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Institute of Medicine (US) Forum on Medical and Public Health Preparedness for Catastrophic Events. Medical Countermeasures Dispensing: Emergency Use Authorization and the Postal Model, Workshop Summary. Washington (DC): National Academies Press (US); 2010.

Emergency Use Authorization

Background

The EUA program was established in 2004, when the *Project BioShield Act*, among other measures, amended Section 564 of the *Federal Food, Drug, and Cosmetic Act* to include this provision (HHS, 2010a). EUA permits the FDA Commissioner to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security (FDA, 2007).

EUA is an important tool for public health officials and physicians involved in an emergency response because it can enable them to use the best countermeasure available to detect, prevent, or treat a disease or injury in certain populations, even if that countermeasure is unapproved by the FDA or not approved for that particular use.

Prior to the response to H1N1 in 2009, only two EUAs had been issued—one for a medication for the prevention of inhalation anthrax (the authorization has since been terminated) and the second for antibiotic emergency kits for the postal model, which was issued in 2008 and is still in effect. The majority of EUAs issued have been in response to 2009 H1N1. At the time of the workshop, one EUA had been issued for N95 respirators, three for antiviral medications, and nine for in vitro diagnostics (FDA, 2010a, 2010b, 2010c, 2010d). Additional EUAs for nine diagnostic tests were issued after the workshop. The declaration of a Public Health Emergency for 2009 H1N1 Influenza expired on June 23, 2010, and, therefore, the EUAs issued for the 2009 H1N1 response have been terminated (CDC, 2010f).

At the workshop, participants noted that EUA has a broader use beyond enabling the use of an unapproved product or extending the use of an approved product to populations for which it was not approved. In particular, it can also be used to address labeling requirements and other challenges that arise because of constraints inherent in a public health response. “From a legal perspective, there are a lot of situations where EUA helps get past all those requirements,” said Sherman of HHS. “You can change the labeling. You can change the information. You can change the dosage. You can give it to populations for which wasn’t approved.” She continued, “In some sense we had to match up in practice a public health response where you might not have the precise labeling that your physician would prescribe to you. There are a lot of variables that are necessary for the public health responders that don’t necessarily match what the approved drug would look like if you just went to your physician and got it because you had that illness.”

This section will begin by outlining the role of EUA within the FDA’s mission and the process by which an EUA may be issued. Following that, the section will consider the EUAs issued in response to 2009 H1N1, highlighting the successes and advances as well as the challenges and the areas identified by participants in which further work could enhance future emergency responses.

The Role of EUA Within the FDA’s Mission

EUAs are issued by the FDA and, therefore, reflect the FDA's mission to protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA is responsible for the following areas related to counterterrorism and emerging threats:

- Facilitating the development and availability of medical countermeasures;
- Protecting the safety and security of regulated medical products;
- Enhancing emergency preparedness and response capabilities;
- Implementing comprehensive food security strategy; and
- Ensuring safety and security of agency assets.

"The bottom line is that the FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of drugs, biologics, and devices," said Carmen Maher, policy analyst/senior nurse officer, Office of Counterterrorism and Emerging Threats, FDA. Included in that broad purview are ventilators and personal protective equipment.

As a general rule, health needs must be met with medical countermeasures that are supported by good science and that follow regulatory requirements. In non-emergency situations, explicit labeling laws and prescription and usage guidelines are required by FDA and state laws to protect the public. During an emergency, the FDA considers the potential benefit that an EUA would provide, while never abandoning its essential mission to ensure the safety, efficacy, and security of the medical countermeasures used. More information on FDA's policy regarding EUA can be found in the FDA guidance document on this topic (FDA, 2007).

The EUA Process

The process of issuing an EUA involves five steps:

1. Determination of an emergency;
2. Declaration of an emergency;
3. Review of the request for EUA by the FDA;
4. Issuance of the EUA or denial of the request; and
5. Termination of the EUA.

The determination of an emergency can be made by HHS, Department of Homeland Security, or Department of Defense. The emergency can be a military, domestic, or public health emergency that affects, or has a significant potential to affect, national security. Agents involved include chemical, biological, radiological, or nuclear agents. Both the determination and the declaration of the emergency must state the nature of the threat involved.

Once a determination of an emergency has been made and an emergency has been declared, the FDA reviews the EUA request and, if feasible and appropriate given the circumstances of the emergency, consults with the National Institutes of Health and the CDC. If the request is found to meet statutory criteria, the FDA Commissioner issues an EUA. The termination of an EUA is linked to the declaration—once the declaration expires, so does the EUA. A single declaration can support multiple EUAs as necessary.

Pre-EUA

Although the law does not allow the FDA to preauthorize an EUA before the determination and declaration of an emergency, the process can begin before the actual emergency occurs. Specifically, a request can be submitted to the FDA regarding situations that may happen, such as potential anthrax attacks or smallpox outbreaks. This is called a pre-EUA. In these instances, informed speculations are made about what the emergency situation might be. Maher explained, "We are already looking at the data for the products that could be used in those situations, including what [are] the science and the data behind [those products] and how [they] would be used, as well as how the EUA would be crafted." A pre-EUA allows the FDA to begin work on fact sheets and other documentation. "What we have done with the pre-EUA situation is get the fact sheets as close as we can to what we think the final fact sheets would be and allow the state to go and reproduce that," Maher said. If an emergency is declared and the EUA is formally requested, final review could be done, and if any substantive changes were needed, the FDA would work with the state to make sure those changes were incorporated.

What Can an EUA Cover?

The development pathway for medical countermeasures (and other drugs) has three phases—pre-IND (investigational new drug), IND, and NDA (new drug application). The NDA is how drug sponsors formally propose that the FDA approve new pharmaceuticals for sale and marketing. It is not a requirement that products be in a specific point of the development pathway to be considered for EUA, but it is implied that the product is currently undergoing development or has been developed and therefore has gone partially down the pathway. It is important to recognize that an EUA is not part of the development pathway; it is an entirely separate entity that is used only during emergency situations and is not part of the drug approval process.

An EUA must meet the following four statutory criteria to be considered. The goal of these criteria is to ensure that even in an emergency, the public is receiving the best, safest, most appropriate care possible.

1. There must be a serious or life-threatening illness caused by a specified chemical, biological, radiological, or nuclear agent.
2. It must be reasonable to believe that the product covered by the EUA is going to be effective for the intended use—diagnosing, treating, or preventing either an illness or condition caused by a specific agent, or an illness or condition caused by an approved or authorized medical countermeasure deployed against the agent.
3. The known and potential benefits need to outweigh the known and potential risks.
4. There must be no adequate approved, alternative medical countermeasures available for the situation.

EUAs may waive a number of regulatory requirements to allow unapproved products or approved products to be used in unapproved situations as emergency medical countermeasures. Typically, for instance, when an unapproved product is used in a clinical setting, it requires either informed consent or review and approval by an institutional review board. EUAs can waive that requirement for the duration of the emergency. For example, one EUA issued for the 2009 H1N1 pandemic allowed the use of the (as-yet-unapproved) peramivir IV in clinical settings to combat severe influenza, without either informed consent or board review. In this case, no other intravenous antivirals were effective against these severe infections, and the FDA determined that there were sufficient data and need to allow administration of peramivir IV under an EUA.

"In the specific situation of EUA or emergency use of any product, we are looking at the emergency, the circumstances of the emergency, the product's regulatory status, proposed indication, safety and efficacy data, adverse events described in the product labeling or in the investigators' brochure if it was there," Maher said.

The FDA also looks at various operational issues and partners with the CDC to consider issues such as:

- When will it be dispensed: before or after the event?
- How will it be dispensed and by whom? In a hospital setting or not, by licensed or non-licensed providers?
- What is the time frame—is there a therapeutic window that needs to be met?
- What are the operational limitations on the ground and how will they be handled?
- Is the product available in sufficient quantities to meet the need or will it be made available? Can it be manufactured in time to meet the need at hand?

"We have to strike that balance to ensure the safe and efficacious use of the product, but [also] to ensure that the right product is getting to the right person at the right time," Maher said.

Conditions of Authorization

The letter of authorization issued by the Commissioner of the FDA includes the conditions of authorization, which address all the elements that are part of the EUA. This is where roles are clarified, and specific conditions are laid out for different parties, such as public health authorities, manufacturers, healthcare facilities and providers, and others who dispense or distribute the products. Examples of what can be addressed within the conditions of authorization include the following:

- Specific information for healthcare practitioners and authorized dispensers;
- Specific information for recipients;
- Adverse event reporting and monitoring;
- Recordkeeping/access;
- Restrictions on distributing and administration;
- Restrictions on advertising;
- Data collection and analysis; and
- Compliance with good manufacturing practice.

Intersection of EUA and the PREP Act

Healthcare providers, manufacturers, and healthcare organizations are often concerned about liability protection during medical countermeasures dispensing campaigns. This is especially true when the use of medical countermeasures is authorized under an EUA. Workshop participants noted that they often receive questions about the relationship between the issuance of an EUA and a PREP Act declaration, which provides immunity from liability claims arising from administration and use of covered countermeasures to manufacturers, distributors, program planners, and other qualified persons.

An EUA is issued separately from a PREP Act declaration. “It’s not automatic that an EUA will have a PREP Act declaration,” Courtney said. It is also not a requirement that a PREP Act declaration be made for an EUA to be issued.

Courtney continued, “In addition, according to the FDA, if a PREP Act declaration does exist for a product that has an EUA, but the terms of the EUA are violated, then the PREP Act protections might not apply.”

The PREP Act itself has sometimes been an additional motivating factor for requesting an EUA. The statute states that coverage is only available for medical countermeasures that are approved and licensed by the FDA under an IND, investigational device exemption (IDE), or EUA. “We have made commitments by issuing these PREP Act declarations to various folks, the manufacturers, the distributors, and everyone in the chain, that they will have this liability protection,” said Sherman of HHS. “If we can’t be sure that the product is covered by one of those FDA mechanisms, we can’t necessarily guarantee that the PREP Act for liability coverage would remain in place.”

Successes in the Response to 2009 H1N1

The response to H1N1 was made possible largely because of the use of multiple EUAs, which allowed use of a yet-unapproved antiviral medication, deemed to be critical in caring for severely ill patients, and extended the use of other antiviral medications and countermeasures to larger populations than would otherwise be allowed. EUAs also assisted public health authorities with addressing challenges such as labeling restrictions and changes in the information provided to recipients of the countermeasures. Although the *Project BioShield Act* granted the authority for EUA in 2004, only 2 EUAs had been issued prior to 2009. In 2009 and 2010, EUAs were issued for 22 products in response to 2009 H1N1. Three were issued for antiviral medications and one for personal respiratory protection devices (Table 2) (FDA, 2010a, 2010b, 2010c). In addition, EUAs were issued for 18 diagnostic tests; some of these were issued after the workshop took place (FDA, 2010d). Because of this, those involved in issuing, interpreting, and using EUAs gained much deeper experience during the year leading up to the workshop, and many new developments emerged.

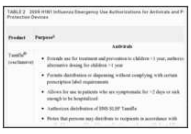

TABLE 2

2009 H1N1 Influenza Emergency Use Authorizations for Antivirals and Personal Respiratory Protection Devices.

The first part of this document described several aspects of medical countermeasures dispensing in response to the 2009 H1N1 pandemic, including distribution from the SNS, challenges faced by public health departments, public–private partnerships, and liability protection. This second look at the response to the 2009 H1N1 influenza pandemic focuses on the use of EUA during the response, improvements to the EUA process based on this experience, and areas that should be addressed when moving forward.

EUAs issued during the 2009 H1N1 response included both unapproved uses of approved drugs as well as the use of an unapproved drug. “We sought to address what we perceived as a drug shortage issue,” said Brad Leissa, deputy director in the Office of Counter-Terrorism and Emergency Coordination at the FDA’s Center for Drug Evaluation and Research. For example, some areas of the country experienced acute shortages of Tamiflu oral suspension that were addressed by making available expired lots of medication that had been tested through the FDA’s Shelf-Life Extension Program (SLEP). These “expired” lots would usually require relabeling

before use. The lots would have needed to be sent to a relabeler, then back to the SNS for redistribution to the states. “If the public health authority wanted to [relabel], they have the authority under the EUA to do that. If they chose not to, they did not have to,” Leissa explained.

The prescribing guidelines for Tamiflu were expanded to include children under a year old and patients who had been symptomatic for more than 2 days or who were sick enough to be hospitalized (FDA, 2010a). These uses were beyond the usual guidelines, but were determined to be necessary for the most people to receive the best care possible. The guidelines for the use of Relenza were also expanded to include patients who were symptomatic for more than 2 days or who were hospitalized, and certain “expired” lots were tested and authorized for use (FDA, 2010a).

The response to 2009 H1N1 also marked the first time that an EUA has covered an unapproved product—peramivir (FDA, 2010b). Peramivir IV is not approved by the FDA for any indication. “Here we had an unmet medical need,” Leissa recalled. There was no approved IV antiviral product that was effective against this virus. In generating the EUA, the FDA put together a 40-page fact sheet that attempted to include the best information available for practitioners, covering what was known of the risks and benefits of the investigational product as well as what was unknown.

The FDA and the CDC put the approved EUAs on their websites for public view, making them easily accessible and completely transparent.[4] Susan Gorman, associate director for science at the SNS, noted it was the first time “we have had such a multifaceted, extensive communication campaign.”

Gorman also noted that the EUA system was flexible enough to enable various amendments to existing EUAs that were needed during the 2009 H1N1 response to allow the use of expired assets that had been tested through SLEP.

Challenges and Areas for Further Work

The 2009 H1N1 response also made clear a number of challenges, gaps, and barriers associated with EUAs, participants noted during the workshop. Over the course of the workshop, participants highlighted some of these challenges and discussed directions for further work. While by no means a comprehensive review, some of the more pressing concerns and needs are described below.

Communication About EUAs

Workshop participants noted that despite efforts by the FDA and the CDC to post EUAs and associated information on their websites, many providers, public health officials, their legal counsels, and members of the public continued to have questions about EUAs in general, and about the specific EUAs issued in response to 2009 H1N1.

The FDA attempted to clarify what the EUAs covered and what they did not by revisiting the questions and answers it published. In an effort to make the process as transparent as possible, Sherman said, the emergency declarations behind the EUAs, which are handled by her office, should be posted in a more timely manner. “Lawyers are a lot happier if they can see every step in the process,” she noted.

Some providers and members of the public were also confused about why an EUA was needed in certain cases and what impact, if any, the EUA had on other regulations, standards, and usual procedures. For example, the release of an EUA for N95 respirators caused some confusion. “As people in occupations were having their respirators fit-tested, and they were using them on a

regular basis, they did not understand why now an EUA would be needed for those things," Gorman explained. Some personnel thought the EUA meant that the respirator-protection standard no longer applied, and the work that employees were doing was no longer protected by Occupational Safety and Health Administration (OSHA) standards. The question became, Did the EUA supersede OSHA's fit-testing requirements for occupations that required these respirators? To clarify matters, the EUA was quickly amended to include the following text: "For the purposes of this letter of authorization, the term 'general public' is broad and includes people performing work-related duties. This authorization affects only requirements applicable under the *Federal Food, Drug and Cosmetic Act*. If respirators are used for people performing work-related duties, employers must comply with the OSHA Respiratory Protection Standard, 29 CFR 1920.134, found at www.osha.gov." That such clarification was needed illustrates the importance of communicating with a wide range of stakeholders during the EUA process.

Providers also need to be better educated about what each new EUA means because it may affect their liability. Gloria Addo-Ayensu, health director of the Fairfax County Health Department in Virginia, suggested that information given to providers be put into simple bullet points, so that when patients ask about the risk associated with the medication that is being prescribed, the physician has a quick and easy reference. She noted, "Patients often ask their providers what the risk of using the drugs are and so on, and many practitioners don't have any idea, which in itself is a liability issue."

Fact Sheets and Documentation

The need to create millions of fact sheets that explain to patients what medication they are taking, how to take it, and what side effects may occur, along with documentation tracking medical countermeasures dispensing, is a major challenge for emergency planners and responders. This problem is exacerbated for countermeasures that are used under an EUA because, as discussed earlier, the EUA cannot be issued prior to the declaration of the emergency. Because of this, the conditions of authorization for that EUA are not known in advance, and these conditions specify the information that must be provided to healthcare practitioners, authorized dispensers, and recipients, as well as requirements for record-keeping and data collection. Therefore, it is impossible to fully produce fact sheets and recordkeeping documentation before the emergency and issuance of the EUA.

Kevin Sell, pharmacist consultant to the Minnesota Department of Health's Office of Emergency Preparedness, illustrated that point using the example of the state of Minnesota. "We are only 1.7 percent of the population in the United States, yet we still potentially have to generate up to 5 million forms in dozens of languages. At a minimum, in our metro area alone, we would have to generate [forms in] at least five different languages beyond English." He went on to say, "Patient information, drug information: We can't wait until game day. We need to have that stuff up front. We simply can't plan in a vacuum. I can't magically generate 5 million forms for a small state."

Many states have already spent significant time, money, and staff resources working on documentation such as screening forms for their emergency preparedness and response plans. But those forms may not be exactly what are required under an EUA. As Sell explained, "We spent years; resources; talent; toil; emotion; bickering; painful, painful, painful hours . . . tens of thousands of hours nationwide developing screening forms at an individual, state level, and now we are being told 'not so fast.' You are going to have to wait. You are going to have to wait for those to become available."

At the workshop, participants discussed potential ways to address this challenge. In some cases, creating templates might make sense, such as in the case of treatment for anthrax. "If the plan is

to do a 10-day regimen of meds and then go back and get a 60-day regimen of meds," said Gretchen Michael, communications director for ASPR/HHS, "why can't the basic fact sheets be created as a template? Don't print it anywhere. Just keep it in the computer. Start translating. There is certain information about taking a pill or doing it whether in a language or in pictures that is going to be factually correct no matter what the situation is." The pre-EUA process available through the FDA could be helpful here, because the FDA could use this process to begin to consider possible scenarios, what medical countermeasures could be needed, and what accompanying fact sheets they are likely to require if an EUA were to be issued. But even if fact sheets could be prepared and translated in advance, if printing had to wait until the EUA was issued in order to confirm the contents, it would still be very difficult to produce the documentation without using up a significant portion of the 48-hour timeframe for anthrax prophylaxis.

Late in 2008, in an effort to standardize and streamline fact sheet production, the SNS committed to leading a project to create fact sheets to replace the ones the states had done, including handling the expense of translating them into multiple languages. The fact sheets would be made available in an electronic form, so that states could print what was needed in a timely manner. Burel said, "We have had this discussion with [the] FDA. [The] FDA understands the need and they are supportive of doing that." Unfortunately, due to the 2009 H1N1 pandemic, those meetings were suspended, but Burel stated, "We do know we owe that to the states and we will get that out to the states as soon as possible."

Shelf-Life Extension Program

SLEP allows the FDA, after extensive safety and potency testing, to extend the shelf life of expired drugs, allowing them to be used instead of discarded. During the response to 2009 H1N1, many lots of drugs such as Tamiflu went through SLEP and became available for distribution. But a number of questions arose about drugs that have gone through SLEP.

Some clinicians and members of the public have reservations about products that have expired dates on them. "Even though you can point back to the website that shows what lots have been tested," Gorman said, "The fact that you are getting a bottle with a date that looks like it is expired is still a problem for some people." Questions are being directed at the FDA about what kinds of testing are being done to ensure the quality of these drugs. Leissa explained, "We need to provide more information up at our website to assure people what kind of testing and what rigor of data we have about the quality of products. That is something that we are working to address."

Labeling

According to Gorman, current legal interpretation of the PREP Act coverage requires EUAs for reasons that have nothing to do with whether a drug is FDA approved for the emergency at hand, but often for simple labeling issues. For example, many medications stored in the SNS have "for SNS use only" on the label. This "SNS use only" notation was not part of the NDA, so it is a labeling deviation. This also applies to items that have gone through SLEP and are extended with a new expiration date, but not relabeled. Additionally, Gorman noted, "Things that have been in storage conditions that may have exceeded label temperature ranges are not part of the approved new drug application. For all these reasons, which would technically apply to every asset in the SNS that has undergone shelf-life extension [or] has 'SNS use only' on the label, we would require an EUA for everything." She went on to note, "That is going to hinder [our ability] to deploy [materials] in a timely manner. . . . We need a better mechanism to be able to use these products that are going to have labeling changes."

EUAs and State Dispensing Laws

Complicating the EUA process, each state may have its own unique requirements for dispensing medications—especially concerning what information must be included on the label. Because of these requirements, many questions have been raised about whether the EUA would supersede the state dispensing law or if state law trumps the EUA. Gorman reported that this issue is being addressed, and no clear guidelines have been provided yet.

Data Collection and Research

The use of unapproved medications and devices under an EUA presents a potential opportunity to collect data on their use and results in clinical settings. However, participants noted that collecting and analyzing data under these circumstances is likely to be very challenging. For example, with peramivir, which was being dispensed under an EUA at the time of the workshop, the letter of authorization included a mechanism to try to obtain the best safety information possible. However, this is not a simple issue: As Leissa said, "These are very sick populations. Many of the patients that are receiving the drug are getting it when they are already near death . . . so being able to learn anything from that is difficult." Additionally, Leissa noted that administering these drugs in an emergency situation is nothing like the randomized, controlled clinical trials that are necessary to evaluate safety and efficacy, making data analysis difficult.

Participants also noted that there is a great need for policy research on the use of EUAs themselves. Leissa asked, "Are we doing *good* things with Emergency Use Authorization?"

Streamlining and Standardizing the EUA Process

Workshop participants acknowledged that, as people have gained more experience with EUAs, the process has become smoother. It is known now what information needs to be provided to the FDA, and the lines of communication are more open. Furthermore, others beyond the provider community are gaining experience with EUAs. "The FDA's experience with EUAs is also something that has risen dramatically with the H1N1 situation," noted Aubrey Miller of the FDA's Office of Counterterrorism and Emerging Threats. "Obviously we have been on a learning curve along with everyone else, and one of our main objectives as this begins to slow down is to actually look at the EUA guidance and reevaluate how to make it a better process and [have] more uniformity with respect to it."

Beyond EUAs

Several workshop participants emphasized that although EUAs facilitate getting appropriate materials where they are needed in a timely fashion, they are not the ideal end solution. As Minson said, "The idea here is not to have an interminable number of EUAs that are being kicked out, but ultimately to say at some point that this is a 'patch.' This gets us to where we might want to be on a permanent footing."

Many workshop participants questioned whether EUAs are currently required for too wide a range of medical countermeasures dispensing situations. Because many of the current EUAs were written to address labeling changes or storage conditions of assets in the SNS, some participants wondered if there was another way to provide PREP Act coverage rather than generating EUAs for everything in the stockpile. Gorman wondered, "Do we need a reinterpretation or an amendment of the PREP Act to include coverage of all those things so they don't need to be a separate EUA for every countermeasure in the SNS?"

Gerald Parker of HHS also raised the question, "Should we engage in a policy discussion about a new legal definition of an approved product that is somewhere between what we consider an

EUA today and an approved product today, somewhere in the middle?" This would be a product approved only for an emergency low probability, but extremely high consequence, event. Workshop participants also discussed the potential for an FDA-approved product list for high-risk threats, such as anthrax.

"As much as we are trying to move toward better processes, better situations, working with our state partners to identify what the limitations are and effect changes to those limitations where we can, you are very limited with an EUA," Maher noted. "The ideal situation is having a marketed product for that emergency use. EUA is not the answer."

Summary

Many workshop participants agreed that EUAs are an important tool in helping to protect public health. "It is clearly better than not having the drugs available and certainly better than investigation of a new drug requirement," Blumenstock said. "The key here is how to take all these new requirements and new challenges, getting a better comfort level—a better understanding—so that we can be more effective and efficient in its administration."

Frustration has grown as people realize that EUAs are needed more often than anticipated, and they are concerned about what would happen if an event occurs before pre-EUA discussions have begun. The need to quickly become knowledgeable in the science, public health needs, and logistics during an unforeseen event will have a steep learning curve, and many fear the compromises that may occur.

Although getting approved medical countermeasures for emergency use will not erase the need for the EUA tool, it would minimize that need and allow countermeasures to be dispensed more quickly to where they are needed. "That is what everybody's goal should be: to get these products in their emergency settings to be approved," Leissa said.

Footnotes

4 Since the termination of the EUAs issued for H1N1, the CDC has removed them from its website. Likewise, the FDA has also updated its website to reflect the termination.

Bookshelf ID: NBK53122