

Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) Medical Countermeasure (MCM) Authorities:

FDA Questions and Answers for Public Health Preparedness and Response Stakeholders

January 2014

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This document responds to questions raised by public health stakeholders about the 2013 enactment of PAHPRA and the law's impact on preparedness and response efforts related to the emergency use of medical countermeasures (MCMs) during chemical, biological, radiological, or nuclear (CBRN) emergencies, including those involving emerging infectious diseases (e.g., pandemic influenza). This document is intended to provide general information about the provisions of PAHPRA. It does not announce FDA interpretations of that statute and does not announce agency policy decisions with respect to implementation of the statutory provisions or their application to particular circumstances. FDA recognizes the need for issuance of a guidance document that will address such interpretations and policy decisions and is working to prepare such a document.

As of the date of this document's posting, FDA is in the process of implementing PAHPRA's MCM-related provisions, which are discussed below. FDA will communicate additional details and materials about PAHPRA as appropriate when such information becomes available. While PAHPRA's MCM provisions are intended to facilitate and support a wide range of preparedness and response efforts, FDA recognizes that changes resulting from PAHPRA may raise additional questions among public health preparedness and response stakeholders, especially during implementation of the law. Stakeholders are welcome to contact FDA directly with specific questions.

A. SUMMARY OF PAHPRA

1. What is PAHPRA?

PAHPRA is the [Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 \(PAHPRA\)](#) (Public Law 113-5).¹ On March 13, 2013, President Obama signed into law the bill H.R. 307 to reauthorize the [Pandemic and All-Hazards Preparedness Act of 2006 \(PAHPA\)](#) (Public Law 109-417) and to develop new authorities to sustain and strengthen national preparedness for public health emergencies involving CBRN agents, including emerging infectious disease threats (e.g., pandemic influenza). This new law is referred to as *PAHPRA*.

2. Does PAHPRA include provisions that are specific to the use of MCMs for emergencies?

Yes. Among its many important provisions focusing on public health and health care preparedness and response, PAHPRA includes language that specifically addresses MCMs. As used in this document, the term "MCMs" means the medical products (i.e., drugs, biologics, and devices) that might be needed to diagnose, prevent, or treat diseases or other conditions resulting from CBRN emergencies. For example, MCMs include medical products such as anti-infective drugs, vaccines, diagnostic tests, ventilators, and personal protective equipment (PPE).

¹ Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) (Public Law 113-5, 127 Stat. 161). <http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf>.

FDA's responsibilities under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) include evaluating medical product safety and effectiveness for regulatory approval, licensure, or clearance and regulating products after they have been approved, licensed, or cleared. These broad responsibilities also apply to MCMs because MCMs are medical products. The new law recognizes the many roles FDA plays in public health emergency preparedness and response by including provisions intended to advance FDA's mission of fostering the development and availability of MCMs for use in CBRN emergencies.

The legislation's FDA-related MCM provisions can be found in Title III of PAHPRA (sections 301-307). As described in greater detail in the following pages, these provisions address a number of activities related to MCMs but can be summarized into provisions that are intended to facilitate:

- MCM emergency preparedness and response efforts (see Section B below), and
- MCM product development (see Section C below).

B. MCM EMERGENCY PREPAREDNESS AND RESPONSE PROVISIONS

Overview:

3. What are PAHPRA's MCM emergency preparedness and response provisions, and how will they affect public health stakeholders' MCM efforts?

PAHPRA affects MCM preparedness and response by providing new flexibilities and authorities based on experience with previous preparedness efforts and emergency responses involving MCMs. Many of these changes are amendments to FDA's existing Emergency Use Authorization (EUA) authority under section 564 of the FD&C Act, but PAHPRA also creates new MCM preparedness and response authorities. Together, these amendments and new authorities are intended to support and facilitate pre-event planning efforts and pre-positioning of MCMs for a range of stakeholders, including federal partners like the Department of Defense (DoD) and the Centers for Disease Control and Prevention (CDC), as well as state, local, tribal, and territorial (SLTT) public health agencies. They also are intended to facilitate stakeholders' efficient and rapid use (i.e., dispensing and administration) of MCMs in the event of an emergency involving a CBRN threat, including an emerging infectious disease threat (e.g., pandemic influenza).

The changes in PAHPRA related to MCM preparedness and response can be summarized as:

- (a) Amending FDA's existing EUA authority;
- (b) Creating several new authorities under the FD&C Act related to the emergency use of approved MCMs; and
- (c) Allowing for pre-positioning of MCMs under the FD&C Act.

These 3 main changes are discussed in additional detail below and are briefly outlined in the following summary table (Table 1).

Table 1. Summary of PAHPRA’s MCM Emergency Preparedness and Response Provisions²

MCM Emergency Preparedness and Response Provisions	MCM Category	FD&C Act Section
Amendments to the Emergency Use Authorization (EUA) Authority	* <i>Unapproved MCMs</i> * <i>Unapproved uses of approved MCMs</i>	§ 564
Determinations for EUA issuance		§§ 564(b)(1)(A)-(D)
Duration of HHS EUA declaration		§ 564(b)(2)
EUAs issued for preparedness purposes		§ 564(b)(1)
Data collection time period		§ 564(e)(1)(B)(iii)
Categorization of in vitro diagnostics (IVDs)		§ 564(m)
New Emergency Use Authorities (No EUA)	* <i>Approved MCMs only</i>	§§ 564A & 505-1
Emergency use instructions (EUI)		§ 564A(e)
Emergency dispensing orders		§ 564A(d)
Expiration dating extensions		§ 564A(b)
CGMP waivers		§ 564A(c)
REMS waivers		§ 505-1
New Pre-Positioning Authority	* <i>Approved MCMs</i> * <i>Unapproved MCMs</i>	§ 564B

Amendments to the EUA Authority (section 564 of the FD&C Act):

Unapproved MCMs & unapproved uses of approved MCMs

4. What is an EUA?

The EUA authority is a legal mechanism that allows FDA to help strengthen the nation’s public health protections against CBRN threats by facilitating the availability of MCMs needed during public health emergencies. Under section 564 of the FD&C Act (21 U.S.C. 360bbb-3), the FDA Commissioner can allow either (a) the *use of an unapproved medical product* (e.g., drug, vaccine, or diagnostic device) or (b) the *unapproved use of an approved medical product* during an emergency to diagnose, treat, or prevent a serious or life-threatening disease or condition caused by a CBRN agent if certain statutory criteria are met.³ When scientific evidence is available to support such a use in an emergency, issuing an EUA enables response stakeholders to use, or prepare to use, an MCM without violating the FD&C Act.

² This table is solely for purposes of outlining the PAHPRA MCM provisions that are likely to be of most interest to stakeholders. For complete information on PAHPRA’s amendments to the FD&C Act, refer to Public Law 113-5. <http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf>.

³ An EUA can also be issued for a product that may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a product that is approved, licensed, or cleared or authorized for use under an EUA for diagnosing, treating, or preventing such a disease or condition caused by a CBRN agent.

Following is a brief summary of the EUA issuance process, which is largely the same as before PAHPRA's enactment. Specific PAHPRA-related changes to this process are discussed in greater detail and summarized in Figure 1 below.

1. DHS, DoD, or HHS Determination. The Secretary of either the Department of Homeland Security (DHS), Department of Defense (DoD), or Department of Health and Human Services (HHS) must make a determination related to a CBRN threat or the Secretary of DHS must make a Material Threat Determination (MTD).
2. HHS EUA Declaration. The HHS Secretary must make a declaration that circumstances exist to justify an EUA based on the determination made by the DHS, DoD, or HHS Secretary. This declaration is specific to EUA issuance; it is different from a public health emergency declaration under section 319 of the PHS Act and other types of declarations.
3. FDA Issuance of EUA. After the HHS declaration is made, the FDA Commissioner can issue an EUA after ensuring that the criteria for issuance (as outlined in section 564(c) of the FD&C Act) of the EUA have been met.

5. How does PAHPRA amend the EUA authority?

The EUA authority is still found in section 564 of the FD&C Act. Although the basic steps for issuing an EUA remain the same, PAHPRA changes the EUA authority in several ways to better facilitate preparedness and response activities. Examples of these amendments include (see also Table 1 and Table 2):

- **Determinations required for EUA issuance.** PAHPRA amends the EUA determination language to provide additional flexibility for issuing an EUA. Under section 564(b)(1) of the FD&C Act, there are now 4 types of determinations about CBRN threats that may be used to support EUA issuance (previously, only 3 types of determinations could support an EUA). The 4 threat determinations that can support the HHS declaration that is required to be made before issuance of an EUA are:
 1. DHS determination. “[A] determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents” [section 564(b)(1)(A)]

- PAHPRA removes the word “specified” before “biological, chemical, radiological, or nuclear agent or agent,” thereby increasing the flexibility of the determination that has to be made.
 2. DoD determination. “[A] determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents” [section 564(b)(1)(B)]

- PAHPRA removes the word “specified” before “biological, chemical, radiological, or nuclear agent or agents,” thereby increasing the flexibility of the determination that has to be made.

3. HHS determination. “[A] determination by the Secretary [of Health and Human Services] that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents” [section 564(b)(1)(C)]

- Before PAHPRA, this HHS determination required a public health emergency declaration under section 319 of the PHS Act. Now, the HHS Secretary’s determination can be based on either an actual or a potential public health emergency. The HHS Secretary can still declare a public health emergency under section 319 of PHS Act, but this now is not required to support an EUA. In addition, the HHS determination now can consider the health and security of U.S. citizens living abroad.⁴ PAHPRA also removes the word “specified” before “biological, chemical, radiological, or nuclear agent or agents” and before “disease or condition that may be attributable to such agent or agents,” thereby increasing the flexibility of the determination that has to be made.

4. DHS identification of a material threat. “[T]he identification of a material threat [by the DHS Secretary] pursuant to section 319F-2 of the [PHS] Act [42 U.S.C. 247d-6b] sufficient to affect national security or the health and security of United States citizens living abroad.” [section 564(b)(1)(D)]

- PAHPRA includes this as an entirely new basis on which the Secretary of HHS can issue a declaration supporting an EUA. DHS refers to this as a Material Threat Determination or MTD.

- **Duration of HHS declaration and EUA.** The duration of an EUA depends in part on the duration of the HHS declaration that supports the EUA. The HHS declaration must be current for an EUA to remain in effect.⁵ Previously, the HHS declaration terminated (a) 1 year after it was issued (but it could be renewed by HHS) or (b) if HHS determined that the emergency circumstances no longer existed, whichever occurred first.

PAHPRA eliminates the 1-year time limit for the HHS declaration so that the HHS declaration now terminates upon the earlier of (a) HHS determining that the circumstances

⁴ For example, refer to the May 29, 2013, HHS determination and declaration related to MERS-CoV. U.S. Department of Health and Human Services. *Determination and Declaration Regarding Emergency Use of In Vitro Diagnostics for Detection of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)*. 78 Fed. Reg. 33842 (June 5, 2013). <http://www.gpo.gov/fdsys/pkg/FR-2013-06-05/pdf/2013-13333.pdf> or <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

⁵ As noted earlier, before an EUA can be issued, the HHS Secretary must make a declaration of an emergency or threat of emergency (based on 1 of the 4 threat determinations listed in the bullets) such that circumstances exist to justify the issuance of an EUA.

justifying the EUA's issuance no longer exist or (b) a change in the approval status of the product such that an EUA would no longer be needed. [section 564(b)(2) of the FD&C Act]

- **EUAs issued for preparedness purposes.** PAHPRA provides clearer authority for FDA to issue an EUA *before* a CBRN emergency occurs to enable stakeholders to better prepare for the use of an MCM if the statutory criteria for issuing an EUA are met. Previously, FDA's authority to issue an EUA was based on a required HHS declaration of emergency, which in most instances limited FDA's issuance of an EUA until the time of an actual emergency.

Now, PAHPRA expressly allows the HHS Secretary to make a declaration that "circumstances exist justifying the authorization" of the emergency use of a product based on 1 of the 4 possible determinations (see above the first bullet in this section for additional details about these 4 determinations). This provides flexibility for MCM preparedness because an EUA now can be issued before or during an emergency. [section 564(b)(1) of the FD&C Act]

- **Data collection time period for EUA products.** Before PAHPRA, data about the safety and effectiveness of the emergency use of an MCM could be collected only during the time period in which the EUA was in effect. This meant that after an EUA terminated (e.g., an emergency ended), this type of data about the product could not continue to be collected under the EUA.

Now, when an EUA is issued for a product, PAHPRA expands the time period for collection and analysis of information about an MCM's safety and effectiveness to include both during the time period when the EUA is in effect *and* a reasonable period of time after the EUA is terminated. [section 564(e)(1)(B)(iii) of the FD&C Act]

- **Categorization of an in vitro diagnostic (IVD) authorized for use under an EUA.** PAHPRA expressly permits FDA, as part of the issuance of an EUA, to categorize the complexity of an IVD to indicate whether the test can be performed at a point-of-care setting or only in a more sophisticated laboratory. [section 564(m) of the FD&C Act]

Figure 1. Overview of Process for Issuing an EUA (under section 564 of the FD&C Act)

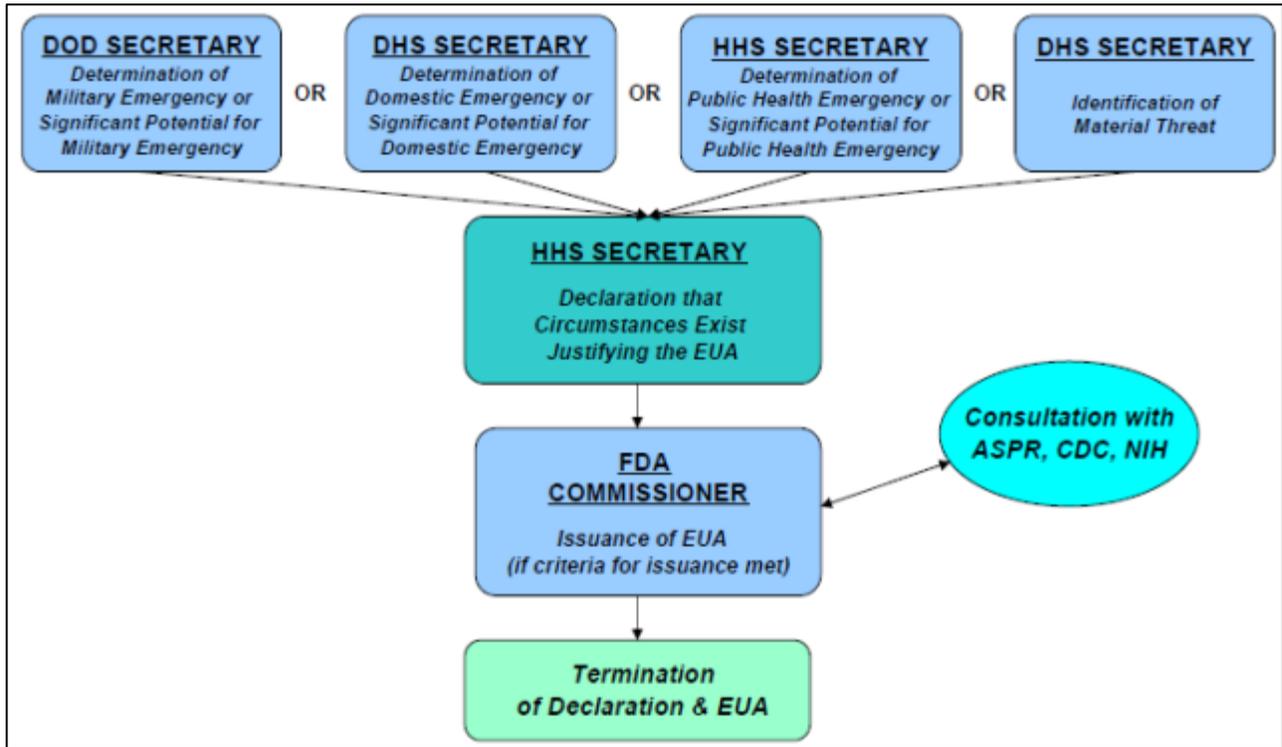


Table 2. Summary of PAHPRA Amendments to the EUA Authority

MCM Emergency Preparedness and Response Provisions	MCM Category	FD&C Act Section
Amendments to the Emergency Use Authorization (EUA) Authority	* <i>Unapproved MCMs</i> * <i>Unapproved uses of approved MCMs</i>	§ 564
Determinations for EUA issuance		§§ 564(b)(1)(A)-(D)
Duration of HHS EUA declaration		§ 564(b)(2)
EUAs issued for preparedness purposes		§ 564(b)(1)
Data collection time period		§ 564(e)(1)(B)(iii)
Categorization of in vitro diagnostics (IVDs)		§ 564(m)

6. What are the criteria FDA has to consider for issuing an EUA in advance of an emergency for preparedness purposes? Since PAHPRA's enactment, have any new EUAs been issued?

As discussed above and summarized in Figure 1, FDA must ensure that certain criteria for issuance of the authorization are met before issuing an EUA, whether or not the EUA is being issued for preparedness purposes in advance of an emergency or issued during a response. These criteria did not change and are outlined in section 564(c) of the FD&C Act—they include findings that:

- The CBRN agent referred to in the HHS EUA declaration can cause a serious or life-threatening disease or condition;
- The product may be effective in diagnosing, treating, or preventing such disease or condition;
- The known and potential benefits of the use of the product outweigh its known and potential risks; and
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such a disease or condition.

Again, PAHPRA does not establish separate or different criteria for FDA to consider for issuing an EUA before an emergency versus issuing an EUA during an emergency—the criteria for issuance are the same as outlined in section 564(c) of the FD&C Act. Issuing an EUA for preparedness purposes simply means issuing an EUA *before* an actual emergency occurs to help facilitate stakeholders' preparedness and rapid response efforts.⁶

Since PAHPRA was enacted in March 2013, FDA has used this clearer authority to authorize the emergency use of certain MCMs in advance of actual CBRN emergencies. Specifically, FDA issued 2 EUAs for preparedness purposes to respond to events that have emerged in other countries:

- H7N9 Influenza. EUA issued for an IVD to detect the novel avian influenza(A) H7N9 virus for preparedness purposes (April 22, 2013).⁷
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV). EUA issued for an IVD to detect MERS-CoV for preparedness purposes (June 5, 2013).⁸

⁶ Although this does not change the criteria for issuance of an EUA, one prerequisite for EUA issuance that might differ from before PAHPRA was enacted is the type of threat determination on which the HHS Secretary bases the declaration that circumstances exist justifying issuance of the EUA. As outlined above, there are now 4 possible types of threat determinations under section 564(b)(1) of the FD&C Act. In other words, depending on the situation, now an EUA can also be supported by the DHS Secretary's identification of a material threat (pursuant to section 319F-2 of the PHS Act) sufficient to affect national security or the health and security of United States citizens living abroad. In addition, depending on the situation, an EUA can now be supported by an HHS Secretary's determination that there is "a significant potential for a public health emergency" (not only an actual emergency) "that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad."

⁷ U.S. Food and Drug Administration. *Authorization of Emergency Use of an In Vitro Diagnostic for Detection of the Novel Avian Influenza A(H7N9) Virus; Availability*. 78 Fed. Reg. 38044 (June 25, 2013). <http://www.gpo.gov/fdsys/pkg/FR-2013-06-25/pdf/2013-15096.pdf> or <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

New Preparedness and Response Authorities for MCM Use (sections 564A & 505-1 of the FD&C Act):

Approved MCMs only

7. Other than amending the EUA authority, what new preparedness and response authorities for approved MCMs does PAHPRA include?

PAHPRA also creates several streamlined authorities to facilitate the emergency use of approved MCMs without the need for an EUA (Table 1 and Table 3). Although they address the emergency use of MCMs during or in preparation for emergencies, these new authorities are entirely separate from the EUA authority under section 564 of the FD&C Act. They are found in different sections of the FD&C Act: section 564A of the FD&C Act and section 505-1 of the FD&C Act. These provisions focus on *FDA-approved* MCMs intended for use during CBRN emergencies.

Previously, in certain cases FDA would have to issue an EUA for use of approved MCMs even if they were intended to be used during an emergency for their approved CBRN indications (e.g., doxycycline for inhalational anthrax post-exposure prophylaxis (PEP)). The rationale was that certain preparedness and response activities otherwise could have violated provisions of the FD&C Act and could have jeopardized any applicable tort liability protections under the Public Readiness and Emergency Preparedness Act (PREP Act).⁹ Examples of such activities included distributing to patients/recipients emergency use fact sheets that differed from the MCM's approved labeling, dispensing MCMs without a prescription, and not complying with certain Current Good Manufacturing Practice (CGMP) requirements.¹⁰

For approved MCMs that will be dispensed or administered for use during a CBRN emergency, PAHPRA establishes new streamlined mechanisms to facilitate such MCM preparedness and response activities without having to issue an EUA and without rendering an MCM unapproved, adulterated, or misbranded under the FD&C Act. When an EUA is not needed, these new flexibilities—which again apply *only* to eligible FDA-approved medical products intended for use during a CBRN emergency—include the following:

- **Authority to issue emergency use instructions (EUI).** PAHPRA allows a designated HHS official/unit to create and issue special emergency use instructions about the conditions of use for such MCMs both (a) before a CBRN event occurs and (b) during a response. These instructions can be used by anyone during a response and can be disseminated by government

⁸ U.S. Food and Drug Administration. *Authorization of Emergency Use of an In Vitro Diagnostic for Detection of Middle East Respiratory Syndrome Coronavirus; Availability*. 78 Fed. Reg. 42779 (July 17, 2013).

<http://www.gpo.gov/fdsys/pkg/FR-2013-07-17/pdf/2013-17103.pdf> or
<http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

⁹ U.S. Department of Health and Human Services. *Public Readiness and Emergency Preparedness Act*.
<http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx>.

¹⁰ For additional information about CGMPs, see, for example, U.S. Food and Drug Administration. *Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs*.
<http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm124740.htm>.

entities (or persons acting on behalf of those entities) in preparation for an emergency response. EUI are intended to be similar to the Fact Sheets for Health Care Professionals and Fact Sheets for Patients/Recipients and Parents/Caregivers that have been authorized in past EUAs.¹¹ The authority to issue EUI has been delegated by the HHS Secretary to CDC.¹² Therefore, stakeholders should consult with CDC on questions related to MCM emergency use instructions. [section 564A(e) of the FD&C Act]

- **Authority to permit emergency dispensing.** The new law also allows for emergency dispensing (including mass dispensing) of approved MCMs during an actual CBRN emergency event without requiring an individual prescription for each recipient of the MCM and without all of the information otherwise required to be provided when dispensing the MCM under section 503(b)(2) or 520(e) of the FD&C Act if (a) permitted by the law of the state in which the emergency dispensing occurs or (b) in accordance with an emergency dispensing order issued by the FDA Commissioner. Emergency dispensing under this provision will not result in the product being considered unapproved or deemed adulterated or misbranded under the FD&C Act because it is not dispensed with an individual patient prescription. [section 564A(d) of the FD&C Act]
- **Authority to extend expiration dating of MCMs.** PAHPRA expressly empowers FDA to extend the expiration dating of an eligible FDA-approved MCM stockpiled for use in a CBRN emergency if the extension is supported by an appropriate scientific evaluation. PAHPRA defines *expiration date* as “the date established through appropriate stability testing...to ensure that the product meets applicable standards of identity, strength, quality, and purity at the time of use.” The new authority allows FDA to require appropriate conditions related to expiry date extensions, including appropriate storage, sampling, and labeling. Previously, FDA issued EUAs to expressly permit the use of an MCM with an extended expiration date (e.g., an extension through the federal Shelf-Life Extension Program (SLEP)) during an emergency response to ensure PREP Act liability protections. [section 564A(b) of the FD&C Act]
- **Authority to waive CGMP requirements.** PAHPRA permits FDA to waive otherwise applicable CGMP requirements (e.g., proper storage or handling requirements) for approved MCMs to accommodate emergency response needs (e.g., temporary storage of products at points of dispensing (PODs)). [section 564A(c) of the FD&C Act]
- **Authority to waive Risk Evaluation and Mitigation Strategies (REMS) requirements.** In the past, a REMS¹³ waiver was permitted only in the event of a declared emergency under section 319(a) of the PHS Act. PAHPRA expands the current REMS waiver authority so that FDA may now allow a waiver based on all of the same types of CBRN emergencies that would trigger an EUA. If it is determined that a waiver is needed, a waiver of REMS

¹¹ For example, the sample fact sheets authorized through the July 2011 doxycycline mass dispensing EUA, which are available at: <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

¹² U.S. Department of Health and Human Services. *Delegation of Authority of section 564A(e) of the Federal Food, Drug, and Cosmetic Act*. December 16, 2013.

¹³ U.S. Food and Drug Administration. *A Brief Overview of Risk Evaluation and Mitigation Strategies (REMS)*. <http://www.fda.gov/downloads/aboutfda/transparency/basics/ucm328784.pdf>.

requirements also now can apply to all REMS elements. Previously, only elements to assure safe use (ETASU) requirements¹⁴ could be waived. [section 505-1 of the FD&C Act]

The processes associated with the use of each of these new authorities are being developed and will be communicated to stakeholders. To summarize, although an EUA may no longer be needed for an FDA-approved MCM that is used during a CBRN emergency, depending on the specific emergency response needs the following new activities authorized by PAHPRA might still need to occur to facilitate the use of the MCM:

- Development, issuance, and distribution of emergency use instructions by CDC;
- Ensuring that an appropriate legal mechanism is in place to authorize emergency dispensing without an individual prescription, either through (1) a mechanism as permitted under the law of the state in which emergency dispensing will occur or (2) an emergency dispensing order issued by FDA;
- Authorization(s) by FDA and engagement in certain activities related to MCM expiry dating;
- Waiver(s) by FDA of otherwise applicable CGMP requirements (e.g., related to storage of an MCM during a response) to accommodate the emergency response if needed; and/or
- Waiver(s) by FDA of otherwise applicable REMS requirements if it is determined that such a waiver is needed.

Table 3. Summary of New MCM Emergency Use Authorities Established by PAHPRA

MCM Emergency Preparedness and Response Provisions	MCM Category	FD&C Act Section
New Emergency Use Authorities (No EUA)	<i>* Approved MCMs only</i> <i>* Before or during an emergency</i>	§§ 564A & 505-1
Emergency use instructions (CDC)		§ 564A(e)
Emergency dispensing orders (FDA)		§ 564A(d)
Expiration dating extensions (FDA)		§ 564A(b)
CGMP waivers (FDA)		§ 564A(c)
REMS waivers (FDA)		§ 505-1

8. What are examples of situations in which EUAs are no longer needed to allow for the emergency use of certain MCMs?

FDA has received questions from stakeholders about why EUAs have been needed to authorize the use of approved MCMs that would be used for approved CBRN indications (e.g., doxycycline for inhalational anthrax PEP) during an emergency response. Before PAHPRA was enacted, FDA issued

¹⁴ ETASU requirements are intended to reduce a specific serious risk listed in the labeling of the drug. They are required medical interventions or other actions health care professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

EUAs for certain approved MCMs, even though they were approved products for the anticipated emergency use, to address activities that might otherwise have violated the FD&C Act (e.g., distribution of fact sheets/emergency instructions that differed from the product's FDA-approved labeling, dispensing without a prescription, etc.). EUAs have also been issued to help ensure PREP Act coverage.

Now, because of PAHPRA, EUAs are no longer needed for certain emergency activities that involve approved MCMs. The key thing to understand is that this applies only to an approved MCM that is intended for use(s) in response to a CBRN emergency. FDA plans to provide guidance, as appropriate, on use of these streamlined authorities to facilitate preparedness and response.

Doxycycline: The doxycycline mass dispensing EUA,¹⁵ issued in July 2011, authorizes certain activities (e.g., issuing emergency fact sheets and allowing mass dispensing without individual patient prescriptions) that no longer necessitate an EUA under PAHPRA. Doxycycline is an FDA-approved product for inhalational anthrax PEP. So long as doxycycline is being used during a CBRN emergency (e.g., for inhalational anthrax PEP), an EUA is no longer needed to permit those activities; rather, it is possible now to rely on the new, streamlined mechanisms described above (e.g., emergency dispensing authority, issuance of emergency use instructions, etc.) to enable activities that used to require an EUA.¹⁶ As of this document's posting, the doxycycline mass dispensing EUA remains in effect and has not been terminated to ensure that ongoing preparedness efforts by stakeholders are not impacted during implementation of the applicable new mechanisms and processes.

Ciprofloxacin: Ciprofloxacin is also approved for PEP of inhalational anthrax. Therefore, like doxycycline, ciprofloxacin dispensed for inhalational anthrax PEP is the type of product for which an EUA is no longer needed to permit certain activities for which an EUA would previously have been needed.¹⁷ In other words, it is possible now to use the new, streamlined mechanisms described above (e.g., emergency/mass dispensing authority, issuance of emergency use instructions, etc.) to enable activities with respect to ciprofloxacin that used to require an EUA.

¹⁵ U.S. Food and Drug Administration. *Authorization of Emergency Use of Oral Formulations of Doxycycline; Availability*. 76 Fed. Reg. 47197 (Aug. 4, 2011). <http://www.gpo.gov/fdsys/pkg/FR-2011-08-04/pdf/2011-19622.pdf>.

¹⁶ However, at this time, the National Postal Model (NPM) EUA, which addresses pre-positioning of 10-day supplies of doxycycline in special kits for United States Postal Service employee volunteers and their household members and includes specific programmatic elements, remains in effect. U.S. Food and Drug Administration. *Amended Authorization of Emergency Use of Doxycycline Hyclate Tablet Emergency Kits for Eligible United States Postal Service Participants and Their Household Members; Availability*. 76 Fed. Reg. 72935 (Nov. 28, 2011). <http://www.gpo.gov/fdsys/pkg/FR-2011-11-28/pdf/2011-30450.pdf>.

¹⁷ Unlike for doxycycline, an EUA for ciprofloxacin mass dispensing was not issued before PAHPRA. Therefore, authorized or example fact sheets—including home preparation instructions for children and adults who cannot swallow pills—for recipients of ciprofloxacin product following an anthrax attack were not available like they were for doxycycline. One of the concerns with home preparation of ciprofloxacin is how to mask the extremely bitter taste of crushed tablets and identifying appropriate foodstuffs that will make palatable, home prepared ciprofloxacin to help ensure adequate adherence to this important MCM. FDA is not aware of solutions to address the palatability problem at this time. Although it does not address home preparation, in the interim stakeholders might find it to be helpful to refer to ciprofloxacin oral suspension's approved labeling for pediatric dosing information (e.g., <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=57611#nmlm34068-7> for Bayer's ciprofloxacin label for tablets and oral suspension).

9. When an EUA is no longer needed for approved MCMs, how will stakeholders be permitted to engage in the types of activities (e.g., dispensing without an individual patient prescription, handing out fact sheets about the emergency use of the product, etc.) that previously would have required an EUA?

As described earlier, only certain activities—that is, those involving only FDA-approved MCMs intended for uses in certain CBRN scenarios—would qualify for the new mechanisms and no longer need an EUA. To summarize, depending on the specific emergency response needs, the following activities authorized by PAHPRA might still need to occur to facilitate the use of an approved MCM:

- Development, issuance, and distribution of emergency use instructions by CDC;
- Ensuring that an appropriate legal mechanism is in place to authorize emergency dispensing without an individual prescription, either through (1) a mechanism as permitted under the law of the state in which emergency dispensing will occur or (2) an emergency dispensing order issued by FDA;
- Authorization(s) by FDA and engagement in certain activities related to MCM expiry dating;
- Waiver(s) by FDA of otherwise applicable CGMP requirements (e.g., related to storage of an MCM during a response) to accommodate the emergency response if needed; and/or
- Waiver(s) by FDA of otherwise applicable REMS requirements if it is determined that such a waiver is needed.

10. What are emergency use instructions (EUI) and who will be responsible for developing and issuing them? Can these instructions be developed for any MCM before an actual emergency? Will state and local stakeholders be permitted to modify or add additional information to emergency use instructions after they have been issued by CDC?

PAHPRA specifies that the HHS Secretary may, acting through an appropriate HHS official, create and issue emergency use instructions about an MCM to inform health care professionals and patients/recipients about the MCM's approved, licensed, or cleared conditions of use (i.e., the information in the product's FDA-approved labeling) before or during an emergency. In general, these instructions could include many of the types of information about FDA-approved products that have been included in the Fact Sheets for Health Care Professionals and Fact Sheets for Recipients/Patients that have been authorized and included in previous EUAs for FDA-approved products, such as doxycycline.¹⁸ The authority to develop EUI was delegated by the HHS Secretary to CDC in December 2013.¹⁹ We anticipate that CDC, in issuing those instructions, will inform stakeholders about what, if any, modifications (such as adding local contact information) will be permissible.

¹⁸ For example, the sample fact sheets authorized through the July 2011 doxycycline mass dispensing EUA, which are available at: <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

¹⁹ U.S. Department of Health and Human Services. *Delegation of Authority of section 564A(e) of the Federal Food, Drug, and Cosmetic Act*. December 16, 2013.

Again, it should be emphasized that the new authority to issue EUI is limited to MCMs that have been approved, licensed, or cleared by FDA and will be dispensed or administered for use during a CBRN emergency. The authority ensures that such instructions do not render such MCMs unapproved, adulterated, or misbranded under the FD&C Act (which is one reason why, in the past, an EUA would have been needed to authorize the emergency unapproved use of an approved product even if it was being used for an approved CBRN use). Another important reason for this authority is for CDC to be able to make available—*before* an emergency occurs—information about the emergency use of an approved product. This will enable stakeholders to be better prepared for and more familiar with the emergency use of the MCM if an emergency were to occur, rather than waiting for an EUA and its accompanying authorized fact sheets to be issued at the time of an event.

11. Is PAHPRA’s new expiration dating authority different from the federal Shelf-Life Extension Program (SLEP) program? Does PAHPRA allow state and local MCM stockpiles to participate in SLEP?

SLEP is the federal, fee-for-service program through which the labeled shelf life of certain federally stockpiled medical materiel (e.g., in the Strategic National Stockpile (SNS)) can be extended after select products undergo periodic stability testing conducted by FDA. The program, which is administered by DoD, was established in 1986 after it was recognized through testing that certain products remained stable beyond their labeled expiration dates when properly stored. Through expiration dating extensions, SLEP helps to defer the replacement costs of certain products in critical federal stockpiles.

Before PAHPRA, the distribution, dispensing, or use of products with extended expiry, and any related labeling adjustments, were possible by FDA’s exercise of its enforcement discretion (which sometimes raised questions about liability protections) or through issuance of an EUA. PAHPRA now provides FDA with the explicit authority to extend the expiration dating of eligible FDA-approved MCMs stockpiled for use in CBRN emergencies. The new expiration dating authority under PAHPRA includes certain limitations. For example, to be eligible, a product must be an approved MCM. In addition to the identification of specific lots, batches, or other units covered and the duration of the extension, FDA can require appropriate conditions related to any extensions under the new authority, including appropriate storage, sampling, recordkeeping, periodic testing or retesting, product disposition, and labeling.

The legislation itself does not extend the existing federal SLEP program to state or local MCM stockpiles and does not create a new SLEP program for non-federal partners. In other words, SLEP is an established program, whereas PAHPRA establishes a new authority for FDA to be able to extend expiry dating under certain circumstances. PAHPRA does not address programmatic elements of SLEP or alter FDA’s role with regard to the SLEP program. Therefore, SLEP remains limited to federal stockpiles at this time. However, FDA has already initiated efforts to develop processes for requests, eligibility, and assessments under the new PAHPRA expiration dating authority.

12. What steps has FDA taken to address MCM expiration dating challenges?

As discussed above, section 564A(b) of the FD&C Act now provides FDA with clearer authority to address stockpiling challenges based on appropriate scientific evidence and labeling flexibilities, as it has done in the past. FDA acknowledges the stockpiling challenges of SLTT stakeholders (e.g., related to doxycycline, ciprofloxacin, and Tamiflu) and remains committed to finding appropriate solutions to address such challenges. Several examples of how FDA has addressed expiry dating challenges following PAHPRA's enactment and before PAHPRA are described below.

After PAHPRA. On September 5, 2013, FDA issued a memorandum for certain DuoDote auto-injector lots manufactured by Meridian Medical Technologies, a Pfizer, Inc., company, stating that “[b]ased on FDA’s review of scientific data, FDA has concluded that, provided the products have been stored under labeled storage conditions, it is scientifically supportable for lots of DuoDote listed in the following table to be used for an additional year (1 year) beyond the manufacturer’s original labeled expiry date...”²⁰ For nerve agent poisoning purposes, FDA authorized such use pursuant to the new expiration dating authority under section 564A of the FD&C Act.

Before PAHPRA. Examples of how FDA addressed stakeholders’ expiry dating challenges before PAHPRA’s enactment include extensions related to antiviral drugs following the 2009-2010 H1N1 influenza pandemic response and spot shortages of Tamiflu during the 2013 seasonal influenza response:

- June 22, 2010. Following the 2009-2010 H1N1 influenza response, FDA issued a letter to CDC leadership regarding the disposition of Tamiflu and Relenza lots. The letter noted that, based on FDA-approved supplemental New Drug Applications for Relenza inhalation powder and Tamiflu capsules that provided an expiration dating period of 7 years, it would be scientifically supportable for the expiry extension (i.e., for a maximum of 7 years) to apply to certain lots of Tamiflu and Relenza that have already been manufactured. FDA also recommended relabeling of such product prior to dispensing.²¹
- January 17, 2013. In addition to FDA’s June 2010 letter above, a CDC message to states in 2013 regarding spot shortages of Tamiflu for seasonal influenza noted that, “[b]ased on FDA’s review of scientific data, FDA has concluded that, provided the products have been stored under labeled storage conditions, it is scientifically supportable for certain lots of Tamiflu capsules held in strategic stockpiles to be used for a maximum of ten [10] years beyond their date of manufacture...”²²

²⁰ U.S. Food and Drug Administration. *Memorandum: DuoDote (atropine and pralidoxime chloride injection) Auto-Injector Expiry Dating*. September 5, 2013. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM376385.pdf>. On December 24, 2013, FDA added additional lots of Duodote to the list.

<http://www.fda.gov/drugs/drugsafety/ucm376367.htm>.

²¹ For complete information on this messaging, refer to

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm216249.htm>.

²² It was also noted that, “at this time...Tamiflu capsules purchased through HHS subsidy program contracts held in state stockpiles should not be used to treat seasonal influenza cases. CDC will provide updates as needed about the use of such product...”

Authority to Pre-Position MCMs (section 564B of the FD&C Act):

Approved & unapproved MCMs

13. How is the PAHPRA provision for pre-positioning different from the other PAHPRA authorities?

PAHPRA’s provision regarding “products held for emergency use” permits federal, state, and local government entities, or persons acting on behalf of a government entity, to pre-position (i.e., stockpile) MCMs regardless of a product’s regulatory status, but in anticipation that use will be permitted under some other mechanism. That is, an MCM can be pre-positioned in anticipation of approval, licensure, or clearance, or in anticipation of being authorized for use under an EUA or for investigational use, without violating the FD&C Act (section 564B of the FD&C Act). The authority to pre-position MCMs in this way applies to all categories of MCMs, including those that are approved, unapproved, investigational, or authorized for use under an EUA. Previously, FDA issued an EUA or exercised its enforcement discretion to allow such activity.

14. How does PAHPRA’s pre-positioning language affect current MCM stockpiles? Does PAHPRA require that stakeholders currently stockpiling MCMs now do anything differently?

PAHPRA’s pre-positioning provision clarifies what stakeholders are lawfully permitted to do to prepare for potential rapid deployment of MCMs during an actual CBRN emergency. This provision means that now it is not a violation of the FD&C Act or PHS Act for stakeholders (e.g., SLTT public health officials) to purchase, ship, or hold MCMs intended for use during an emergency. This provision applies whether the product is approved, anticipated to be approved, or anticipated to be authorized for use under an EUA or for investigational use, as long as the MCM is in fact held and not used until permitted under FDA approval, licensure, or clearance; under an investigational new drug application (IND) or investigational device exemption (IDE); or pursuant to an EUA. Stakeholders should continue to properly store any product they might be stockpiling in accordance with CGMPs; FDA intends to provide additional information about pre-positioning when available.

Table 4. Summary of PAHPRA’s Pre-Positioning Authority

MCM Emergency Preparedness and Response Provisions	MCM Category	FD&C Act Section
New Pre-Positioning Authority	* <i>Approved MCMs</i> * <i>Unapproved MCMs</i>	§ 564B

C. ADDITIONAL INFORMATION ABOUT PAHPRA AND MCMs

MCM Product Development Provisions:

15. How is PAHPRA intended to improve MCM product development?

Although the focus of this question and answer document is on MCM preparedness and response activities, public health stakeholders have also expressed interest in FDA's roles in MCM product development. PAHPRA recognizes that FDA has key responsibilities in the development and approval, licensure, or clearance of MCMs and in the regulation of MCMs after they have been approved, licensed, or cleared or otherwise authorized for emergency use.

PAHPRA builds on FDA's ongoing efforts to enhance product review processes and to advance regulatory science for the development of MCMs. This includes new provisions that focus on FDA's interactions with government and industry stakeholders working to develop MCMs. For example, provisions include ensuring that FDA holds certain types of meetings with MCM product sponsors and provides final guidance to industry on the use of animal models for establishing claims of an MCM's efficacy when human efficacy testing is not ethical or feasible.

For additional information about FDA's MCM product development activities under PAHPRA and the Medical Countermeasures Initiative (MCMi), refer to FDA's PAHPRA²³ and MCMi Websites.²⁴

Next Steps:

16. How is FDA working to implement PAHPRA's MCM provisions?

Since the enactment of PAHPRA in March 2013, FDA has been working with its federal partners on interpreting and implementing PAHPRA's MCM-related provisions. As this process continues, FDA intends to issue guidance and/or other informational materials as appropriate. FDA will also work with its federal partners and other key preparedness and response stakeholders at all levels to optimize and, as new information becomes available, communicate the impact of PAHPRA on MCM-related preparedness and response activities.

Although PAHPRA's MCM provisions are intended to facilitate and support a wide range of preparedness and response efforts, FDA recognizes that changes resulting from PAHPRA may raise questions among public health preparedness and response stakeholders, especially during implementation of the law. Public health stakeholders should feel free to contact FDA with any questions about PAHPRA's changes and about implementation through AskMCMi@fda.hhs.gov or brooke.courtney@fda.hhs.gov.

²³ U.S. Food and Drug Administration. *Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)*. <http://www.fda.gov/EmergencyPreparedness/MedicalCountermeasures/ucm359581.htm>.

²⁴ U.S. Food and Drug Administration. Medical Countermeasures Initiative. <http://www.fda.gov/medicalcountermeasures>.

Online Resources:

17. Where can I find additional information about MCMs and PAHPRA?

- PAHPRA (Public Law 113-5):
<http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf>
- FDA's PAHPRA Website (*including updates as they become available*):
<http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm359581.htm>
- EUA Official Website (*including current and archived/terminated EUAs*):
<http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm>
- FDA Medical Countermeasures Initiative (MCMi):
<http://www.fda.gov/medicalcountermeasures>
- Public Readiness and Emergency Preparedness (PREP) Act:
<http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx>
- FDA MCMi Twitter:
[@FDA_MCMi](https://twitter.com/FDA_MCMi)