Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax

Guidance for Industry

DRAFT GUIDANCE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)

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Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax Guidance for Industry[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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to assist sponsors in the development of drugs for the indication of prophylaxis of inhalational anthrax[2] in persons who have inhaled aerosolized *Bacillus anthracis* spores but who have not yet manifested clinical evidence of disease.[3] The indication also applies to persons with probable imminent exposure to *B. anthracis* spores (e.g., first responders), although in such cases initiation of antibacterial therapy begins immediately before entering the *B. anthracis*-contaminated environment. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[4]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] The indication of prophylaxis of inhalational anthrax was previously known as inhalational anthrax (post-exposure) — to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. The indication has been revised; see section II.B., Indication for Prophylaxis of Inhalational Anthrax.

[3] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products such as therapeutic proteins and monoclonal antibodies, unless otherwise specified, and references to *approval* include new drug application approval for drugs or biologics license application licensure for therapeutic proteins and monoclonal antibodies. Sponsors interested in developing other types of biological products, such as vaccines and immunoglobulin preparations, should contact the appropriate review division in the Center for Biologics Evaluation and Research.

[4] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the indication of prophylaxis of inhalational anthrax.

Principles for Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[5]

This guidance supersedes the draft guidance for industry *Inhalational Anthrax (Post-Exposure) — Developing Antimicrobial Drugs* issued in March 2002 (2002 draft guidance). The specific regulations under which drugs for prophylaxis of inhalational anthrax are approved have changed in the last decade. This guidance clarifies that drugs developed for prophylaxis of inhalational anthrax are to be considered for approval under the animal rule.[6] Other changes from the 2002 draft guidance are incorporated into the appropriate sections of this guidance and are based on comments received for the 2002 draft guidance. In addition, this guidance reflects recent developments in scientific information that pertain to drugs being developed for prophylaxis of inhalational anthrax.

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. Historical Background

In the fall of 2001, *B. anthracis* spores (Ames strain) were used as an agent of bioterrorism and sent through the U.S. mail, resulting in cases of inhalational and cutaneous anthrax. Post-exposure prophylaxis of inhalational anthrax was administered to thousands of persons, most of whom received ciprofloxacin or doxycycline (Jernigan, Stephens, et al. 2002; Martin, Tierney, et al. 2005; Doolan, Freilich, et al. 2007; Ingelsby, O'Toole, et al. 2002).

At the time of the anthrax attacks, ciprofloxacin was already approved (in August 2000) for post-exposure prophylaxis of inhalational anthrax under the accelerated approval regulations. In November 2001, a notice in the *Federal Register* clarified that penicillin G procaine and doxycycline, both of which included anthrax or *B. anthracis* in their previously approved labeling, are indicated for prophylaxis of inhalational anthrax.[7] Levofloxacin also was approved under the accelerated approval regulations in November 2004. In December 2012, raxibacumab was approved under the animal rule regulations for the treatment of inhalational anthrax caused

[5] We update 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.

[6] The animal rule sets forth a pathway for approval of drug or biological products when human efficacy studies are not ethical or feasible. See 21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biological products. See also the guidance for industry *Product Development Under the Animal Rule*.

[7] See "Prescription Drug Products; Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure)" (66 FR 55679, November 2, 2001).

by *B. anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

B. Indication for Prophylaxis of Inhalational Anthrax

A window of opportunity for preventing illness and reducing mortality exists between the time of inhalation of aerosolized *B. anthracis* spores and the development of signs and symptoms of inhalational anthrax. The indication for drugs to prevent the development of disease in persons who have inhaled aerosolized *B. anthracis* spores, but who do not yet have the established disease, is referred to as *prophylaxis of inhalational anthrax.*

This indication means that drug administration starts after a known or suspected exposure to aerosolized *B. anthracis* spores, but before clinical symptoms of the disease develop. The indication also includes anticipated exposure (e.g., first responders), when the first few doses may be taken pre-exposure, but the remainder of the course of prophylaxis is administered post-exposure.

III. DEVELOPMENT PROGRAM

A. General Considerations

The antibacterial drugs that have been approved for prophylaxis of inhalational anthrax were found to be safe and effective in a number of indications, marketed for many years, and prescribed to millions of patients before their approvals of prophylaxis of inhalational anthrax. Therefore, the level of experience with these drugs was quite extensive and adverse effects were well-characterized. Because it is expected that a large number of persons may receive these drugs as prophylaxis, it is recommended that antibacterial drugs being developed for this indication have sufficient safety experiences to assess the risk and benefit among persons who are defined to be at high risk for exposure to and inhalation of *B. anthracis* spores. It is unlikely that sufficient human safety experience can be obtained for an investigational antibacterial drug for which prophylaxis of inhalational anthrax is the only indication under development. Thus, an indication for prophylaxis of inhalational anthrax will be reserved almost exclusively for antibacterial drugs for which widespread use in other infectious diseases has been established.[8]

The extent of available safety and efficacy information from use of the drug for other indications can provide information for sponsors about the potential for drug development for this indication under the animal rule regulations. If there is substantially limited human safety and efficacy information available for evaluation of an investigational drug, sponsors should provide justification for the anticipated benefit that will offset the risk of the investigational drug for prophylaxis of inhalational anthrax.

[8] In some circumstances when a drug appears to offer potential benefit complementary to drugs already approved for the proposed indication but may not be studied for broader indications in other diseases, a more limited (e.g., second-line) indication for prophylaxis of inhalational anthrax may be considered (e.g., raxibacumab).

1. Efficacy Considerations

Definitive human efficacy studies cannot be conducted because naturally occurring inhalational anthrax is extremely rare and it would be unethical to deliberately expose healthy human volunteers to *B. anthracis* spores; thus, as previously noted, drugs developed for prophylaxis of inhalational anthrax should be developed for consideration of approval under the animal rule.[9] FDA can rely on evidence from animal studies to provide substantial evidence of effectiveness to support approval only when all four criteria listed in the animal rule regulations, as follows, are met:[10]

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

FDA emphasizes that development proposals for prophylaxis of inhalational anthrax may be more convincing if the drug has been shown to be safe and effective in the treatment of other infectious diseases.

2. Human Safety Considerations

Drugs evaluated for efficacy under the animal rule are evaluated for safety under the existing requirements for establishing the safety of new drugs (21 CFR 314.50(d)(5)(vi) and 21 CFR 314.610(a) for drugs and 21 CFR 601.2(a) and 21 CFR 601.91 for biologics). The risks of the use of any drug are weighed against its benefits in the populations likely to use the drug for the stated purpose. For antibacterial drugs, the anticipated duration of therapy for prophylaxis of inhalational anthrax is 60 days. Safety concerns arising from shorter-duration or lower-dose uses of previously approved or studied drugs will contribute to the overall safety database, but the development plan should address plans for assembling a safety database adequate to support the proposed dose and duration for prophylaxis of inhalational anthrax. Sponsors should discuss with FDA the appropriate size and nature of the preapproval safety database.

[9] See 21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biological products. See also the guidance for industry *Product Development Under the Animal Rule*.

[10] See 21 CFR 314.610 and 601.91.

3. Nonclinical Safety Considerations

Guidances for industry are available to provide information for sponsors on general nonclinical safety considerations for drug development.[11] To support the indication for prophylaxis of inhalational anthrax, animal toxicity studies in two or more species (e.g., rat, mouse, dog, and monkey) are recommended to characterize nonclinical safety. For a previously approved antibacterial drug for which the nonclinical safety characterization and accumulated clinical data on the use of the drug support a 60-day duration of therapy the available nonclinical safety data are usually sufficient.

4. Clinical Pharmacology Considerations

An important component to establishing substantial evidence of effectiveness of a drug approved according to the animal rule regulations is the selection of an effective dose in humans based on pharmacokinetics and pharmacodynamics of the drug in animals and humans, or other relevant information (21 CFR 314.610(a)(4) for drugs and 21 CFR 601.91(a)(4) for biological products). Because effectiveness of drugs for prophylaxis of inhalational anthrax cannot be tested in humans, a comparison of systemic drug exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax obtained in the adequate and well-controlled animal efficacy studies is used to support the selection of an effective dose in humans. This comparison should take into account the variability of exposure parameters in both animals and humans, and any outlying values of exposure in humans should be greater than those associated with efficacy in animals, to minimize the possibility of subtherapeutic exposures in humans.[12] Sponsors should discuss with FDA whether information other than pharmacokinetics and pharmacodynamics can support the selection of an effective dose and regimen in humans.

The drug's absorption, distribution, metabolism, and excretion characteristics should be characterized and plasma protein binding determined both in the animal species selected for efficacy testing and in humans. Obtaining pharmacokinetic (PK) data for specific populations (i.e., geriatrics, pregnant women, patients with renal or hepatic impairment, and pediatrics, if possible (see section III.C.1., Pediatrics)) is recommended, as well as conducting studies to investigate the potential for drug-drug interactions with medicinal products likely to be co-administered in the clinical scenario.

5. Microbiology Considerations

Sponsors should provide information on the in vitro susceptibility of a spectrum of *B. anthracis* isolates to the investigational drug. This testing should be performed on approximately 50 isolates, provided there is evidence that all isolates have uniformly low variability in minimum inhibitory concentrations (MICs) to the investigational drug. If there is multiple-fold variability

[11] See the Pharmacology/Toxicology guidance Web Page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm; for example, see the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*.

[12] See the guidance for industry *Product Development Under the Animal Rule*.

in the MIC results, data on a larger number of isolates should be submitted (up to 100 isolates). A variety of strains should be selected to represent geographic diversity, human and animal isolates, and naturally occurring antibacterial resistance. In addition, susceptibility testing to several known strains (including Vollum, Ames, and Sterne) should be performed. Susceptibility testing should be performed in several laboratories to demonstrate reproducibility of the results.

Bacteria cultured from animals that develop infection during treatment or in the follow-up period should be tested for in vitro susceptibility. Post-treatment MIC values should be compared to the baseline MIC values.

Drugs that have an indication for prophylaxis of inhalational anthrax (such as ciprofloxacin, levofloxacin, doxycycline, and/or penicillin G procaine) should be included in susceptibility tests as control drugs.

The details of the procedure and methods for susceptibility testing should be provided. Susceptibility testing should be performed using a standardized method, such as that recommended by the Clinical and Laboratory Standards Institute (CLSI).[13] If an alternative or experimental testing method is used, then details of the method and performance characteristics should be provided. The range of concentrations to be tested should be sufficiently broad to ensure that MICs are reported as a specific value.

Laboratory work with *B. anthracis* must be conducted in compliance with the requirements of the select agent regulations (42 CFR part 73) and should incorporate relevant biosafety procedures. Sponsors should contact the Centers for Disease Control and Prevention (CDC) (http://www.CDC.gov) and the National Institutes of Health (http://www.nih.gov/research-training) for more information regarding biosafety procedures (CDC 1999).

If antibacterial resistance develops spontaneously following exposure to the investigational drug, the mechanism of resistance should be characterized, when possible.

B. Considerations for the Adequate and Well-Controlled Animal Efficacy Studies

1. Animal Models

Sponsors should discuss with FDA the proposed animal models in which efficacy will be tested and the study designs for the adequate and well-controlled animal efficacy studies and obtain concurrence on the details of the models and the design of the studies before the studies are initiated.[14] In the past, a rhesus macaque model (e.g., Friedlander, Welkos, et al. 1993) was used as the animal model of infection for prophylaxis of inhalational anthrax for selected drugs.

[13] CLSI publishes documents that describe standardized susceptibility testing that are updated periodically. These documents can be found at http://clsi.org.

[14] See the guidance for industry *Product Development Under the Animal Rule*.

Sponsors can discuss with FDA the use of other animal models in their drug development program.

2. Study Conduct

FDA considers the good laboratory practice for nonclinical laboratory studies (GLP) regulations to be an established and relevant system for ensuring data quality and integrity. FDA recommends the use of GLP, to the extent practicable, for these studies.[15] Before initiating the studies, sponsors should identify exceptions to GLP regulations, if any, and seek concurrence from FDA on alternative methods to ensure data quality and integrity in the event of such exceptions.

Animal studies must comply with the applicable laws and regulations as outlined in the Animal Welfare Act (7 U.S.C. 2131 et seq.) and the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals.[16]

3. Bacterial Challenge

Strains of *B. anthracis* with known virulence in humans and the chosen animal species should be used for challenge. It is expected that mortality will be greater than or equal to 90 percent in the infected, untreated control group.

The route of *B. anthracis* exposure in the animal efficacy studies should be aerosol inhalation, as is anticipated in humans from an intentional release. Sponsors wishing to explore the possibility of administering spores via direct placement into the trachea or nasal passages should discuss these plans with FDA early in the development program.

The preparation of the inoculum of spores to be used for the inhalational challenge should be standardized and validated in the laboratory where such testing will be done for the first time. Standardization and optimization of the inoculum concentration are important because the animal survival time may vary with the experimental conditions (e.g., animal species, strain of *B. anthracis*, method of inoculum preparation, inoculum size, and exposure time).[17]

4. Selection of the Dose for the Investigational Drug

The selection of the dose for the investigational drug to be studied in the adequate and well-controlled animal studies should be based on an understanding of the exposure-response relationship in the proposed animal model and an understanding of the differences in absorption,

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[15] See 21 CFR part 58.

[16] The policy document is accessible at http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf.

[17] For example, in the Friedlander and colleagues study (Friedlander, Welkos, et al. 1993), rhesus monkeys were infected with approximately 5.5×10^5 spores, a mean of 11 times the amount that kills 50 percent of the test animals (LD_{50}), with a range of 5 to 30 times the LD_{50} of Vollum 1B strain of *B. anthracis*. In another animal study included in labeling for levofloxacin, rhesus monkeys were infected with approximately 2.7×10^6 spores (a mean of 49 times the LD_{50}, with a range of 17 to 118 times the LD_{50}) of Ames strain of *B. anthracis*.

distribution, metabolism, and excretion of the drug between humans and the proposed animal species.[18] Sponsors should provide evidence to support a conclusion that humans receiving the dose proposed for this indication would safely and reliably have exposure to the drug greater than exposures observed in the animals in the efficacy studies used to support approval. Achieving a higher exposure in humans is important to minimize the possibility of subtherapeutic exposures in humans, particularly if there is adequate human safety information to support the proposed dose, as may sometimes occur based on use of the drug for other conditions. In general for antibacterial drugs, the duration of administration in the adequate and well-controlled animal studies has been approximately 30 days; this has allowed for demonstration of robust protective effects in the nonhuman primate model, whereas the 60-day recommended human antibacterial drug regimen addresses the possibility of occasional later spore germination.[19]

Before conducting the adequate and well-controlled animal efficacy studies, sponsors may find in vitro PK/pharmacodynamic (PD) approaches to be helpful in determining an appropriate dose (see, for example, Louie, Vanscoy, et al. 2013). Use of PK/PD parameters such as the ratio of the area under the curve to the MIC or the ratio of the maximal concentration (C_{max}) to the MIC may be useful for antibacterial drugs with concentration-dependent mechanisms of bacterial killing, whereas the time above the MIC may be useful for antibacterial drugs with time-dependent mechanisms of bacterial killing.

5. Choice of Comparators

A vehicle control group should be included. This can serve as an untreated control to verify aspects of study conduct and bacterial inoculum preparation by comparing the progression of disease in the absence of treatment to what is anticipated based on previous experience with that animal model. A randomized, masked (blinded) design is particularly important for this type of animal study to minimize the risk that comparisons between treatment and control groups could be affected by differences in baseline characteristics, supportive care, clinical evaluation, or use of euthanasia criteria based on treatment group designation.

6. Efficacy Endpoints

The primary endpoint should be survival to the end of the study. The proportion of animals achieving the primary endpoint should be compared between the drug group and the control group. Secondary endpoints should include bacteremia at different time intervals during or after treatment and a quantitation of the microbial burden in infected organs and/or tissues (e.g., blood, spleen, liver, brain, lymph nodes, cerebrospinal fluid) collected at the time of necropsy.

FDA recommends the assessment of the primary efficacy endpoint (survival) after a period of observation following completion of treatment (e.g., 30 days following the end of treatment). A complete histopathologic evaluation should be performed on animals that die during the study,

[18] See 21 CFR 314.610(a)(4) and 21 CFR 601.91(a)(4).

[19] See discussions of the duration of antibacterial drug dosing in the July 28, 2000, Anti-Infective Drugs Advisory Committee transcript found at http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective.

including animals that met prespecified criteria for euthanasia (Bregman, Alder, et al. 2003; Jacobs, El Hage, et al. 2003).

7. Study Pharmacokinetic Assessments

PK data should be collected for the drugs tested in the adequate and well-controlled animal studies. Determining the systemic exposure that was achieved in animals and that prevented the inhalational anthrax infection and consequent death is necessary for comparison to human exposures for the determination of a human dose (see 21 CFR 314.610(a)(4) and section III.A.4., Clinical Pharmacology Considerations). Therefore, blood samples for PK analysis should be collected from each animal and sample size and PK sampling strategies should be adequate to characterize relevant exposure parameters.

8. Statistical Considerations

The goal of the adequate and well-controlled animal studies should be to demonstrate that the investigational drug is statistically superior to placebo and confers a treatment effect considered likely to be clinically meaningful. Standard supportive care should be provided consistently across treatment groups in the studies.[20] Power considerations and proposed statistical analysis should be discussed with FDA before intended studies are initiated.

C. Other Considerations

1. Pediatrics

Sponsors are encouraged to begin discussions about their pediatric clinical development plan as early as is feasible because pediatric studies are a required part of the overall drug development program. Sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting or such other time as may be agreed upon by FDA and the sponsor.[21]

Obtaining data to support pediatric dosing is challenging. Because administration of an investigational drug presents more than minimal risk, and because naturally occurring exposure to aerosolized *B. anthracis* spores is unlikely to occur in children in the United States, it is considered unethical under 21 CFR part 50, subpart D,[22] to obtain PK data following administration of a drug used to treat or protect against inhalational anthrax from healthy children who do not have a prospect of direct benefit from the drug. Accordingly, other approaches to pediatric dose selection should be explored such as applying PK data from the use

[20] See the guidance for industry *Product Development Under the Animal Rule* for definitions of supportive care.

[21] See the Pediatric Research Equity Act (Public Law 108-155; section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144). See also the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

[22] See 21 CFR 50.52, Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

of the investigational drug for other more common diseases, obtaining population PK data during use of the investigational drug if specific situations warranting pediatric use arise during drug development, modeling pediatric exposure from existing adult data from the investigational drug, or using data available from other sufficiently similar drugs. For example, PK modeling served as the basis for raxibacumab's pediatric dosing recommendations based on existing adult raxibacumab exposure data in combination with PK data in adults and pediatric patients from other monoclonal antibodies. Regardless of the chosen approach, the objective is to derive the dose and administration regimens that are predicted to provide the pediatric population with adequate drug exposure.[23]

The Best Pharmaceuticals for Children Act (Public Law 107-109) may apply to drugs approved for prophylaxis of inhalational anthrax.

2. Postapproval Trials

If a drug is approved under the animal rule regulations, postmarketing studies (e.g., field studies) are required to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (in the case of a drug for prophylaxis of inhalational anthrax, if the drug is used in the event of an accidental or intentional exposure to aerosolized *B. anthracis*).[24] A plan for a postmarketing study is required as part of a new drug application or biologics license application under the animal rule.[25]

3. Labeling

The indication granted will be *prophylaxis of inhalational anthrax*. In addition to providing the appropriate dosing regimen in the DOSAGE AND ADMINISTRATION section, the prescribing information should also provide a summary of the efficacy data that served as the basis of approval (section 14, CLINICAL STUDIES). Patient labeling (e.g., Medication Guide, patient information) should also be drafted and discussed with FDA, including, but not necessarily limited to, the explanation that, for ethical and feasibility reasons, the drug's approval is based on efficacy studies conducted in animals alone (21 CFR 314.610(b)(3) for drugs and 21 CFR 601.91(b)(3) for biological products). The prescribing information should list the organism *Bacillus anthracis* in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section.

[23] See, for example, discussions at the Anti-Infective Drugs Advisory Committee meeting of November 2, 2012, found at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm; and the biologics license application review documents of raxibacumab found on the Drugs@FDA Web page (enter "raxibacumab" in the search bar to locate review documents at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm).

[24] 21 CFR 314.610(b)(1) for drugs and 21 CFR 601.91(b)(1) for biologics

[25] Ibid.

REFERENCES

Brachman PS, 1980, Inhalational Anthrax, Ann NY Acad Sci, 353:83-93.

Bregman CL, Alder RR, Morton DG, et al., 2003, Recommended Tissue List for Histopathologic Examination in Repeat-dose Toxicity and Carcinogenicity Studies: A Proposal of the Society of Toxicologic Pathology (STP), Toxicol Pathol, 31:252-253.

CDC, 1999, Biosafety in Microbiological and Biomedical Laboratories (BMBL) 4th Edition.

CDC, 2006, Inhalation Anthrax Associated with Dried Animal Hides — Pennsylvania and New York City, 2006, Morbidity and Mortality Weekly Report, 55(10):280-282.

Doolan DL, Freilich DA, Brice GT, et al., 2007, The U.S. Capital Bioterrorism Anthrax Exposures: Clinical Epidemiological and Immunological Characteristics, J Infect Dis, 195(2):174-184.

Friedlander AM, Welkos SL, Pitt MLM, et al., 1993, Post-Exposure Prophylaxis Against Experimental Inhalation Anthrax, J Infect Dis., 167:1239-1243.

Henderson DW, Peacock S, and Belton FC, 1956, Observations on the Prophylaxis of Experimental Pulmonary Anthrax in the Monkey, J Hyg, 54:28-36.

Inglesby TV, Henderson DA, Bartlett JG, et al., 1999, Anthrax as a Biological Weapon, JAMA, 281(18):1735-1745.

Inglesby TV, O'Toole T, Henderson DA, et al., 2002, Anthrax as a Biological Weapon; Updated Recommendations for Management, JAMA, 288:2236-2252.

Jacobs A, El Hage J, Hastings K, et al., 2003, Recommended Tissue List for Histopathologic Examination: Letters to the Editor, Toxicol Pathol, 31:571.

Jernigan DB, Stephens DS, Ashford DA, et al., 2002, Investigation of Bioterrorism-related Anthrax, United States, 2001: Epidemiologic Findings, Emerg Infect Dis, 8(10):1019-1028.

Louie A, Vanscoy B, Liu W, Kulawy R, Drusano GL, 2013, Hollow-fiber Pharmacodynamics Studies and Mathematical Modeling to Predict the Efficacy of Amoxicillin for Anthrax Postexposure Prophylaxis in Pregnant Women and Children, Antimicrob Agents Chemother, 57(12):5946-60.

Martin SW, Tierney BC, Aranas A, et.al., 2005, An Overview of Adverse Events Reported by Participants in CDC's Anthrax Vaccine and Antimicrobial Availability Program, Pharmacoepidemiol Drug Saf, 14(6):393-401.

Meselson M, Guillemin J, Hugh-Jones M, et al., 1994, The Sverdlovsk Anthrax Outbreak of 1979, Science 266:1202-1208.

Plotkin SA, Brachman PS, Utell M, Bumford FH, and Atchison MM, 2002, An Epidemic of Inhalation Anthrax, The First in the Twentieth Century: I. Clinical Features, Am J Med, 112;4-12 (originally published as Am J Med 1960;29:992-1001).

Suffin SC, Carnes WH, Kaufmann AF, et al., 1978, Inhalational Anthrax in a Home Craftsman, Hum Pathol, 9(5):594-597.