DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

April 13, 2016

RADM Nicole Lurie, M.D., M.S.P.H.
Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
1600 Clifton Road MS-D-14
Atlanta, GA 30333

RE: Order Permitting Emergency Dispensing of Oral Formulations of Ciprofloxacin and Waiver of CGMP Requirements during an Anthrax Emergency

Dear RADM Lurie and Dr. Frieden:

This letter is to notify you that for preparedness purposes, pursuant to section 564A(d) of the Federal Food, Drug, and Cosmetic (FD&C) Act, the Food and Drug Administration (FDA) is hereby issuing this order to permit emergency dispensing[1] of FDA-approved oral dosage forms of ciprofloxacin products ("eligible ciprofloxacin products") for the post-exposure prophylaxis (PEP)[2] of inhalational anthrax during an emergency involving *Bacillus anthracis* (*B. anthracis*), the biological agent that causes anthrax disease. Although there is not currently an active emergency involving *B. anthracis* ("anthrax emergency"), this order will allow stakeholders[3] to implement plans for emergency dispensing of eligible ciprofloxacin products without individual prescriptions in the future if they reasonably believe there is a need to do so because of their constituents' known, suspected, or likely imminent exposure to *B. anthracis*. This order also

[1] For purposes of this order, the term "emergency dispensing" includes, but is not limited to, the public health response activities of dispensing medical countermeasures (MCMs) under a medical model and of "mass dispensing" MCMs to large populations under a non-medical model (e.g., through points of dispensing, also referred to as "PODs").

[2] Prophylaxis is generally considered to refer to certain situations in which the person receiving the drug has not exhibited symptoms. In some instances in which ciprofloxacin may be used as an MCM pursuant to this order, it may not be feasible to distinguish between persons without symptoms and some who have begun to exhibit symptoms; however, the Food and Drug Administration (FDA) would expect that the applicable public health authorities would direct any persons with evidence of symptomatic anthrax illness to appropriate medical care as expeditiously as possible.

[3] As used in this order, the term "stakeholder(s)" means the public agency or its delegate that has legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to prescribe, administer, deliver, distribute, or dispense oral ciprofloxacin products in an emergency situation.

permits dispensing of product without a prescription or other information otherwise required by section 503(b) of the FD&C Act by health care professionals and authorized dispensers[4] who are acting as part of a stakeholder's official emergency response as described below.

In addition, under section 564A(c) of the FD&C Act, FDA is waiving certain current good manufacturing practice (CGMP) requirements to further facilitate rapid distribution and dispensing of eligible ciprofloxacin products during an anthrax emergency response.

This order and waiver, in conjunction with Emergency Use Instructions (EUI) for oral dosage forms of ciprofloxacin that the Centers for Disease Control and Prevention (CDC) may create and issue under section 564A(e) of the FD&C Act,[5] render a ciprofloxacin mass dispensing Emergency Use Authorization (EUA) for PEP under section 564 of the FD&C Act unnecessary.

Background

In 2004, the Secretary of the Department of Homeland Security (DHS) issued a Material Threat Determination indicating that *B. anthracis*, the biological agent that causes anthrax disease, presents a material threat against the population of the United States sufficient to affect national security. In 2008, the Secretary of DHS also determined, pursuant to section 564(b)(1)(A) of the FD&C Act, that there is significant potential for a domestic emergency involving a heightened risk of attack with *B. anthracis*.[6]

Section 564A(d) of the FD&C Act, which was added to the FD&C Act by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), allows for emergency dispensing of eligible, approved medical countermeasures (MCMs) during an actual chemical, biological, radiological, or nuclear (CBRN) emergency[7] without requiring an individual prescription for each recipient of the MCM and/or without prescription information otherwise required to be provided when dispensing the MCM under section 503(b) of the FD&C Act, to be exempt from provisions of that Act that would otherwise prohibit such dispensing, if (1) permitted by the law of the State in which the emergency dispensing occurs or (2) in accordance with an emergency dispensing order issued by FDA. In addition, section 564A(c), also added by PAHPRA, permits FDA to waive otherwise applicable CGMP requirements (e.g., proper storage

[4] For purposes of this order, the term "authorized dispensers" refers to individuals who are not health care professionals (e.g., certain public health agency staff, volunteers, etc.), and to certain health care professionals (e.g., first responders, nurses, pharmacists) who otherwise might be acting outside of their professional scope of practice in dispensing the MCM, who are acting under the authority of the applicable stakeholder's official emergency response plans.

[5] Section 564A(e) of the Federal Food, Drug, and Cosmetic (FD&C) Act allows, without having to issue an Emergency Use Authorization (EUA), the creation and issuance of Emergency Use Instructions (EUI) to inform health care providers or individuals to whom an eligible product is to be administered concerning such product's approved, licensed, or cleared conditions of use. The Secretary of Health and Human Services (HHS) delegated the EUI authority to the Director of the Centers for Disease Control and Prevention (CDC). HHS. *Delegation of Authority of section 564A(e) of the Federal Food, Drug, and Cosmetic Act*. December 16, 2013.

[6] U.S. Department of Homeland Security (DHS). *Memorandum from Michael Chertoff to Michael O. Leavitt, Determination Pursuant to §564 of the Federal Food, Drug, and Cosmetic Act*. September 23, 2008.

[7] Under section 564A(d)(1) of the FD&C Act, eligible MCMs may be dispensed under an emergency dispensing order only during the circumstances under which (1) one of three determinations have been made by either the Secretary of DHS, Department of Defense, or HHS under section 564(b)(1) of the FD&C Act or (2) a Material Threat Determination has been made by the DHS Secretary, as described in section 564A(a)(1)(C) of the FD&C Act.

and handling requirements) for eligible, approved MCMs to accommodate emergency response needs (e.g., temporary storage of product at points of dispensing (PODs)). Notably, FDA may issue an order to allow emergency dispensing of eligible products and waive CGMP requirements without having to issue an EUA.

Based on the anthrax determinations and the authorities added by PAHPRA, as well as available information about stakeholder emergency response plans and operational needs, FDA concludes that it is reasonable to permit emergency dispensing of eligible ciprofloxacin products to facilitate an emergency response in the event of an anthrax emergency. Specifically, current public health emergency response plans throughout the United States anticipate that oral ciprofloxacin products may be stored and distributed by various stakeholders for preparedness purposes in advance of an actual anthrax emergency, so that they may be dispensed to impacted individuals rapidly during an event or post-event as part of a mass dispensing strategy. This order is important for emergency response purposes because it enables rapid initiation of antimicrobial therapy through various dispensing modalities during an anthrax emergency without FDA or stakeholders having to take further action with respect to otherwise applicable prescription requirements under federal law.

Emergency Dispensing Authorized

Therefore, FDA is hereby authorizing the emergency dispensing of eligible ciprofloxacin products during an anthrax emergency without a prescription and without all of the information otherwise required to be provided with the product pursuant to section 503(b) of the FD&C Act.[8] Depending on the circumstances of an anthrax emergency and response needs, individuals responsible for dispensing a product might include (1) licensed health care professionals who are acting within their professional scope of practice (e.g., physicians; nurse practitioners and physician assistants in certain states) and (2) authorized dispensers who, for purposes of this order, include (a) licensed health care professionals who might otherwise be acting outside of their professional scope of practice in dispensing the MCM (e.g., physicians not licensed in the state, nurses, pharmacists, emergency medical technicians) and (b) individuals who are not health care professionals (e.g., certain public health agency staff, volunteers, agents, or contractors).[9] Therefore, this order also permits emergency dispensing by health care professionals and authorized dispensers, provided that the products are dispensed in accordance with the applicable stakeholder's official emergency response plan(s) during an anthrax emergency.

This order applies in all circumstances and in any jurisdiction(s) within the United States, its territories, or possessions, when a stakeholder reasonably believes that there is a need to dispense

[8] This includes, for instance, name and address of dispenser; serial number and date of prescription or of its filling; name of prescriber; name of patient, if stated on prescription; and directions for use and cautionary statements, if contained in the prescription.

[9] In the interest of the public's health, FDA nevertheless also strongly recommends and expects that, to the fullest extent possible under the circumstances, stakeholder emergency plans and response activities will involve guidance from the impacted jurisdiction's official medical authority (e.g., state or local health officer, chief medical officer, etc.) or, as appropriate, other licensed health care professionals in the dispensing of eligible ciprofloxacin products in response to an anthrax emergency.

eligible ciprofloxacin products in an emergency because of their constituents' known, suspected, or likely imminent exposure to *B. anthracis*.[10]

Eligible Ciprofloxacin Products

This order applies to all oral dosage forms of ciprofloxacin that have been approved by FDA for an anthrax indication.[11] This includes products in tablet form and powder for oral suspension. The products identified above are "eligible products" within the meaning of section 564A(a) of the FD&C Act.

These products are authorized for emergency dispensing when they are either packaged in their original manufacturers' packaging or repackaged for emergency distribution and/or dispensing with (1) their original FDA-approved labeling and/or (2) EUI created and issued by CDC pursuant to section 564A(e) of the FD&C Act to facilitate health care professionals', authorized dispensers', and recipients' understanding of anthrax disease and the risks and benefits of the use of ciprofloxacin. During an anthrax emergency, this order allows dispensing of FDA-approved ciprofloxacin products that are not supplied in a unit-of-use (UoU) container, as well as partial (e.g., 10-day) supplies, if necessary.[12]

CGMP Requirements and Waiver

This order covers eligible ciprofloxacin products that have been manufactured, packaged, and labeled (and where applicable repackaged and/or relabeled) under CGMP requirements and, unless otherwise authorized by FDA, stored in compliance with the manufacturers' labeled storage conditions for the products to ensure potency.[13]

Section 501 of the FD&C Act requires that the controls for holding of a drug be operated or administered in conformity with good manufacturing practice in such a manner that does not affect the identity, strength, quality, or purity of the drug. In general, drugs should be held under labeled storage conditions to assure stability over their labeled shelf-life. Certain drugs are more susceptible to degradation, while some drugs, including the eligible ciprofloxacin drugs identified in this order, remain sufficiently stable even when temporarily held under temperatures exceeding labeled conditions and when such excursions occur in the days preceding dispensing and use.

[10] This may involve all dispensing within a jurisdiction or across jurisdictional lines (e.g., across state lines to address a geographical response need).

[11] FDA-approved drug products can be identified at: FDA. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. http://www.accessdata.fda.gov/scripts/cder/ob/. Extended release oral tablets are not eligible products.

[12] This may include, for example, ciprofloxacin product from the Strategic National Stockpile (SNS), from strategic stockpiles in states, and in pre-positioned individual supplies of ciprofloxacin (e.g., "medkits") that are available under certain jurisdictions' emergency response plans (e.g., for first responders), subject to any applicable CGMP requirements and waiver as described in this document.

[13] This may include eligible ciprofloxacin product that has received an expiry dating extension (i.e., to allow use of the product beyond the manufacturer's labeled expiry date) under the federal Shelf-Life Extension Program (SLEP) or otherwise under section 564A(b) of the FD&C Act, but which might, or might not, be relabeled with the new use date.

In the event of an anthrax emergency, emergency response operations to enable use of oral ciprofloxacin might require transportation, storage, or handling for rapid dispensing without the capability to maintain certain otherwise applicable CGMP conditions during the response. During the period this order is in effect, FDA is hereby permitting temperature excursions that do not exceed 40°C for a total period of less than 7 days during an anthrax emergency response for the shipment and storage of eligible ciprofloxacin products. Products meeting these conditions will not be deemed adulterated or misbranded under the FD&C Act.

Duration

This emergency dispensing order and CGMP waiver will remain in effect until revised or revoked by FDA by a subsequent order or waiver.

Effect on State Law

Sections 564A(c) and (d) of the FD&C Act are intended to protect the public health by enabling rapid access to potentially life-saving medical products during a CBRN emergency. State laws that govern dispensing of covered products but impose different or additional conditions that would limit the access to eligible ciprofloxacin products allowed by this order would be an "obstacle to the accomplishment and execution of the full purposes and objectives of Congress" in enacting these provisions.[14] Therefore, FDA believes that state laws within the jurisdictional coverage of this order that impose more restrictive conditions or requirements on dispensing products covered by this order will be preempted.[15]

However, certain states within the jurisdictional coverage of this order may have in effect—or may choose to enact—laws that permit emergency dispensing of eligible MCMs as provided by section 564A(d) of the FD&C Act. This order is not intended to replace those frameworks as long as they are not more restrictive than this order in providing for access to the FDA-approved products covered by this order.[16]

---

[14] *See Arizona v. United States*, 132 S. Ct. 2492, 2501, 2505, 2507 (2012); *Crosby v. National Foreign Trade Council*, 530 U.S. 363, 373 (2000); *Geier v. American Honda Motor Company, Inc.*, 529 U.S. 861, 873 (2000); *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). We note that the Congressional objective that any conflicting state restrictions on dispensing would be preempted by this provision is demonstrated by its enactment of section 564A(d)(2)(B), which is the basis for this order. Because section 564A(d)(2)(A) would permit dispensing "as permitted under the law of the State in which the product is dispensed," the alternative of section 564A(d)(2)(B) is clearly intended to permit such dispensing that is not permitted under the laws of that state.

[15] While FDA believes that preemption applies here, it recognizes that this is a controversial area of the law. Because the attorneys advising some state response programs may take a different view than that expressed here, FDA encourages state programs to consult with their legal counsel as to whether they believe that their states would need to take complementary legal action to assure that their state laws would not conflict with this order. If such state action is considered to be necessary, it will be important that any required changes in state law, or any steps necessary to implement state laws to permit emergency dispensing consistent with this order, be determined as part of the state's emergency planning for an anthrax response. For additional background, see: FDA. *Emergency Use Authorization of Medical Products and Related Authorities Guidance for Industry and Public Health Stakeholders: Draft Guidance.* April 2016. http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm.

[16] Whether or not a particular state legal provision or action is sufficient to permit the emergency dispensing strategy state or local stakeholders anticipate conducting within their state rests in large part on the interpretation of that state law, which is a matter that should first be directed to the appropriate legal authority within the relevant jurisdiction (e.g., the state Attorney General). To ensure clarity, and perhaps increase the likelihood state laws, regulations, orders, or other legal actions to permit emergency dispensing are deemed sufficient, it is recommended that such

Communication to Stakeholders

FDA plans to post a copy of this order and waiver on its Internet website for stakeholder and public access. In addition, it is suggested that you notify affected stakeholders in all states (and in other relevant jurisdictions as you deem appropriate) who may be engaged in preparing for, or involved in an actual response to, an anthrax emergency covered by this order and waiver so that public health and other applicable emergency response plans may be coordinated and/or revised as appropriate.

Sincerely,

--/S/--
Luciana Borio, M.D.
Acting Chief Scientist

actions address the same eligibility, scope, duration, and other elements FDA addresses in this emergency dispensing order.