DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

August 23, 2010

Robin Robinson, Ph.D.
Director
Biomedical Advanced Research and Development Authority (BARDA)
330 Independence Avenue SW
Room G640
Washington, DC 20201

Dear Dr. Robinson:

This letter is in response to BARDA's October 1, 2008 submission, as amended,[1] requesting that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for the pre-event provision and potential use of doxycycline hyclate tablet emergency kits[2] for inhalational anthrax, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act). Your request is specifically for eligible[3] United States Postal Service (USPS) participants in the Cities Readiness Initiative (CRI) (hereinafter USPS participants) and their household members.[4]

On September 23, 2008, pursuant to section 564(b)(1)(A) of the Act, 21 U.S.C. § 360bbb-3(b)(1)(A), the Secretary of the Department of Homeland Security determined that there is a significant potential for a domestic emergency, involving a heightened risk of attack with a

[1] BARDA submitted an amendment on October 3, 2008. Following issuance of FDA's October 3, 2008, authorization letter, BARDA submitted a request on behalf of the Office of the Assistant Secretary for Preparedness and Response (ASPR) on February 19, 2009, to further amend the authorization. On February 25, 2009, an amended authorization letter responding to that request was issued. That letter specified that the doxycycline hyclate tablets to be utilized would be manufactured by West-Ward Pharmaceuticals and repackaged by PD-Rx. On August 4, 2010, BARDA requested that the EUA be further amended to permit the use of Mutual Pharmaceutical Company Inc. as a manufacturer and the Department of Health and Human Services Supply Service Center at Perry Point, Maryland, as a repackager under the EUA. This letter grants that request.

[2] Your submissions refer to a Household Antibiotic Kit (HAK), which would be stored in an eligible United States Postal Service (USPS) participant's home and would contain unit-of-use bottles of doxycycline hyclate tablets (100 mg) and both emergency use instructions and home preparation instructions. Your submissions also refer to an individual Household Antibiotic Kit (iHAK), which would be stored at an eligible USPS participant's workplace and would contain only one unit-of-use bottle of doxycycline hyclate tablets (100 mg) and emergency use instructions. For ease of reference, this letter of authorization will use the term "doxycycline hyclate tablet emergency kit(s)" to refer to both types of kits, unless otherwise specified. When referring to the kits separately, this letter will use the term "household doxycycline hyclate tablet emergency kit" to refer to the HAK and the term "individual doxycycline hyclate tablet emergency kit" to refer to the iHAK.

[3] The term "eligible" refers to USPS participants who have agreed in writing to participate in the Postal Module of CRI, have been screened for fitness to receive OSHA-required personal protective equipment, have (including household members) been medically screened for contraindications based on completed health assessment forms, have (including household members) been given a valid prescription, and have (including household members) not otherwise been determined to be ineligible to receive doxycycline hyclate tablet emergency kits.

[4] Your submissions define "household member" as "anyone that considers that address as his or her permanent place of residence."

specified biological, chemical, radiological, or nuclear agent or agents--in this case, Bacillus anthracis.[5] On October 1, 2008, pursuant to section 564(b) of the Act, and on the basis of such determination, the Secretary of the Department of Health and Human Services declared an emergency justifying the authorization of the emergency use of doxycycline hyclate tablets accompanied by emergency use information subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a), and on October 1, 2009 the Secretary renewed that declaration.[6,7] Having consulted with the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), and having concluded that the criteria for issuance of this authorization under section 564(c) of the Act are met, I am authorizing the emergency use of doxycycline hyclate tablet emergency kits for the post-exposure prophylaxis of inhalational anthrax for eligible USPS participants and their household members,[8] subject to the terms of this authorization.

The remainder of this letter is organized into four sections: Background, Criteria for Issuance of Authorization, Scope of Authorization, Conditions of Authorization, and Duration of Authorization.

I. Background

CRI involves 72 major metropolitan areas and all 50 states. The primary goal of CRI is to develop the ability to provide mass prophylaxis to 100% of the identified population within 48 hours of notification to do so.

On February 18, 2004, the Secretary of the Department of Health and Human Services (HHS), the Secretary of the Department of Homeland Security (DHS), and the Postmaster General signed a Memorandum of Agreement to explore how the resources of the USPS could be made available to help deliver oral antibiotics in response to a biological terrorism incident. Subsequently, HHS launched CRI and asked the USPS to participate in what has been referred to as the CRI Postal Module (or Postal Plan). The Postal Module involves the delivery of antibiotics to residential households within pre-determined zip codes by USPS participants where there may be an intentional release of Bacillus anthracis in their geographic area. The CRI Postal Module could be activated and executed while the municipality is establishing its points-of-dispensing (POD) network for the remainder of the emergency response which, in the

[5] Memorandum from Michael Chertoff to Michael O. Leavitt, Determination Pursuant to § 564 of the Federal Food, Drug, and Cosmetic Act (Sept. 23, 2008).

[6] Declaration of Emergency Pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 360bbb-3(b) (Oct. 1, 2008); renewed October 1, 2009. 74 FR 51279 (Oct. 6, 2009)

[7] The doxycycline hyclate tablet emergency kits for eligible USPS participants and their household members referenced and authorized in this letter fall within the scope of the Secretary of the Department of Health and Human Services' declaration.

[8] Doxycycline hyclate tablets are indicated for treatment of infections caused by "Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*." This indication generally means that drug administration is expected to start after a known or suspected exposure to aerosolized *Bacillus anthracis* spores, but before clinical symptoms of the disease develop. The indication includes presumed exposure, since it is often difficult to know whether and when exposure has actually occurred. The indication also encompasses instances where *Bacillus anthracis* exposure via inhalation is expected and will be imminent. In such cases, the first few doses of prophylaxis may be taken pre-exposure, but the remainder of the course would be taken post-exposure. The indication is commonly referred to as "post-exposure prophylaxis of inhalational anthrax," and this term will be used throughout this letter for ease of reference.

case of a wide-area anthrax event, could continue for 1-2 months. The postal carriers' role is voluntary because emergency response is neither part of the basic mission of USPS nor a provision of the contracts between USPS and the unions representing the carriers. USPS has made its participation in the CRI Postal Module contingent on the pre-event provision of prescription antibiotic countermeasures to USPS participants and their household members.

Your request relates to a potential EUA for the pre-event provision and potential use of doxycycline hyclate tablets (100 mg) in the form of emergency kit(s) for eligible USPS participants and their household members. Although doxycycline hyclate tablets are approved for the post-exposure prophylaxis of inhalational anthrax, the emergency kits you describe in your submissions would require an EUA because they would include certain written information that is not currently part of the approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for doxycycline hyclate tablets (100 mg). Specifically, you indicated that the following pieces of written information would accompany the doxycycline hyclate tablets:

- Fact Sheet for Recipients
- For the household doxycycline hyclate tablet emergency kit, home preparation instructions for recipients who cannot swallow pills (hereinafter home preparation instructions)
- Information placard (unless the bag is pre-printed with placard information)
- MedWatch Form 3500 for the reporting of any adverse events associated with the doxycycline hyclate tablet emergency kit

In addition, a Fact Sheet for Health Care Providers would be distributed to health care providers and authorized dispensers of the doxycycline hyclate tablet emergency kits.

You propose to use doxycycline hyclate tablets (100 mg) that were manufactured by West-Ward Pharmaceutical Corp. or Mutual Pharmaceutical Co., Inc., and repackaged by PD-Rx Pharmaceuticals or Department of Health and Human Services Supply Service Center at Perry Point, Maryland into unit-of-use bottles containing 20 oral tablets each, a 10-day supply.[9]

The doxycycline hyclate tablet emergency kit(s) that are the subject of your request would come in two forms. The first, which you describe as a Household Antibiotic Kit (HAK), would contain a unit-of-use bottle of doxycycline hyclate tablets for each eligible USPS participant and each eligible household member, as well as the Fact Sheet for Recipients, home preparation instructions, MedWatch Form 3500, and information placard (unless bag is pre-printed with placard information) described above. All of these items would be placed in one tamper-evident, clear plastic bag for home storage. The second, which you describe as an individual Household Antibiotic Kit (iHAK), would contain one unit-of-use bottle of doxycycline hyclate tablets for the eligible USPS participant and the Fact Sheet for Recipients, MedWatch Form 3500, and information placard (unless the bag is pre-printed with placard information) described above. All of these items would be placed in a separate tamper-evident, clear plastic bag for secure storage at the USPS participant's workplace, should the USPS participant need to deploy emergently.

[9] We note that the full course of doxycycline hyclate tablets for adults for the post-exposure prophylaxis of inhalational anthrax is 100 mg twice daily for 60 days. The corresponding oral dosing regimen for children under 100 pounds is 1 mg per pound of body weight twice daily for 60 days.

II. Criteria for Issuance of Authorization

Having considered the September 23, 2008 determination by the Secretary of the Department of Homeland Security that there is a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents--in this case, Bacillus anthracis, and the October 1, 2008 declaration of emergency by the Secretary of Health and Human Services and the October 1 renewal of that declaration, and having consulted with NIH and CDC, I have concluded that the emergency use of doxycycline hyclate tablet emergency kits for the post-exposure prophylaxis of inhalational anthrax for eligible USPS participants and their household members meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

(1) Bacillus anthracis can cause anthrax, a serious or life-threatening disease or condition;

(2) based on the totality of scientific evidence available to FDA, it is reasonable to believe that doxycycline hyclate tablet emergency kits may be effective for post-exposure prophylaxis of inhalational anthrax,[10] and that the known and potential benefits of doxycycline hyclate tablet emergency kits, when used for the post-exposure prophylaxis of inhalational anthrax in the specified population, outweigh the known and potential risks of the product; and

(3) there is no adequate, approved, and available alternative to doxycycline hyclate tablet emergency kits for the post-exposure prophylaxis of inhalational anthrax.[11]

Specifically, I have concluded, pursuant to section 564(c)(1) of the Act, that Bacillus anthracis can cause inhalational anthrax, which is a serious or life-threatening disease or condition. The fatality rate for inhalational anthrax in the United States is estimated to be approximately 45 percent to 90 percent. From 1900 to October 2001, there were 18 identified cases of inhalational anthrax in the United States, the latest of which was reported in 1976, with an 89 percent (16/18) mortality rate. Most of these exposures occurred in industrial settings, i.e., textile mills. From October 4, 2001, to December 5, 2001, a total of 11 cases of inhalational anthrax linked to intentional dissemination of Bacillus anthracis spores were identified in the United States. Five of these cases were fatal. These fatalities occurred despite aggressive medical care, including treatment with antimicrobial drugs.

I have also concluded that, based on the totality of the scientific evidence available to FDA, including data supporting the safe and effective use of doxycycline hyclate tablets (100 mg) for the post-exposure prophylaxis of inhalational anthrax, the results of CDC's home MedKit study, and information associated with the development of the home preparation instructions, it is reasonable to believe that doxycycline hyclate tablet emergency kits may be effective for the post-exposure prophylaxis of inhalational anthrax pursuant to section 564(c)(2)(A) of the Act.

[10] The Act uses the terms "diagnosing, treating, or preventing" in Section 564(c)(2)(A). Post-exposure prophylaxis is encompassed by these statutory terms.

[11] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

The above conclusion is largely based on the fact that FDA has previously approved a number of NDAs and ANDAs for doxycycline hyclate tablets for the treatment and post-exposure prophylaxis of inhalational anthrax, as summarized below.

In November 2001, as part of a public health response to the use of anthrax spores as a bioterrorism agent, the Agency published a notice in the Federal Register that clarified the dosing recommendations for, among others, doxycycline hyclate products, in the management of patients with inhalational anthrax who had been exposed to spores of Bacillus anthracis, but who did not manifest clinical disease.[12] In that notice, FDA announced that it had determined that the language in the labeling of certain drug products, including those containing doxycycline hyclate, is intended to, and does, cover all forms of anthrax, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease exposure to aerosolized B. anthracis. FDA also announced that the appropriate dosing regimen for adults is 100 mg of doxycycline, taken orally twice daily for 60 days; and the corresponding oral dosing regimen for children under 100 pounds is 1 mg per pound (1 mg/lb) of body weight (2.2 mg/kilogram (kg)), given twice daily for 60 days.[13] FDA based these conclusions on the following:

- Effectiveness was supported by minimal inhibitory concentration (MIC) data for the tetracycline class and Bacillus anthracis, pharmacokinetic data, data from the Sverdlovsk incident, and the outcome data from a study of inhalational exposure to Bacillus anthracis in rhesus monkeys.

- With respect to safety, FDA noted that doxycycline drug products have been used for over 30 years and the literature on the products is voluminous. FDA previously reviewed the literature dealing with the long-term administration of doxycycline for treatment of diseases other than anthrax. Several articles reported the results of studies involving the administration of doxycycline in amounts comparable to the recommended doses. They also involved administration of doxycycline for 60 days and periods approaching and exceeding 60 days. FDA also reviewed data from the Adverse Event Reporting System (AERS). Analysis of these articles and data indicated no pattern of unlabeled adverse events associated with the long-term use of doxycycline.

- FDA also noted that doxycycline and other members of the tetracycline class of antibiotics are not generally indicated for the treatment of any patients under the age of 8 years. Tetracyclines are known to be associated with teeth discoloration and enamel hypoplasia in children and delays in bone development in premature infants after prolonged use. FDA balanced the nature of the effect on teeth and the fact that this delay in bone development is apparently reversible against the lethality of inhalational anthrax, and concluded that doxycycline drug products can be labeled with a pediatric dosing regimen for inhalational anthrax (post-exposure).

[12] *See* 66 Fed. Reg. 55679 (Nov. 2, 2001); Docket 01N-0494.
[13] *Id.* The *Federal Register* notice further requested that applicants for these products submit labeling supplements to update their package inserts with this information.

As noted above, FDA has approved, under section 505(j) of the Act, a number of abbreviated new drug applications (ANDAs), including West-Ward's ANDA (#65-095) and Mutual's ANDA (62-677) for doxycycline hyclate tablets (100 mg) for treatment and post-exposure prophylaxis of inhalational anthrax on July 2, 2003. Doxycycline hyclate tablets (100 mg) manufactured by West-Ward or Mutual, which have been repackaged and re-labeled by PD-Rx Pharmaceuticals, or by Department of Health and Human Services Supply Service Center at Perry Point, Maryland are the subject of this emergency use authorization. This product is the same as the reference listed drug, Vibra-Tabs (doxycycline hyclate tablets, 100 mg; NDA #50-333), within the meaning of section 505(j) of the Act.

I have also considered CDC's home MedKit study and information associated with the development of the home preparation instructions as part of the totality of the scientific evidence available to FDA, and have determined that this information helps to support the conclusion that it is reasonable to believe that doxycycline hyclate tablet emergency kits may be effective for post-exposure prophylaxis of inhalational anthrax, as summarized below.

The CDC study evaluated the ability of study participants to receive what was referred to as a MedKit -- doxycycline[14] with certain written information, including emergency use instructions and home preparation instructions similar to those being authorized here. A convenience sample of 4,250 St. Louis area households, divided among three cohorts, was enrolled in the study after medical screening and informed consent. The primary outcomes for this evaluation were to determine the extent to which participants would follow instructions for appropriately keeping the MedKits intact and reserving them for emergency use until directed by a local government official. Although this study had a number of limitations as explained below, approximately 97% of all study respondents returned the MedKits upon completion of the study.

Finally, FDA considered information associated with the development of the home preparation instructions for doxycycline hyclate tablets. FDA had previously developed home preparation instructions and these instructions were tested by the Chicago Department of Public Health, which provided its results to FDA. The Agency revised the home preparation instructions based on these findings and performed additional laboratory tests and limited palatability testing. FDA also worked with CDC to improve the readability of the instructions.

Although FDA has approved a number of NDAs and ANDAs for doxycycline hyclate tablets (100 mg) for the treatment and post-exposure prophylaxis of inhalational anthrax, these products are not approved with emergency use instructions and home preparation instructions. The amount and nature of the scientific evidence regarding the ability to use emergency use instructions and home preparation instructions is more limited than the scientific evidence supporting the approval of doxycycline hyclate tablets for the post-exposure prophylaxis of inhalational anthrax. However, taking into consideration the potentially fatal nature of anthrax disease, the CDC home MedKit study and the information associated with the development of the home preparation instructions also helps to support a conclusion that it is reasonable to believe that doxycycline hyclate tablet emergency kits may be effective for the post-exposure prophylaxis of inhalational anthrax. Accordingly, based on the totality of the scientific evidence

[14] In this study, participants who were allergic to doxycycline or for whom doxycycline was otherwise contraindicated received ciprofloxacin.