majority of Emergency Use Authorizations (EUAs) for COVID-19 diagnostics were based on preliminary data, raising concerns about their accuracy and reliability. The FDA must balance the need for rapid adoption of new technologies with ensuring safety and efficacy. This study highlights the need for improved evidence standards for EUAs in future public health emergencies.

Keywords:COVID-19, WHO, public health, Emergency Use Authorization, FDA.

Access this article online	
Home Page: **www.mcmed.us/journal/abs**	**Quick Response code**

Received:22.05.2024	**Revised**:12.06.2024	**Accepted**:10.07.2024

INTRODUCTION

The emergence of the COVID-19 pandemic has underscored the critical need for rapid and effective response mechanisms to address public health emergencies [1]. One such mechanism is the Emergency Use Authorization (EUA) [2], a legal provision that allows for the use of unapproved medical products or unapproved uses of approved medical products during declared emergencies [3]. This process, sometimes referred to as "compassionate use," provides a pathway for accessing potentially life-saving treatments before they undergo the standard, lengthy approval process [4].

The COVID-19 pandemic, which began in December 2019 in Wuhan, China, and quickly spread globally, has necessitated the use of EUAs to manage the outbreak effectively. As the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern in January 2020, and later a pandemic in March 2020 [5], the urgent need for effective treatments and preventive measures became evident. COVID-19 presents a spectrum of symptoms, from mild respiratory issues to severe illness resulting in pneumonia [6], respiratory failure, and death, emphasizing the need for timely medical interventions. Vaccines have been one of the most critical tools in combating the pandemic. Among the various types of vaccines developed, the mRNA vaccines have gained prominence for their innovative approach and rapid development timeline. The EUA process has facilitated

Corresponding Author: **Avinash Kumar G,** Email:dravinashreddy88@gmail.com

the expedited availability of these vaccines, which have undergone rigorous evaluation by regulatory bodies such as the FDA [7], the European Medicines Agency (EMEA), and the WHO. In India, the Central Drugs Standard Control Organization (CDSCO) has granted EUAs for several COVID-19 treatments and vaccines, including Remdesivir and Favipiravir, under specific conditions to manage the health crisis effectively [8].

Despite the benefits, the EUA process poses significant challenges, including ensuring the safety, efficacy, and quality of the medical products distributed under these authorizations. The FDA and other regulatory agencies must balance the urgent need for medical countermeasures with their responsibility to safeguard public health [9]. Historical precedents, such as the EUAs issued during the H1N1 influenza pandemic in 2009, provide valuable lessons on the complexities and considerations involved in emergency authorizations.

As the world continues to grapple with COVID-19, understanding the role and impact of EUAs is crucial. This introduction sets the stage for a detailed examination of the EUA process, its application during the COVID-19 pandemic [10], and the broader implications for public health policy and practice.

METHODOLOGY

Emergency Use Authorization (EUA) Pathway

An Emergency Use Authorization (EUA) is an expedited regulatory mechanism utilized during a public health emergency (PHE) to authorize the use of vaccines and other medical products, such as drugs, diagnostics, devices, and biologics. This pathway is particularly relevant in situations like the COVID-19 pandemic. The U.S. Food and Drug Administration (FDA) grants EUAs after thoroughly evaluating all available evidence, carefully balancing the known or potential risks against the potential benefits of using the product in an emergency. In the case of COVID-19, the FDA determined that the known and potential advantages of detecting COVID-19 infections in the specified target population outweighed the associated risks.

Pre-Emergency Submissions

The Agency recommends that, whenever feasible and appropriate, a pre-emergency submission be made through existing protocols (such as IND or IDE) to enable the FDA to begin its review before an actual or potential emergency is identified. The scope and timing of the evaluation of such submissions will vary based on the nature of the submission (including whether there is an existing IND or IDE for the product) and the workload of the reviewing Center. The FDA believes that pre-emergency submissions for high-priority activities can be reviewed within weeks to months, depending on these factors and other urgent circumstances beyond the Agency's control [11].

Submission of EUA

The relevant FDA Center will collaborate closely with the entity submitting the EUA request, overseeing the Agency's response. If practical and appropriate, the Office of the Commissioner will facilitate meetings with the NIH and CDC Directors. Technical feedback from the EUA Working Group will be conveyed to the FDA review division, with coordination by the Commissioner's Office and ASPR [12]. The review division may also consult other countermeasures working groups and external experts as needed.

The FDA recognizes that the data required to support an EUA will vary based on the emergency and product specifics. Each request will be assessed according to relevant facts and legal requirements. The FDA Center will review the request, consult with experts, and make recommendations to the Commissioner [13]. The Office of the Commissioner will issue a letter approving or disapproving the emergency use, detailing the product's intended use and indications. Upon EUA issuance, the relevant Center will work with the Office of the Commissioner to develop and publish a Federal Register notice and update the FDA website with EUA information.

Emergency use listing

On March 27, 2020, the WHO introduced the Emergency Use Listing (EUL) method to provide guidance on validation data required for emergency use authorization. The EUL, replacing the 2014-2016 EUAL procedure, accelerates the availability of unlicensed vaccines, therapies, and diagnostics during public health emergencies (PHEs). This risk-based system evaluates products based on performance, quality, safety, and efficacy, aiding submission to Member States and UN procurement bodies [14].

An emergency declaration by a government authority is often required to issue an EUA. This may involve consulting other agencies and meeting specific criteria, such as the emergence of a life-threatening contagious disease without approved treatments. Emergency declarations for EUA pathways can differ from those by other authorities.

Eligibility of candidate products

The EUL concerns three product streams (vaccines, therapeutics and IVDs). For IVDs, the specific requirements for products to be eligible for evaluation under the EUL procedure are:

1. The disease for which the product is intended is serious or immediately life threatening; has the

potential of causing an outbreak, epidemic or pandemic; and there are no licensed products for the indication or for a critical subpopulation (e.g., children).
2. The applicant undertakes to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for WHO prequalification (WHO PQ) once the product is licensed [15]
3. The product is manufactured in compliance with current good manufacturing practices (GMPs) under a functional quality management system (QMS

Eligibility for An Eua

Under Section 564, the FDA Commissioner can authorize the use of a medication, device, or biological product during an emergency. EUA candidates are products not approved under sections 505, 510(k), and 515 of the FD&C Act or section 351 of the PHS Act. The Commissioner must determine that the emergency agent can cause a serious or life-threatening disease or condition, that scientific evidence, including clinical trial data, shows that the benefits outweigh the risks, and that there is no adequate, approved, and available alternative for diagnosing, preventing, or treating the condition.

Processing of an Eua

The FDA's role in pre-emergency actions for potential EUA products, detailing the steps the Agency will take to process an EUA request once the Secretary has made a declaration of emergency

Emergency Use Authorization of Medical Products By Different Regulatory Agencies

The FDA can streamline the availability and deployment of medical countermeasures (MCMs) during public health emergencies, enhancing defenses against chemical, biological, radiological, and nuclear (CBRN) threats, including infectious diseases. According to Section 564 of the FD&C Act, unapproved medical products or unapproved uses of approved products can be authorized for emergency use to diagnose, treat, or prevent serious or life-threatening conditions caused by CBRN agents if the Secretary of HHS determines an emergency use authorization is appropriate. This determination must be based on one of four assessments of threats made by the Secretary of HHS, Homeland Security, or Defense [16].

On February 4, 2020, the Secretary of Health and Human Services (HHS) determined that a public health emergency existed due to the COVID-19 virus, which posed a significant potential impact on national security and the health of Americans, both domestically and abroad. This declaration by the HHS Secretary paved the way for subsequent pronouncements supporting the use of Emergency Use Authorizations (EUAs) based on the identified public health emergency related to COVID-19.

Vaccines

The COVID-19 pandemic, caused by the highly transmissible SARS-CoV-2 virus, has profoundly impacted global society and economies. Originating from a bat coronavirus, SARS-CoV-2 shares genetic similarities with other coronaviruses like SARS-CoV, belonging to the Sarbecovirus subgenus. Studies reveal its strong binding affinity to the human ACE2 receptor, facilitating its rapid spread and zoonotic transmission. By March 2021, the pandemic had resulted in over 121 million confirmed cases and 2.7 million deaths worldwide, necessitating stringent public health measures and accelerated research for effective vaccines and treatments to mitigate its impact and restore normalcy globally [17].

Live Virus Vaccines and Inactivated Vaccines

In the biomedical sector, highly immunogenic vaccines like inactivated and live vaccines are extensively used. Inactivated vaccines contain non-infectious viruses that cannot replicate in the body, ensuring safety. Live vaccines use attenuated viruses with reduced virulence, closely monitored to maintain safety during clinical trials and commercial use. Currently, Codagenix and the Serum Institute of India are conducting Phase I trials for a live attenuated vaccine using CodaVax technology [18].

Vector Vaccines

Live attenuated vector-based vaccines use modified harmless viruses like adenovirus, measles, or influenza as vectors to express coronavirus proteins during immunization. These vaccines can be replicating or non-replicating, with safety concerns minimized as many viral vectors cannot fully replicate in human cells. However, pre-existing immunity to the vector can reduce vaccine effectiveness if the individual has been previously vaccinated with the same vector. Currently, Oxford University and the Massachusetts Institute of Technology (MIT) are collaborating on a chimpanzee adenovirus-based vaccine for SARS-CoV-2. Additionally, the Pasteur Institute, Themis, and the University of Pittsburgh Vaccine Research Center are developing a measles viral vector vaccine expressing the SARS-CoV-2 spike protein [19].

Safety and Efficacy of Vaccines

Thirteen vaccines were approved globally by March 2021, with varying effectiveness against COVID-19. Comirnaty (BNT162b2) showed 95% efficacy against symptoms, while Moderna's mRNA-1273 and BBIBP-

CorV were 94.5% and 86% effective, respectively, with BBIBP-CorV being more effective (100%) in preventing severe disease. AstraZeneca's AZD1222 produced specific antibodies peaking at 28 days post-immunization, and use of paracetamol mitigated mild side effects. Sputnik V and EpiVacCorona vaccines reported no unexpected adverse events, while Convidicea showed strong T-cell and antibody responses. Various vaccines, like CoviVac and ZF2001, were approved or under trial in different countries, with ongoing assessments of efficacy and safety [20].

Regulatory Authorities

The COVID-19 pandemic has significantly impacted citizens, patients, and businesses worldwide. Regulatory agencies and pharmaceutical companies with marketing authorizations are operating in continuity mode, adapting to unprecedented challenges. Urgent interventions and reprioritized operations are necessary to address public health needs effectively. Maintaining a stable supply of medicines remains crucial for public health, requiring solutions that minimize shortages while upholding high standards of quality, safety, and efficacy in EU-approved medicines. This guidance advises marketing authorization holders (MAHs) on regulatory expectations and flexibility during the pandemic, emphasizing ongoing adaptation to evolving circumstances. MAHs are encouraged to consult with the European Medicines Agency or national competent authorities for specific product inquiries not covered in this document.

Legal Regulatory Guidance

In the EU, pharmaceutical products must obtain marketing authorization before they can be sold. This authorization can either be granted by the European Commission, allowing marketing across all Member States (centralized marketing authorization), or by a National Competent Authority (NCA) in an individual Member State, allowing marketing only within that specific country (national marketing authorization). Processes are in place to facilitate the granting of national marketing authorizations for pharmaceuticals that have already been authorized by another EU/EEA Member State, ensuring efficient access to medicines across the region [18,20].

RESULT AND DISCUSSION

The COVID-19 pandemic has had devastating global consequences, resulting in unprecedented loss of life and posing serious threats to food security, public health, and economies worldwide. The impact has been profound, pushing tens of millions into poverty and potentially increasing the number of undernourished people by millions. Businesses are facing existential threats, and job losses are affecting nearly half of the global workforce, particularly those in the informal economy without social protections or access to healthcare. Lockdowns have exacerbated these challenges, limiting people's ability to earn income and feed their families adequately.

Moreover, countries like Brazil and Russia are experiencing alarming increases in infection rates, prompting heightened surveillance and preventive measures to avoid further outbreaks. Efforts to develop vaccines and treatments have intensified, yet the pandemic's persistence remains evident. Experts warn that COVID-19 is likely to endure for years, with uncertain patterns of resurgence potentially affecting different regions cyclically. Recent developments, such as the discovery of multisystem inflammatory syndrome in children and analyses suggesting potential benefits of earlier lockdowns, underscore the ongoing complexities and lessons of this crisis.

Amid these challenges, there has been contentious debate over the scientific responses and policy decisions, highlighting the critical role of scientific expertise and evidence-based approaches in navigating this "new normal." As societies adapt to post-pandemic realities, there is a growing recognition of the need to prioritize scientific guidance and rational strategies to mitigate future health crises effectively.

EUA Pathway

The process of issuing an Emergency Use Authorization (EUA) involves several key steps. First, an emergency situation must be identified and declared by HHS, the Department of Homeland Security, or the Department of Defense. This could involve a military, domestic, or public health crisis that threatens national security or has a high potential to do so, often involving chemical, biological, radiological, or nuclear agents. Once declared, the FDA reviews the EUA request, consulting with agencies like the CDC and NIH as needed. If the FDA Commissioner determines that the request meets legal requirements, an EUA is issued. The EUA remains in effect until the emergency declaration expires; multiple EUAs can be authorized under a single declaration as needed.

Pre EUA

The procedure for issuing an Emergency Use Authorization (EUA) can begin even before an actual emergency arises, though the statute prevents the FDA from preauthorizing an EUA before an official emergency declaration. This is referred to as a pre-EUA. For example, requests can be made to the FDA in anticipation of hypothetical events like smallpox outbreaks or anthrax attacks. In these cases, educated guesses are made about the potential emergency, and the

FDA starts evaluating the data and science behind the products that might be used, determining how they would be utilized and how the EUA would be created.

State Dispensing Laws and EUAs

Each state may have its own specific rules for dispensing pharmaceuticals, especially regarding label information, complicating the EUA process. This raises the question of whether the EUA overrides state dispensing laws or if state laws take precedence. Gorman noted that this issue is being addressed, but no clear guidelines have been provided yet. The risk analysis shows that authorizations related to PPE and diagnostic procedures pose the least danger but have the greatest impact on the public and healthcare efficiency. A standardized approach to diagnostic testing is crucial to ensure more reliable tests are conducted. There was global panic regarding ventilators during the COVID-19 pandemic. National regulatory bodies often failed to consult relevant experts when setting technical requirements and procedures for procurement and installation, leading to wasted tax dollars on ineffective medical devices. The key lesson from the COVID-19 pandemic is the vital importance of an evidence-based regulatory system.

CONCLUSION

The collaborative effort between the International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO) has highlighted critical insights and recommendations for emergency medical product authorizations during the COVID-19 pandemic. The evaluation revealed that many Emergency Use Authorizations (EUAs) were issued based on limited or nonclinical data, raising concerns about the reliability and safety of these products. Moving forward, it is essential for regulatory bodies to strengthen evidence requirements and resist political pressure to ensure that authorized products are both safe and effective. This study underscores the need for robust, evidence-based regulatory frameworks and highlights the importance of international cooperation in addressing global health emergencies. Despite the challenges, improving regulatory practices can enhance public trust and ensure the efficacy and safety of medical products in future health crises.

REFERENCES

1. Rizk JG , Forthal DN , Kalantar-Zadeh K. (2021). Expanded access programs, compassionate drug use, and emergency use authorizations during the COVID-19 pandemic. *Drug Discov Today*. 26(2), 593-603.
2. Woloshin S , Patel N , Kesselheim AS. (2020). False negative tests for SARSCmoV- 2 infection—challenges and implications. *N Engl J Med*. 383(6), 38.
3. Tau N, Shepshelovich D. (2020). Assessment of data sources that support US Food and Drug Administration medical devices safety communications. *JAMA Intern Med*. 180(11), 1420-1426.
4. Zhai MZ , Lye CT , Kesselheim AS. (2020). Need for transparency and reliable evidence in emergency use authorizations for Coronavirus Disease 2019 (COVID-19) therapies. *JAMA Intern Med*. 180(9), 1145-1146.
5. Saag MS. (2020). Misguided use of hydroxychloroquine for COVID-19: the infusion of politics into science. *JAMA*. 324(21), 2161-2162.
6. Spoorthi V, Sasank S. (2020). Utility of ivermectin and doxycycline combination for the treatment of SARS-CoV-2. *Int Arch Integrated Med.* 7(10), 117- 182.
7. Camprubi D, Almuedo-Riera A, Marti-Soler H. (2020). Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. *PLoS One*. 15(11), 0242184.
8. Bhattacharya R, Ray I, Mukherjee R. (2020). Observational study on clinical features, treatment and outcome of COVID-19 in a tertiary care centre in India—a retrospective case series. *Int J Sci Res*. 9(10).
9. Cadegiani FA, Goren A, Wambier CG, McCoy J. (2021). Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients. *New Microbes New Infect.* 43, 100915.
10. Elalfy H, Besheer T, El-Mesery A. (2021). Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. *J Med Virol*. 93(5), 3176- 3183.
11. Shahbaznejad L, Davoudi A, Eslami G. (2021). Effects of ivermectin in patients with COVID-19: a multicenter, double-blind, randomized, controlled clinical trial. *Clin Ther*. 43(6), 1007-1019.
12. Ahmed S, Karim MM, Ross AG. (2021). A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 103, 214-216.
13. Chachar AZK, Khan KA, Asif M. (2020). Effectiveness of ivermectin in SARSCOV- 2/COVID-19 patients. *Int J Sci*. 9, 31-35.
14. Lopez-Medina E, Lopez P, Hurtado IC. (2021). Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA*. 325(14), 1426-1435.

15. Abd-Elsalam S, Noor RA, Badawi R. (2021). Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: a randomized controlled study. *J Med Virol*. 93(10), 5833-5838.
16. Ravikirti, Roy R, Pattadar C. (2021). Evaluation of ivermectin as a potential treatment for mild to moderate COVID-19: a double-blind randomized placebo controlled trial in Eastern India. *J Pharm Pharm Sci*. 24, 343-350.
17. Buonfrate D, Chesini F, Martini D. (2022). High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. *Int J Antimicrob Agents*. 59(2), 106516.
18. Krolewiecki A, Lifschitz A, Moragas M. (2021). Antiviral effect of high-dose ivermectin in adults with COVID-19: a proof-of-concept randomized trial. *EClinicalMedicine*. 37, 100959.
19. Okumus N, Demirturk N, Cetinkaya RA. (2021). Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect Dis*. 21(1), 411.
20. Podder CS, Chowdhury N, Sina MI, Haque W. (2021). Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomized controlled study. *IMC J Med Sci*. 14(2).

Cite this article:
Peethala Harshini, G Avinash Kumar, E.Manasa, E Divya. (2024). Study Of Various Pathways Of Emergency Authorization Of Corona Medications By Various Regulatory Agencies Around In The World: *ActaBiomedicaScientia*, 11(1), 61-66.