

PHARMACEUTICAL AND MEDICAL DEVICE RESILIENCE: IMPLEMENTATION OF EMERGENCY USE AUTHORIZATION IN PHARMACEUTICALS AND MEDICAL DEVICES DURING THE COVID-19 PANDEMIC: A LITERATURE REVIEW

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ABSTRACT

The COVID-19 pandemic has caused an urgent need for pharmaceuticals and medical devices used for testing, treatment, and prevention. The policy of issuing an Emergency Use Authorization (EUA) for COVID-19 handling products is carried out to fulfill these needs. This study aims to describe and analyze how the EUA mechanism can be used as resilience during the pandemic. The study used Pubmed and ScienceDirect databases to search all articles using inclusion and exclusion criteria. The inclusion criteria were articles in English and Indonesian, national and international research articles covering the application of the EUA, searches limited to the last 3 years, and articles not limited to one study design. The exclusion criteria were articles not available in full text and topics unrelated to EUA in pharmaceuticals and medical devices. A total of 1,009 articles were identified using the keywords “Emergency Use Authorization”, “drug or medical device”, “COVID-19”. Finally, 11 articles that met the criteria were analyzed. The EUA approval for pharmaceuticals and medical devices is a form of resilience in the face of a pandemic and is an effective way to meet increasing needs while looking at clinical evidence and evidence of use in the field. The ability and experience in implementing the EUA can be a guide for learning in dealing with pandemics in the future.

Keywords: *COVID-19, emergency use authorization, implementation, resilience*

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INTRODUCTION

Health is one of the human rights which is not only assessed as a state free from disease or disability. But also a state of complete physical, mental, and social health, so productivity can be achieved optimally (World Health Organization, 2023). One of the things supporting this health status is the availability of pharmaceuticals and medical devices with guaranteed safety, quality, and efficacy.

New emerging diseases and re-emerging diseases are the main causes of morbidity and mortality worldwide. Some diseases can spread quickly and become pandemic, such as COVID-19, which has occurred since the beginning of 2020. Prevention and treatment efforts continue to be carried out to deal with the pandemic. The government also issues policies in dealing with pandemics that are continuously adapted to current national and international conditions (Satuan Tugas Penanganan COVID-19, 2022).

The availability of pharmaceuticals and medical devices plays an important role in supporting the treatment and prevention of COVID-19. Along with the increase in patients, the need for medical devices and special drugs for COVID-19 increases, so the accuracy and availability of pharmaceuticals and medical devices are needed (Huda R et al., 2021). The urgent need has prompted the government to issue policies that support the fulfillment of the need for pharmaceuticals and medical devices during the pandemic. One of these policies is granting an Emergency Use Authorization for certain COVID-19 handling products that are

indispensable in health services. The FDA as the food and drug regulatory agency in the United States has given this EUA approval for several therapies (US FDA, 2022b). In Indonesia, Badan Pengawas Obat dan Makanan (BPOM) is authorized to issue emergency use approvals for the use of drugs during public health emergencies (BPOM, 2021). For certain medical devices used in handling COVID-19, approval for emergency use is given by the Ministry of Health (Kementerian Kesehatan RI, 2021). The implementation of EUA has been carried out as an effort to overcome the COVID-19 pandemic. Therefore, we did this literature review to describe and analyze how the EUA implementation policy can be used as resilience during the pandemic.

METHOD

This literature review was conducted by searching for articles through online databases such as Pubmed and ScienceDirect. Article searches were conducted using the keywords “Emergency Use Authorization”, “drug or medical device”, “COVID-19”. The inclusion criteria for obtaining the related articles were 1) articles in English, 2) national and international research articles covering the application of the EUA, 3) search journals limited to the period of 3 years, and 4) articles not limited to one research design. Exclusion criteria in the article search were articles that were not available in full text and topics not related to EUA in pharmaceuticals and medical devices. Articles obtained from the database are then screened based on duplication, title, abstract, and article content that match the predetermined criteria. The next step is to download the articles that have been screened. The downloaded articles are extracted and analyzed by topic, and then the data are organized in a narrative review.

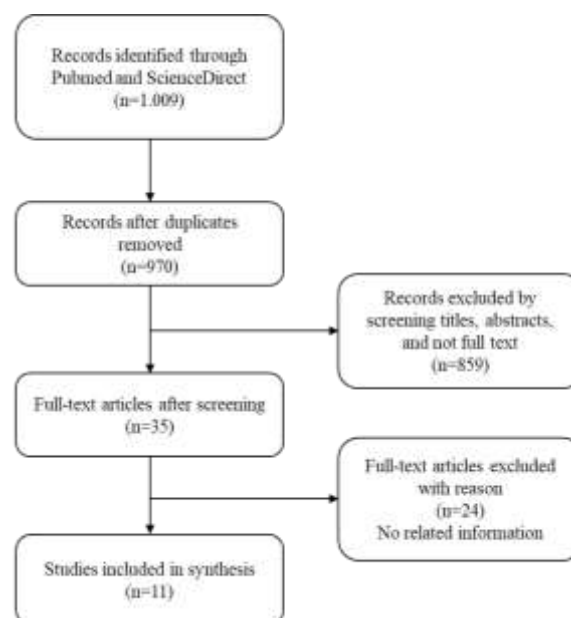


Figure 1. Article search flow

RESULTS AND DISCUSSION

An article search using keywords on the Pubmed and ScienceDirect websites yielded 1,009 articles. After screening for duplication and excluding articles that do not fit the topic to be discussed, a total of 11 articles will be analyzed.

Table 1. Article search results

No.	Title	Author	Year	Result
1.	The Emergency Use Authorization of Pharmaceuticals: History and Utility During the COVID-19 Pandemic	Tran A., Witek T.J.	2021	Before its implementation during the COVID-19 pandemic, the initial purpose of implementing the EUA was to strengthen defenses against bioterrorism. Marketing approval as a new drug can be issued to therapies that previously received EUA approval when clinical evidence is available, such as remdesivir for the treatment of COVID-19.
2.	Understanding, Verifying and Implementing Emergency Use Authorization Molecular Diagnostics for the Detection of SARS-CoV-2 RNA	Mitchell S.L., et al	2020	The SARS-CoV-2 nucleic acid detector is the first medical device to get EUA approval.
3.	Implementation of an Emergency Use Authorization Test During an Impending National Crisis	Lefferts J.A., et al	2020	The FDA publishes guidelines for SARS-CoV-2 test kits that can obtain EUA approval.
4.	The Dynamics of SARS-CoV-2 (RT-PCR) Testing	Joyce N., Seim L., Smerina M.	2021	The absence of sensitivity or specificity standards for SARS-CoV-2 test kits has resulted in a large number of false-positive

					and false-negative cases. However, combining test results with clinical symptoms at the time of diagnosis is necessary.
5.	Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic	Rizk J.G., et al	2021		The EUA approval is given for medical products that do not yet have a distribution permit in certain emergency conditions, including accelerating the handling of the COVID-19 pandemic. Although the Randomized Controlled Trial (RCT) has become the standard for assessing the safety and effectiveness of a therapy, the application of EUA can provide a quick answer in the face of a pandemic.
6.	Lessons Learned from Coronavirus Disease 2019 (COVID-19) Therapies: Critical Perspectives From the Infectious Diseases Society of America (IDSA) COVID-19 Treatment Guideline Panel	Bhimraj A, et al	2022		The FDA has issued EUA for several COVID-19 therapies, including hydroxychloroquine, convalescent plasma, remdesivir, bamlanivimab, baricitinib with remdesivir, casirivimab/imdevimab, and bamlanivimab/etesevimab. The EUA may be published before evidence of routine use of the therapy is available, making it potentially ineffective, or even dangerous for the

				<p>patient. Therefore, cooperation and collaboration between the government and relevant stakeholders is needed in the implementation of EUA.</p>
7.	FDA efficiency for approval process of COVID-19 therapeutics	Cassidy C., et al	2020	<p>Time constraints and pressure from the public to find a COVID-19 therapy have caused some studies to be less robust and have no control group. However, the EUA approval of several COVID-19 therapies in a short period demonstrates the FDA's ability to focus resources and manpower on specific issues, including in collaboration with various stakeholders.</p>
8.	The Rise and Fall of Chloroquine/ Hydroxychloroquine as Compassionate Therapy of COVID-19	Manivannan E., Karthikeyan C., Moorthy NSHN., Chaturvedi S.C.	2021	<p>Hydroxychloroquine received EUA approval at the beginning of the COVID-19 period based on some literature regarding its potential against several types of viruses. The clinical observations and RCT results on hydroxychloroquine did not show the expected clinical benefit, so the EUA permit was revoked.</p>
9.	Emergency Approvals for COVID-19: Evolving Impact on Obligations to	Lynch H.F., Bateman-House A., Joffe S.	2021	<p>Therapy using EUA products that have not been proven through clinical trials is ethically</p>

	Patients in Clinical Care and Research			permissible, but still consider the use of evidence-based therapy.
10.	First Full Regulatory Approval of a COVID-19 Vaccine, the BNT162b2 Pfizer-BioNTech Vaccine, and the Real-World Implications for Public Health Policy	Parums D.V.	2021	The Pfizer-BioNTech vaccine received EUA approval from the FDA in December 2020. After passing phase 3 clinical trials, it received full regulatory authorization.
11.	A low-cost, highly functional, emergency use ventilator for the COVID-19 crisis	Raymond S.J., et al.	2022	The FDA publishes EUA guidelines that can encourage researchers and manufacturers to create effective COVID-19 medical devices at affordable prices. One of the medical devices that were made based on these guidelines and successfully obtained EUA approval is a mechanical ventilator designed specifically for handling the COVID-19 pandemic.

The FDA enacts Emergency Use Authorizations to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear threats, including infectious disease, by facilitating the availability and use of necessary medical precautions during times of public health emergencies. The FDA may allow unapproved medical products or the unapproved use of medical products approved for use in an emergency to diagnose, treat, or prevent disease, serious or life-threatening conditions caused by threatening agents when certain criteria are met, such as the absence of adequate or agreed terms and no alternatives available (US FDA, 2022a).

The initial purpose of implementing the EUA was as a step to accelerate and improve national security against potential bioterrorist attacks. During the COVID-19 pandemic, this mechanism was used as an important regulatory pathway in providing needed pharmaceuticals and medical devices as a form of resilience in dealing with a pandemic. Products that receive EUA approval can get extended for the EUA period, withdraw the EUA approval, or receive full regulatory approval as new drugs or medical devices (Tran & Witek, 2021).

To handle the COVID-19 pandemic, the US FDA first issued an emergency use authorization on test kits used to detect nucleic acid SARS-CoV-2 (Mitchell et al., 2020). On February 29, 2020, the FDA issued a “Policy for Diagnostics Testing in Laboratories Certified to Perform High-Complexity Testing Under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency” which serves as a guide for laboratory testing of SARS-CoV-2 test kits that can be submitted for EUA approval (Lefferts et al., 2020). As the test was developed under the EUA, there is no standardized sensitivity or specificity data for the test kit. False positive and false negative cases that occur during clinical practice make it necessary to combine test results with clinical symptoms to establish an accurate diagnosis (Joyce et al., 2021).

The EUA approval on diagnostic medical devices during the COVID-19 pandemic set a precedent for issuing EUA for COVID-19 treatment therapies, such as remdesivir, convalescent plasma, propofol 2%, hydroxychloroquine, ruxolitinib, bamlanivimab, etesevimab, baricitinib, casirivimab, and imdevimab (Bhimraj et al., 2022; Rizk et al., 2021). Time constraints and high pressure from the public to find rapid COVID-19 therapies have led to EUA approval being based on research that is less robust and often does not have a control group. Cooperation and collaboration between governments, manufacturers, and the clinical research community are needed to develop safe and effective therapies. Despite these shortcomings, the rapid expansion of the trial as a whole could help researchers draw important preliminary conclusions, such as treatment with remdesivir requires further investigation and the use of hydroxychloroquine, which was later found to be not as effective as in preclinical testing (Bhimraj et al., 2022; Cassidy et al., 2020).

There is sufficient clinical evidence available for therapy using remdesivir so the FDA has issued a New Drug Application approval for remdesivir (Tran & Witek, 2021). This is different from hydroxychloroquine therapy. The EUA approval of hydroxychloroquine is based on a large body of literature regarding its potency against several strains of viruses and preliminary clinical data on its therapeutic benefit in the treatment of COVID-19 patients. Although preliminary clinical data support its use for the treatment of COVID-19, hospital observations and clinical evidence from large-scale randomized clinical trials do not demonstrate a clinical benefit of hydroxychloroquine. In the end, the FDA revoked hydroxychloroquine's EUA authorization and no longer used it as a COVID-19 therapy (Manivannan et al., 2021).

Although the Randomized Controlled Trial remains the gold standard for assessing the safety and effectiveness of a therapy, implementing the EUA can help provide a fast and timely response to a pandemic (Rizk et al., 2021). EUA approval makes needed drugs quickly available and expands treatment options. However, only evidence-based treatment should be the standard of care. Notwithstanding EUA approval, healthcare facilities and physicians are under no obligation to offer unproven interventions. But rather they must assess the available evidence and treat patients accordingly. Therefore, the decision to offer EUA products that have not been proven exclusively through clinical trials is ethically permissible. But it is still important to make evidence-based treatment decisions (Lynch et al., 2021).

For vaccines, one of the vaccines that were granted EUA approval by the FDA was the Pfizer-BioNTech COVID-19 vaccine, which was administered in December 2020. In addition to the FDA, the European Medicines Agency (EMA) in Europe and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK also gave EUA approval for this

vaccine. In its development, this vaccine has successfully passed phase 3 clinical trials, so the FDA finally gave full regulatory authorization approval (Parums, 2021). This shows that the EUA approval can become a full regulatory approval if it can submit the required data.

The EUA guidelines that are issued by the FDA encourage researchers and manufacturers to create effective products at affordable prices and comply with EUA guidelines. One of the products designed based on these guidelines is a mechanical ventilator that applies an efficient design and is specifically designed for its application in handling the COVID-19 pandemic. The test results for precision, safety, and reliability meet the requirements of the emergency use guidelines, so this ventilator received EUA approval from the FDA (Raymond et al., 2022)

CONCLUSION

The EUA approval for pharmaceuticals and medical devices is a form of resilience in the face of a pandemic and is an effective way to meet increasing needs. The EUA approval must be accompanied by clinical evidence and evidence in the field so that pharmaceuticals and medical devices on the market have safety, quality, and efficacy. The ability and experience in implementing the EUA, including during the rapid data collection process, as well as collaboration with manufacturers and researchers, can be a guide for learning in dealing with pandemics in the future.

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