Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles

Draft Guidance for Government Public Health and Emergency Response Stakeholders

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2017
Procedural

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Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles
Draft Guidance for Government Public Health and Emergency Response Stakeholders[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

A number of government public health and emergency response stakeholders[2] maintain stockpiles of doxycycline[3] tablets or capsules for post-exposure prophylaxis (PEP) or treatment of inhalational anthrax in the event of an anthrax emergency. States have asked FDA what would be necessary to provide confidence that stockpiled doxycycline tablets and capsules have retained their original quality (i.e., purity and potency) beyond the manufacturer's labeled expiration date so the replacement of stockpiled product could be deferred.[4]

This document, once finalized, will provide guidance to government stakeholders on testing to extend the shelf life (i.e., expiration date) under section 564A(b) of the Federal Food, Drug, and Cosmetic Act (FD&C) Act[5] of stockpiled doxycycline tablets and capsules for public health emergency preparedness and response purposes for an anthrax emergency.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, the term *government stakeholders* refers to the public health and/or emergency response agencies or their agents/delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundaries (e.g., city, county, tribal, territorial, State, or Federal), or functional range or sphere of authority (e.g., law enforcement, public health, military health) to prescribe, administer, deliver, distribute, hold, or dispense a medical product during an emergency situation.

[3] For the purposes of this guidance, *doxycycline* refers to both doxycycline monohydrate and doxycycline hyclate.

[4] This is, in part, based on guidance FDA issued in 2004 for government agencies to conduct shelf-life testing of stockpiled potassium iodide (KI): *Guidance for Federal Agencies and State and Local Governments: Potassium Iodide Tablets Shelf Life Extension*. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] 21 U.S.C. 360bbb-3a(b).

This guidance applies to both doxycycline monohydrate and doxycycline hyclate tablets and capsules equivalent to 50 mg and 100 mg of doxycycline that are indicated for PEP or treatment of inhalational anthrax. Where doxycycline is mentioned throughout this guidance, it is meant to include both the hyclate and monohydrate forms of the drug that are indicated for PEP or treatment of inhalational anthrax.

This guidance provides background information on the doxycycline drug product, the recommended protocol to support extending the expiration dates of specific doxycycline lots, how to identify a suitable laboratory to conduct testing, and the process for requesting and receiving an authorized expiration date extension for an identified lot of doxycycline. The criteria for an authorized extension include the requirements and conditions under section 564A(b) of the FD&C Act for any expiration date extensions authorized by FDA based on testing conducted following this guidance.

This guidance and any resulting expiration date extensions authorized by FDA do not apply to doxycycline available commercially or otherwise held for any other non-emergency purpose.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Doxycycline Drug Product

Doxycycline is a bacteriostatic tetracycline antibiotic prescribed mainly for the treatment of urinary, respiratory, and gastrointestinal (GI) tract infections and also is approved for PEP and treatment of inhalational anthrax due to *Bacillus anthracis*.

Commercially, doxycycline is available by prescription as capsules, delayed-release capsules, tablets, delayed-release tablets, powder for oral suspension, oral suspension, periodontal systems, and injectable dosage forms with strengths ranging from 20 mg to 200 mg (equivalent to base doxycycline). FDA has approved multiple new drug applications (NDAs) and abbreviated NDAs (ANDAs) for doxycycline tablets and capsules.[6] The applications currently provide for marketing of tablets or capsules by prescription.[7]

[6] For an up-to-date listing of all approved doxycycline products, consult the online version of FDA's Approved Drug Products With Therapeutic Equivalence Evaluations (Electronic Orange Book) at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[7] However, during an anthrax emergency and if appropriate, FDA may authorize dispensing without individual patient prescriptions to facilitate official public health responses. Section 564A(d) of the FD&C Act.

B. FDA Information on the Safe and Effective Use of Doxycycline Tablets and Capsules for Inhalational Anthrax Post-Exposure Prophylaxis or Treatment

Among other things, doxycycline is approved by FDA for treatment of anthrax due to *B. anthracis;* the approved indication also includes PEP, to reduce the incidence or progression of disease following exposure.[8] Based on national preparedness for chemical, biological, radiological, and nuclear (CBRN) emergencies and doxycycline's anthrax indication, a number of government stakeholders stockpile doxycycline tablets or capsules that are generally stored under controlled conditions. For example, the Strategic National Stockpile (SNS), which is managed by the Centers for Disease Control and Prevention (CDC), stockpiles doxycycline, among other medical countermeasures (MCMs), to distribute to states to rapidly dispense as PEP to impacted populations during an anthrax emergency. Also, some states and local jurisdictions stockpile doxycycline for use for PEP before arrival of SNS assets (e.g., as a quick strike force for protecting first responders and health care professionals) or if SNS assets are not provided.

Additionally, to help facilitate anthrax preparedness and public health interest in the emergency use of doxycycline for anthrax responses, FDA has issued an emergency dispensing order (FDA 2016) and CDC has issued Emergency Use Instructions (EUI) to facilitate doxycycline mass dispensing efforts by government stakeholders.[9] FDA also coordinates with CDC on clinical and scientific issues related to the use of doxycycline for anthrax preparedness, including conducting Shelf-Life Extension Program (SLEP) testing of doxycycline held in the SNS.

C. Approaches to Drug Product Expiration Date Changes and Extensions

Although there are several possible approaches to changing or extending the expiration date for approved drugs, the most appropriate or feasible approach depends on factors such as whether the extension is initiated by the manufacturer, is for certain drugs held in critical Federal stockpiles, or is for certain MCMs under section 564A(b) of the FD&C Act.

1. Expiration Date Changes Initiated by the Manufacturer

The manufacturer of an approved drug product may extend the expiration date for the drug product based on acceptable data from full, long-term stability studies on at least three pilot or production batches in accordance with a protocol approved in the NDA or ANDA. FDA should be notified of the extension of the expiration dating period. The data can be submitted in an annual report to the NDA or ANDA if, after obtaining and analyzing the data in accordance with the protocol, the criteria set forth in the approved stability protocol are met.[10] Such extended

[8] Labeling can be found by searching for doxycycline on the FDA Approved Drug Products Web site, http://www.accessdata.fda.gov/scripts/cder/daf.

[9] CDC's doxycycline EUI are available to state and local public health officials via a password-protected CDC JOIN Web site. During an anthrax emergency, the EUI materials will be posted on https://www.cdc.gov for the general public.

[10] See the guidance for industry *Changes to an Approved NDA or ANDA.*

dating typically is applied prospectively to newly manufactured lots and generally not retrospectively applied to lots manufactured before the newly determined dating period.[11]

2. Federal Shelf-Life Extension Program

The Federal Shelf-Life Extension Program (SLEP) is another approach, but it is limited to specific drug products. SLEP is the Federal, fee-for-service program through which the labeled shelf life of certain federally stockpiled medical materiel (e.g., in the SNS) may be extended after select drug products undergo periodic stability testing conducted by FDA (Khan, Kona, et al. 2014). The program, which is administered by the Department of Defense (DoD), was established in 1986 after it was recognized through testing that certain drug products remained stable beyond their labeled expiration dates when properly stored. Through expiration date extensions, SLEP helps to defer the replacement costs of certain drug products, including doxycycline, in critical Federal stockpiles. Testing under SLEP is limited to drug products in Federal stockpiles.

3. Section 564A(b) of the Food, Drug, and Cosmetic Act

Under section 564A(b) of the FD&C Act, FDA has the authority to extend the manufacturer-provided expiration date of eligible FDA-approved medical products stockpiled for use in CBRN emergencies if the extension is intended to help facilitate the Nation's ability to protect the public health or military preparedness and effectiveness and is ensured by an appropriate scientific evaluation conducted or accepted by FDA.[12,13,14,15] To be an eligible product under section 564A of the FD&C Act, a product must be an approved, cleared, or licensed medical product; intended for use to prevent, diagnose, or treat a disease or condition involving a CBRN agent(s); and intended for use during certain emergency circumstances.[16,17]

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[11] However, in certain cases for emergency preparedness purposes, manufacturers may agree to permit the use of their stability data to permit FDA extensions of expiration dates for existing products, or FDA may rely on other data that will support extensions.

[12] In March 2013, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) was enacted, in part to develop new authorities to sustain and strengthen national preparedness for public health emergencies involving CBRN agents, including emerging infectious disease threats (e.g., pandemic influenza). Among its many provisions, PAHPRA gives FDA the authority to extend, based on an appropriate scientific evaluation, the expiration date of certain approved MCMs for emergency response purposes under section 564A(b) of the FD&C Act. See http://www.gpo.gov/fdsys/pkg/PLAW-113publ5/pdf/PLAW-113publ5.pdf.

[13] Under section 564A(b)(4) of the FD&C Act, *expiration date* is the date established through appropriate stability testing required by the regulations issued by FDA to ensure that the product meets applicable standards of identity, strength, quality, and purity at the time of use.

[14] See the guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities*.

[15] Before PAHPRA's enactment, for the distribution, dispensing, or use of products with extended expiration, and any related labeling adjustments, the only available mechanisms to allow for use beyond the labeled expiration date were under FDA's exercise of its enforcement discretion or through issuance of an EUA under section 564 of the FD&C Act.

[16] This includes the circumstances under which a specific type of emergency or threat determination has been made by the Secretary of the Department of Homeland Security (DHS), DoD, or Health and Human Services (HHS) under section 564(b)(1) of the FD&C Act. Section 564A(a) of the FD&C Act.

Under section 564A(b), FDA must identify specific lots, batches, or other units of the product for which extended expiration is authorized and the duration of each extension. FDA also may identify any other requirements or conditions for an extension as FDA may deem appropriate for the protection of the public health. This may include requirements for, or conditions on, product sampling, storage, packaging or repackaging, transport, labeling, notice to product recipients, recordkeeping, periodic testing or retesting, or product disposition. Eligible products with authorized expiration date extensions may be introduced, or delivered for introduction, into interstate commerce after the expiration date provided by the manufacturer. These products will not be considered unapproved products (as defined in section 564(a)(2)(A)) or deemed adulterated or misbranded under the FD&C Act.

The expiration date extension authority under section 564A(b) of the FD&C Act does not codify the existing SLEP program, extend SLEP to State or local MCM stockpiles, create a new SLEP program for non-Federal government stakeholders, or otherwise address programmatic elements of SLEP. It does not alter FDA's role with regard to SLEP. SLEP remains limited to Federal stockpiles at this time. However, section 564A(b) of the FD&C Act provides FDA with the authority to extend the expiration date(s) of certain eligible medical products, thereby eliminating any uncertainty about the legal status of such products when FDA authorizes an extended expiration date and helping to address MCM stockpiling challenges such as those faced by non-Federal government stakeholders.

As noted earlier, the DoD SLEP program remains limited to Federal stockpiles, so non-federally stockpiled products are not eligible for testing under that program. To help address this public health need, FDA is providing this guidance on testing to support expiration date extensions under section 564A(b) of the FD&C Act of doxycycline tablets and capsules being stockpiled for emergency purposes usually under controlled conditions by government stakeholders.

III. DISCUSSION

Studies conducted through SLEP on a variety of drug products have shown that the expiration dates for most drug products can be extended. For certain products that are generally known to be stable, such as doxycycline tablets and capsules, test results may be extrapolated for emergency use. Government stakeholders are expected to store stockpiled products according to manufacturer's labeled storage conditions (Kahn, Kona, et al. 2014). However, if stockpiled doxycycline tablets and capsules have not been stored under storage conditions as specified in the product's approved labeling or if storage conditions cannot be verified, suitability of

[17] Eligible products authorized for emergency use under section 564A of the FD&C Act, including those with extended expiration dates under section 564A(b) of the FD&C Act, are considered covered countermeasures for purposes of liability protection under the Public Readiness and Emergency Preparedness (PREP) Act. For additional information on the PREP Act and current PREP Act declarations, see http://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx.

stockpiled lots may be determined through accelerated studies[18] that include confirmatory testing over the study period.

A. Observations About Doxycycline Tablet and Capsule Stability Based on Historical Data

Doxycycline tablets and capsules are compendial drug products that are manufactured to meet the recommended tests and criteria of the U.S. Pharmacopeia (USP)/National Formulary (NF) monographs and FDA-approved specifications. Specification attributes include assay, dissolution, and degradant[19] limits, which may be stability-indicating and relevant for stability studies. Stability studies reviewed by FDA over many years have confirmed that none of the components of approved doxycycline tablets and capsules, including the active ingredient, has significant potential for chemical degradation or interaction with other components in the formulation or with components of the container closure system when stored according to labeled directions.

Based on historical data, doxycycline tablets and capsules are expected to remain within USP assay and dissolution acceptance criteria beyond their labeled expiration dates. Degradants are also expected to show minimal increase over time when stored according to the labeled storage conditions. From a pharmacology/toxicology perspective, the acceptable limits for degradants in doxycycline tablets and capsules should be restricted to the existing limits in the USP monographs. For purposes of this guidance, current USP monographs should be referenced for tablets and capsules. However, in the absence of a USP limit and method for degradants, including 4-epidoxycycline, the British Pharmacopoeia (BP) Doxycycline Capsule monograph limits and method may be used.

B. Discussion About Bioavailability

Based on the available information on solubility, intrinsic dissolution, complete absorption of doxycycline in the GI tract, and published relative bioavailability studies in a small number of subjects, both forms of doxycycline, monohydrate and hyclate, have comparable bioavailability (Jantratid, Strauch, et al. 2010; Bogardus and Blackwood 1979; Kitzes-Cohen, Farin, et al. 1998; Saux, Mosser, et al. 1981; Malmborg 1984).[20] Although there is a solubility difference between the two forms, both monohydrate and hyclate can be considered highly soluble according to the Biopharmaceutics Classification System.[21] Even if formulation-related factors should result in

[18] *Accelerated studies* are studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.

[19] The term *degradant* is used to mean an impurity that may increase over shelf life. *Impurity* and *related substance* are terms sometimes used in USP and the British Pharmacopoeia monographs to denote degradants. Where the term degradant is used in this guidance, it should be considered to mean the same as impurity or related substance in a compendial monograph.

[20] See also Doxycycline Monohydrate Properties at Drug Bank, http://www.drugbank.ca/drugs/DB00254 (accessed on July 16, 2015).

[21] See the draft guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.* When final, this guidance will represent the FDA's current thinking on this topic.

dissolution and absorption rate differences, significant exposure differences between the two forms are not expected. Additionally, there have not been reports of absorption rate effects for any of the wide range of excipients used for doxycycline hyclate and monohydrate products. In conclusion, doxycycline monohydrate and hyclate are likely to provide similar systemic exposure based on our current knowledge. Based on this evidence, the recommended acceptance criteria, analytical methods, and shelf-life extension procedures outlined in this guidance may be applied to either form of the drug.

C. Recommended Protocol for Shelf-Life Extension of Doxycycline Tablets and Capsules

Before testing is conducted to extend expiration dates, government stakeholders should determine whether all stockpiled product for which they seek an expiration date extension and from which testing samples are selected has been and will continue to be stored under the manufacturer's labeled storage conditions. If proper storage conditions have been maintained and lots are less than 6 years beyond the manufacturers' original labeled expiration dates, then government stakeholders should follow the testing protocol described in Table 1 (see Attachment).

If appropriate storage conditions of the stockpiled product have not been maintained or cannot be confirmed to have been maintained during any time the product has been stockpiled, accelerated stability testing should be performed following the testing protocol in Table 2 (see Attachment) to evaluate the continued suitability of the lot and its eligibility for expiration extension. Similarly, regardless of storage conditions, any lots that are 6 years or more beyond the manufacturer's original labeled expiration dates should be placed on accelerated stability testing to extend their expiration dates following the testing protocol described in Table 2.

After testing is completed, if government stakeholders would like to request an expiration date extension for tested lots, they must submit to FDA certain information, as described below in section III.E, to enable FDA to authorize an extension for the stakeholders' tested drug products (section 564A(b) of the FD&C Act). Also as described in section III.E, FDA will identify on its Web site each lot of doxycycline for which it authorizes an extension, which will enable other government stakeholders who might stockpile the same lot to apply an existing extension to their lot if stored according to the drug product's labeled storage conditions. Irrespective of whether an extension is authorized under the testing performed within sections III.C.1 or III.C.2, FDA expects that, moving forward, any lots for which an extension has been authorized will be stored according to the manufacturer's labeled storage conditions.

Stockpiles should be checked routinely for lots nearing their labeled expiration date. These lots should be tested within a reasonable time frame (e.g., 6 months) that allows government stakeholders to submit requests to FDA for consideration of an expiration date extension authorization before reaching the labeled expiration date. This will help to ensure that such stakeholders hold product that is authorized by FDA for use beyond its labeled expiration date during an anthrax emergency. For lots tested before their expiration dates that FDA has authorized for use beyond the labeled expiration date, the 2-year extension will begin from the labeled expiration date rather than from the date of testing.

1. Lots Stored According to Labeled Storage Conditions and Less than 6 Years Beyond Their Labeled Expiration Dates (Including Lots That Are Nearing Their Labeled Expiration Dates)

For lots that have been stored according to the manufacturer's labeled storage conditions for the entire time they have been stockpiled and are less than 6 years beyond their manufacturer labeled expiration dates, including those lots that are approaching (i.e., have not yet reached) their labeled expiration dates, expiration dates may be extended for 2 years based on acceptable test results (see Table 1). If three or fewer lots are stockpiled from a single manufacturer, then every lot should be tested to extend the expiration date. If more than three stockpiled lots are supplied by a single manufacturer, then the three oldest lots should be tested to extend the expiration date of all lots held from that manufacturer. If any of the three lots fail, then all lots from that manufacturer should be tested and expiration dates should only be extended for those lots that pass all criteria. Testing of lots from one manufacturer may not be used to extend the expiration dates of lots from another manufacturer.

The number of tablets or capsules withdrawn from each lot for testing should be sufficient to perform the test procedures described in the referenced monograph. Compliance with the USP criteria for assay, degradants, and dissolution should be confirmed by the designated laboratory. Additionally, a visual inspection of the product is recommended to verify product integrity. Government stakeholders are encouraged to retain the manufacturer's labeling (i.e., package insert) so that the product description and storage conditions are readily available. If, however, the label is unavailable at the time of testing, the National Institutes of Health[22] has links to most FDA-approved product labels for reference.

For lots that have been stored under the manufacturer's labeled storage conditions and are less than 6 years beyond their manufacturer labeled expiration date, including lots that have not yet reached their labeled expiration date, a 2-year extension of the expiration date may be approved upon receipt of acceptable test results as follows:

- The Table 1 testing protocol should be followed for a 2-year extension of the expiration date for individual tested lots. If testing results are acceptable from individual tested lots, then those tested lots can be considered qualified for a 2-year extension of the expiration date.

- The Table 1 testing protocol should be followed for a 2-year expiration extension for representative lots used to qualify multiple lots from the same supplier. If testing results are acceptable from at least the three oldest lots from the same manufacturer, then all of the same-manufacturer lots of doxycycline can qualify for a 2-year extension of the expiration date.

[22] NIH, U.S. National Library of Medicine, DailyMed, http://dailymed.nlm.nih.gov/dailymed/index.cfm.

- After this initial confirmation, additional 2-year extensions of the expiration date would be qualified by following the Table 1 testing protocol and obtaining passing test results. However, for product that is 6 years beyond the manufacturer's labeled expiration date, continued 2-year extension of the expiration date must be determined by accelerated stability studies following the testing protocol described in Table 2.

- For lots that have not yet reached but are nearing the manufacturer's labeled expiration date, testing should be performed within a reasonable time frame (e.g., 6 months) before their labeled expiration dates to allow adequate time for conducting the testing and requesting an authorization of expiration date extension for lots that pass testing. If such lots pass testing before their labeled expiration date, then the initial **2-year extension time frame may begin on the labeled expiration date** (i.e., rather than the date the testing was performed). Testing for all subsequent extension periods should also be performed within a reasonable time frame (e.g., 6 months before the extended lot reaches its new expiration date). The new expiration date for these subsequent extension periods will begin 2 years from the expiration date that was established for the previous extension period (i.e., rather than the date the testing was performed).

- For lots that have reached the manufacturer's labeled expiration date and have been stored according to labeled storage conditions and are less than 6 years beyond their labeled expiration dates, authorization of expiration date extension for lots that pass testing will begin **2 years from the date of testing**. Subsequent expiration date extensions will begin on the expiration date associated with the initial 2-year extension **only if** subsequent stability testing is performed before lots have reached the expiration date of the initial 2-year extension. Otherwise, subsequent extension periods will begin 2 years from the testing date of each subsequent extension.

- As described below in section III.E, adequate records of all testing should be kept, even when a lot fails stability testing.

2. Lots Not Stored According to Labeled Storage Conditions or 6 Years or More Beyond Their Labeled Expiration Dates

If stockpiled lots have not been stored in accordance with the manufacturer's labeled storage conditions or if the lots are 6 years or more beyond the manufacturer's labeled expiration date, the expiration date may be extended only if the lots are shown to meet the acceptance criteria indicated in the testing protocol described in Table 2 after 3 months of storage at accelerated stability testing conditions. If three or fewer lots are from a single manufacturer, then every lot should be placed on accelerated stability testing to extend the expiration date. If more than three stockpiled lots are supplied by a single manufacturer, at least the three oldest lots should be placed in the accelerated stability study to extend the expiration dates of all lots held from that manufacturer. Testing lots from one manufacturer may not be used to extend the expiration date of lots from another manufacturer.

Accelerated stability testing storage conditions are 40°C ± 2°C /75% ± 5% relative humidity. These conditions stress the product and are thought to be conservatively predictive of future

stability for a period of time under room temperature conditions. The long-term stability data in conjunction with accelerated stability data are commonly used initially to establish tentative expiration dates for pharmaceuticals. The tentative expiration dates are confirmed with full long-term stability data post approval. For products in government stockpiles, performance of long-term stability studies is not expected. However, accelerated studies should be performed for cases in which lots have not been stored according to manufacturer's labeled storage conditions or when stockpiled lots are 6 years or more beyond the manufacturer's labeled expiration date.

For lots that have not been stored in accordance with the manufacturer's labeled storage conditions or that are 6 years or more beyond the manufacturer's labeled expiration date, results of these tests can qualify expiration date extensions as follows:

- The Table 2 testing protocol should be followed for a 2-year expiration date extension for individual tested lots. If testing results are acceptable from individual tested lots after 3 months of storage under accelerated storage conditions, then those tested lots can be considered qualified for a 2-year extension of the expiration date **beyond the expiration date from the initial sampling point** in the accelerated stability study (month 0) for the initial 2-year extension of the expiration date.

- The Table 2 testing protocol should be followed for representative lots used to qualify multiple lots from the same manufacturer. If the testing results are acceptable after 3 months of storage under accelerated storage conditions, then all lots of doxycycline tablets or capsules stockpiled from that manufacturer can be qualified a 2-year extension of the expiration date **from the initial sampling point** in the accelerated stability study (month 0) for the initial 2-year expiration extension.

- After this confirmation, additional 2 year extensions of the expiration date **from the initial sampling point** in the accelerated stability study (month 0) can be qualified through accelerated studies (i.e., 3 months storage at accelerated conditions). The additional 2 year extension of the expiration date qualified by an additional accelerated study would begin from the initial sampling point (month 0) of the additional study.

- Records of all testing should be kept, even when a lot fails stability testing.

D. Identifying a Suitable Laboratory To Conduct Doxycycline Tablets and Capsules Testing

Government stakeholders may conduct their own stability testing if they have labs that meet the elements of a suitable laboratory. Alternatively, if a government stakeholder chooses to have stability testing performed by a contractor, a suitable laboratory should be identified. Most suitable laboratories should be capable of performing the testing described in this guidance. A *suitable laboratory* for purposes of this guidance is one that follows all relevant current good manufacturing practices requirements as cited in 21 CFR parts 210 and 211. In addition, the recommended assay and degradant tests should follow USP or BP (for testing 4-epidoxycycline) high performance liquid chromatography (HPLC) methods and dissolution testing should be performed using the methods and requisite apparatus as described in USP. Because these are

compendial tests, the validation of methodology is straightforward (i.e., typical parameters are listed in USP General Chapter <1225>).

E. Process for Requesting and Receiving an Authorized Expiration Date Extension for an Identified Lot of Doxycycline Tablets or Capsules

1. Overview

Based on FDA's understanding of the stability of doxycycline products and the testing methodology described in this guidance, when testing conducted by a suitable laboratory demonstrates the product is stable at the time of testing, FDA may accept these results as an appropriate scientific evaluation under section 564A(b) of the FD&C Act. In general, we anticipate that we will accept a government stakeholder's self-certification that appropriate testing has been conducted on a specified lot of stockpiled doxycycline tablets or capsules. However, FDA reserves the right to deny a request for an expiration date extension of a specific lot of doxycycline tablets or capsules for the protection of the public health.

Each lot of doxycycline tablets or capsules that has undergone testing in accordance with this guidance and is found to be stable at the time of testing may be eligible to be authorized by FDA for a 2-year expiration date extension each time the product is tested under section 564A(b) and other conditions under section 564A(b) are met.[23] The doxycycline product tested must be FDA-approved and intended for use to prevent or treat a disease or condition involving *B. anthracis* during the circumstances under which (1) a determination under section 564(b)(1) of the FD&C Act has been made by the Secretary of DoD, DHS, or HHS or (2) a Material Threat Determination (MTD) pursuant to section 319F-2 of the Public Health Service Act has been made by the Secretary of DHS.[24] Furthermore, doxycycline tablets or capsules available commercially, or stockpiled, for other non-CBRN emergency purposes are not eligible for expiration date extensions under section 564A(b) of the FD&C Act or this guidance.

As described below, before FDA may authorize an expiration date extension under section 564A(b), government stakeholders must submit certain information to FDA to enable FDA to identify each specific lot for which extended expiration is authorized. Before such stakeholders may use tested products for anthrax emergency purposes, they first must receive notification that FDA has authorized the expiration date extension of each lot. Also, certain requirements and conditions under section 564A(b) will apply to any doxycycline expiration date extension FDA authorizes based on government stakeholder testing conducted in accordance with this guidance.

[23] See sections III.C and III.D of this guidance.

[24] On September 23, 2008, pursuant to section 564(b)(1)(A) of the FD&C Act, in a memorandum to Michael O. Leavitt, the Secretary of DHS determined that there is a significant potential for a domestic emergency involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent or agents—in this case, *B. anthracis* (http://www.dhs.gov/xlibrary/assets/ofsec_signed_determination092308.pdf).

2. Format of Submissions

Submissions, including a cover letter, may be provided in electronic or paper format. General information on electronic submissions, as well as links to CDER-specific submission preparation guidelines, may be obtained at FDA's Electronic Submission Gateway Web site: http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm113200.htm.

To facilitate timely consideration of requests, FDA strongly recommends that government stakeholders submit the following information in any request for a doxycycline expiration date extension based on testing conducted in accordance with this guidance:

- Requester's name, title, affiliation, and contact information (i.e., mailing address, email address, telephone number, and fax number) and requester's preferred way to be contacted by FDA.

- Date of request.

- Statement of the request for an FDA expiration date extension for a specific lot of doxycycline tablets or capsules stockpiled for anthrax preparedness and tested under this guidance.

  - A single request letter may include a government stakeholder's request for extensions of more than one lot, including other lots that either the stakeholder has tested in accordance with this guidance or to which the requesting stakeholder would like their test results to be extrapolated.

- Statement that the government stakeholder certifies the test results and resulting new expiration dates are based on testing conducted in accordance with the testing methodology and any other requirements or conditions described in this guidance.

- Information about the tested doxycycline product:

  - Dosage form of doxycycline product (e.g., tablets or capsules).
  - Strength (e.g., 100 mg).
  - Name of manufacturer.
  - Lot number.
  - Manufacturer's labeled expiration date (original and last extended dates, if applicable).
  - Quantity of lots and number of units of the product in each lot stockpiled.
  - Unit of product stockpiled (e.g., 20-count unit-of-use bottle (packaging configuration)).
  - Whether the lot previously has undergone expiration date extension testing under this guidance (and, if so, a brief summary of the findings of the previous testing, including whether the product was found to be stable at the time of testing).
  - Past and current storage conditions (i.e., whether the lot has been and continues to be properly stored according to the manufacturer labeled storage conditions).

- The report from the laboratory that conducted the testing that includes the following information about the doxycycline testing:
    - Test methods and validation reports of the test methods.
    - Name and contact information of the suitable laboratory that conducted the testing.
    - Test date.
    - Lot(s) and batch(es) tested.
    - Whether the tested product was found to be stable at the time of testing or failed testing results and any observations that may have occurred while testing the product.
    - Proposed new expiration date based on the date of testing and criteria described in this guidance (if the laboratory report does not already include such information).
- Other information the government stakeholder believes would be important to inform FDA's review of the doxycycline expiration date extension request.

When submitting a request in paper format, provide a minimum of three copies to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, send an email that includes the submission cover letter to the following address to highlight the urgency of the request (e.g., if related to an imminent or ongoing emergency): CDEREUA@fda.hhs.gov (cc: EUA.OCET@fda.hhs.gov).

3. Notification of Authorization Decision to Requesters and Public Notice of Extensions for Government Stakeholders To Apply an Authorization to Untested Lots

After receiving and reviewing a government stakeholder's request to extend an expiration date for doxycycline based on testing conducted in accordance with this guidance, FDA will notify (e.g., by email) the requester of the expiration date extension decision (i.e., whether FDA authorizes the requested extension and the specific lot(s) for which an extended expiration date is authorized and new expiration period). FDA may decline to authorize the request based on a number of factors (e.g., if the doxycycline product fails to meet the necessary criteria identified in section 564A of the FD&C Act or as described in section III.E.4 of this guidance). FDA also will notify the requester when FDA declines to authorize the extension for the product, including whether or not the product should be properly disposed of.

In addition, FDA will provide public notice (e.g., a memorandum posted on the FDA Web site) of each expiration date extension (e.g., manufacturer name, lot number, original manufacturer

labeled expiration date, new expiration date) that the product is authorized under section 564A(b) of the FD&C Act and in accordance with this guidance.[25] This notification will enable other government stakeholders holding the same lot(s) of the product to apply an applicable extension of shelf life to their own stockpiled lot(s) of doxycycline without testing such lot(s), as long as the stakeholders follow other applicable requirements and conditions described below in section III.E.4.[26]

4. Other Requirements and Conditions Under Section 564A(b) of the FD&C Act

In addition to the identification of specific lots, batches, or other units of the product for which extended expiration is authorized and the duration of such an extension, FDA may identify any other requirements or conditions as deemed appropriate for the protection of the public health, including related to product sampling, storage, packaging or repackaging, transport, labeling, notice to product recipients, recordkeeping, periodic testing or retesting, or product disposition.[27]

The following is a list of other requirements and conditions that apply to any expiration date extensions FDA authorizes based on stockpiled doxycycline tablet or capsule testing conducted following this guidance:

- **Testing**: Test results may be considered an appropriate scientific evaluation that may be accepted by FDA for purposes of an expiration date extension under section 564A(b) of the FD&C Act if government stakeholders ensure that the doxycycline testing is conducted by a suitable laboratory and in accordance with the testing methodology, as described in this guidance. FDA reserves the right to conduct inspections of laboratories conducting testing under this guidance. Government stakeholders must secure agreements from such laboratories that the laboratories will permit FDA inspection, as appropriate.

- **Periodic testing or retesting**: Government stakeholders are not required to conduct periodic testing or retesting. However, if such stakeholders are interested in requesting an additional 2-year extension of the expiration date for a previously tested lot, such lot, if eligible for an additional 2-year extension of the expiration date, must be retested according to the testing protocol outlined in this guidance. In addition, the government stakeholder must submit a new 2-year extension of the expiration date request to FDA, and FDA must authorize the new 2-year extension of the expiration date (including for any lots to which test results are extrapolated).

[25] Section 564A(b)(2) of the FD&C Act.

[26] For a list of doxycycline expiration date extensions authorized by FDA under section 564A(b) before issuance of this guidance, refer to the 2015 memo from FDA's Acting Chief Scientist to State and local public health and first responder stakeholders titled *Expiry Date Extensions of Certain Lots of Doxycycline Hyclate 100mg Capsules Held in Strategic Stockpiles* (http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM462484.pdf).

[27] Section 564A(b)(2) of the FD&C Act.

- **Storage**: Government stakeholders should have stored, and should continue to store, their stockpiled doxycycline tablets or capsules according to the manufacturer's labeled storage conditions until the time of emergency use.[28] As described earlier in this guidance, testing may be permitted on certain lots that have not been stored according to their labeled storage conditions up to the time of testing. However, FDA expects that all such lots will, moving forward, be stored according to their labeled storage conditions if testing finds such product to be stable at the time of testing and if FDA authorizes an expiration date extension for such lots. FDA reserves the right to conduct audits or inspections of stockpiled product, as appropriate.

- **Recordkeeping**: Government stakeholders should keep detailed records about storage and any testing they conduct or have conducted under this guidance (e.g., manufacturer name, lot number, and original manufacturer labeled expiration date; date of testing; any additional lots to which the test results apply; name and contact information of the laboratory that conducted the testing; results of the testing, including whether any lots failed testing and, if known, the reason why a specific lot failed testing; number of times each lot was tested; any correspondence from FDA). Through a process of inventory control, government stakeholders also should maintain records of emergency use of any doxycycline lots that have received an expiration date extension from FDA. All such records described in this paragraph will be made available to FDA for inspection or audit upon request.

- **Labeling**: Although government stakeholders may choose to re-label each individual container (e.g., unit-of-use bottle, bulk bottle) of product that has been authorized for an expiration date extension, FDA is not recommending or requiring that each individual container be relabeled with the new expiration date. However, government stakeholders should distinguish the doxycycline tablet or capsule lots that have new expiration dates or that have undergone stability testing (e.g., by shrink wrapping a pallet and placing a single marking on a centrally stockpiled lot with the authorized extended expiration date).

- **Notice to product holders**: Although FDA is not requiring doxycycline product that has undergone testing and received an expiration date extension under this guidance to be relabeled with the new expiration date, government stakeholders will inform any holders of such product that the product's labeled expiration date has been extended by FDA through appropriate scientific testing accepted by FDA (e.g., if the testing is conducted or supported by the State public health agency, the State will notify any applicable sub-state jurisdictions or other government stakeholders that stockpile the same lot(s) of doxycycline in the State of any applicable extension(s)).

- **Notice to product recipients**: Although FDA is not requiring products that have undergone testing and received expiration date extensions from FDA in accordance with

[28] However, under section 564 of the FD&C Act and section 564A(c) of the FD&C Act, FDA may, as appropriate and under certain circumstances, waive certain current good manufacturing practice (CGMP) requirements (e.g., related to storage temperature) temporarily to facilitate an emergency response.

this guidance to be relabeled with the new expiration date, government stakeholders will inform any recipients (i.e., individuals in the impacted population to whom the drug is being dispensed) of such product at the time of dispensing (i.e., during or in anticipation of an anthrax emergency) that the product's labeled expiration date has been extended through appropriate scientific testing accepted by FDA.[29]

- **Product disposition**: If a government stakeholder submits to FDA test results that do not initially appear to be favorable for supporting an expiry date extension, it should continue to properly store the applicable lot(s) and should not dispose of such lot(s) until receiving notification from FDA. Government stakeholders who do not submit such data to FDA, or who otherwise receive notification from FDA to dispose of their lot(s) after FDA reviews their test data, should properly dispose of any such lot to prevent potential misuse, environmental contamination, or antimicrobial resistance.

- **Other**: FDA may identify any other requirements or conditions as FDA may deem appropriate for the protection of the public health.

IV. REFERENCES

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[29] The recipient notice requirement may be met if applicable CDC-issued EUI under section 564A(e) of the FD&C Act for doxycycline address the use of such product beyond its labeled expiration date.

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ATTACHMENT

Each table includes examples of how to present data as well as the protocol to follow as referenced in section III. This format should be followed for recording test results. The test results and specifications below are provided for illustration. Test methods and acceptance criteria should follow the appropriate monograph for each product as described in section III.

Table 1. Testing Protocol for Expiration Date Extension of Doxycycline Tablets and Capsules Meeting Criteria Under III.C.1*

Product Name and Strength	Lot Identification (number and manufacturer)	Storage** [Y/N]	Test Date	Specifications	Test Result	Manufacturer's Labeled Expiration Date (original and last extended dates, if applicable)	Proposed New Expiration Date
Doxycycline Hyclate Capsules 100 mg, USP	Lot #Abc0123 AB Manufacturing	Y	1/01/2017	Assay: 90.0-120.0% labeled amount	100.0%	6/2017 manufacturer's labeled expiration date	6/2019
				Dissolution: NLT 80%(Q) in 30 min. Mean: High: Low:	 99% 101% 98%		
				Degradants: 4-Epidoxycycline: NMT 0.5% Any other individual: NMT 0.5% Total: NMT 2.0%	 0.10% 0.09% 0.19%		
				Appearance: Conforms with label description and maintains integrity***	Conforms		

*Product has been continuously stored according to manufacturer's labeled storage conditions and is less than 6 years beyond manufacturer's labeled expiration date.

** Has the product been stored continuously under manufacturer's labeled storage conditions before testing? The response should be yes (Y) or no (N). If the response is no (N), then accelerated studies should be performed or an extension cannot be considered. Refer to Table 2.

***Conformance to the product label description. Evaluation of the general integrity of the product should be made. This result can be denoted as conforms or does not conform.

Table 2. Testing Protocol for Expiration Date Extension of Doxycycline Tablets and Capsules Under III.C.2 *

Product Name and Strength	Lot Identification (number and manufacturer)	Storage** [Y/N]	Test Station and Test Date	Specifications	Test Result	Manufacturer's Labeled Expiration Date (original or last extended)	Proposed New Expiration Date
Doxycycline Hyclate Capsules 100 mg, USP	Lot #Abc0123 AB Manufacturing	N	Month 0 1/01/2017	Assay: 90.0-120.0% labeled amount	100.0%		
				Dissolution: NLT 80%(Q) in 30 min. Mean: High: Low"	 99% 101% 98%		
				Degradants: 4-Epidoxycycline: NMT 0.5% Any other individual: NMT 0.5% Total: NMT 2.0%	 0.10% 0.09% 0.19%		
				Appearance: Conforms with label description and maintains integrity***	Conforms		
			Month 1 2/01/2017	Assay	97.0%		
				Dissolution Mean/High/Low	98%/ 100%/ 97%		
				Degradants 4-Epi/other/total	0.10%/0.09%/ 0.19%		
				Appearance	Conforms		
			Month 2 3/01/2017	Assay	97.5%		
				Dissolution Mean/High/Low	98%/ 100%/ 97%		
				Degradants 4-Epi/other/total	0.20%/0.09%/ 0.29%		
				Appearance	Conforms		
			Month 3 4/01/2017	Assay	95.0%	6/2017 Manufacturer's labeled expiration date	1/2019
				Dissolution Mean/High/Low	97%/ 98%/ 95%		
				Degradants 4-Epi/other/total	0.30%/0.10%/ 0.40%		
				Appearance	Conforms		

*Continuous storage according to manufacturer's labeled storage conditions cannot be confirmed or lots are 6 years or more beyond the manufacturer's labeled expiration date. Accelerated studies should be continued for at least 3 months or an extension cannot be considered. Testing under accelerated conditions (40°C ± 2°C/75% ± 5% relative humidity).

** Has the product been stored continuously under manufacturer's labeled storage conditions before testing? The response should be yes (Y) or no (N). If the response is no (N), then please explain.

***Conformance to the product label description. Evaluation of the general integrity of the product should be made. This result can be denoted as conforms or does not conform.