Anti-Infective Drugs Advisory Committee

Doxycycline Medkits for Public Health Preparedness for an Anthrax Attack

April 2, 2012
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>ARES</td>
<td>Anthrax Response Exercise Series</td>
</tr>
<tr>
<td>ASPR</td>
<td>Assistant Secretary for Preparedness and Response</td>
</tr>
<tr>
<td>ASTHO</td>
<td>Association of State and Territorial Health Officials</td>
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<tr>
<td>B. anthracis</td>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>BARDA</td>
<td>Biomedical Advanced Research and Development Authority</td>
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<tr>
<td>BLA</td>
<td>Biologics License Application</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
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<tr>
<td>CRI</td>
<td>Cities Readiness Initiative</td>
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<tr>
<td>CRO</td>
<td>Clinical Research Organization</td>
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<tr>
<td>DHS</td>
<td>US Department of Homeland Security</td>
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<tr>
<td>EO</td>
<td>Executive Order</td>
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<tr>
<td>ER/LA</td>
<td>Extended Release/Long Acting</td>
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<tr>
<td>EUA</td>
<td>Emergency Use Authorization</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDAAA</td>
<td>Food and Drug Administration Amendments Act of 2007</td>
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<tr>
<td>HAK</td>
<td>Household Antibiotic Kit</td>
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<tr>
<td>HHS</td>
<td>US Department of Health and Human Services</td>
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<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>IAK</td>
<td>Individual Antibiotic Kit</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>MCM</td>
<td>Medical Countermeasures</td>
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<td>MDH</td>
<td>Minnesota Department of Health</td>
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<tr>
<td>MTD</td>
<td>Material Threat Determination</td>
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<tr>
<td>MOA</td>
<td>Memorandum of Agreement</td>
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<tr>
<td>NACCHO</td>
<td>National Association of County &amp; City Health Officials</td>
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<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<td>NDMS</td>
<td>National Disaster Medical System</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NLM</td>
<td>National Library of Medicine</td>
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<tr>
<td>NPM</td>
<td>National Postal Model</td>
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<tr>
<td>OHA</td>
<td>Office of Health Affairs</td>
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<tr>
<td>OPEO</td>
<td>Office of Preparedness and Emergency Operations</td>
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<tr>
<td>OTC</td>
<td>Over-the-Counter</td>
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<tr>
<td>PEP</td>
<td>Post-exposure Prophylaxis</td>
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<td>PHEP</td>
<td>Public Health Emergency Preparedness</td>
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<tr>
<td>POD</td>
<td>Point of Dispensing</td>
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<td>PPHA</td>
<td>Participating Public Health Authorities</td>
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<tr>
<td>RFP</td>
<td>Request for Proposal</td>
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<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>RSS</td>
<td>Receipt, Store, and Stage</td>
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Doxycycline Medkits for Public Health Preparedness for an Anthrax Attack
April 2, 2012

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

<table>
<thead>
<tr>
<th>SNS</th>
<th>Strategic National Stockpile</th>
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<tr>
<td>TEP</td>
<td>Technical Evaluation Panel</td>
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<tr>
<td>UOU</td>
<td>Unit of Use</td>
</tr>
<tr>
<td>USG</td>
<td>US Government</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
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<td>USPS</td>
<td>US Postal Service</td>
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III. Purpose

On September 23, 2008, the US Department of Homeland Security (DHS) determined that significant potential exists for a domestic emergency involving Bacillus anthracis (B. anthracis), the bacterium that causes anthrax. Then on October 1, 2008, the Secretary of Health and Human Services (HHS) declared an emergency and on October 3, 2008, the use of doxycycline hyclate tablets was authorized as part of home antibiotic medkits for US Postal Service (USPS) employees and their household members. Because of this ongoing potential, a declaration of emergency was renewed in subsequent years: October 1, 2009; October 1, 2010; and July 18, 2011.

The availability of personal antibiotic medkits could significantly prepare a ready workforce of first responders by eliminating their need to queue at community point-of-care or point-of-dispensing (PODs) locations. It is expected that PODs will be overwhelmed the first several days; therefore, the pre-incident, far-forward positioning of medical countermeasures (MCMs) will lessen the time required for first responders to obtain life-saving antibiotics enabling them to help affected communities more rapidly.

Our proposal is a step-wise approach to make antibiotic medkits commercially available to those first responder communities and their households (e.g., responder community of 3.2 million and an average household size of 3 equals a population of approximately 10 million) to increase preparedness of this group, which may increase willingness of the first responders to report to work in the event of an anthrax attack.

The purpose of this document is to provide information to the Food and Drug Administration’s (FDA) Anti-Infective Drugs Advisory Committee on the preparedness efforts for anthrax post-exposure prophylaxis (PEP), description of the initial dataset to support a regulatory development plan of an FDA-approved medkit, and to seek guidance from this Committee on the feasibility of an FDA-approved medkit. We believe that this approval is appropriate because of, but not limited to, the following:

- HHS response required for the December 30, 2009, Executive Order (EO) 13527, Establishing Federal Capability for the Timely Provision of Medical Countermeasures Following a Biological Attack. Pre-positioned medkits are just one mechanism for getting critical MCMs to people with the added benefit to potentially decrease the initial stress on PODs.

- Based on recent USPS Emergency Use Authorization (EUA) experience, it is expected that the household antibiotic kits will stay intact, will not be used inappropriately, and will be viable for use during an anthrax event.

- By employing appropriate labeling/packaging, the first responder community will be well informed on the proper storage and disposal of these kits.

- Valuable tools used for traditional drug approvals, such as Risk Evaluation and Mitigation Strategy (REMS) and product registries, already exist for drugs that have a greater potential for inappropriate use.
• We propose taking a measured approach with the initial indication so that medkits would only be available to the first responder community and their household members. First responders will be defined by appropriate professional responder organizations and not dictated by the USG. This proposed indication is a conservative approach that offers a level of vigilance to a population that is fully engaged in preparedness and response activities. The indicated population could be deliberately expanded as knowledge and experience is gained from this initial effort.

• Distribution of medkits would not be done as part of a federal program. A medkit would be a commercially available drug product via prescription and dispensed by a pharmacist.

• Doxycycline is an equally effective and inexpensive alternative to ciprofloxacin, which is also FDA-approved for anthrax post-exposure prophylaxis.

• To date, a thorough search of the US literature does not provide data that suggest there would be rampant misuse of antibiotics in the medkit by self medication; a comprehensive study or studies that span multiple ethnic, educational, and socioeconomic groups is needed to fully understand self-medication practices in the general population. Without such studies, the negative assumption that people will misuse these products cannot be touted fairly.

IV. Background

1. Anthrax Disease
Anthrax is a zoonotic disease caused by the spore-forming bacterium, B. anthracis. The disease most commonly occurs in wild and domestic mammals (e.g., cattle, sheep, goats, camels, antelope, and other herbivores). Anthrax occurs in humans when they are exposed to infected animals or tissue from infected animals or when they are directly exposed to B. anthracis spores. Depending on the route of exposure, anthrax can occur in three forms: cutaneous, gastrointestinal, or inhalation. The case-fatality rate for anthrax ranges from <1% (for cutaneous anthrax treated with appropriate antimicrobial agents) to 86-89% (during the 1979 outbreak of inhalation anthrax in the former Soviet Union and in the United States during the 20th century, respectively).1

The precise infectious dose of B. anthracis in humans by the various routes is not known; however, inhalation anthrax can develop in susceptible hosts after exposure to a relatively small number of spores. Based on data from studies of nonhuman primates, the lethal inhalation dose has been estimated to range from 2,500 to 760,000 spores.

After B. anthracis spores were sent through the US mail in 2001, twenty-two cases of anthrax resulted (11 inhalational, 11 cutaneous) and five persons died from inhalation anthrax (almost 50% of those exposed to inhalation anthrax). These fatal cases had an insidious onset consisting of nonspecific complaints of malaise, fatigue, chills, fever, nausea, vomiting, diarrhea, abdominal pain, headache,

cough, chest pain, myalgias, and profound sweating lasting several days\textsuperscript{2}, which abruptly progressed to fulminant respiratory distress and shock.\textsuperscript{3}

The prognosis for patients with symptomatic anthrax varies by clinical presentation. Cutaneous disease tends to evolve over days to weeks, and once recognized, can be effectively treated with appropriate oral antimicrobials. Gastrointestinal and inhalational exposure to \textit{B. anthracis} spores can rapidly result in severe systemic disease. Inhalation anthrax is the most severe form of anthrax because of the rapid progression of the disease to involve hemorrhagic mediastinitis, toxemia, and massive pulmonary edema; and the difficulty in establishing the diagnosis quickly.\textsuperscript{4} Historical mortality rates for untreated anthrax disease are 10-20\% for cutaneous anthrax, 25-50\% for gastrointestinal anthrax, and essentially 100\% for inhalational anthrax.\textsuperscript{5}

\textit{B. anthracis} is considered one of the most serious biowarfare or bioterrorism agents because of the ability of the spores to persist in the environment, the ability of the aerosolized spores to readily cause infection via respiratory (inhalation) exposure, and the high mortality of resulting inhalation anthrax. The Centers for Disease Control and Prevention (CDC) has classified anthrax as a Category A biological warfare agent, meaning it has great potential to adversely affect public health. The lethality of aerosolized \textit{B. anthracis} spores was demonstrated in 1979 when an unintentional release of \textit{B. anthracis} spores from a military microbiology facility in the former Soviet Union resulted in 64 deaths. The cases of anthrax that occurred after \textit{B. anthracis} spores were distributed through the US mail in 2001 further underscore the potential dangers of this organism as a bioterrorism threat.

CDC defines the incubation period of inhalational anthrax as usually less than one week but may be prolonged for weeks (up to two months). Regardless of this broad incubation period, the US policy is to deploy antimicrobials for post-exposure prophylaxis within 48 hours from the decision to dispense.

HHS medical consequences modeling studies demonstrate that the lag time between the release of the spores and the initiation of an antimicrobial PEP campaign is the key parameter that determines the quantity of exposed individuals who develop serious infection and die.\textsuperscript{6} That is, the longer the time delay in starting prophylaxis after exposure, the greater the chance that an exposed person will develop lethal disease. Furthermore, it is significantly more cost-effective and less resource-intensive to prevent morbidity and mortality via oral antimicrobial and vaccination PEP campaigns than to provide complicated and lengthy treatment regimens to symptomatic patients.\textsuperscript{7}

\textsuperscript{3}Jernigan JA, Stephens DS, Ashford, DA, \textit{et al.} Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. Emerging Infectious Diseases 2001;7(6):933-944
\textsuperscript{5}Knudson GB. Treatment of anthrax in man: history and current concepts. Mil Med 1986;151(2):71-7
PEP is effective in preventing anthrax disease. The FDA has approved the administration of four antimicrobials for use for PEP following exposure to aerosolized *B. anthracis* spores: ciprofloxacin, doxycycline, levofloxacin, and parenteral procaine penicillin G.

As proposed, the antibiotic medkits herein discussed contain only doxycycline hyclate due to initial concerns about including ciprofloxacin. Concerns were based on the potential for development of antimicrobial resistance to ciprofloxacin. Doxycycline is a semisynthetic tetracycline antibacterial drug approved for prescription use by FDA for treatment and post-exposure prophylaxis of anthrax due to *B. anthracis*, including inhalation anthrax, to reduce the incidence or progression of disease following exposure to aerosolized *B. anthracis*. The recommended PEP regimen for anthrax includes a 60-day course of doxycycline or ciprofloxacin concurrent with three doses of anthrax vaccine adsorbed (AVA, BioThrax®) at 0, 2, and 4 weeks.8,9

2. Anthrax Preparedness Milestones

2004

- February 18, 2004: The DHS Secretary issued a Material Threat Determination (MTD) indicating that *B. anthracis* presents a material threat against the population of the United States sufficient to affect national security.

- In response to bioterrorism concerns, HHS created the Cities Readiness Initiative (CRI) as part of the Cooperative Agreement on Public Health Emergency Preparedness (PHEP) to help the nation's largest metropolitan areas develop the ability to provide life-saving medications in the event of a large-scale biological terrorist attack or naturally occurring disease outbreak.

- February 18, 2004: The HHS Secretary, DHS Secretary, and Postmaster General signed a Memorandum of Agreement (MOA) to make resources of the USPS available to help dispense oral antimicrobials in response to a biological terrorism incident. This offer of USPS assistance came to be known as the Postal Plan. The MOA outlined the framework for delivery of antimicrobials from the Strategic National Stockpile (SNS) to the general population.

2005

- July 2005: The HHS Secretary raised the concept of household emergency pharmaceutical stockpiles during a speech to the Association of State and Territorial Health Officials (ASTHO)-National Association of County & City Health Officials (NACCHO) Joint Conference. This concept was subsequently referred to as the “Home Medkit”10 and launched a myriad of activities within HHS including:
  - CDC funded an Investigational New Drug (IND) research project known as the Emergency MedKit Evaluation Study (CDC/St. Louis Study).

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9 Because AVA is not licensed for post-exposure use, administration of AVA as a component of PEP is available under an Investigational New Drug (IND) application (IND #10061, held by CDC) and may be made available under an Emergency Use Authorization (EUA).

HHS/USPS collaboration began to define the National Postal Model (NPM) and the request from USPS and their Unions for the provision of anthrax PEP in the form of a Household Antibiotic Kit (HAK) was made for the mail carriers and their household members.

- HHS asked FDA to opine on what studies would be necessary to obtain FDA approval for such a medkit.

2006 - 2007

- The CDC-sponsored St. Louis Study concluded with the initial evidence that almost all (97%) of those entrusted with a HAK cared for it appropriately.

- FDA composed the Project Plan Outlining Components to Support a MedKit New Drug Application (NDA)\(^\text{11}\).

2008

- September 23, 2008: The DHS Secretary determined that there is a significant potential for a domestic emergency involving a heightened risk of attack with \textit{B. anthracis}\(^\text{12}\).

- October 1, 2008: The HHS Secretary declared an emergency justifying the authorization of the emergency use of doxycycline hyclate tablets for anthrax PEP\(^\text{13}\).

- October 3, 2008: The FDA Commissioner, in consultation with the CDC and the National Institutes of Health (NIH), concluded that the criteria for issuance of the authorization under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)) were met and authorized the emergency use of doxycycline hyclate tablet emergency kits, for inhalation anthrax PEP for eligible USPS participants and their household members in the event of a public health emergency involving \textit{B. anthracis}.

2009

- October 1, 2009: The HHS Secretary renewed an emergency justifying the authorization of the emergency use of doxycycline hyclate tablets for anthrax PEP\(^\text{14}\).

- December 30, 2009: The US President signed Executive Order (EO) 13527, \textit{Establishing Federal Capability for the Timely Provision of Medical Countermeasures Following a Biological Attack} (Appendix 1). This EO spells out the US Government’s policy of public health preparedness: “It is the policy of the United States to plan and prepare for the timely provision of medical countermeasures to the American people in the event of a biological attack in the United States through a rapid Federal response in coordination with State, local, territorial, and tribal governments.”


2010

- October 1, 2010: The HHS Secretary renewed the emergency declaration justifying the authorization of the emergency use of doxycycline hyclate tablets for anthrax PEP.\(^\text{15}\)

2011

- July 18, 2011: The HHS Secretary renewed the emergency declaration justifying the authorization of the emergency use of doxycycline hyclate tablets for anthrax PEP.\(^\text{16}\)

- At the request of the HHS Assistant Secretary for Preparedness and Response (ASPR), the Institute of Medicine (IOM) performed and published a study on the use of prepositioned antibiotics for protection against anthrax.\(^\text{17}\)

- ASPR/HHS conducted outreach via a Public Survey on Medical Countermeasures, Seattle-King County Washington, November 5-6, 2011. The Executive Summary is currently in the clearance process.

- Via pre-IND meeting package and further discussions with FDA, the Biomedical Advanced Research and Development Authority (BARDA) in the ASPR at HHS, requested that FDA convene an Advisory Committee Meeting to have the Committee consider the feasibility of an FDA-approved medkit.

- December 1, 2011: BARDA submitted an IND for stability and observational studies of doxycycline and ciprofloxacin mixed in pre-identified foodstuffs and was notified by FDA after the 30-day safety review that the IND was in effect. The intent of the studies current and planned is to create the foundation based on the 2006 guidance from FDA to help support a regulatory development plan for an eventual approved medkit.

2012

- April 2012: FDA Anti-Infective Drugs Advisory Committee meeting on medkits.

3. **Anthrax Preparedness Activities**

Current MCM strategies in a case of *B. anthracis* attack include distribution and dispensing systems that involve federal, state, Tribal, and local governments distributing vaccine and drugs to PODS and pre-deployed, community-based caches. Thus far, only the National Postal Model (NPM) includes prepositioning of antibiotics in homes.


Cities Readiness Initiative

In 2004, the HHS created the CRI as part of the Cooperative Agreement on PHEP to help the nation’s largest metropolitan regions develop the ability to provide life-saving medications in the event of a large-scale bioterrorist attack or naturally occurring disease outbreak. Administered by the CDC’s SNS, CRI assists awardees in preparing for a large-scale anthrax attack or other large-scale public health emergency by providing antimicrobials and other life-saving medical supplies to 100 percent of a planning jurisdiction’s population within a 48-hour time frame. The program currently includes 72 metropolitan regions and covers an estimated 57 percent of the US population.

PODs are designated dispensing locations for persons who are currently healthy but who may have been "exposed" and need prophylactic medication. PODs are the traditional method of providing prophylaxis in CRI.

National Postal Model

The NPM was conceptualized as a way of reducing the general population surge at PODs. With this modality, mail carriers deliver antibiotics to the homes in pre-determined zip codes. The NPM is entirely voluntary for the employees of the USPS and only available to the jurisdictions with an approved USPS Dispensing Plan. Based on February 18, 2004, MOA, the USPS, in conjunction with HHS, local and state public health and law enforcement partners, and its letter carrier unions, developed a prototype by planning and executing three CRI proof-of-concept drills (in Seattle, Boston, and Philadelphia) and a comprehensive NPM pilot in Minneapolis/St. Paul. Presently, operational capability to distribute MCMs now exists in the Minneapolis/St. Paul area and recently launched in the Louisville, Kentucky area. In December 2009, Section 2 of the EO 13527 directed the establishment of a national USPS model for residential delivery of antibiotics following a biological attack. The resulting NPM sets forth the method for establishing USPS MCM distribution and delivery to residential addresses, guiding local planning for venue-specific Postal Plans. The future plans include Boston, Philadelphia, and San Diego.

The NPM is one of several methods of antibiotic delivery intended to reach the general population within 48 hours of the decision to release SNS assets. In conjunction with other local emergency response plans, the NPM will augment, not replace, the dispensing of oral antibiotics via PODs. The NPM can be efficient because pre-event preparation enables USPS participants to be involved in the earliest phase of the public health response to an anthrax event by delivering PEP on an emergency basis as a quick strike force directly to residences throughout an at-risk geographic area(s). Thus, given adequate planning and preparation, a venue-specific Postal Plan could be activated and executed while the municipality is putting its POD network into play for the remainder of the response. Most programmatic and operational responsibilities for the NPM are supported by the HHS Office of Preparedness and Emergency Operations (OPEO) and the National Disaster Medical System (NDMS) and in conjunction with participating Public Health Authorities (PPHA). This responsibility was recently transferred to OPEO and NDMS from the only participating public health authority at the time, Minnesota Department of Health (MDH), because of the exhaustive effect a program this size had on the staff in MDH.

The two unions that represent USPS carriers (the National Association of Letter Carriers and the National Rural Letter Carriers Association) are staunch supporters of the NPM. However, their endorsement is
contingent not only upon compliance with all applicable health recommendations pertinent to the carriers but also upon pre-event provision of prescription antibiotic drugs to the carriers as well as to other members of the carriers’ households. Thus, in order to participate in NPM, it is critical that the USPS volunteer participants and their household members be appropriately protected via chemoprophylaxis (e.g., begin PEP regimen as soon as instructed by the appropriate healthcare provider). Therefore, OPEO/NDMS screens each participant and his/her household member(s) and issues doxycycline in medkits, by prescription only, to eligible participants. Although doxycycline is FDA-approved for PEP, the written information included in the medkit is not; therefore, prepositioning of doxycycline in the NPM is authorized by the FDA under an EUA.

The doxycycline medkits for the NPM include (1) Household Antibiotic Kits (HAKs), to be stored at home and used by the USPS participant and anyone having permanent residence at the USPS participant’s primary residential address, and (2) Individual Antibiotic Kits (IAKs) to be stored and used by the USPS participant at his/her workplace.

HAK and IAK contain the following (Appendix 2):

- Plastic bag with information printed on exterior
- Unit of Use (UOU) bottle with 10-day supply of doxycycline hyclate
- Fact Sheet for Recipients
- Instructions - *In an Emergency: How to Prepare Doxycycline for Children and Adults Who Cannot Swallow Pills*
- MedWatch Form 3500

Each HAK contains UOU bottles for the participant and each household member.

V. Building the Initial Medkit Dataset

In accordance with medkit activities (Section III) and based on 2006 FDA’s *Project Plan Outlining Components to Support a MedKit NDA*, BARDA started pursuing a step-wise development program to help build the initial set of data in support of a potential FDA-approved medkit.

1. Proposed Contents of Antibiotic Medkit

Each medkit will only be available through a prescription from a licensed physician and dispensed from a pharmacy according to applicable federal and state regulations. It is too soon to speculate what an actual commercially available kit could look like; however, it could be very similar to what has been utilized in the USPS EUA (Appendix 2), which is outlined below.

- Depending on the household makeup, a pharmacist would “kit” specific doxycycline UOU or blister packs in the medkit for dispensing. Thus, it could be an individually sealed transparent bag with instructions printed on the exterior specifying that the medkit should be opened only in the event of a declared public health emergency. The transparency feature will enable participating households to satisfy their curiosity about the contents of the kit without having to open it. Warning statements along with an approved Medication Guide about proper use of the contents will be placed both inside the bag and in an outside pocket of the bag. In addition, the commercial manufacturer will provide an information contact telephone number that individuals
may call if they have questions regarding instructions (if discarded by accident), or if they have used the contents and are concerned about a possible medical problem associated with the use of doxycycline.

- A UOU bottle or a blister pack containing twenty doxycycline hyclate 100-milligram tablets.
- 10ml oral syringe (for administering crushed tablets, if needed)
- The medkit labeling (i.e., all written, printed, and/or graphic information that accompanies the product). These instructions are written close to an 8th grade reading level for ease of understanding. With the instructions on the outside, recipients will be less likely to feel they must open the transparent plastic bag to learn more about its proper use. The following will be included:
  - Approved Medication Guide
    - appropriate storage conditions
    - information about anthrax
    - information about doxycycline
    - when not to take doxycycline
    - when to stop taking doxycycline
  - Instructions for children and adults who cannot swallow pills
    - tablet crushing and mixing instructions with water and foods
    - dosing instructions for children and adults

2. **Doxycycline Medkit Development and Regulatory Pathway**

Although doxycycline is approved for treating anthrax, the labeling information that accompanies doxycycline tablets in a medkit is not. The data to support the potential further development of a doxycycline medkit is being carried out in two stages. In stage one, several pilot studies have been initiated by BARDA in order to provide preliminary data regarding stability of doxycycline mixed with water and food matrices, observation of home preparation, and label comprehension for stage two, which will include commercially sponsored studies. (See Section a. Stage I below for study descriptions.)

a. **Stage I**

Utilizing the 2006 FDA’s *Project Plan Outlining Components to Support a MedKit NDA* (See excerpt from that guidance in Table 1 below) on regulatory development of a home medkit, BARDA submitted an IND to begin to establish a regulatory development pathway for an eventual commercially available medkit. A palatability study was conducted prior to IND submission. Currently BARDA has developed and submitted two protocols to the IND. The purpose of these studies is to generate an initial data set regarding observation of mixing, stability in the food matrices, and label comprehension. The label comprehension study protocol is currently in development and is yet to be submitted to the FDA.
### Table 1. Excerpt from FDA Guidance

<table>
<thead>
<tr>
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<tr>
<td><strong>Palatability</strong></td>
<td>Evaluate the palatability of doxycycline and ciprofloxacin when mixed with each of several food substances. Include evaluation of the previously tested food substances and other food substances in order to further evaluate the ability to mask the taste of doxycycline and ciprofloxacin and to provide a range of food options; providing a range of food options will increase the choices in order to meet taste preferences and increase the likelihood of finding a listed food substance in a particular home.</td>
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</tbody>
</table>
| **Evaluation of the Home Preparation Instructions: Label Comprehension** | Performed by laboratory personnel:  
- Data needed with regard to the ability of individuals to follow/adhere to instructions  
  - To include the soaking step adequately addresses prior difficulties reported with crushing the tablets, and evaluation of content uniformity, dose recovery, and dose fractionation (ability to deliver intended dose).  
- This type of study, including stability assessments for the approx. 24 hour period that the prepared material may be utilized, needs to be done for each manufacturer’s formulation.  
- If there is a desire to add a new food substance to the list of food substances in which the drug may be mixed, additional stability testing would be needed to support use of that new food substance. |
| **When Performed by Subjects Representative of the General Population:** | This study would be done in a “home-like” or “kitchen-like” setting to evaluate whether persons of different literacy levels can successfully perform the crushing and mixing instructions:  
- Estimated number of study subjects (N) = 100 to 150  
- The study should enroll persons with different literacy levels, specifically including patients with low literacy. Ideally, 50% of persons enrolled in the study would be of low literacy level. In this study, it will be very important to adequately evaluate groups of different literacy levels and their performance.  
- One might also consider studying / enrolling persons who are first responders, if the medkit might be directed primarily at first responders. |
| **Bioavailability Assessment for the Drug in the Food Substance(s) Admixture** | At the time of the 2006 guidance, FDA was not sure if this study would be needed because, according to the data the Agency had, crushed oral doxycycline and ciprofloxacin had similar bioavailability to that of the intact solid oral dosage forms; therefore, in vivo studies may not be necessary. |

While most adults can take the required solid oral dosage formulation of these antibiotics, children and dysphagic individuals can present unique problems for compliance. Therefore, tablets need to be crushed and added to solutions and/or food matrices to administer the required dose of medication to these individuals. It is this mixture that may have a disagreeable taste, especially to children. Addressing the
disagreeable flavor characteristics of doxycycline and ciprofloxacin may enhance compliance with the recommended treatment regime, particularly among the young population, which is why BARDA funded the first study (non-IND) assessing the palatability of ciprofloxacin and doxycycline in various foodstuffs.

Protocol C-2010-01: Palatability Study for Masking the Respective Tastes of Ciprofloxacin and Doxycycline
Northland Laboratories, Chicago, conducted this study. The PI was Dr. Brian Pfister, Laboratory Director.

The goal of this study was to identify foods and/or pharmaceutical flavoring additives that most successfully mask the unpleasant tastes of ciprofloxacin and doxycycline solid oral dosage forms.

Respectively, ciprofloxacin and doxycycline were crushed and pre-mixed with foodstuffs or pharmaceutical flavorings. Only information regarding doxycycline is provided here. The Doxycycline Group had 61 panelists who tasted 16 foodstuffs and two pharmaceutical flavorings with one repetition. Panelists were asked to taste up to four different food products per sitting containing a known dosage of doxycycline. Chocolate pudding, peanut butter, low fat and regular chocolate milk, cherry yogurt, cherry gelatin, low fat milk, simple syrup with sour apple, and apple juice were among the highest in overall opinion scoring above a 5.0 (good) and had the highest percentages of “yes” (at or above 85%) when asked if they were a good option to cover up the taste of the medication.

Protocol C-2011-2: Study to Evaluate the Stability of Ciprofloxacin and Doxycycline Mixed in Pre-Identified Foodstuffs
Northland Laboratories, Chicago, is conducted this study under BARDA-sponsored IND, and the PI is Ms. Gretchen Gutierrez, Laboratory Director.

The objective of this study was to evaluate the stability of ciprofloxacin and doxycycline solid oral dosage when dissolved/suspended in tap water and mixed with food matrices, and milk and soy infant formula. Testing frequency of the tap water and drug mixtures was evaluated at 0, 1, 12, 18, 24, 36, 48, and 60 hours; and the food and drug mixtures was evaluated at 0, 1, 2, and 4 hours.

The stability evaluation included assessment of each drug compound in a drug and tap water mixture across a pH range of 3.0-8.5 and over a temperature range of 41-77°F (5-25°C). The analytical testing scheme resulted in 240 analytical samples for each drug evaluated for concentration (assay), degradation/impurities, and appearance for the tap water and drug mixtures. The analytical scheme for the food matrices resulted in 147 analytical samples for doxycycline (144 food and drug mixtures and 3 food preparations without the drug to be used as a control for degradation/impurity assessment).

Doxycycline was mixed with the following foods: chocolate pudding, smooth peanut butter, chocolate milk, simple syrup, and apple juice.

SUMMARY OF DOXYCYCLINE STABILITY DATA
The stability of doxycycline was measured in each of the pH-adjusted water solution/suspensions at time points of 0, 1, 12, 18, 24, 36, 48, 60 hours and evaluated for concentration (assay) and degradation
compounds. Doxycycline in the pH adjusted water solutions remained stable at both room temperature (25°C) and at refrigerated conditions (5°C) over the course of 60 hours at pH levels of 2.75 (as is), 3.2, and 4.6. There is evidence of degradation at pH of 6.5 and significant degradation at 8.5 at room temperature which suggest that doxycycline may not be stable in neutral or alkaline conditions. At refrigerated temperatures, pH of 6.5 was stable and pH 8.5 had much slower degradation which suggests that the cooler conditions slow the reaction.

The stability of doxycycline was measured in each of the food-drug matrices at time points of 0, 1, 2, and 4 hours and evaluated for concentration (assay) and degradation compounds. Doxycycline remained stable at both room temperature (25°C) and at refrigerated conditions (5°C) over the course of 4 hours for apple juice and simple syrup, and both cow derived and soy derived infant formula. It was stable in chocolate milk at refrigerated conditions but not at room temperature. Peanut butter was not stable with only 85.9% recovery at room temperature and 87.8% recovery at refrigerated conditions after one hour and decreasing from there. The chocolate pudding had questionable stability results but also had significant drug recovery issues. For purposes of this protocol, the choice was made to use 90-110% of the target concentration of the drug in the food matrix as acceptance criteria, in line with USP requirements. Since the drug tablets themselves are not assessed for content, drug recovery is being reported as a percentage based on the analytical method work completed prior to the stability study for the food matrices.

The final three matrices chosen for inclusion into the doxycycline mixing instructions are apple juice, chocolate milk, and simple syrup.

Protocol C-2011-3: Study to Observe Home Preparation of Ciprofloxacin and Doxycycline Mixed in Pre-Identified Foodstuffs
Northland Laboratories, Chicago, is conducting this study under BARDA-sponsored IND, and the PI is Ms. Gretchen Gutierrez, Laboratory Director.

The purpose of this study is to test written instructions for the home preparation of ciprofloxacin and doxycycline solid oral dosage forms into foodstuffs. The doxycycline arm of this study will include selected food matrices from the stability study (apple juice, chocolate milk, and simple syrup). Mixing instructions will also include infant formula as an option for infants only taking formula. The foodstuffs selected are also expected to be commonly found in a household and/or readily available throughout the US.

This protocol will be a single-center, observational, performance-based study to 1) observe participants using the home preparation instructions for adequate preparation; 2) test foods mixed by study participants for homogeneity and correct dose of drug, and 3) recommend further revisions to the preparation instructions if results from 1 and/or 2 indicate changes are needed to improve user comprehension and/or ensuring the dose prepared is the dose that is available within the food mixture for administration.

Upon arriving for a study session, a study participant will be brought to the area where the study will be conducted. The laboratory staff will read the same introductory statement to each study participant.
Each study participant will be in his/her station and will not be able to see other participants. In addition, participants will be instructed not to discuss the study activities with other participants at any time. The table in front of each participant will have four small bowls, metal spoons, a set of measuring spoons, a 10 mL dosing syringe, instructions for preparation, an assignment sheet, water, drug tablets/pills, a simple kitchen timer, selected foodstuffs for that session, paper towels, and an assortment of typical kitchen utensils. The additional utensils not necessarily intended for use in the mixing protocol will be provided to test participant performance in a realistic setting where he/she will likely have to choose appropriate implements from those on hand. Utensils will be cleaned by staff after each session for reuse in future sessions or replaced. All study participants will be given the same instructions.

A video recording device such as a web cam connected to a computer, or a video camera will be positioned at the booth where participants will work and will record their session. This method of observing their work will be used so that participants are not distracted by an observer being physically present and do not receive inadvertent or perceived queues from an observer. From the video of each session, the following quantitative observations will be documented:

- Time spent reading instructions before beginning to prepare the mixture
- Correct tool selected for measuring the antibiotic dose
- Number of uses of the dosing syringe to measure out the antibiotic dose to be mixed with food
- Time spent stirring the antibiotic dose and food together
- Number of times the participant interrupts his/her activities to reread the instructions.

These quantitative observations are intended to be an objective evaluation of performance and compliance with instructions. With these observations it may be possible to distinguish performance/compliance differences among different literacy groups. It may also be possible to identify aspects of the preparation process that are inherently challenging or error prone.

Antibiotic-food mixtures made by the participants will be evaluated analytically to determine correct dosage and homogeneity of the mixture. Homogeneity is a critical characteristic in the administration of drug products particularly in infants and small children to confirm that they are indeed getting the appropriate dose. To address this, each prepared foodstuff will be evaluated in duplicate using random sampling. The analytical testing will be according to the methods listed in the current United States Pharmacopoeia (USP) for Assay and are High Performance Liquid Chromatography (HPLC) methods. Slight modifications to the methods will be required in order to account for the matrices. Modifications may include solvent changes, adjustments in solvent-sample ratios, or centrifugation to remove solid matter from solvent-sample mixtures.

Protocol C-2011-4: Label Comprehension Assessment of an Emergency Use Household Antibiotic Kit

SNBL Clinical Pharmacology Center, Baltimore, Maryland, will conduct this study under BARDA-sponsored IND, and the PI will be Dr. Mohamed Al-Ibrahim.

This is a prospective, open label, cross-sectional study. Comprehension of the label and instructions will be assessed by a structured one-on-one interview based on a questionnaire designed to assess comprehension of key communication messages. The questionnaire will first be evaluated by focus group interviews and modified accordingly for ease of use and understandability. Study procedures and
structured interviews will be assessed in a training session and refined, if necessary, prior to use in this study.

Community liaisons for selected study centers will be selected and trained to assist in recruiting at their respective sites. Research associates will be formally trained to administer the interview, and their technique will be assessed prior to commencing the study.

Study participants will meet at a selected venue in their community for one study visit during which they will complete all study procedures, including the one-on-one structured interview to assess comprehension of the doxycycline label and instructions.

The primary objective is to assess the percentage of all study participants that understands the primary communication messages found on the label and instructions, i.e., indication, dosing instructions, contraindications, and warnings. The secondary objective is to assess comprehension of the overall messages relating to the safe and appropriate use of the drug.

This study will include 600 participants (including 100 emergency first responders identified for the purpose of this study as police, fire, and emergency medical technicians) of a demographically diverse population of adults with varying levels of education and English language literacy from a variety of rural, urban, and suburban sites across Maryland.

Approximately 8-10 sites across Maryland are targeted to obtain representation of a demographically diverse population of adults with varying literacy levels, to include various regions in Baltimore City, Baltimore County, rural northwest Maryland, rural Eastern Shore of Maryland and rural southwest Maryland.

Inclusion criteria will include males or females, 18 years or older (currently living in the state of Maryland) who can read, write, and understand English; are willing and able to complete all study procedures; and are able to understand and sign the informed consent form.

Exclusion criteria will exclude participants with visual problems that deter them from reading study materials, who have received prior Disaster Preparedness Training (does not apply to first responders cohort); who are physicians, nurse practitioners, registered nurses, physician’s assistants, or dentists; and who have had prior participation in this study.

Each participant will receive a complete medkit bag. The medkit bag will be identical to the medkit bag used in the NPM EUA. The bag will contain an empty sample doxycycline bottle with label, fact sheet entitled, “Emergency: Mixing Doxycycline Hyclate with Food for Children & Adults Who Cannot Swallow Pills”, 10ml oral syringe, and the MedWatch 3500 Form.

Each study participant will meet one-on-one with a research associate and will complete an informed consent form. The interviewer will complete an eligibility checklist and demographic form and then administer the Rapid Estimate of Adult Literacy in Medicine (REALM) test. Subjects will then be provided with the medkit, after which they will be interviewed by the research associate to assess their understanding using the predefined script and comprehension questionnaire. Participants will be given the opportunity to suggest ways to improve the label and instructions.
b. **Stage II**

Taking into consideration FDA’s *Project Plan Outlining Components to Support a MedKit NDA* and recommendations of the FDA Anti-Infective Drugs Advisory Committee on medkits, future HHS and/or USG policy may include the decision to pursue a commercial FDA-approved doxycycline medkit. These in-home stockpiles would be intended to supplement, not replace, medical countermeasure dispensed through community-based PODs.

Should the medkit development proceed to Stage II, BARDA (see Appendix 3) will publish a Request for Proposal (RFP) for a commercial, FDA-approved medkit.

The commercial manufacturer will have to meet all applicable FDA regulatory requirements for approval. The commercial manufacturer will need to file an IND to begin the process, and subsequently submit the NDA. The manufacturer will be obligated to conduct the appropriate studies under IND, for example, but not limited to, the following: assess the comprehension of the product labeling, conduct a palatability study, and perform an observational “actual use” study. These studies should address what is in the medkit, when it should be used, where and how it should be stored, and how it should be used.

If this Committee finds an FDA-approved medkit is feasible and a step-wise indication to the responder community acceptable, there will need to be well-crafted, targeted messages to this population with regard to, but not limited to, the following:

- product availability and process (i.e., medical screening, prescription, dispensing at retail pharmacy)
- the appropriate storage conditions
- guidance on the triggers for use of the medkit
- caution not to use the medkit contents except when directed to do so by public health officials in the event of an anthrax emergency.

**VI. Proposed Medkit Logistics**

This Section contains ideas and suggestions on how FDA-approved medkits could be dispensed and stored for the indicated population within the responder community. The final logistics would require in-depth deliberations with FDA and the commercial manufacturer including, but not limited to, the following: prescribing via a medical director for household members, storage, national registry for medkits, and collection or disposal of expired kits. All details will be included in the approved label, labeling, and any post marketing commitments.

We propose that the FDA-approved medkits have an initial restricted approval to be made available to those professional responder organization-identified first responders and their household members. Thus, the medkit will not initially be available to the general population. The USG will not mandate that the responder organizations make medkits available to their first responders and household members; that will be a decision left to that organization and/or individual responder. The responsibility will lie with the responder organizations to increase their own preparedness for an anthrax emergency.
1. Proposed Definition of First Responders and Household Members
The USG will not dictate what individuals and/or organizations are first responders; therefore, professional responder organizations could assist this effort by drafting a vetted definition of first responder. These may include emergency medical technicians, police officers, and health care workers. However, it is assumed that these personnel are trained and certified according to all applicable laws, regulations, and standards.

A household member is anyone who considers that address as his or her permanent place of residence.

2. Proposed Program Schema for Use of the Responder Antibiotic Kits
a. The Prescribing and Dispensing of Doxycycline Via the Responder Doxycycline Medkit
One possible scenario could include a licensed physician acting as a Medical Director for a responder organization who will review the medical history information with the responder and prescribe doxycycline for the responder as well as each household member who has supplied the requisite medical history. Those for whom the prescribing physician determines that doxycycline is contraindicated (e.g., history of allergy or significant adverse reaction to a tetracycline) will be considered not applicable to receive doxycycline to be contained within the home antibiotic kit. Although tetracycline antibiotics are not recommended during pregnancy, their use may be indicated for a life-threatening illness. During the bioterrorist event of 2001 with anthrax, the CDC recommended the use of doxycycline in pregnant women and children for the treatment and prevention of inhalation anthrax because the high death rate from the infection outweighed the risks posed by the antibiotics.18

If the contraindication applies to any member of the household, the responder still can elect to have a medkit; however, s/he makes that decision as an informed choice. The responder will have the opportunity to apprise the healthcare entity in writing that s/he (a) is prepared to accept an incomplete (i.e., medication in kit does not represent every household member) antibiotic kit and (b) understands that, during a public health emergency involving exposure of his/her household to the anthrax organism, the household members not covered by the household kit will have the same dependency as does the rest of the community upon whatever emergency mass chemoprophylaxis the public health authority is able to provide. That is, s/he will have the option to (a) participate and accept whatever degree of pre-event antimicrobial drug coverage is medically appropriate for the household or (b) decline to participate and accept for his/her entire household the same dependency upon the public health authorities for emergency chemoprophylaxis as has the overwhelming majority of the community, which will not have access to household kits of antibiotic drugs.

Each prescription for a medkit will be available commercially and, therefore, will be dispensed by a pharmacist according to applicable federal and state pharmacy regulations. It is important to understand that the final format of the medkit is outside the scope of this document and will require the traditional relationship that every manufacturer and FDA has in bringing products into the commercial market.

b. **Qualification and Registration of the Responder Organizations and Medical Directors**

It may be necessary for the responder organization to have to register with the manufacturer or a third party vendor in order to obtain doxycycline medkits for identified first responders. The credentialing of the responder organization may require information along with written verification of participation of the named Medical Director on organization letterhead for review by the manufacturer or the third party vendor. These documents should be reviewed to ensure the credentials of the responder organization and the Medical Director are accurate prior to acceptance of the participation of the responder organization.

c. **National Registry for Medkits**

Registries are collections of data related to patients with a specific diagnosis, condition, or procedure. A registry is a study that actively collects data and information on medical products during product use. Registries differ from post-marketing surveillance techniques in that patients are enrolled before the outcome, such as an adverse event, is known. Registries have become a popular manner to collect real-time data, such as pregnancy registries to monitor women who become pregnant after exposure to an investigational drug in a clinical trial; voluntary drug product registries to supplement on-going long-term post-approval studies to monitor rare serious adverse events noted during a clinical study; and to provide additional safety and efficacy data on products that receive approval through accelerated approval mechanisms, such as drugs for rare diseases. Registries may be an important tool for the availability of this product.

d. **Required Visit to PODs**

Since this proposed medkit only has the first 10 days of oral PEP, the first responders and their household members will need to visit community-based PODs or follow other available mechanisms to receive the 50-days follow-on of the antibiotic therapy and the 3-dose series of PEP anthrax vaccination, if appropriate.

e. **_EXPIRY**

As doxycycline in medkits expires, the responder organizations will develop their own plans for collecting expired doxycycline as potentially outlined in the FDA-approved labeling. Alternatively, the kit could come with its own disposal mechanism or instructions.

Once the medkits have been dispensed, a program internal to that responder organization may be necessary to maintain operational readiness. This may include attention to situations that might affect the continued availability or contents of the doxycycline kits and may require written procedures to address the following: employee departure, survey of viable kits, loss and/or inappropriate use of the contents of the kit.

VII. **Advantages of Prepositioning Doxycycline Medkits**

DHS issued respective MTD for *B. anthracis* in 2004 and multidrug-resistant *B. anthracis* in 2006. *B. anthracis* is considered one of the most serious bioterrorism agents because of the ability of the spores to persist in the environment, the ability of the aerosolized spores to readily cause infection via respiratory exposure, and the high mortality of resulting inhalation anthrax. In the absence of rapid and effective public health intervention, the successful execution of a large-scale anthrax attack in a major metropolitan area could have disastrous effects.
Two factors are the primary determinants of how quickly the PEP regimen can be initiated. The first factor is detection and confirmation of a *B. anthracis* release. This may occur within a few hours if the release of the aerosol is witnessed; within 24-36 hours if BioWatch environmental sampling is the first source of evidence; or after 2 or more days if the first evidence is the appearance and correct diagnosis of symptomatic individuals presenting for healthcare.

The second factor determining the speed of initiating PEP is the time needed following detection to move antimicrobial drugs (a) from the SNS to State-operated Receipt, Store, and Stage (RSS) warehouses; (b) from the RSS to PODs; and (c) from the PODs to the at-risk population. The length of time needed depends on how quickly PODs can be set up and begin operations, how many PODs can be operated simultaneously, and the aggregate throughput of the POD network. The PODs are likely to be the rate limiter in that generally they depend heavily on the availability of volunteer workers and must be set up on a just-in-time basis in facilities that normally are used for other purposes. PODs throughput could greatly vary, from 162 to 1,700 persons per hour, depending on the size and number of PODs. This is based on modeling and published reports of mass vaccination and antibiotic dispensing campaigns for naturally occurring infectious diseases. Therefore, it may be impossible to meet the timeline required to provide prophylaxis to the citizens of a large city or other densely populated region within 48 hours, as required by the CRI. Thus, in the wake of a wide-area release of the anthrax organism, the sooner mass PEP begins and the more rapidly it is executed, the more lives can be saved.

Recent preparedness exercises, including the DHS Anthrax Response Exercise Series (ARES) and the HHS Dark Zephyr senior-level exercise, underscore the significant progress the US has made in planning for rapid dispensing of oral antimicrobial drugs, but exercises also reveal continued areas for improvement, particularly the need to improve how the nation moves emergency medical countermeasures into a community. Feedback from these preparedness exercises has raised concerns that the nation does not have adequate operational capability to provide antimicrobial prophylaxis to entire communities within 48 hours of the decision to do so.

Houck and Herrmann developed a compartmental model that includes both the progression of the disease and the logistics of treatment, which could estimate the impact of deploying medkits in a community. The model used the following parameters: population size (5,000,000); time to detect attack (48 hours); delay until local supplies are available (5 hours); delay until push pack is available = 12 and 24 hours; number exposed (50,000, 500,000, and 1,250,000); percentage of non-exposed persons who will seek

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prophylaxis (1%, 10%, and 50%); and, adherence rate (65% and 90%). The number of medkits distributed varied prior to an attack scenario. They considered increments of 500,000 medkits from 0 to 5,000,000. The medkit model showed that as more medkits are pre-positioned, the mortality rate decreases and the fewer deaths occur. In some scenarios the mortality rate was substantial while in others it was minimal. When the number of potential exposures was high and medication not immediately available for those who truly needed it, then providing medkits would save many lives.24

The IOM (see Appendix 4), in its 2011 study on prepositioning antibiotics for anthrax, recognized the potential benefits of pre-positioning medkits with first responders. Widespread use of prepositioned medkits could significantly prepare a ready workforce of first responders by eliminating the need for first responders to initially queue at community PODs and therefore preventing delays in response time. Providing responders with anthrax antibiotics prophylaxis regimens, such as doxycycline medkit, in advance of an event increases the likelihood that they will be available to perform their vital functions. This plan allows first responders to be directly involved in their own resilience, and, thereby they will be more prepared to help citizens. In addition, they may be more likely to participate knowing that their household members are protected as well.

The responder community plays an important role during an anthrax attack in maintaining law and order (e.g., police), protecting infrastructure (e.g., fire fighters, police), and providing healthcare (e.g., emergency medical services). By making doxycycline medkits available to first responders and their household members for personal preparedness, nationwide preparedness for an anthrax attack would be improved since a proportion of communities would not have to visit PODs. Pre-positioned medkits can relieve pressure on community PODs; thus prepositioned medkits can benefit those who have them as well as those who do not.

Stakeholder Support

The Emergency Services Coalition for Medical Preparedness

The Emergency Services Coalition for Medical Preparedness (Coalition) comprises all the national associations representing emergency services organizations and personnel. The Coalition represents millions of highly skilled career and volunteer personnel in the disciplines of Law Enforcement, Fire and Emergency Services, Emergency Medical Services, Emergency Management, and Public Works.

Several recent studies examined the ability and willingness of responders to report in a variety of disaster situations. These studies reveal willingness to respond at a mere 50 percent for biological events. These studies have shown increased responder willingness to report when countermeasures are made available for themselves and their families in advance of the emergency event. Increased resilience requires the development and deployment of protections to ensure emergency services will continue during large-scale attacks.25,26,27,28

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An FDA-approved antibiotic medkit supports the continuity of emergency services operations in disaster situations by addressing concerns of responders in reporting for duty during medical-based emergencies. The Coalition advocates for increasing the national resilience by providing additional protections for emergency services personnel and their families. One component of this protection is to distribute FDA-approved antibiotics medkits pre-event to support the protection of responders whose mission is to save lives, protect property and the environment, assist communities impacted by disasters, and aid recovery during emergencies.

Department of Homeland Security Office of Health Affairs
The DHS Office of Health Affairs (OHA) mission is to provide medical, health, and scientific expertise in support of the DHS mission to prepare for, respond to, and recover from all hazards impacting the Nation. Within that mission are four goals: to provide expert health and medical advice to DHS leadership; to build national resilience against health incidents; to enhance national and DHS medical first responder capabilities; and to protect the DHS workforce against health threats.

OHA has been highly involved in federal activities surrounding Executive Order 13527, “Establishing Federal Capability For The Timely Provision of Medical Countermeasures Following A Biological Attack.” Working in close collaboration with the FDA to address the different Sections of this EO, both OHA and FDA consider the preparedness of our nation’s first responders a priority. An FDA-approved antibiotic medkit would add another layer of preparedness to ensure the responders with critical duties in the immediate aftermath of an anthrax attack are able and willing to continue working; an advancement with the potential to support a portion of DHS employees with responder duties.

VIII. Perspectives on or from Public Health

1. Potential for Possible Antibiotic Misuse Leading to Adverse Events
Although the 2011 IOM study recognizes the potential benefits of pre-positioning medkits with first responders, the study does not recommend development of public health strategies that involve broad use of prepositioned MCMs for the general population because of the associated risk such as inappropriate use, to treat cold for example, or use in an event of distant attack. See Appendix 4 for the other IOM recommendations.

Although this is a serious concern, the medkit will contain a limited number of tablets (20 per person – one tablet twice a day for 10 days). This limited quantity makes the likelihood of adverse effects due to accidental or intentional overdosing lower than would be the case if a full course of anthrax PEP (120 tablets – one tablet twice a day for 60 days) were provided. If a wide-area anthrax emergency were to require PEP beyond 10 days, first responders would be directed to obtain the requisite medications through whatever means public health authorities are using to provide PEP to the rest of the population.

Pandemic Influenza Using a Threat-and Efficacy-Based Assessment Framework.” PLoS ONE 5: e9856.
Doi:10.1371/journal.pone.0009856


Furthermore, this section discusses data on antibiotic misuse in the US found in scientific literature, the actual data collected from the USPS participants under the NPM EUA for the use of doxycycline contained in HAKs, the St. Louis Home MedKit Evaluation Pilot Study, and FDA regulatory mechanisms for risk mitigation.

a. **Scientific Literature on Antibiotic Misuse**

To further investigate the potential misuse of antibiotics in general, BARDA has consulted the National Library of Medicine (NLM). The NLM librarians conducted a search using the following databases: MEDLINE/PubMed, Web of Science, Embase, and Google/Google scholar. See Appendix 5 for the complete list of search criteria and scientific databases searched. Using the established search criteria and databases, a one hundred eighteen-page list of references was identified. All references were determined to include data from either within the US or outside the US. Those from outside the US were excluded from assessment since findings in other countries do not necessarily translate to US culture. Studies in Europe, for example, show substantial variation of antibiotic misuse in various European countries (e.g. lower rates of misuse in Northern and Western Europe and high rates of misuse in Southern and Eastern Europe): thus, it would be difficult to interpret which of these finding would be applicable to US population. References from data within the US were categorized into the following groups based on their general subject matter: (1) Anthrax release 2001, (2) Antibiotic regimen compliance, (3) Latino immigrant antibiotic use and acquisition behavior, (4) Self medication, (5) Emergency response studies, and (6) Miscellaneous. The Miscellaneous category included subject matter related to antibiotic insurance issues, physician antibiotic prescribing, dental antibiotic prophylaxis, and patient expectations for antibiotic prescribing. It was determined that the antibiotic misuse of most concern with medkit pre-positioning would involve self medication; therefore, self medication was the focus of the data assessment. Although non-compliance is a serious issue, it could happen whether doxycycline is obtained from prepositioned medkits, from PODs, or by physician prescription. Self medication was a common theme in the nine references targeting Latino immigrants, so these data were also included in the assessment.

Of these references with data from within the US that pertained to self medication, there were no comprehensive studies that span multiple ethnic, educational, and socioeconomic groups to help paint a picture of the US general population self-medication practices. Instead data were gathered from specific study populations such as emergency department patients, sexually transmitted disease patients, college students visiting student health clinic, Latino immigrants, injection drug users, and upper

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respiratory infection patients.\textsuperscript{35} Publication dates for these studies range from 1975 to 2010. In all studies, there were portions of the study populations who reported as having taken antibiotics not prescribed by a physician to treat a perceived condition. The percentages of those from some of the sub-populations reported as self medicating are as follows:

- Emergency department patients: 17\% (232 out of 1363) and 6\% (17 out of 270)
- Sexually transmitted disease patients: 14\% (75 out of 551)
- College students visiting student health clinic: 2.4\% (62 out of 2,624)
- Injection drug users: 25\% (3 out of 12)
- Upper respiratory infection patients: 24\% (50 out of 192).

These antibiotics could have been obtained from a variety of sources such as leftover from previous prescription, from family member, directly from pharmacist without prescription, or from outside the US.

Some references in the self-medication category examined antibiotic sources other than physician prescription. A study from 2009 investigated the availability of antibiotics for purchase without a prescription on the internet and concluded that antibiotics are freely available for purchase on the internet without a prescription, a phenomenon that encourages self-medication and low quality of care. They identified 138 unique vendors selling antibiotics without a prescription. Of those vendors, 36.2\% sold antibiotics without a prescription, and 63.8\% provided an online prescription. Vendors who sell antibiotics without a prescription were more likely to sell quantities in excess of a single course, and the antibiotics were more likely to take more than 7 days to reach the customer. This suggests that these transactions are most likely for storing the drug for future self diagnosis and use.\textsuperscript{36}

Another reference, published in 2002, provides information regarding the availability of certain antibiotics from pet stores without a prescription. The author found a broad range of antibiotics available without a prescription at pet stores to include erythromycin in 200-mg tablets; kanamycin in 150-mg capsules; penicillin in 250-mg tablets; ampicillin in 250-mg capsules; tetracycline in 250-mg tablets or capsules; minocycline in 10-mg tablets; triple sulfa-combination capsules containing 84 mg of sulfamethazine, 84 mg of sulfacetamide, and 332 mg of sulfathiazole; urinary antiseptic combination capsules containing 60 mg of nitrofurazone and 25 mg of furazolidone; and metronidazole in 250-mg capsules. Since these medications are not regulated for use in humans, there are no guarantees as to their quality or potency.\textsuperscript{37}

Published in 2010, an investigation of nonprescription antibiotic therapy from US-Mexico border pharmacies involving Mexicans and US medical tourists reported that self medication with antibiotics tends to be concentrated where antibiotics are readily and cheaply available over-the-counter (OTC); this includes Mexico along with most of Latin America. They identify common users of border pharmacies to be the large medical tourist population who cross the border to make OTC purchases of drugs that are otherwise prescription only and more expensive in the US. Their results show that Mexican clients were more likely to engage in risky antibiotic use and reported twice the use of antibiotics than the US tourists,

which stands to reason that those with the most access to the border pharmacies and unregulated purchasing will engage in risky behavior. They did find, however, that levels of public health knowledge about antibiotic risks did predict lower overall levels of antibiotic saving, sharing, and OTC purchasing across and within all groups. Research conducted directly after the anthrax event of 2001 revealed an alarming number of pharmacists displaying banners proclaiming “Prevent Anthrax; Buy Cipro Cheap.” US tourists, concerned with the possibility of an antibiotic shortage in the case of an anthrax “epidemic,” visited Mexican pharmacies to stock up on “Cipro.” Although Mexican pharmacists were promoting the sale of “Cipro,” Mexican consumers were much less concerned with contracting anthrax than were Americans, according to interviews conducted with the pharmacists. Fear of a shortage of ciprofloxin in the US and the refusal of physicians to prescribe prophylactic antibiotics to “prevent” anthrax led Americans to cross the border to hoard these antibiotics. “Cipro” was displayed in pharmacy windows and sold in boxes of 10 or 12 to US tourists.  

Multiple studies have been done investigating US Latino immigrant antibiotic use behavior. One review published in 2006 concluded that self-prescribing of antibiotics is common among Latinos in the US Latino communities, and that Latinos obtain these antibiotics from sources outside the US, independently owned grocery stores or bodegas in their US communities, family members, previous illnesses for which antibiotics were prescribed, and pharmacists without prescription. The self-prescribing practices of many Latinos were most commonly based on the belief that antibiotics help treat viral infections. Common themes among most studies in this category were that participants’ previous experiences in countries with limited restrictions on antibiotics influenced acquisition of antibiotics without a prescription in the US. Participants described the roles of grocers, family, and social networks in accessing treatment advice and prescription drugs. Prescription medicines, such as antibiotics, and medical advice were identified as readily available from nonmedical sources. Data indicate that this population experiences significant barriers to accessing health care, forcing them to seek treatment alternatives including the purchase and use of drugs manufactured in Mexico.

While there are portions of the targeted study populations in each self-medication category article who are identified as having self medicated, it is not clear that these data are an indication of how the general US population may misuse a home medkit. References do point to the notion that if people are inclined to self medicate with antibiotics, there currently are multiple antibiotic sources available, often without prescription. Through this thorough search of the US literature, it would seem that further studies need to be done to conclusively state that self medication of the contents from an FDA-approved and appropriately packaged medkit would be a realistic risk that would outweigh the benefit of prepositioning this medical countermeasure.

b. **USPS Six-Month Household Antibiotic Kit Survey Data Reports**

As part of the conditions of authorization from the EUA, each city participating in the venue-specific Postal Plan is required to perform a six-month survey on the status of HAKs that were distributed to the USPS volunteer participants. MDH collected data on the status of HAKs in the Minneapolis/St. Paul area every six months since the EUA authorization, and the reports below cover the following reporting periods: April 2010 through September 2010, October 2010 through March 2011, and April 2011 through September 2011.

Data from these three surveys show that all participants and their household members who returned their surveys still had their HAKs and did not open them. As USPS participants are volunteers, there are no financial or social incentives for them and their household members not to open their HAKs. To date, no reports of misuse of doxycycline in medkits have been received.

**April 2010 through September 2010 Reporting Period**

- Of 377 active participants at survey mailing, 12 participants (3%) were deactivated for not returning a six-month HAK Status form. Of the 12 deactivated volunteers who did not return their form, 9 returned their HAK and 3 did not return their HAK at the time of doxycycline refresh.

- Data was collected on the 365 participants who returned the HAK Status forms, which indicated that the entire cohort (n=365, 100%) of the responding USPS volunteers still had their HAK, knew where they were stored, and reported them as unopened. (See Table 2 below)

- Of the 365 forms that were collected, 328 people (89.9%) had neither change in the composition of their household nor any change in health status for themselves or their household members.

**Table 2. HAK Status April 2010 – September 2010**

<table>
<thead>
<tr>
<th>Health and Household Status</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in household members and health status</td>
<td>328</td>
<td>89.9</td>
</tr>
<tr>
<td>Change in household composition</td>
<td>23</td>
<td>6.3</td>
</tr>
<tr>
<td>Change in health status</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>Change in household composition and the health status</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Incomplete forms (see the note below)</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>365</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Note: At the time of doxycycline refresh, MDH contacted four volunteers who submitted incomplete forms. Two volunteers had no changes in their household or health status; one had a new household member; and one opted out of the program and returned his/her kit at the time of the six-month follow-up.*

**Additional Information from the Doxycycline Refresh in August 2010**

Because the doxycycline in the initial HAK distribution expired on September 30, 2010, MDH developed a process to collect and replace the fielded kits and termed this process “refresh.” MDH collected 358 HAKs from the active volunteers and 9 from the deactivated volunteers. However, 10 HAKs were missing at the conclusion of the refresh activities from active, deactivated, and inactive volunteers. Table 3 provides additional information on the status of returned and missing HAKs.
Table 3. HAK Status from August 2010 Refresh

<table>
<thead>
<tr>
<th>Returned HAKs</th>
<th>n=367</th>
</tr>
</thead>
<tbody>
<tr>
<td>From active volunteers</td>
<td>358</td>
</tr>
<tr>
<td>From deactivated volunteers (forms were not returned)</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing HAKs</th>
<th>n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>From active volunteers</td>
<td>5</td>
</tr>
<tr>
<td>From deactivated volunteers who did not return their Kit Status form</td>
<td>3</td>
</tr>
<tr>
<td>From volunteers who initially returned their Kit Status form but subsequently left the Program</td>
<td>2</td>
</tr>
</tbody>
</table>

Ten HAKs were reported missing for the reasons outlined below.

Active Volunteers:
Five currently active volunteers reported missing HAKs. Based on reasons described below, MDH, in consultation with the USPS, decided not to deactivate these volunteers, as the loss of the HAK was out of their control.
- One volunteer reported that the HAK was thrown out during a renovation of the area of the home where it had been stored.
- One volunteer reported driving to the office to return HAK for the refresh when a car accident took place. The car was totaled and towed before the kit was removed. The kit could not be retrieved.
- One volunteer lost the HAK during a move.
- One volunteer, who has many children, had hidden the HAK so the children could not find it and, subsequently, had forgotten where he placed the HAK.
- One volunteer was unable to find the HAK.

Inactive Volunteers:
Five inactive volunteers reported missing HAKs for the following reasons:
- Three deactivated volunteers, who did not return their Kit Status form, reported missing HAKs.
- One volunteer transferred and did not return the HAK.
- One volunteer opted out of the program and reported the HAK lost.

October 2010 through March 2011

- Out of 327 forum participants, a six-month HAK Status form was collected from 310 (94.8%) participants. Of the 17 volunteers who did not return their HAK Status form, seven volunteers did not receive their HAK from the doxycycline refresh in August 2010 and 10 did not return their forms.
- Data was collected on the 310 participants who returned the HAK Status forms. The entire cohort (n=310, 100%) of the USPS volunteers still had their HAK, knew where they were stored, and reported them as unopened. Please see Table 4 below.
• Of the 310 forms that were collected, 283 people (91.2%) had no change in the composition of their household or any change in health status for themselves or their household members.

Table 4. HAK Status October 2010 – March 2011

<table>
<thead>
<tr>
<th>Health and Household Status</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in household members and health status</td>
<td>283</td>
<td>91.2%</td>
</tr>
<tr>
<td>Change in household composition</td>
<td>22</td>
<td>7.1%</td>
</tr>
<tr>
<td>Change in health status</td>
<td>5</td>
<td>1.6%</td>
</tr>
<tr>
<td>Change in household composition and the health status</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>310</td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

April 2011 through September 2011

As of December 8, 2011, of the 337 participants, 268 (79.5%) submitted completed six-month HAK Status forms. Additionally, 30 participants (8.9%) returned forms without a name. USPS sent a follow-up mailing. Once a reasonable deadline for response had passed, MDH sent a letter to non-responding participants terminating their participation in this volunteer program. At the time this document was prepared, no further information was received.

• Data was collected on the 268 participants who returned the HAK Status forms. 262 (97.8%) of the USPS volunteers still had their HAK, knew where they were stored, and reported them as unopened.
• Of the 268 forms that were collected, 233 people (86.9%) had no change in the composition of their household or any change in health status for themselves or their household members. Table 5 below provides information on composition and health status of surveyed participants’ household members.

Table 5. HAK Status April 2011 – September 2011

<table>
<thead>
<tr>
<th>Health and Household Status</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in household members and health status</td>
<td>233</td>
<td>90.8%</td>
</tr>
<tr>
<td>Change in household composition</td>
<td>26</td>
<td>9.7%</td>
</tr>
<tr>
<td>Change in health status</td>
<td>5</td>
<td>1.9%</td>
</tr>
<tr>
<td>Change in household composition and the health status</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>Incomplete forms</td>
<td>3</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>268</td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

c. **St. Louis Home MedKit Evaluation Pilot Study**

CDC conducted a Home MedKit Evaluation Pilot Study in St. Louis and published the summary results in November 2007.43 The overarching aim of the study was to evaluate a strategy that would provide medicines to individual households prior to any direct bioterrorism threat and for use only as directed in

a declared public health emergency. Specifically, the study was designed to (1) assess the ability of households to maintain medkits in the home as directed and to reserve them for emergency use; (2) explore attitudes, perceptions, and other social factors that may influence participant behavior regarding storage and proper use of the medkits; and (3) provide information about the acceptability of the household medkit prototype.

The study design was prospective over a period of eight months. A baseline interview was conducted in-person, and each household member was medically screened. Because the study was conducted under an IND, informed consent was required for each member. At the time of enrollment, households were randomly assigned to a two-, four-, or eight-month time interval for a follow-up interview and the return of their medkit. There were 174 households lost to follow-up; data were complete for 4,076 households (12,040 persons). Participants received financial compensation for the study.

Regarding the ability of households to maintain medkits in the home as directed and to reserve them for emergency use, 97% (3,946 out of 4,076) of all study respondents returned the household medkits upon completion of the study. Of the 130 (3%) households that did not return their medkits, 125 of these households could not locate their medkits and five simply refused to return them. Four households reported having used their medkits: an elderly woman used hers during a declared emergency for a storm; two households reported having had a member with “sore throat;” and one household refused to state why the pills were taken. Among the medkits that were returned, all but 34 of the medkit bags were intact (i.e., more than 99% had no pills missing). Curiosity about the contents was the most frequently mentioned reason (55%) given for opening the medkit bag.

Regarding the attitudes, perceptions, and other social factors that may influence participant behavior regarding storage and proper use of the medkits, more than 75% (n = 3,086) of participants reported that having the emergency medkit in their homes increased their awareness of the need to prepare for a public health emergency, including a terrorist attack. Overall, 75% (n = 3,059) of all respondents reported that they feel “not too prepared” or “not at all prepared” for such an attack. An overwhelming majority of study participants reported that, based on their experience with the study, they would like to have a medkit in their home. The majority of respondents stated that they would pay for a medkit, and the average price that households would pay per person was $23.

d. FDA Regulatory Mechanisms for Risk Mitigation

Based on the study sponsored and conducted by the CDC and the current experience in Minnesota for the USPS EUA, it is highly unlikely that doxycycline would be improperly used when dispensed as a packaged medkit and under the control of the responders and their family members. Thus, the benefits of doxycycline dispensed as medkits to be used in the event of an anthrax incident outweigh the risks of the drug being misused. However, it must be noted that, under both of these programs, the kits were provided free of charge and monitoring and reporting on the status of the kits was included as part of the program. It is possible that these factors contributed to proper use and storage. Under this proposal, product purchase would be the responsibility of the responder family and monitoring and reporting of medkit status is not anticipated to occur.

A concern is that this risk:benefit ratio will change. FDA has many ways to monitor and manage this risk:benefit ratio, to include appropriate product labeling, post-market surveillance, Medication Guides,
and risk evaluation and mitigation strategies (REMS). FDA also has the ability to collaborate with other stakeholders to insure the safe use of doxycycline in medkits.\textsuperscript{44} 

FDA can require that companies conduct a post-approval study or clinical trial to assess a known serious risk related to the use of a drug, to assess signals of serious risks related to the use of the drug, or to identify an unexpected serious risk when available data indicates that there is a potential for a serious risk. This ability was given to the Agency through the FDA Amendments Act of 2007 (FDAAA).\textsuperscript{45} This law requires that persons submit a proposed REMS as part of a NDA or Biologics License Application (BLA) if required by FDA. FDA may require applications approved without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. Once the holder of an approved application is notified by FDA that a REMS is necessary, the holder must submit a proposed REMS within 120 days, or within such other reasonable time as FDA requires to protect the public health. Failure to submit a REMS can result in enforcement action.\textsuperscript{46} 

Thus, FDA has a regulatory mechanism in place to identify and assess the risks of misuse of doxycycline in medkits if there is a concern that this misuse changes the benefit:risk ratio profile. 

FDA is using REMS to balance the benefits of prescribing a controlled substance, extended release/long acting (ER/LA) opioids, to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death.\textsuperscript{47} Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem. The central component of the opioid REMS is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants) so that these drugs can be prescribed and used safely.\textsuperscript{48} Prescribers need to understand how to assess patients for treatment with ER/LA opioids; be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids; be knowledgeable about how to manage ongoing therapy; know how to counsel patients and caregivers about the safe use of these products, including proper storage and disposal; and be familiar with general and product specific drug information concerning ER/LA opioids.\textsuperscript{49} 

The opioid REMS also includes educational materials that prescribers can provide to patients on how to use and store these products safely. These materials will allow prescribers to properly counsel patients on safe use and the responsibilities associated with using these products. One such educational material

is a Medication Guide\(^{50}\) that patients pick up with their prescriptions. Medication Guides provide information in patient-friendly language about the drug’s risks and how to use the drug.

Manufacturers of ER/LA opioids are required to monitor their REMS program to determine, among other things, how many prescribers are completing the educational programs and whether the REMS is adversely affecting patient access to necessary pain medications.\(^{51}\) Thus, if FDA has the ability to monitor and mitigate the risks of a controlled substance with a long history of misuse, then this same program can be expected to monitor and mitigate the risks of doxycycline misuse when packaged and delivered in medkits.

An applicant does not have to wait for FDA to require that a REMS be submitted; the applicant may voluntarily submit a proposed REMS to the FDA. For instance, an applicant may submit a proposed REMS to the FDA if the applicant believes a REMS would be necessary to ensure that the benefits of the drug outweigh its risks. An approved REMS that is voluntarily submitted is subject to the same requirements and enforcement as a REMS that was originally submitted as a FDA-required proposed REMS. In addition, if the FDA determines that a REMS is not required, an applicant may undertake voluntary risk management measures that would be performed outside of a REMS\(^{52}\), such as physician and consumer education, language in the package insert (see antibiotic labeling below), and active post-marketing surveillance.

Through the Safe Use Initiative,\(^{53}\) FDA has the ability to collaborate to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners and stakeholders who are committed to safe medication use. These stakeholders include Federal agencies, such as CDC, pharmacies, healthcare professionals, and patients.\(^{54}\) FDA has already collaborated with a broad group of stakeholders to address safety issues associated with, for example, acetaminophen toxicity due to daily dosing in excess of the recommended maximum labeled dose; the association of a rare, but serious, disease with benzocaine, the main ingredient in OTC gels and liquids applied to the gums or mouth to reduce pain; and unintentional medication overdoses in children by children’s gaining access to medication when their caregivers weren’t looking.\(^{55}\)


2. Misuse of Doxycycline in Medkits Could Lead to Antibiotic Resistance

The development of antibiotic resistance is an issue for all antibiotics. Almost all important bacterial infections in the US and throughout the world are becoming resistant to antibiotics. Antibiotic resistance has been called one of the world's most pressing public health problems. The FDA is addressing antibiotic resistance through activities that include awareness and partnering with the CDC.

Antibiotic labeling contains required statements in several places advising health care professionals to prescribe these drugs only to treat infections that are believed to be caused by bacteria. Labeling also encourages health care professionals to counsel patients about proper use. For example, the labeling for doxycycline products states that patients should be counseled that antibacterial drugs should only be used to treat bacterial infections as they do not treat viral infections. When the product is prescribed, patients should be told that the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the immediate treatment and increase the likelihood that bacteria will develop resistance; therefore, bacterial infections may not be treatable by the drug or other antibacterial drugs in the future. This information is located on the first page of the labeling giving it prime importance and a location where a healthcare provider will readily see it. In addition, a post-approval requirement for a recently approved antibiotic, DIFICID® (fidaxomicin), requires the post-approval monitoring for the development of resistance. This was required as an analysis of spontaneous postmarketing adverse events reports will not be sufficient to assess a signal of a serious risk of development of bacterial resistance. The company must conduct a prospective study over a five-year period after introduction of DIFICID® to the market to determine if decreased susceptibility to DIFICID® is occurring in C. difficile.

FDA has partnered with CDC on "Get Smart: Know When Antibiotics Work," a campaign that offers Web pages, brochures, fact sheets, and other information sources aimed at helping the public learn about preventing antibiotic-resistant infections.

Antibiotic resistance is an issue for doxycycline in medkits as it is for all antibiotics. Doxycycline contains labeling for physicians and patients which cautions against use of the drug for indications other than bacterial infections. In addition, as the above studies demonstrate, first responders are not likely to lose control of their medkit or take doxycycline before the need arises. Therefore, the risk of the development of antibiotic resistance does not outweigh the benefit of use of doxycycline during a pre- or post-anthrax event.

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Appendix 1

December 30, 2009

Executive Order 13527 -- Medical Countermeasures Following a Biological Attack

ESTABLISHING FEDERAL CAPABILITY FOR THE TIMELY PROVISION OF MEDICAL COUNTERMEASURES FOLLOWING A BIOLOGICAL ATTACK

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Policy. It is the policy of the United States to plan and prepare for the timely provision of medical countermeasures to the American people in the event of a biological attack in the United States through a rapid Federal response in coordination with State, local, territorial, and tribal governments.

This policy would seek to: (1) mitigate illness and prevent death; (2) sustain critical infrastructure; and (3) complement and supplement State, local, territorial, and tribal government medical countermeasure distribution capacity.

Sec. 2. United States Postal Service Delivery of Medical Countermeasures. (a) The U.S. Postal Service has the capacity for rapid residential delivery of medical countermeasures for self administration across all communities in the United States. The Federal Government shall pursue a national U.S. Postal Service medical countermeasures dispensing model to respond to a large-scale biological attack.

(b) The Secretaries of Health and Human Services and Homeland Security, in coordination with the U.S. Postal Service, within 180 days of the date of this order, shall establish a national U.S. Postal Service medical countermeasures dispensing model for U.S. cities to respond to a large-scale biological attack, with anthrax as the primary threat consideration.

(c) In support of the national U.S. Postal Service model, the Secretaries of Homeland Security, Health and Human Services, and Defense, and the Attorney General, in coordination with the U.S. Postal Service, and in consultation with State and local public health, emergency management, and law enforcement officials, within 180 days of the date of this order, shall develop an accompanying plan for supplementing local law enforcement personnel, as necessary and appropriate, with local Federal law enforcement, as well as other appropriate personnel, to escort U.S. Postal workers delivering medical countermeasures.

Sec. 3. Federal Rapid Response. (a) The Federal Government must develop the capacity to anticipate and immediately supplement the capabilities of affected jurisdictions to rapidly distribute medical countermeasures following a biological attack. Implementation of a Federal strategy to rapidly dispense medical countermeasures requires establishment of a Federal rapid response capability.

(b) The Secretaries of Homeland Security and Health and Human Services, in coordination with the Secretary of Defense, within 90 days of the date of this order, shall develop a concept of operations and establish requirements for a Federal rapid response to dispense medical countermeasures to an affected population following a large-scale biological attack.
Sec. 4. Continuity of Operations. (a) The Federal Government must establish mechanisms for the provision of medical countermeasures to personnel performing missionessential functions to ensure that mission-essential functions of Federal agencies continue to be performed following a biological attack.

(b) The Secretaries of Health and Human Services and Homeland Security, within 180 days of the date of this order, shall develop a plan for the provision of medical countermeasures to ensure that mission-essential functions of executive branch departments and agencies continue to be performed following a large-scale biological attack.

Sec. 5. General Provisions.

(a) Nothing in this order shall be construed to impair or otherwise affect:

(i) authority granted by law to a department or agency, or the head thereof; or
(ii) functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity, by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

BARACK OBAMA

THE WHITE HOUSE,
December 30, 2009.
Appendix 2

NPM EUA Medkit Content
In an Emergency: How to Prepare Doxycycline for Children and Adults Who Cannot Swallow Pills

Mixing Doxycycline Hyclate 100mg Tablets with Food

Once you have been notified by your federal, state or local authorities that you need to take doxycycline for a public health emergency, it may be necessary to prepare emergency doses of doxycycline for children and adults who cannot swallow pills.

June 2006
Prepared by the U.S. Food and Drug Administration
In an Emergency: How to Prepare Doxycycline for Children and Adults Who Cannot Swallow Pills

Mixing Doxycycline Hyclate 100mg Tablets with Food

Once you have been notified by your federal, state or local authorities that you need to take doxycycline for a public health emergency, it may be necessary to prepare emergency doses of doxycycline for children and adults who cannot swallow pills.

June 2008
Prepared by the U.S. Food and Drug Administration

Supplies You Will Need
You will need these items to make doses of doxycycline for adults and children who cannot swallow pills:

- 1 doxycycline pill (100 mg)
- (Do not take doxycycline if you are allergic to tetracyclines)
- a metal teaspoon
- 2 small bowls
- Water
- one of these foods or drinks to hide the bitter taste of crushed doxycycline:
  - milk or chocolate milk
  - chocolate pudding
  - apple juice and sugar

Crushing the Pill and Mixing with Water

1. Put 1 doxycycline pill in a small bowl.
2. Add 4 full teaspoons of water to the same bowl.
3. Let the pill soak in the water for 5 minutes so it will be soft.
4. Use the back of a metal teaspoon to crush the pill in the water. Crush the pill until no visible pieces remain.
5. Stir the pill and water so it is well mixed.

You have now made the Doxycycline and Water Mixture.
Child’s weight: ________

Adding Food to the Doxycycline and Water Mixture to Make It Taste Better

1. Weigh your child.
2. Find your child’s weight on the left side of the chart below.
3. Next, look on the right side of the chart to find the amount of the Doxycycline and Water Mixture to mix with food. The chart shows you the amount to give your child for 1 dose. (For a ½ teaspoon dose, fill the metal teaspoon half way. It is better to give a little more of the medicine than not enough).

<table>
<thead>
<tr>
<th>Child’s Weight</th>
<th>Amount of Doxycycline and Water Mixture</th>
<th>Teaspoons</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 pounds or less</td>
<td>½ teaspoon</td>
<td>1</td>
</tr>
<tr>
<td>13 to 25 pounds</td>
<td>1 teaspoon</td>
<td>2</td>
</tr>
<tr>
<td>26 to 30 pounds</td>
<td>1½ teaspoons</td>
<td>3</td>
</tr>
<tr>
<td>31 to 50 pounds</td>
<td>2 teaspoons</td>
<td>4</td>
</tr>
<tr>
<td>51 to 63 pounds</td>
<td>2½ teaspoons</td>
<td>5</td>
</tr>
<tr>
<td>64 to 75 pounds</td>
<td>3 teaspoons</td>
<td>6</td>
</tr>
<tr>
<td>76 to 88 pounds</td>
<td>3½ teaspoons</td>
<td>7</td>
</tr>
<tr>
<td>89 pounds or more</td>
<td>Use the entire mixture</td>
<td>Entire mixture</td>
</tr>
<tr>
<td>and adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Add the right amount of the Doxycycline and Water Mixture from the chart above to the second bowl. For adults and children 89 pounds and more, use the entire mixture.
5. Add 3 teaspoons of milk or chocolate milk or chocolate pudding or apple juice to the second bowl. If you use apple juice, also add 4 teaspoons of sugar to the second bowl. • Stir well.
6. Go to Step 2 for dosing.

Dosing the Doxycycline and Water Mixture Mixed With Food

1. Give all of the Doxycycline and Water and food mixture in the second bowl. This is one dose.
2. Each child or adult should take 1 dose in the morning and 1 dose at night each day.

Storing the Doxycycline and Water Mixture (If There Is Enough for Another Dose)

- If you have enough leftover doxycycline and water mixture for another dose, you can keep it for the next dose.
- The doxycycline and water mixture can be stored in a covered bowl or cup. Label and date.
- Keep the mixture in a safe place out of the reach of children.
- Store the Doxycycline and Water Mixture at room temperature for up to 24 hours.
- Throw away any unused mixture after 24 hours and make a new Doxycycline and Water Mixture before the next dose.

Do not take doxycycline if you have an allergy to tetracyclines.
Get emergency help if you have any signs of an allergic reaction including hives, difficulty breathing, or swelling of your face, lips, tongue or throat.

Doxycycline may cause diarrhea, skin reaction to the sun, loss of appetite, nausea and vomiting. Birth control pills may not work as well if you take doxycycline.

Report any reaction to the medication to MedWatch at www.fda.gov/medwatch or 1-800-FDA-1088
BACKGROUND

This fact sheet provides background about the National Postal Model (NPM) that would be used to respond to a large-scale airborne anthrax attack, including information about Household Antibiotic Kits (kits for eligible United States Postal Service [USPS] participants and household members) and Individual Antibiotic Kits (kits stored at the workplace only for eligible USPS participants). The first part gives background information and important details to be considered while completing the USPS NPM Health Assessment Form. The second part gives detailed instructions about what the USPS participant and their household members should do if they are instructed to take the antibiotics in the kits because of an actual anthrax attack.

The National Postal Model is a system to distribute medications door-to-door in certain emergency situations. This program was developed by security and public health officials and the USPS. USPS employee volunteers (referred to as “USPS participants”) who are participating in a venue-specific adaptation of the National Postal Model are capable of rapidly distributing antibiotics to people exposed to the anthrax bacteria germ to prevent inhalational anthrax disease in people. The U.S. Department of Health and Human Services (HHS) is coordinating the packaging and dispensing of the Household Antibiotic Kits and Individual Antibiotic Kits.

What if I do not want to be a part of the USPS National Postal Model?

The National Postal Model is a volunteer program. There is no penalty for deciding not to participate. If you decide not to participate, you and your household members may receive antibiotics through other ways the government would distribute them to the public to prevent anthrax disease in an anthrax emergency.

IMPORTANT INFORMATION

Read this fact sheet so you will be ready to use your Household Antibiotic Kit or Individual Antibiotic Kit if you are told by a public health official to use it. The HHS Secretary has declared an emergency and the Food and Drug Administration (FDA) Commissioner has issued an Emergency Use Authorization (EUA) to authorize the pre-event storage and post-event use of Household Antibiotic Kits and Individual Antibiotic Kits. The emergency was declared because the Secretary of Homeland Security has determined that there is a significant potential for a domestic emergency involving a heightened risk of attack with anthrax. These actions allowed the Food and Drug Administration (FDA) Commissioner to authorize the distribution and potential use during an emergency of Household Antibiotic Kits and Individual Antibiotic Kits for USPS employee volunteers participating in the National Postal Model and their household members to prevent inhalational anthrax disease.

Doxycycline is a prescription medicine approved by the FDA to prevent and treat infections caused by certain bacteria (germs), including the life-threatening bacterial germ that causes anthrax disease. However, a special legal permission called an FDA Emergency Use Authorization is needed to allow for emergency use instructions, home preparation instructions, and other information to be provided to you. The specific emergency use instructions in this fact sheet are new and so have not been studied in the past. Some persons may have to
prepare doxycycline dosages at home from the Household Antibiotic Kit. The home preparation instructions are also new and so have not been evaluated for use in a home setting. You will receive more information and instructions for use at the time of exposure to anthrax. The Emergency Use Authorization may be revoked if the criteria for issuing it are no longer met or other circumstances make revocation appropriate to protect public health or safety.

NOTE: This emergency declaration and Emergency Use Authorization do not mean that an actual anthrax emergency has happened or that there is currently an exposure that can make you sick. If an actual anthrax emergency happens in your area, you will be instructed by a public official to start taking the doxycycline in the Household Antibiotic Kit or Individual Antibiotic Kit. Do not use the Household Antibiotic Kit or Individual Antibiotic Kit unless you have been told to start using it by a public official. Taking doxycycline at that time can help keep you from getting sick if you have been exposed to certain bacteria germs, such as the one that causes anthrax.

If you have been exposed to the anthrax bacteria germ, are taking doxycycline as directed, and begin to have the symptoms of anthrax described below, get medical care right away. Do not delay getting medical care.

<table>
<thead>
<tr>
<th>FACTS ABOUT ANTHRAX AND DOXACYCLINE</th>
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**What is anthrax?**

Anthrax is a serious disease caused by the bacterial germ *Bacillus anthracis*. This bacterial germ forms spores. A spore is a cell that is asleep (inactive) but may become active under the right conditions. Anthrax spores can cause anthrax disease if they get into your lungs, skin, or stomach and become active. People who breathe in (inhale) anthrax spores are at risk of getting serious inhalational anthrax disease. Taking antibiotics soon after exposure to anthrax germs may prevent getting anthrax disease. Anthrax disease can cause death even if you are treated. Anthrax disease affects children and adults in much the same way. However, children may be more likely than adults to suffer bad effects from some of the antibiotics used to prevent the disease.

**What are the symptoms of breathing in (inhalational) anthrax?**

The first symptoms of breathing in (inhalational) anthrax are cold-like or flu-like symptoms and can include a sore throat, mild fever, and muscle aches. Later symptoms include cough, chest discomfort, shortness of breath, tiredness, and muscle aches. *(Caution: Do not assume that just because a person has cold or flu symptoms that they have breathed in, i.e., inhalational, anthrax.)*

**If I get anthrax, will I make others sick with anthrax?**

No, anthrax is not a disease where there is person-to-person spread like the flu.

**What is doxycycline?**

Doxycycline is an antibiotic medicine that is used to treat infections caused by certain bacterial germs, including life-threatening germs such as anthrax.
Who should not take doxycycline?

Do not take doxycycline if you:

- Are allergic to doxycycline
- Are allergic to any antibiotic known as a tetracycline. Ask your doctor if you are not sure. A partial list of tetracycline drugs includes:
  - Chlortetracycline (Aureomycin)
  - Demeclocycline (Declomycin)
  - Doxycycline (Adoxa, Atridox, Bio-Tab, Doryx, Doxychel, Doxy, Monodox, Periostat, Vibra-Tabs, Vibramycin)
  - Minocycline (Arestin, Dynacin, Minocin, Vectrin)
  - Oxytetracycline (Terak, Terra-Cortril, Terramycin, Urobiotic-250)
  - Tetracycline (Achromycin V, Bistracycline, Sumycin, Tetrax, Topicycline, Helida)

How do I report side effects or problems with using the medicine in the Household Antibiotic Kit or Individual Antibiotic Kit?

For life-threatening emergencies, call 911. If you take doxycycline and if you experience any adverse event or a medication error, contact your personal physician or emergency department. You or your personal physician should report side effects or medication errors by any of these methods:

- Reporting to MedWatch via the MedWatch website at: [www.fda.gov/medwatch](http://www.fda.gov/medwatch); www.fda.gov/medwatch;
- Submitting a MedWatch Form 3500 with the report (one is included with the information in your Household Antibiotic Kit or Individual Antibiotic Kit); it is also available at [http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf](http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf); or
- Reporting to MedWatch using the “800” number: 1-800-FDA-1088.

When you report side effects or errors to your personal physician and via MedWatch, state that you have used a “doxycycline hyclate tablet emergency kit” received under the “USPS-NPM EUA” (United States Postal Service National Postal Model Emergency Use Authorization) by including in the description of the event the abbreviations “USPS-NPM EUA” or the words “USPS-NPM Emergency Use Authorization.” In addition, report adverse effects to a designated National Disaster Medical System (NDMS) clinician at 800-place holder.

What if I do not take the antibiotic in the kit when told to do so?

It is your choice to take the preventative antibiotic or not. Note that Postal workers will not be allowed to be a part of the USPS National Postal Model if they do not take the antibiotic following an anthrax event. If you do not take the antibiotic in the Household Antibiotic Kit or Individual Antibiotic Kit, you may develop or die from severe anthrax disease if you are exposed to the anthrax germ.

Are there other medicines for preventing or treating anthrax?

Other FDA-approved antibiotic medicines approved by the FDA to prevent or treat anthrax that are not a part of the Household Antibiotic Kit or Individual Antibiotic Kit include: ciprofloxacin, levofloxacin, and penicillin G
These antibiotic medicines require a prescription from your doctor and are not part of the EUA. Each of these other medicines, like all medicines, can have side effects. Ciprofloxacin and levofloxacin can cause adverse effects including: tendon rupture, convulsions, hallucinations (seeing things that are not there), depression, abnormal heartbeats, and a severe type of diarrhea. Penicillins can cause a number of adverse effects including serious allergic reactions, skin rashes, and a severe type of diarrhea.

BioThrax (Anthrax Vaccine Adsorbed) may be given to protect adults ages 18 to 65 years old who may come in contact with animal products, such as hides, hair, or bones from areas where anthrax germs are found, and that may be contaminated with anthrax germ (*Bacillus anthracis*) spores. The vaccine may also be given to people such as veterinarians and laboratory workers whose job may involve touching animals or other materials that may be infected. It is not clear if BioThrax works or is safe for people after they have been contaminated with anthrax germ (*Bacillus anthracis*) spores. Side effects of BioThrax are muscle or joint aches, headache, tiredness, chills, rashes, and low fever. BioThrax is not covered in this Emergency Use Authorization because the vaccine does not provide protection for several weeks. If you have questions about these other medicines, talk with your doctor.

What if I use other medicines?

Doxycycline and other medicines may affect each other, causing side effects. Doxycycline may affect the way other medicines work and other medicines may affect how doxycycline works. The doses of some medicines may need to be changed while you take doxycycline. You should prepare a list of the medications that you or your household members take, including prescription and non-prescription medicines, vitamins, and herbal supplements. It is especially important to discuss with the medical screener if anyone takes:

- medicine to thin your blood known as warfarin (Coumadin, Jantoven). People who take a blood thinner (anticoagulant therapy) may need a different dose when taking doxycycline.
- seizure medicine such as phenobarbital, phenytoin (Dilantin), fosphenytoin (Cerebyx), or carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, or Teril)
- isotretinoin (Accutane) or acitretin (Soriatane)
- methotrexate
- oral contraceptives (birth control pills may not work as well when you take doxycycline; use condoms or another form of birth control to prevent pregnancy until you finish taking doxycycline.)
- lithium
- ciprofloxacin, levofloxacin, or other quinolone antibiotics

How can I learn more?

The Department of Health and Human Services, in collaboration with USPS and the public health authority, will make you aware of any important new information found during the time of emergency use of the Household Antibiotic Kit or Individual Antibiotic Kit.
WHAT SHOULD I CONSIDER ABOUT DOXYCYCLINE AFTER I RECEIVE MY HOUSEHOLD ANTIBIOTIC KIT OR INDIVIDUAL ANTIBIOTIC KIT?

Upon receiving a Household Antibiotic Kit or Individual Antibiotic Kit:

As soon as you receive a Household Antibiotic Kit or Individual Antibiotic Kit, review the list of drugs directly above. If you currently are taking any of them, ask your regular health care provider whether you should continue to take it/them during an emergency for which public health authorities instruct you to take the doxycycline in your kit. Also ask your health care provider if there are additional measures you should take if you are recommended to continue with your ongoing medications as well as the doxycycline.

Upon a change in health status after receiving a Household Antibiotic Kit or Individual Antibiotic Kit:

If, after your receive a kit, you experience any of the following changes in health status, ask your regular health care provider whether you should take the doxycycline in your Household Antibiotic Kit or Individual Antibiotic Kit during an emergency for which public health authorities instruct you to do so:

- develop a serious liver or kidney problem
- develop an allergy to doxycycline or tetracycline
- become pregnant
- are breast feeding.

Upon starting a medication on the list above:

If, after you receive a Household Antibiotic Kit or Individual Antibiotic Kit, you begin taking any of the drugs listed above, ask your regular health care provider whether you should continue to take it/them during an emergency for which public health authorities instruct you to take the doxycycline in your kit.

How should I store doxycycline?

- Store doxycycline between 68°F and 77°F (20°-25°C).
- Keep doxycycline in the container it comes in.
- Keep doxycycline dry.
- Keep the container closed tightly.
- Keep doxycycline and all medicines out of the reach of children.
- A good storage place in many homes is on an upper shelf in a bedroom closet that is kept off-limits to children.

How should I dispose of the doxycycline when it reaches its expiration date, when I change jobs or move, when I no longer want to be a part of the USPS National Postal Model, or when the emergency ends?

You should contact ________________________________ to get information on how to return your Household Antibiotic Kit or Individual Antibiotic Kit for proper disposal.
DURING AN ANTHRAX EMERGENCY: USE OF HOUSEHOLD ANTIBIOTIC KITS OR INDIVIDUAL ANTIBIOTIC KITS

The following information should be reviewed prior to taking the medicine during an emergency caused by anthrax exposure. If an actual anthrax emergency happens in your area, you will be instructed by a public health official to start taking the doxycycline in the Household Antibiotic Kit or Individual Antibiotic Kit. ** Do not use your kit unless you have been told to start by a public health official. **

This kit contains only enough medicine for 10 days. This is not a full course of preventive therapy. You need to take a full course of medication, which is usually 60 days. It is important to complete the full course of medication to help protect you from getting anthrax disease. Public officials will announce where you can get the rest of the medicine that you and your household members will need to complete your preventive therapy.

You have received a Household Antibiotic Kit or Individual Antibiotic Kit containing a 10-day supply of doxycycline in the event you are exposed to the anthrax germ, which can be deadly. You do not have to take this drug, but taking doxycycline (when told to start taking it by a public health official) to treat anthrax will reduce your risk of getting sick and dying. If possible, you may want to discuss with a health care professional the benefits and risks described in this fact sheet, or any available alternatives.

The full course of treatment is usually 60 days. Public officials will announce where you can get the rest of the medicine.

What is anthrax?
Anthrax is a serious disease caused by the germ Bacillus anthracis. People who breathe in (inhale) anthrax germs are at risk of serious illness, including death. However, you can’t get anthrax from another person.

- First symptoms are cold-like or flu-like symptoms, e.g., a sore throat, mild fever, muscle aches.
- Later symptoms are cough, chest discomfort, shortness of breath, tiredness, muscle aches. Symptoms usually occur within 7 days of inhaling anthrax germs, but can take up to 42 days to appear. See a doctor immediately if you have symptoms.

What is doxycycline?
Doxycycline is a prescription drug approved by the Food and Drug Administration (FDA) to prevent anthrax. Federal authorities have specially authorized certain uses of doxycycline, including use with associated with kits and emergency information, for this emergency situation. If you take doxycycline as directed and begin to feel sick anyway, get medical care right away.

How do I take doxycycline?

- Adults and those 8 years and older and children 89 lbs (40 kg) or more – take one pill (100 mg) in the morning and one pill in the evening on an empty stomach with a full glass of water.
- If you get an upset stomach or indigestion, take it with some food or milk. Be sure to drink lots of fluids.
- Children under 89 lbs (40 kg) and adults who can’t swallow a pill – Follow the directions provided to you on crushing and mixing doxycycline.
- If you miss a dose, take only the next scheduled dose – Do not take two doses at one time.
- Doxycycline may not work as well when taken with some medicines. Take it 2 hours before or 2 hours after taking: antacids; multivitamins or supplements with calcium, iron, magnesium, or sodium bicarbonate; Sucralfate (Carafate); Colestipol (Colestid); cholestyramine; Didanosine; Bismuth subsalicylate (Helidac) (Pepto Bismol) (Kaopectate); or any other products to treat indigestion, nausea, or diarrhea.
- Doxycycline may affect dosing of certain blood thinners or seizure medicines; call your doctor if you are on these medications.
- Keep the pills dry; store them between 68–77°F (20–25°C).
- Keep containers out of the reach of children and pets; call the poison control center if accidental ingestion occurs (1-800-222-1222).
Who should NOT take doxycycline?
Do not take doxycycline if you have had a severe allergic reaction to doxycycline or another tetracycline drug. If you or other household members have begun taking new drugs since you received your kit and have not already consulted your regular health care provider, ask the provider—or report to one of the local public health agency medication dispensing centers—to determine whether to continue to take those medications and whether there are additional health measures you should follow.

STOP taking the medicine if you get any of these serious, but rare, side effects; get medical help right away (go to the Emergency Room or call 911):
- swelling of the tongue, hands, or feet
- closing of the throat
- trouble breathing
- severe itching or rash, especially hives and welts
- severe stomach cramps with high fever or bloody diarrhea
- yellowing of the eyes or skin or dark-colored urine
- pain when swallowing
- unusual bleeding or bruising
- severe headaches, dizziness, or double vision

Keep taking the medicine if you have:
- mild nausea or vomiting, upset stomach, loose stools
- vaginal yeast infection

Are there other possible severe side effects?
- Serious liver problems (liver failure)
- Sensitivity to the sun
- Discolored teeth, poor tooth enamel in children under the age of 8 or when taken by their mothers during the last half of pregnancy or while nursing
- Slowed bone growth in children
- Birth control pills stop working. Use another form of birth control until you finish taking all of your doxycycline

What is unknown about the emergency use of doxycycline?
The benefit of providing you with emergency access to an initial supply of doxycycline is expected to outweigh the risks. However, it is unknown how well these emergency instructions will be used, how many individuals will receive the full, 60-day course of post-exposure prophylaxis (PEP).

How do I report side effects or errors?
Tell your doctor right away. You or your personal physician may report side effects or medication errors by:
- Reporting to MedWatch via the MedWatch website at: www.fda.gov/medwatch;
- Submitting a MedWatch Form 3500 with the report (one is included with the information in your kit); it is also available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf; or
- Reporting to MedWatch using the “800” number: 1-800-FDA-1088.

When you report side effects or errors to your personal physician and via MedWatch, state that you have used a “doxycycline hyclate tablet emergency kit” received under the “USPS-NPM EUA” (United States Postal Service National Postal Model Emergency Use Authorization) by including in the description of the event the abbreviations “USPS-NPM EUA” or the words “USPS-NPM Emergency Use Authorization.” Adverse events and medication errors must be documented and reported promptly (within 15 days) to MedWatch.

Reports of adverse effects should also be made to the designated NDMS clinician at: 800-Place Holder.

CONTACTS: If you have any questions, please contact XXXXX (placeholder for HHS/OPEO/NDMS specific contact information). The Department of Health and Human Services (HHS), in collaboration with USPS and the public health authority, will make you aware of any important new information found during the time of emergency use of the Household Antibiotic Kit or Individual Antibiotic Kit.
Appendix 3

BARDA’s Mission

BARDA is a core component of the Office of the Assistant Secretary for Preparedness and Response (ASPR) and as such contributes to the broader ASPR mission to “Lead the country in preparing for, responding to, and recovering from the adverse health effects of emergencies and disasters by supporting our communities’ ability to withstand adversity, strengthening our health and response systems, and enhancing national health security.

BARDA’s mission is to develop and procure medical countermeasures that address the public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases.

Specifically, BARDA supports the advanced development and procurement of drugs, vaccines and other products that are considered priorities for national health security. BARDA funding bridges the “valley of death” characterizing the late stages of product development. BARDA’s support ensures continuity of funding at a critical point for medical countermeasures developed by industry or emerging from the basic research and preclinical development activities sponsored by the National Institutes of Health (NIH). In procuring medical countermeasures for the Strategic National Stockpile, BARDA enhances the capabilities of the Centers for Disease Control and Prevention (CDC) to organize an effective response.

BARDA is the component of the Public Health Emergency Medical Countermeasures Enterprise that focuses on the advanced development, manufacturing and acquisition of medical countermeasures against CBRN threats, pandemic influenza, and emerging infectious diseases. BARDA’s staff includes experts in the fields of physical, chemical and biological sciences, engineering, clinical medicine, public health, product development, regulatory affairs, and program management.

The Pandemic and All-Hazards Preparedness Act (PAHPA) established BARDA in December 2006. BARDA oversees the Project BioShield program and Special Reserve Fund and is charged by statute with (1) promoting collaboration and communication between the US Government and interested parties in the advanced development and licensure of needed medical countermeasures; (2) directing and coordinating the countermeasure and product advanced research and development activities of the HHS; (3) facilitating medical countermeasure development by providing advice or directing interested parties to the relevant Centers of the FDA; and (4) supporting innovation through strategic initiatives and investment in technologies and research tools that facilitate countermeasure development.

PAHPA established a dual mandate for BARDA. BARDA is charged with coordinating the development of, and bridging the “valley of death” for, MCMs determined to be critical to the Nation’s health security. It is important to note that many such MCMs lack meaningful commercial markets and without US Government support would be unlikely candidates for development. In supporting their development, BARDA fills the gap between NIH, which
supports basic and preclinical research, and CDC, which develops utilization plans and deploys MCMs during public health emergencies. BARDA fulfills its mission by supporting advanced research and development of needed medical countermeasures; working in collaboration with manufacturers, the NIH, the CDC, the FDA, and the Departments of Defense (DoD) and Homeland Security (DHS); supporting technology innovation through strategic initiatives; and overseeing Project BioShield acquisitions.
Appendix 4

ASPR’s Commissioning of the Institutes of Medicine

Aware that one strategy will not meet every community’s medical countermeasure needs, the U.S. Government, in partnership with its State, local, tribal, and territorial partners, is investigating a variety of strategies for maximizing the nation’s capacity to respond to a large-scale bioterrorism attack. A combination of innovative distribution strategies has been proposed to meet the varied needs of the nation’s many population subgroups: community-based PODs for antimicrobials and vaccines; direct residential delivery of antibiotics via the U.S. Postal Service; pre-deployed, community-based caches of medical countermeasures for emergency use; pre-event dispensing of medical countermeasures as equipment to first responders; pre-deployed workplace caches of medical countermeasures; and pre-event placement of medical countermeasures in individual households for use only as directed.

The Office of the Assistant Secretary for Preparedness and Response (ASPR) within the Department of Health and Human Services (HHS) continues its assessment of these multiple methods of dispensing antibiotics, looking to build on best practices and to learn from stakeholder input. In addition to working with each state’s public health officials in support of community-based distribution of medical countermeasures through PODs, for example, HHS is collaborating with the Minnesota Department of Health to pilot test the postal distribution model. Private employers and the federal government have investigated establishing workplace distribution sites for employees, customers, and families; and HHS has met with emergency services providers to discuss the feasibility and desirability of providing pre-positioned antibiotics to first responders and their families.

In December 2010, ASPR commissioned the Institute of Medicine (IOM) to examine the potential uses, benefits, and disadvantages of various strategies for prepositioning antibiotics. ASPR was not looking for the identification of a single, best strategy, but looking for input on the positives and negatives of the variety of available and hypothesized strategies, including the use of commercially available, FDA-approved kits of antibiotics for home stockpiling. The IOM’s report, *Pre-Positioning Antibiotics for Anthrax*, was released in September 2011. The IOM identified challenges to achieving the capability to pre-position medical countermeasures and stressed the importance of best stewardship of scarce funding at local public health levels. In addition to the input from the IOM report, in November 2011, ASPR convened public focus groups to hear from individual citizens on their preferences and attitudes about the availability of pre-positioned medical countermeasures and their personal preparedness for a biological attack.

The ASPR, in concert with Presidential Policy Directive (PPD) 8, which challenges not only Federal, State, local, Tribal stakeholders but individual US citizens to build and sustain national preparedness thus enhancing national resilience, will continue to assess current and hypothesized medical countermeasure distribution strategies and will share its findings and recommendations on pre-positioning strategies with all stakeholders.
Recommendation 4-1: Develop national guidance for public-private coordination in the prepositioning, distribution, and dispensing of medical countermeasures.

- The Department of Health and Human Services should convene state, local, and tribal governments and private-sector organizations to develop national guidance that will facilitate and ensure consistency for public-private cooperation in the prepositioning, distribution, and dispensing of medical countermeasures and help leverage existing private-sector systems and networks.

Recommendation 5-1: Enhance assessment of performance in implementing distribution and dispensing plans for medical countermeasures.

- The Centers for Disease Control and Prevention should continue to facilitate assessment of state, local and tribal jurisdictions’ performance in implementing dispensing plans for medical countermeasures, in addition to assessing planning efforts. More specifically, the Centers for Disease Control and Prevention, in collaboration with state, local, and tribal jurisdictions, should facilitate assessment of the entire distribution and dispensing system by:
  - demonstrating Strategic National Stockpile distribution capabilities to high-risk jurisdictions;
  - facilitating large-scale, realistic exercises in high-risk jurisdictions to test dispensing capability; and
  - continuing efforts to identify objective criteria and metrics for evaluating the performance of jurisdictions in implementing mass dispensing.

Recommendation 5-2: Integrate ethical principles and public engagement into the development of prepositioning strategies within the overall context of public health planning for bioterrorism response.

- State, local, and tribal governments should use the following principles as an ethical framework for public health planning of prepositioning strategies:
  - Promotion of public health—Strive for the most favorable balance of public health benefits and harms based on the best available research and data.
  - Stewardship—Demonstrate stewardship of public health resources.
  - Distributive justice—Distribute benefits and harms fairly, without unduly imposing burdens on any one population group.
  - Reciprocal obligations—recognize the professional’s duty to serve and the reciprocal obligation to protect those who serve.
  - Transparency and accountability—Maintain public accountability and transparency so that community members grasp relevant policies and know from whom they may request explanation, information, or revision.
  - Proportionality—Use burdensome measures, such as those that restrict liberty, only when they offer a commensurate gain in public health and when no less onerous alternatives are both available and feasible.
  - Community engagement—Engage the public in the development of ethically sound dispensing plans for medical countermeasures, including plans to preposition antibiotics, so as to ensure the incorporation of community values.
Recommendation 5-3: Consider the risk of attack, assess detection and dispensing capability, and evaluate the use of prepositioning strategies to complement points of dispensing.

- State, local, and tribal governments should, in partnership with each other and with the federal government, the private sector, and community organizations:
  - Consider their risk of a potential anthrax attack.
  - Assess their current detection and surveillance capability.
  - Assess the current capability of and gaps in their medical countermeasures dispensing system.
  - Based on their risk and capability assessment, evaluate whether specific prepositioning strategies will fill identified gaps and/or improve effectiveness and efficiency. The decision-making framework should include, for a range of anthrax attack scenarios:
    - evaluation of the potential health benefits and health risks of alternative prepositioning strategies
    - evaluation of the relative economic costs of alternative prepositioning strategies;
    - comparison of the strategies with respect to health benefits, health risks, and costs, taking into account available resources; and
    - consideration of ethical principles and incorporation of community values (see Recommendation 5-2).

Recommendation 5-4: Give priority to improving dispensing capability and developing prepositioning strategies such as forward-deployed or cached medical countermeasures.

- In public health planning efforts, state, local, and tribal jurisdictions should give priority to improving the dispensing capability of points of dispensing and push strategies and to developing forward-deployed or cached prepositioning strategies. The committee does not recommend the development of public health strategies that involve broad use of predispensed medical countermeasures for the general population. In some cases, however, targeted predispensed medical countermeasures might be used to address specific gaps in jurisdictions’ dispensing plans for certain subpopulations that lack access to antibiotics via other timely dispensing mechanisms. These might include, for example, some first responders, health care providers, and other workers who support critical infrastructure, as well as their families.

- Personal stockpiling might also be used for certain individuals who lack access to antibiotics via other timely dispensing mechanisms (for example, because of their medical condition and/or social situation) and who decide—in conjunction with their physicians—that this is an appropriate personal strategy. This is allowed under current prescribing practice and would usually be done independently of a jurisdiction’s public health strategy for dispensing medical countermeasures.
**Recommendation 5-5: Do not pursue development of a Food and Drug Administration-approved MedKit unless this is supported by additional safety and cost research.**

- The committee does not recommend the development of a Food and Drug Administration-approved MedKit designed for prepositioning for an anthrax attack until and unless research demonstrates that MedKits are significantly less likely to be used inappropriately than a standard prescription and can be produced at costs comparable to those of standard prescription antibiotics.

**Recommendation 6-1: Perform additional research to better inform decision making about prepositioning strategies.**

- Results of such research would strengthen the decision-aiding framework proposed in this report for determining whether prepositioning strategies would be beneficial within a community. The Department of Health and Human Services should conduct additional research in the following broad areas: epidemiological and medical issues regarding anthrax and post-exposure prophylaxis for anthrax, operations and logistics, behavior and communications, safety, and cost-effectiveness.
Appendix 5
NIH Library (NIHL) Search Request

Requested By: BARDA

Completed By: NIH Library for OS/ASPR

Date Requested: 9/28/11  Date Delivered: 10/20/11

Search Request(s): Misuse of antibiotics (specifically doxycycline or ciprofloxacin)

Search Strategy:

Database searched: MEDLINE/PubMed; Web of Science; Embase; Google/Google scholar

Limits used:

MEDLINE/PubMed


FDA Advisory Committee Meeting on Medkits
April 2, 2012

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION


"medication adherence" AND antibiotic = 153

**Antibiotic Prophylaxis** AND **Medication Adherence** = 23

("medication misuse" OR "patient misuse" OR "non-compliance") AND antibiotic = 166

Related Citations for PubMed (Select 10915402)11:40:17 = 108

Antibiotic consumption patterns and drug leftovers in 6000 Brazilian households.


("antibiotic consumption" OR "self-medication") AND antibiotic AND "united states"[tiab] = 9

"united states" ("antibiotic consumption" OR "self-medication" OR "non-prescribed") AND (antibiotic OR "doxycycline"[MeSH Terms] OR "doxycycline"[All Fields] OR "ciprofloxacin"[MeSH Terms] OR "ciprofloxacin"[All Fields]) = 31

("Antibiotic consumption" OR "self-medication" OR "non-prescribed") AND antibiotic = 594

("antibiotic consumption" OR "self-medication" OR "non-prescribed") AND (antibiotic OR "doxycycline"[MeSH Terms] OR "doxycycline"[All Fields] OR "ciprofloxacin"[MeSH Terms] OR "ciprofloxacin"[All Fields]) = 595

**Embase**

442 = 'antibiotic consumption' OR 'self-medication'/exp/mj OR 'self-medication'/mj OR 'non-prescribed' AND ('antibiotic'/exp/mj OR 'antibiotic'/mj) AND [{embase}/lim OR {embase classic}/lim)

1,346 = 'antibiotic consumption' OR 'self-medication'/exp OR 'self-medication' OR 'non-prescribed' AND ('antibiotic'/exp OR antibiotic)

164 = 'self medication'/exp/mj OR 'patient compliance'/exp/mj OR 'non adherence' AND ('antibiotic agent'/mj OR 'doxycycline'/exp/mj OR 'ciprofloxacin'/exp/mj) AND [{embase}/lim OR {embase classic}/lim)

**Web of Science**

Topic=(("antibiotic consumption" OR "self-medication") AND antibiotic) = 579

**Google/Google Scholar**
"self-medication" ("home storage" OR "medicine cabinet" OR "medicine chest") AND antibiotic

"united states" ("antibiotic consumption" OR "self-medication" OR "non-prescribed") AND (antibiotic OR "doxycycline" OR "doxycycline" OR "ciprofloxacin" OR "ciprofloxacyn")

**Keywords of interest included:**

Home storage
Medicine cabinet/medicine chest
Antibiotic over-use
Drug hoarding
Self-care
Unprescribed/Non-Prescribed Drugs
Self-Medication
Non-adherence