

Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies, United States

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The US Emergency Use Authorization (EUA) is a critical new tool for medical and public health communities and is applicable for both civilian and military use. It fills the need for timely and practical medical treatment under emergency conditions and authorizes use of the best product available for treatment or prevention when the relevant product has not already been approved or approved for this specific use by the US Food and Drug Administration. The need for and genesis of the EUA, its requirements, its broad application to civilian and military populations, and its features of particular importance to physicians and public health officials are detailed.

The Project BioShield Act of 2004 (Public Law 108–276; “the Act”), among other provisions, established the comprehensive Emergency Use Authorization (EUA) program. EUA permits the US Food and Drug Administration (FDA) to approve the emergency use of drugs, devices, and medical products (including diagnostics) that were not previously approved, cleared, or licensed by FDA (hereafter, “unapproved”) or the off-label use of approved products in certain well-defined emergency situations. EUA provides physicians and public health officials with an important new tool with wide-reaching implications for medical care under emergency conditions. More detailed information on FDA’s policies for authorizing the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency can be found in the draft FDA guidance document made available on July 5, 2005 (*1*).

Government Need for EUA Authority

After the events of September 11, 2001, and the anthrax postal attacks <1 month later, the US Department of

Health and Human Services (HHS) began developing plans for large-scale off-label use of FDA-approved pharmaceutical products, and in some cases of unapproved products, during a national emergency. This undertaking was especially important at the time because critical components of the biodefense armamentarium were, for various reasons, either unapproved products or approved products whose use as countermeasures was not approved by FDA. At the time, the sole mechanism for making unapproved products available in an emergency was through an Investigational New Drug (IND) protocol or an Investigational Device Exemption.

The medical and public health communities have long recognized that, regardless of how swiftly FDA approves drugs and other medical products, there will always be promising drugs, biologic products (e.g., vaccines, blood products, and biologic therapeutics), and devices (e.g., in vitro diagnostics) that do not have FDA approval (unapproved products) as well as promising off-label uses of drugs, biologic products, and devices that are approved by FDA for other indications. These unapproved or off-label products may be the very best preventive, diagnostic, or therapeutic options available. A physician in practice can prescribe an approved drug for an off-label use or an unapproved drug (subject to state practice of medicine statutes and regulations and FDA policy and legislation) on a patient-by-patient basis. However, large-scale use of unapproved drugs or off-label use of approved drugs, before passage of the Act, could only be carried out under an IND protocol.

IND requirements include Institutional Review Board (IRB) approval of the investigational protocol, documented

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informed consent from all patients describing, among other things, the research purposes of the protocol, substantial record keeping, and patient follow-up requirements. Although an IND mechanism is well-suited for a clinical study and can be used in an emergency situation for an individual patient, the mechanism is ill-suited for situations such as a universal vaccination campaign against a life-threatening infectious disease taking place in the context of a national emergency.

In 1987, FDA issued regulations to establish the Treatment IND as a new regulatory category of INDs (2). The purposes, requirements, and implications for physicians of the Treatment IND are described in the medical literature (3,4). The Treatment IND allows the more extensive use of an investigational product for treatment of life-threatening or serious diseases; however, it did not eliminate the clinical study nature of an IND or the practical aspects that could prove problematic in a national emergency situation. Public health officials would most likely be unable, for example, to comply with the requirements of an IND protocol if smallpox vaccine needed to be administered quickly to a large population during a smallpox epidemic or if an approaching influenza pandemic required widespread distribution and unapproved or off-label use of critical antiviral medications. Experience with attempts to use an IND to offer the licensed anthrax vaccine off-label in a postexposure setting to postal workers possibly exposed to anthrax in the 2001 anthrax postal attack highlighted substantial shortcomings with this approach. While important steps would be taken in good faith to make the IND mechanism work in a national emergency, an alternative was needed: something short of licensure that included specific safety, efficacy, and quality requirements in a manner less administratively burdensome than the IND mechanism. The country needed an emergency mechanism built not on a clinical research model, but on a public health model.

Previous Approaches to Large-Scale Treatment Use of Unapproved Products and Approved Products Off-label

The first widespread use of an IND protocol was in 1971 for admitting narcotics addicts into methadone treatment programs authorized by the US government. Methadone had already long been marketed as a narcotic analgesic and as a cough suppressant, and it was subsequently approved for narcotic maintenance treatment in 1972 (5). More than 80,000 patients are estimated to have entered the IND program. This closed distribution system for both the IND and the newly approved use was strictly controlled by FDA and the Drug Enforcement Administration because methadone for narcotic maintenance treatment was only available in programs licensed for this purpose by the government.

During the 1980s, FDA developed several new programs to accommodate the need to make the newest drugs to combat HIV/AIDS and cancer available as quickly as possible (3). All of these large programs required IRB review, written informed consent, and reporting that are mandated for other INDs and that could be fulfilled in the context of an ongoing public health situation that, while grave, did not rise to the level of an immediate national security emergency. These programs included the Treatment IND and a new regulatory approach permitting accelerated approval of new drugs.

During the preparations for the Persian Gulf War, the Department of Defense (DoD) determined that several important medical countermeasures would be needed to protect troops in the Gulf. Two of these products were under INDs for these uses at the time: botulinum toxoid to prevent botulism, and pyridostigmine bromide to protect against a chemical nerve agent. Pyridostigmine bromide was already approved by FDA, but the approved indication and dosage formulation were different from those sought for use by DoD. DoD determined that the INDs were needed for force protection in response to specific threats and, on DoD's request, FDA issued an interim final regulation that established a special IND process that included the waiver of informed consent (6). This policy evolved on the basis of the danger that individual refusal to take these medications would threaten the well-being of not only that soldier but also others in the unit, thus compromising force protection and the success of the military mission (7). This regulation was later rescinded (8) and replaced with new legislation for DoD that requires specific presidential approval for waiving informed consent in each military emergency (9). The EUA, with its provisions for both military and civilian uses, would later provide an alternative to this special IND process.

For civilian defense, HHS has developed over the past decade a national stockpile of medical countermeasures that could be used in the event of a biological, chemical, radiologic, or nuclear attack. More recently, the national stockpile has been acquiring antiviral drugs, investigational and approved influenza vaccines based on highly pathogenic avian influenza (H5N1) strains, respirators, masks, and other items to prepare the United States to respond to pandemic influenza. Since many of the drugs and other medical products in the national stockpile were either unapproved or were not approved for the countermeasure indication, the Centers for Disease Control and Prevention (CDC) developed protocols for their use under the IND mechanism. As discussed above, however, these protocols would most likely fall short in providing the flexibility needed for effective use in national emergency situations.

Requirements for Granting and Implementing an EUA

The Project BioShield Act of 2004 included new language for section 564 of the Food, Drug and Cosmetic (FD&C) Act that created the EUA in a provision entitled Authorization for Medical Products for Use in Emergencies (10). The EUA provides an effective solution to the challenges posed by emergencies involving both civilian and military populations. It addresses the off-label use of FDA-approved products and the use of unapproved products for prevention, treatment, or diagnosis under emergency circumstances. The steps required by the Act before issuance of an EUA are shown in the Table.

Issuance of an EUA is predicated on a Declaration of Emergency that justifies the authorization of the EUA by the secretary of HHS. The secretary may declare such an emergency on the basis of any of the following: 1) the secretary of Homeland Security determines there is a “domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a specified biological, chemical, radiologic, or nuclear agent or agents”; 2) the secretary of defense determines that there is a similar emergency or potential emergency threatening military forces; or 3) the secretary of HHS determines that there is a “public health emergency under section 319 of the Public Health Service Act that affects, or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents” (10). The Act has no requirement that the emergency be the result of a deliberate attack with a CBRN agent to permit use of the EUA. For example, the secretary of HHS could find that an emerging infectious disease or pandemic (such as pandemic influenza) is so serious that it could rise to the level of affecting national security and thus declare a public health emergency under the terms of the Act.

Following the HHS secretary’s Declaration of Emergency justifying issuance of the EUA, the FDA commissioner, under delegated authority from the secretary of HHS, may issue an EUA after consultation, to the extent feasible and appropriate given the circumstances of the emergency, with the directors of the National Institutes

of Health (NIH) and CDC, if he or she concludes that 1) the agent listed in the emergency declaration can cause a serious or life-threatening disease or condition; 2) on the basis of the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the medical product may be effective in diagnosing, treating or preventing this disease or condition or a serious or life-threatening disease or condition caused by another EUA-authorized product or an otherwise approved or licensed product; 3) the known and potential benefits of the medical product, when used to diagnose, prevent, or treat the disease or condition, outweigh the risks, both known and potential; and 4) no adequate, approved, alternative medical product is available.

In addition to these statutory requirements, HHS, through its Office of the Assistant Secretary for Preparedness and Response (formerly the Office of Public Health Emergency Preparedness), has established the Secretary’s Emergency Use Authorization Working Group (EUA WG). This is an interagency committee consisting of federal officials with expertise in public health, medicine, law, ethics, and risk communication. It provides recommendations to both the secretary and the FDA commissioner on use of the EUA, as well as facilitating education and communication about the EUA with healthcare professionals and the public.

Although an EUA may not be issued until after an emergency has been declared by the secretary, FDA recognizes that during such exigent circumstances, the time available for the submission and review of an EUA request may be severely limited. Therefore, FDA strongly encourages an entity with a possible candidate product, particularly one at an advanced stage of development, to contact the FDA center responsible for the candidate product even before a determination of an actual or potential emergency is made. The types of information FDA believes are important to allow an assessment of safety and effectiveness of a product and to make an adequate risk-benefit determination to support issuance of an EUA are provided in the FDA draft EUA guidance previously mentioned (1). If, before the Declaration of Emergency, FDA believes that a candidate product may meet the criteria for an EUA, the agency may share appropriate information on such product with the secretary’s EUA WG.

Table. Actions required before issuance of an EUA*

Step	Required action	Responsible authority
1	Determination of an emergency justifying issuance of an EUA	Secretary of Homeland Security OR Secretary of Defense OR Secretary of Health and Human Services
2	Declaration of emergency	Secretary of Health and Human Services
3	Consultation (to the extent feasible) between the FDA, NIH, and CDC	FDA commissioner, NIH director, CDC director
4	Issuance of an EUA	FDA commissioner (under delegated authority from Secretary of Health and Human Services)

*EUA, Emergency Use Authorization; FDA, US Food and Drug Administration; NIH, National Institutes of Health; CDC, Centers for Disease Control and Prevention.

If the decision is made to issue an EUA, to the extent practicable given the circumstances of the emergency, the FDA commissioner must prescribe certain conditions of use aimed at protecting public health and may prescribe additional conditions for protecting public health. These conditions, and which ones are mandatory, differ depending on whether the EUA authorizes use of an unapproved product or authorizes an off-label use of an FDA-approved product. However, certain basic provisions must be met under all cases, examples of which are described below (a more detailed description of conditions of use that may be applied can be found in the draft FDA guidance [1]).

For example, to the extent practicable given the circumstances of the emergency, both healthcare providers and their patients must be made aware that the product has been authorized for emergency use, must know the “significant known and potential benefits and risks” of emergency use of the product and extent to which such benefits and risks are unknown, and must be informed of any alternatives that may be available and their benefits and risks. Additionally, as a general rule, persons must be made aware of their right to refuse the product (or to refuse it for their children or others without the capacity to consent) and of the potential consequences, if any, of this choice. An exception to this rule is that the president, as commander in chief, can waive military personnel’s right to refuse this product. If the right is not specifically waived by the president for a particular product given under EUA, military personnel have the same right to refuse as civilians. FDA expects that such information will be disseminated to healthcare providers and the general public in the most effective and expeditious way possible, including use of informational leaflets, the media, Internet, videos, and direct communications from public health officials.

During administration of an EUA product, a system would be developed to collect and analyze safety and efficacy information on unapproved products, and such a system may also be developed for unapproved uses of approved products. Adverse events arising from use of the product would be carefully monitored and reported. The FDA commissioner would periodically review the safety and efficacy data collected on EUA products and could revoke the EUA at any time if the criteria for the EUA are no longer met or to protect public health and safety. For unapproved products, the commissioner may choose to designate the persons or entities that may distribute and administer the product for emergency use. For example, the commissioner may choose either to route products under an EUA to central dispensing sites or, in cases where the transportation and congregation of large populations are either dangerous or impractical, allow for distribution of required medications and appropriate product information by postal workers or others. Unless previously revoked or

renewed, an EUA will expire 1 year after the Declaration of Emergency.

Implications of the EUA for Physicians

Although similarities exist, use of a product under an EUA is substantially different from use of a product under an IND protocol. For example, EUA products do not require the detailed, formal, informed-consent process used for human research study participants. However, to the extent practicable given the circumstances of the emergency, prospective patients will always be informed about the opportunity to accept or refuse an EUA product (except for those cases noted above in which the president has specifically waived this right for military personnel) and be given all the information necessary to make this informed choice, as they would for any product offered to them by their healthcare provider. Other unique features of medical product distribution under an EUA include the fact that requirements for the distribution and administration of a EUA product will be determined by the FDA commissioner, in consultation with the directors of CDC and NIH, on a case-by-case basis for each EUA requested. In addition, EUAs do not have to be reviewed by an IRB when they are used for public health purposes. Also, there is no requirement that would prevent EUA products from being dispensed without a physician’s prescription; thus, in a national emergency, prescription products could be provided by a nonlicensed provider or any distribution method or location approved by the FDA commissioner in issuing the EUA.

Concerns have been raised about the liability and compensation protections associated with potential use of a medical product under an EUA. The Public Readiness and Emergency Preparedness Act of 2005 (Public Law 109–148), provides immunity from liability claims arising from administration and use of covered countermeasures to involved manufacturers, distributors, program planners, and qualified persons (with the exception of claims arising from willful misconduct). Covered countermeasures are those that address a disease or condition that the HHS secretary has determined poses a public health emergency or a credible risk of causing a public health emergency in the future. The first such declaration supporting liability protection was made by the secretary in February 2007 regarding vaccines to address pandemic influenza (11). This same coverage could be used for other medical countermeasures in the future, including those that would be used under an EUA.

Although we describe recent legislation in the United States that enables emergency use of products not yet approved by the FDA, or approved only for uses or administration not suitable for emergency situations, we are aware that some other countries have developed procedures

to permit such use. We are also aware that various other countries' national legislation would not restrict such off-label use, or even use of unapproved products, in emergency situations. We believe that sharing general information on potential mechanisms for addressing these issues can help all countries better prepare for, and respond to, emergencies of all types. Most importantly, sharing experiences in the authorization and use of particular products to address emergency needs will be especially helpful to other countries as they identify countermeasures for their own stockpiles.

EUA for Anthrax Vaccine Adsorbed (AVA)

The first use of the EUA authority was in 2005. It occurred in response to a unique set of circumstances, but nonetheless stands as an example of an effective public health response to a need for large-scale use of a medical countermeasure to a biologic agent. Since 1998, to protect against the threat of anthrax attack, the armed forces have vaccinated a substantial number of their members with AVA, a vaccine licensed since 1970 but not originally contemplated as a biowarfare or bioterrorism countermeasure. The program has had detractors and has been the subject of litigation. In late 2004, a federal court issued an injunction against the DoD program on the grounds that the FDA should have obtained public comments before issuing a determination confirming that the AVA license included use for prevention of inhalation anthrax. The court decision effectively deemed use of AVA to prevent inhalation anthrax an unapproved use of an approved drug.

While awaiting the conclusion of the public comment process, DoD, to address what it considered to be the adverse effect of the injunction on military readiness, asked for an EUA to allow a continuation of military vaccinations against anthrax. Then Deputy Defense Secretary Paul Wolfowitz (with assigned authority from the secretary of defense) determined on December 22, 2004, pursuant to the Act, that there was a significant potential for a military emergency involving anthrax and requested that an EUA be issued for AVA. Then-HHS Secretary Tommy G. Thompson issued a Declaration of Emergency on January 14, 2005 (12). On the basis of this declaration and having concluded that the criteria for issuance of an EUA were met, then-Acting FDA Commissioner Lester Crawford, in consultation with the directors of NIH and CDC, issued an EUA for AVA on January 27, 2005 (13). In this instance, therefore, the time from request for an EUA to issuance of the EUA was 5 weeks. The timelines for FDA review and action on a request for consideration for an EUA will depend on the product profile; the existence, if any, of pending pre-EUA applications for the product; the nature of the emergency; and other relevant factors. Although the time required for FDA action will vary, FDA recognizes that it

is likely that, in an emergency situation that is occurring or believed imminent, a request for consideration for an EUA will be acted upon within a matter of hours or days.

Importantly, the EUA issued by Dr. Crawford required DoD to inform military members that they had an option to refuse the vaccine and that no adverse action would be taken against those who declined the vaccine under the EUA. The issuance of this EUA cleared the way for DoD to resume anthrax vaccinations to protect military personnel assigned to certain higher threat areas. This first use of the EUA authority illustrates its important statutory purpose: FDA determined that anthrax vaccine was the best available medical countermeasure to the potential military emergency posed by the risk for attack with anthrax and allowed DoD to use it.

The EUA for AVA was originally issued for 6 months on the request of DoD. Under the Act, an EUA can be extended within the duration of the Declaration of Emergency if the criteria under Section 564(c) of the FD&C Act for issuance of such authorization are still met. On July 22, 2005, the then-FDA commissioner extended the EUA for the duration of the Declaration of Emergency, which terminated on January 14, 2006. During the period of the EUA, more than 100,000 anthrax vaccinations were given. The EUA was allowed to expire on January 14 because FDA, on December 19, 2005, issued a final order concluding that AVA is safe and effective for its labeled indication, to protect persons at high risk for anthrax disease. This action permitted DoD to resume vaccination with AVA for its licensed indication, and an EUA was no longer required.

Conclusions

EUA is a critical new tool for the medical and public health communities and is applicable for both civilian and military use. It fills the need for timely and practical medical treatment when the relevant product has not already been approved or approved for this specific use by the FDA. An understanding of this new product category and its implementation is important to those who will be on the frontlines providing direct care, as well as to those who will be managing mass care situations.

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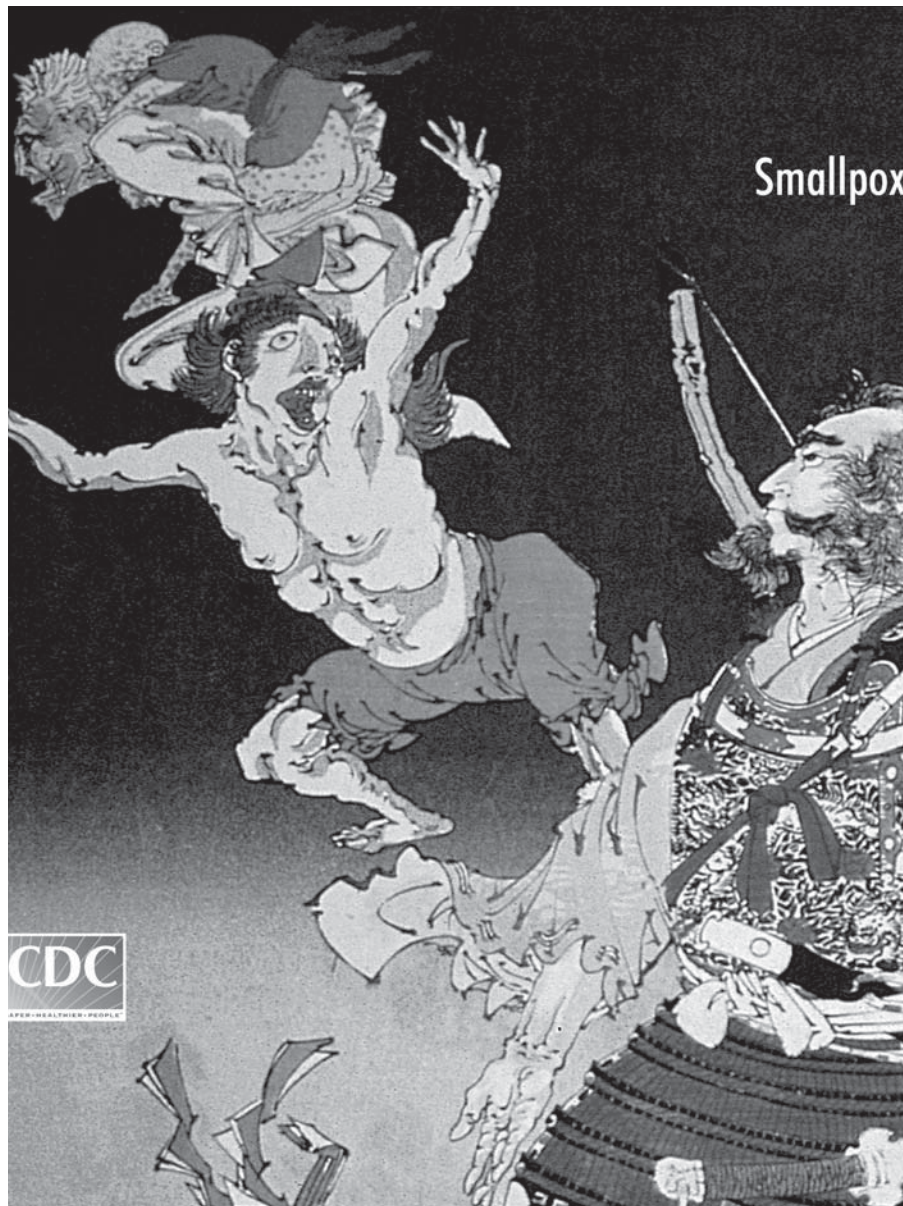
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