Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax

Guidance for Industry

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

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Clinical/Antimicrobial

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Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax Guidance for Industry[1]

This guidance represents 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 office 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 in persons who have or may have inhaled aerosolized *Bacillus anthracis* spores but who have not yet manifested clinical evidence of disease.[2] The indication also applies to persons with anticipated exposure to *B. anthracis* spores (e.g., first responders for anthrax incidents); in such cases, initiation of antibacterial therapy would begin immediately before entering the *B. anthracis*-contaminated environment. For more information regarding the indication, see section II.B., Indication for Prophylaxis of Inhalational Anthrax.

This guidance clarifies that drugs developed for the prophylaxis of inhalational anthrax are to be considered for approval under the animal rule.[3]

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] 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.

[3] 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*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

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; Inglesby, 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 FDA's 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 labelings, are indicated for prophylaxis of inhalational anthrax.[4] Levofloxacin also was approved (in November 2004) for this indication under the accelerated approval regulations. Subsequently, some drugs approved under the animal rule regulations received an indication for prophylaxis of inhalational anthrax but with a more limited indication as follows:

> *for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.*[5]

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 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 *B. anthracis.* However, situations can arise in which persons (e.g., first responders) anticipate an imminent risk of exposure to aerosolized *B.*

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

[5] In 2012 and 2016, respectively, raxibacumab and obiltoxaximab were approved for treatment of inhalational anthrax caused 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. See section III.A., General Considerations.

anthracis spores. Starting therapy immediately before the anticipated or potential exposure can reduce the risk of illness and reduce mortality from inhalational anthrax. Therefore, the indication has been revised. The indication for drugs to reduce the risk of disease in persons who have inhaled, or are likely to imminently inhale, aerosolized *B. anthracis* spores, but who do not yet have the established disease, is now referred to as *prophylaxis of inhalational anthrax.*

III. DEVELOPMENT PROGRAM

A. General Considerations

The antibacterial drugs recently 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 being approved for prophylaxis of inhalational anthrax. Therefore, the level of experience with these drugs was quite extensive, and the safety profiles were well-characterized beforehand. Because a large number of people are expected to possibly receive these drugs as prophylaxis, FDA recommends that antibacterial drugs being developed for this indication have sufficient safety experience to assess the risk and benefit among people who are determined to be at risk for inhalational exposure to *B. anthracis* spores. Sufficient human safety experience is unlikely to 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 is likely to be reserved almost exclusively for antibacterial drugs that have established uses and safety data in other infectious diseases.[6]

Safety and efficacy information derived from the development and use of a drug for other indications may provide additional information for developing a drug for the prophylaxis of inhalational anthrax indication. If there is substantially limited human safety and efficacy information available for evaluation of an investigational drug, sponsors should provide a proposed justification for the anticipated benefit that will offset the risk of the investigational drug for prophylaxis of inhalational anthrax.

An anthrax vaccine may be administered to persons receiving a drug for prophylaxis of inhalational anthrax. Sponsors should discuss with FDA the data that would be collected to assess whether there are drug-vaccine interactions..

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

[6] In addition, 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 indication (e.g., reserved for use when an effective treatment regimen cannot be otherwise provided) for prophylaxis of inhalational anthrax may be considered (e.g., raxibacumab).

inhalational anthrax should be developed for approval consideration under the animal rule.[7] In general, FDA relies on evidence from animal studies to provide substantial evidence of effectiveness to support approval only when the four criteria listed in the animal rule regulations, as follows, are met:[8]

(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 is shown to be safe and effective in the treatment of other relevant infectious diseases (e.g., certain types of pneumonia).

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 biological products). 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. The drug development plan should address assembling a safety database adequate to support the proposed dose and duration for prophylaxis of inhalational anthrax. This is important because shorter-duration or lower-dose uses of previously approved or studied antibacterial drugs may demonstrate safety concerns relevant for both short- and long-term therapy, but those uses cannot rule out additional safety concerns with longer-duration or higher-dose uses of the drug. Sponsors should discuss with FDA the appropriate size and nature of the preapproval safety database.

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[7] 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.*

[8] See 21 CFR 314.610 and 601.91. For this guidance, the term *substance* refers to *B. anthracis,* and the term *product* refers to an investigational drug being evaluated for prophylaxis of inhalational anthrax.

3. Nonclinical Safety Considerations

Guidances for industry are available to provide information for sponsors on general nonclinical safety considerations for drug development.[9] To support the indication for prophylaxis of inhalational anthrax, animal toxicity studies in two or more species (e.g., rat, mouse, dog, or 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 between systemic drug exposures achieved in healthy human subjects and 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.[10] 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 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 (e.g., geriatrics, pregnant women, obese/morbidly obese patients, 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

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[9] See the Pharmacology/Toxicology guidance web page at https://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* and the ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

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

in the MICs, data on a larger number of isolates should be submitted (up to 100 isolates). A variety of isolates should be selected to represent geographic diversity, human and animal isolates, and naturally occurring antibacterial resistance. In addition, susceptibility testing using several well-characterized strains (including Vollum, Ames, and Sterne) and genetically diverse strains from an established repository should be performed. Sponsors should discuss with the FDA if they believe that the breadth of genetic variation can be captured using a different or smaller number of strains/isolates or if there are difficulties obtaining an adequate number of isolates for testing. Reproducibility of the results should be demonstrated at different laboratories. For example, testing should be performed in at least two laboratories with three or more of the same isolates tested in each laboratory.[11]

Initial susceptibility testing of genetically diverse repository isolates might provide some initial insight into potential mechanisms of resistance to the investigational drug if not already known. Sponsors should discuss with FDA their proposed approaches for further assessment of the potential for resistance emergence and should obtain appropriate review (including through their institutions and funding agencies) of any elements that might raise dual-use issues of concern.[12] This discussion should include plans for susceptibility assessment of any bacteria cultured from animals that develop anthrax disease during prophylaxis or in the follow-up period. Post-treatment MIC values should be compared to the baseline MIC values. This information may be important for understanding the mechanism of prophylaxis failures and its relevance to dosing considerations. If antibacterial resistance develops spontaneously following exposure to the investigational drug, the mechanism of resistance should be characterized, when possible.

Drugs that have an FDA-approved indication for prophylaxis of inhalational anthrax (such as ciprofloxacin, levofloxacin, doxycycline, 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. For more information regarding biosafety procedures, sponsors should contact the

[11] For more information about microbiology considerations, see the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs —– Development, Analysis, and Presentation.*

[12] See the Dual Use of Concern web page on the Department of Health and Human Services Public Health Emergency website available at https://www.phe.gov/s3/dualuse/Pages/default.aspx.

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

Centers for Disease Control and Prevention (CDC) (https://www.CDC.gov) and the National Institutes of Health (https://www.nih.gov/research-training) (CDC 2009).

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

1. Animal Models

Before initiating the animal studies, 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 to obtain concurrence on the details of the models and the design of the studies.[14] Nonhuman primate study data together with extensive human experience in other infections contributed to the approvals of ciprofloxacin and levofloxacin discussed above, while combinations of nonhuman primate and rabbit data contributed to more recent development plans for anthrax treatment and prophylaxis under the animal rule. Sponsors should discuss with FDA the appropriateness of specific animal models and combinations of models for proposed drug development programs, including the time of initiation of the investigational therapy for the prophylaxis of inhalational anthrax.

2. Study Conduct

FDA considers the good laboratory practice (GLP) for nonclinical laboratory studies 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] FDA recommends following the principles of replacement, reduction, and refinement of the use of animals in biomedical research (Russell and Burch 1959).

3. Bacterial Challenge

Well-characterized strains of *B. anthracis* with known virulence in humans and the chosen animal species should be used for challenge. Mortality is expected to be greater than or equal to 90 percent in the infected, untreated control group.

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

[15] See 21 CFR part 58 and the guidance for industry *Product Development Under the Animal Rule*.

[16] The policy document is accessible at https://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf. See also Appendix A in the guidance for industry *Product Development Under the Animal Rule*.

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 well characterized. 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 any differences in absorption, 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 proposed dose would safely and reliably have exposures to the drug greater than therapeutic 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. The human dose selected for this indication should also be adequately supported by human safety data. 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, the PK/pharmacodynamic (PD) parameters that correlate with activity and efficacy of the drug

[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*.

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

[19] Discussions of the duration of dosing of antibacterial drugs after inhalational exposure to anthrax spores have focused on the objective of preventing disease arising from germination of inhaled spores until sufficient spore clearance occurs to substantially reduce the risk of disease developing after drug cessation. For example, during the Anti-Infective Drugs Advisory Committee meeting on July 28, 2000 (transcript available at https://wayback.archive-it.org/7993/20170403222328/https://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective), discussions suggested that post-exposure prophylaxis durations up to 20 days might delay but not prevent disease and death in nonhuman primates, while 30 days might provide statistically significant but not complete protection. A total of 60 days was agreed upon as a reasonable duration to recommend for humans based on the combination of animal survival and spore clearance data. Drugs with major differences in mechanism of action, dosing feasibility, or risk-benefit assessment might raise additional considerations that sponsors should discuss with FDA on a case-by-case basis (Bell, Kozarsky, et al. 2002; Inglesby, Henderson, et al. 1999).

should be identified via in vitro PK/PD approaches and in animal models. This information can guide the selection of doses to be tested in adequate and well-controlled animal studies to evaluate efficacy. In vitro studies can be used to determine potentially relevant PK/PD relationships between PK parameters, for example the maximal concentration (C_{max}) and the area under the curve (AUC) and susceptibility based on the MIC. Nonclinical studies then can be used to identify potentially relevant PK/PD parameters (e.g., C_{max}/MIC ratio, AUC/MIC ratio, the time the concentration remains above the MIC) that could correlate with an effective response. Similar PK/PD parameters should be identified for humans to support human dose selection.

5. Choice of Comparators

A control group should be included. This can serve as an untreated control, or placebo/vehicle 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. Sponsors may wish to consider and discuss with FDA when to include an adequately powered third active control arm.

6. Efficacy Endpoints

The primary endpoint should be survival to the end of the study. When survival is used as an endpoint in animal studies, sponsors should prospectively define and include in the protocol euthanasia criteria to reduce or eliminate unnecessary terminal distress and to support study goals. Furthermore, sponsors should consider incorporating telemetry with real-time monitoring into euthanasia criteria, if feasible. Sponsors should increase observation frequency around the time of major morbidity or death to prevent unrelieved pain or distress and to minimize a potential compromise or loss of data. 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., up to and including 30 days following the end of treatment). A complete histopathologic evaluation should be performed on animals that die during the study, including animals that met prespecified criteria for euthanasia (Bregman, Alder, et al. 2003; Jacobs, El Hage, et al. 2003). Sponsors should provide a justification for their euthanasia criteria and discuss them with FDA before initiating the protocol.[20]

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

7. Study Pharmacokinetic Assessments

PK data should be collected for the antibacterial drugs tested in the adequate and well-controlled animal studies. Determining the systemic exposure that was achieved in surviving animals exposed to *B. anthracis* spores 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 (number of animals) and PK sampling strategies should be adequate to characterize relevant exposure parameters. For nonantibacterial drugs, sponsors should discuss with FDA whether other important assessments are also needed to allow for the selection of an effective dose in humans.

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. Sponsors should ensure that euthanasia criteria and any appropriate and needed supportive care are justified, adequately described in the protocol, and applied consistently across treatment groups through measures such as investigator blinding.[21] These considerations, power calculations, and proposed statistical analyses should be discussed with FDA before studies are initiated.

C. Other Considerations

1. Pediatrics

Sponsors are encouraged to begin discussions about their pediatric clinical development plans 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.[22]

Obtaining data to support pediatric dosing is challenging. A study giving healthy children an investigational drug for the purpose of obtaining PK data would not likely meet the criteria for institutional review board approval of pediatric studies under 21 CFR part 50, subpart D, for several reasons including that the administration of an investigational drug would present more than minimal risk, that healthy, unexposed children would have no prospect of direct benefit from the administration of the investigational drug, and that naturally occurring exposure to anthrax spores would be unlikely for children in the United States.

[21] For definitions of supportive care, see the guidance for industry *Product Development Under the Animal Rule*.

[22] 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 Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Accordingly, other approaches to pediatric dose selection should be explored, such as applying PK data from the use 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]

2. Postapproval Studies

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 list the organism *Bacillus anthracis* under the Antimicrobial Activity heading in the *Microbiology* subsection and provide a summary of the efficacy data that served as the basis of approval in the CLINICAL STUDIES section. 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).

[23] See, for example, documents for the Anti-Infective Drugs Advisory Committee meeting of November 2, 2012 (available at https://wayback.archive-it.org/7993/20170403223651/https://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 (available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125349).

[24] 21 CFR 314.610(b)(1) for drugs and 21 CFR 601.91(b)(1) for biological products.

[25] Ibid.

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