Guidance for Industry

Inhalational Anthrax (Post-Exposure) — Developing Antimicrobial Drugs

DRAFT GUIDANCE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)

March 2002
Clinical Antimicrobial

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> This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

In response to the recent bioterrorism event involving exposure to *Bacillus anthracis,* FDA has been approached by a number of firms seeking guidance on how to develop additional therapies and ultimately to receive FDA-approved labeling for anthrax. This guidance focuses on the development of antimicrobial drugs for administration to persons who have inhaled aerosolized *Bacillus anthracis,* but who do not yet have the established disease. The treatment goal would be to prevent the development of disease in such persons following exposure to *B. anthracis* spores.

This guidance is ***not*** intended to provide recommendations on how to treat the established disease, whether inhalational anthrax, gastrointestinal anthrax, or cutaneous anthrax. This guidance also does ***not*** address the use of other means of managing patient exposure, public health agency roles, drug stockpiles, or deployment of agents following an exposure to *B. anthracis.*

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment or prevention of infections. The information presented here should help applicants plan, design, conduct, and appropriately monitor the studies, including clinical studies, to collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Before a drug can receive a labeled indication for inhalational anthrax (post-exposure), the sponsor should have extensive postmarketing experience with their drug, including, ideally, prolonged drug dosing safety information. For an intended use where large populations may be indicated to receive prolonged antimicrobial drug dosing, extensive post-marketing safety experience is needed to formulate a risk-benefit analysis between the potential benefit of effective drug therapy and the risks of inhalational anthrax spore exposure and prolonged drug dosing.

[1] This guidance has been prepared by the Office of Drug Evaluation IV and the Office of Program Initiatives, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogen and Immunologic Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration.

Applications submitted to the Agency on studies conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective for use in persons exposed to aerosolized *B. anthracis* who do not yet have established disease. For general information on antimicrobial drug development, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials* (*General Considerations).*

II. BACKGROUND

In the fall of 2001, *B. anthracis,* the bacterium that causes anthrax, was used as a bioterrorism agent and sent through the U.S. mail, resulting in cases of cutaneous and inhalational anthrax in New York, New Jersey, the District of Columbia, Maryland, Virginia, Florida, and Connecticut. Until this time, anthrax was exceedingly rare in the United States. Approximately 220 cases of cutaneous anthrax (CDC 2000) and 18 cases of inhalational anthrax (Brachman 1980) were reported in the United States in the 20th century. Before 2001, the last reported case of inhalational anthrax occurred in 1976 (Suffin et al., 1978). More recent recognized outbreaks were reported in other parts of the world, including an outbreak in 1979, when in Sverdlovsk (currently Ekaterinburg), Russia, 66 people died of inhalational anthrax after *B. anthracis* spores were accidentally released from a Soviet military laboratory (Meselson et al., 1979). Data available from 41 autopsies have contributed to our present knowledge concerning disease pathogenesis.

A window of opportunity for preventive therapy exists between the time of inhalation of aerosolized spores of *B. anthracis* and development of signs and symptoms of disease. Evidence from animal models and recent human experience has demonstrated use of certain antimicrobial agents ***after*** the inhalational exposure to *B. anthracis* spores, but ***before*** the development of disease symptoms can be effective in preventing the disease and reducing mortality. As a result, the Agency is encouraging the development of antimicrobial agents to be used in the event of inhalational exposure to *B. anthracis.* This guidance provides recommendations on how to develop such agents and gives examples of agents that have met approval criteria.

A. Disease Description

Anthrax is a bacterial infection caused by the gram-positive bacillus, *B. anthracis*. A disease of antiquity, anthrax was responsible for major epidemics and mortality. The incidence of the disease declined rapidly after the etiologic role of *B. anthracis* was recognized and scientists such as Robert Koch and Louis Pasteur worked to introduce control measures and animal vaccination.

Three types of infections are recognized in humans: cutaneous, gastrointestinal, and inhalational disease. Cutaneous anthrax occurs when spores gain access through a cut or abrasion in the skin. The organisms germinate and produce toxins that result in a local reaction with swelling and eschar formation. The disease may progress to bacteremia, and mortality is reported in up to 20 percent of untreated cutaneous cases. Cutaneous anthrax can be recognized clinically, and morbidity and mortality are low with appropriate antimicrobial therapy. Gastrointestinal disease is usually associated with the ingestion of anthrax-contaminated meat. Gastrointestinal disease can be prevented through the effective inspection of livestock and meat products entering the marketplace. Inhalational anthrax follows aerosolized exposure to the spores of *B. anthracis* with subsequent germination of the spores, toxin production, and invasion of the tissues and blood stream by the organism. After a usual incubation period of 2 to 6 days, exposed individuals develop symptomatic disease with very high mortality.

Inhalational anthrax was encountered as recently as the 19th century in industrial settings when large numbers of spores were aerosolized in certain factories (e.g., woolsorter's disease or ragpicker's disease) (Plotkin et al., 1960). Mortality for established disease, even after treatment, was 80 to 100 percent in the 20th century. These rates may change as established disease is treated in the 21st century.

B. Histology

Extensive edema, necrosis, and hemorrhage into affected tissues, including the mediastinal and hilar lymph nodes, the gastrointestinal tract, and the meninges characterize histopathologic changes in human anthrax. Notably, given the respiratory route of entry of the spores and deposition within the alveoli, there are only rare reports of pulmonary bacterial pneumonia, such as consolidation, and inflammation within the pulmonary parenchyma. However, pleural effusions are common.

C. Microbiology

1. In vitro susceptibility testing

Currently, there are no standardized methods (e.g., disk diffusion, broth dilution, or agar dilution) for the susceptibility testing of *B. anthracis*. During the bioterrorism events of 2001, the Centers for Disease Control and Prevention (CDC) evaluated the minimal inhibitory concentrations (MICs) of several antimicrobials against the causative strains of *B. anthracis* using the current National Committee for Clinical Laboratory Standards (NCCLS) broth dilution method (NCCLS 2000). The suitability of the current NCCLS broth dilution testing method for susceptibility testing of drugs against *B. anthracis* is under evaluation by the FDA, CDC, and NCCLS. Interpretive criteria by which an isolate of *B. anthracis* may be defined as susceptible or resistant to a particular antimicrobial have not been determined. The Agency recommends that applicants contact the NCCLS for the latest information on susceptibility testing of *B. anthracis*.[2]

[2] NCCLS can be contacted at www.NCCLS.org.

2. Mechanisms of resistance

The isolates of *B. anthracis* used during the Fall 2001 bioterrorism episodes have not demonstrated high minimum inhibitory concentrations (MICs) to any of the antimicrobials tested. However, the existing literature on the susceptibility of *B. anthracis* suggests that some strains may be penicillin resistant (Lightfoot et al., 1990). In addition, the potential for multi-drug resistant strains of *B. anthracis* exists (Inglesley et al., 1999). Russian scientists claim to have produced a vaccine strain of *B. anthracis* that is resistant to penicillin and doxycycline (Stepanov et al., 1996). The potential for drug resistance supports the study of several classes of antimicrobials to prevent the development of inhalational anthrax.

The clinical relevance and importance of resistance mechanisms in strains of *B. anthracis* remains unclear. For example, certain strains of *B. anthracis* may produce beta-lactamases but administration of penicillin in animal models appears to prevent disease with these same strains. It is clear that microbiologic testing of isolates should be performed before and after drug exposure as part of the evaluation of products for prevention of inhalational anthrax. However, although the MICs for the extended-spectrum cephalopsporins are not high, the efficacy of these drugs for the treatment of *B. anthracis* infection is unclear (Inglesby, et al., 1999).

III. THE MONKEY MODEL — APPLICABILITY TO THE HUMAN DISEASE

Because clinical studies of inhalational anthrax cannot be performed in humans (one cannot ethically intentionally expose patients to *B. anthracis* spores and randomize to active or placebo arms), the Agency has to rely on other evidence of efficacy for this indication. After much discussion and consideration, including input from the Anti-Infective Advisory Committee, the Agency believes that the use of the rhesus (macaque) monkey disease and treatment model for inhalational anthrax (post-exposure) provides convincing evidence of efficacy for regulatory purposes. The parallels, summarized here, between the rhesus monkey disease and treatment model and the human circumstance were noted by the Committee:

Exposure: The spores gained access to the respiratory tract via an aerosol as would be expected in human inhalational anthrax.

Antimicrobial use: The antimicrobials currently approved or found effective (ciprofloxacin, doxycycline, penicillin G procaine) were administered by the same route (oral or IM) and in the same q12h regimen in monkeys as was ultimately the recommended route and frequency in humans.

Antimicrobial Pharmacokinetics: For the drugs that have been granted regulatory approval for this indication, the peak and trough plasma concentrations measured in the rhesus model were similar to peak and trough plasma concentrations measured in humans.

Time course: The time course of the disease among untreated animals — short incubation, rapid down hill course, mortality — is similar to that among people who died of inhalational anthrax in Sverdlovsk in 1979 and in the United States in the fall of 2001.

Histopathology: The autopsy findings of inhalational anthrax reported from the Sverdlovsk experience and reviewed by Dr. Walker at the July 28, 2000, Anti-Infective Advisory Committee meeting are strikingly similar to the necropsy findings reported by Dr. Friedlander in the monkeys that died of inhalational anthrax. Other published literature support these comparative histopathological findings. (Fritz et al, 1995; Gleiser et al, 1967.)

Antimicrobial Activity in Monkey Model: For the drugs currently approved for this indication, the efficacy of the antimicrobial product (ciprofloxacin, doxycycline, penicillin G procaine) compared to saline placebo showed a statistically significant difference in favor of antimicrobial administration, whether one looked at the intent to treat analysis (all animals studied) or the per protocol analysis (anthrax deaths).

A study indicating that another species of monkey was interchangeable with rhesus monkeys would be considered by the Agency. The data from a monkey study could be submitted as long as the model is used in conjunction with data from other sources, including:

- in vitro sensitivity data on *B. anthracis*
- pharmacokinetic data in animals and in humans
- information on drug efficacy in treating other infections
- evidence of safety up to and exceeding 60 days

This information, as well as convincing evidence from the rhesus monkey model, should be submitted in the application for approval.

IV. DRUGS EFFECTIVE IN MANAGING PATIENTS

On August 30, 2000, the Agency approved ciprofloxacin hydrochloride tablets, ciprofloxacin intravenous (IV) solution, ciprofloxacin IV in 5 percent dextrose, ciprofloxacin IV in 0.9 percent saline, and ciprofloxacin oral suspension for use in the management of patients who have been exposed to aerosolized spores of *B. anthracis* as a 60-day regimen. The new drug applications (NDAs) submitted by the sponsor for these products included in vitro activity information, pharmacokinetic data in humans and monkeys, long-term safety data on ciprofloxacin, and the results of an efficacy study in nonhuman primates. This information was brought before the Anti-Infective Advisory Committee with a recommendation for approval of the indication and a dosing duration of 60 days.[3]

On November 2, 2001, in a public health response to the use of anthrax spores as a bioterrorism agent, the Agency published a notice in the *Federal Register* (66 FR 55679) that clarified the

[3] See transcript of meeting at http://www.fda.gov/cder/drug/infopage/cipro/default.htm.

dosing recommendations for doxycycline products and penicillin G procaine in the management of patients with inhalational anthrax who had been exposed to the spores of *B. anthracis*, but who did not manifest clinical disease.[4] Drug products containing doxycycline, doxycycline calcium, doxycycline hyclate, and penicillin G procaine had already been approved with indications for anthrax. The *Federal Register* notice stated that the Agency "determined that the language in the labeling of drug products containing doxycycline, doxycycline calcium, doxycycline hyclate, and penicillin G procaine is intended to, and does, cover all forms of anthrax, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *B. anthracis.*" The *Federal Register* notice further requested that applicants for these products submit labeling supplements to update their package inserts with this information.

It is relevant to the above information on ciprofloxacin, doxycycline, and penicillin G procaine that the rhesus monkey study supporting the approval of ciprofloxacin also included separate doxycycline and penicillin G procaine treatment arms. Each of these arms showed a survival advantage over placebo (Friedlander et al., 1993). No other antimicrobial drugs were tested in this study.[5]

The *Federal Register* notice also explained that other drug products are currently approved with indications for anthrax or infections caused by *B. anthracis* (i.e., minocycline, tetracycline, oxytetracycline, demeclocycline, and penicillin G potassium), that data on these other drugs were undergoing review, and that additional data might be needed to make an explicit labeling recommendation for their use in inhalational anthrax (post-exposure). This notice served to guide the regulatory decisions regarding ciprofloxacin, doxycycline, and penicillin G procaine.

V. INHALATIONAL ANTHRAX (POST-EXPOSURE)

The safety and effectiveness of an antimicrobial to either prevent or treat disease following aerosolized exposure to *B. anthracis* cannot be tested in humans because the naturally occurring disease is rare, and it is unethical to expose humans to the bacteria intentionally. As a result, an application requesting approval of a drug for the indication INHALATIONAL ANTHRAX (POST-EXPOSURE) should contain the elements discussed in detail in this section. Studies planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the management of this condition.

This guidance serves as our best advice under the current scenario where approved therapies are available and the country is not in a state of massive-scale exposure to *B. anthracis*. In the event of a large-scale exposure or absence of other approved therapies (e.g., because supplies are exhausted or otherwise unavailable), the Agency would provide emergency guidance on an alternative approach.

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[4] See information at http://www.fda.gov/cder/drug/infopage/penG_doxy/default.htm or www.gpo.gov.

[5] See July 28, 2000, Advisory Committee transcript http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective.

Applications that can meet some of the elements listed below can request fast track designation while completing the development of data on the other elements.[6]

A. The Indication: Regulatory Synonyms

The Agency has determined that the indication should be designated INHALATIONAL ANTHRAX (POST-EXPOSURE) with further clarification that administration of an antimicrobial is intended "to reduce the incidence or progression of disease following exposure to aerosolized *B. anthracis*."

Specifically, this means that drug administration should start ***after*** a known or suspected exposure to the aerosolized spores of *B. anthracis*, but ***before*** clinical symptoms of the disease develop. Some refer to this intended indication *as post-exposure prophylaxis* even though the intended administration of drug is after the exposure to *B. anthracis*.

The purpose of specifying this indication is to distinguish it from (1) the treatment of symptomatic, established inhalational anthrax infection, which is accompanied by a substantial morbidity and (2) prophylaxis of the disease, namely, administering the drug before exposure to *B. anthracis.*

B. Chemistry

There are no expected chemistry issues because it is anticipated that the drug product already will have been approved in the United States.

C. Preclinical Toxicology Data

It is anticipated that the drug product under development already will have been approved for marketing and that data are available in the approved NDA on animal toxicity in at least two species (e.g., rat, mouse, dog, monkey) for durations up to 6 months. If clinical data and experience demonstrate that a 60-day course of therapy would be reasonably safe to administer to humans, long-term animal toxicology data would not be necessary. (The drugs currently approved have been on the market from 10 to 50 years and already exceed 100 million treatment courses in the United States with additional experience worldwide.) Carcinogenicity studies may provide useful information, but are not necessary for the same reason.

D. In Vitro Microbiology Data

When ciprofloxacin was approved and the findings of efficacy published for doxycycline and penicillin G procaine, the available information on in vitro sensitivity of *B. anthracis* to these antimicrobials was extensive. The Agency had information on more than 90 isolates. When submitting a supplemental application for this indication, it would be

[6] See guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review* (September 1998).

reasonable to submit a smaller number of isolates, particularly if there is evidence that all isolates have uniformly low MICs to the drug of interest.

Note: The term *low MICs* is used because the FDA and NCCLS have not established susceptibility breakpoints for this organism. Therefore, it would be inappropriate to state that the isolates are uniformly susceptible. The goal of the in vitro testing is to demonstrate that low concentrations of a drug (below those that could be achieved in dosing in humans) reliably inhibit growth of *B. anthracis*. Depending on the consistency and uniformity of MICs determined when testing a particular drug, it is possible that 30 to 50 isolates would be adequate. With multiple-fold variability in the MIC results, data on a larger number of isolates should be submitted.

In summary, we recommend the following:

- Several strains (including Vollum, Ames, Sterne, and others) and multiple isolates (from 30 to 90, as discussed above) should be tested.
- Testing should be done in at least two to three laboratories, and at least some of the same isolates should be tested by these laboratories to demonstrate reproducibility of MIC results.
- During testing, ciprofloxacin, doxycycline and/or penicillin G should be used as control drugs.
- All susceptibility testing should include a wide enough range of concentrations so that all MICs have an exact quantitative value instead of < *some value* or > *some value*.
- The details of the testing should be documented (e.g., a protocol should be provided).
- If antimicrobial resistance is detected, the mechanism should be characterized.
- Efforts should be made to measure the potential for development of resistance in vitro. This testing should include studies to determine the frequency of spontaneous mutation and the emergence of multistep resistance in the presence of the compound. Another drug such as ciprofloxacin, doxycycline, or penicillin should be included as a comparator. Once such information is available, attempts should be made to correlate the mutation frequency with clinical outcome.
- Studies to measure reciprocal cross-resistance should also be considered using other drugs such as ciprofloxacin, doxycycline, and penicillin G (the three drugs now found to be effective for post-exposure inhalational anthrax).

E. Rhesus Monkey and Other Animal Models of Efficacy

The Agency believes that until a better approach can be identified to approve drugs for use in persons exposed to aerosolized *B. anthracis*, the rhesus monkey model (Friedlander 1993) should be used for testing additional drugs. A study or data indicating that another species of monkey is interchangeable with rhesus monkeys would be considered by the Agency. The value of using this model is the similarity of (1) the disease, (2) the response to therapy, and (3) systemic drug exposure in the primate model when compared to humans. There also is value in replicating the efficacy results shown

in the original study. Study results should be available at the time the supplement is submitted, not as part of a phase 4 commitment.

In summary, the following general recommendations should be followed:

- The drug should be tested in a nonhuman primate model.
- A vehicle control group should be included. This would serve as a negative control to determine the progression of disease in the absence of treatment.
- Consider using penicillin, doxycycline, and/or ciprofloxacin as a positive control. This approach can serve as an active control and provide for replication of results from the initial study conducted by Friedlander et al., (1993).
- At least 10 animals per arm should be studied.
- Treatment should continue for 30 days.
- There should be a 70-day follow-up observation period after treatment is completed, for a total study duration of 100 days.
- Specify dose and dosage regimen. Animal dosages should be determined based on the anticipated human dosage regimen. The animal dose should give systemic exposures comparable to the anticipated human exposure, and the drug regimen (e.g., QD, BID) should be the same as anticipated in humans. In addition, periodic measurement of peak and trough levels should be done in animals during the study to confirm the level of drug exposure.
- The route of drug administration in animals should be applicable to human use.
- Blood samples for pharmacokinetic (PK) analysis should be collected from each drug-treated monkey. At a minimum, blood samples should be collected to determine plasma drug concentrations at the approximate time of maximum concentration (peak or Cmax) and at the end of the dosing interval (trough or Cmin), after first dose administration and for several successive days after steady state has been attained (at least 5 Cmax and 5 Cmin determinations).
- End points should include survival, bacteremia at different time intervals during or after treatment, and microbial burden in infected organs and/or tissues (e.g., blood, spleen, liver) collected at the time of necropsy.
- Bacteria cultured from animals that develop infection either on treatment or in the 60-day followup period should be tested for in vitro sensitivity to determine MICs. The MICs after treatment should be compared to the baseline values.
- Histopathology data on animals that died during the study should be recorded.

Applicants should also consider developing models using small animals (e.g., guinea pigs), which may be more readily available and which could be used for further study of drugs, drug dosing, drug regimens, and drug duration, as well as exploring drug regimens and drug combinations for treatment of established disease. Although not required, the development of such models would benefit public health by advancing the science and knowledge in the area of animal models for the study of disease caused by *B. anthracis*.

In addition, applicants may wish to explore the possibility of studies in other nonhuman primates such as cynomologous or African green monkeys.

F. Clinical Pharmacology

It is important to obtain complete pharmacokinetic data on the drug in human volunteers or patients and pharmacokinetic data in the rhesus monkey in the efficacy study of inhalational anthrax (post-exposure). The purpose of obtaining these data is to demonstrate that the desired systemic exposure achieved in humans after the anticipated dosage regimen can actually be achieved and is effective in the animal model in preventing inhalational anthrax infection and consequent mortality. Alternatively, it is important to demonstrate that the systemic exposure to the antimicrobial achieved in the rhesus monkey and found effective in preventing infection and death is an exposure that is achievable in humans with an approved and/or otherwise safe-to-use dosage.

In summary, we recommend the following:

- The doses to be tested in animals and in humans should be determined. A pharmacokinetic/pharmacodynamic (PK/PD) approach may be helpful in the determination of an appropriate dosage regimen. For example, use of PK/PD parameters such as AUC/MIC and/or Cmax/MIC may be useful for antimicrobial drugs with concentration-dependent mechanisms of bacterial killing, while the time above the MIC (T_{MIC}) may be useful for antimicrobial drugs with time-dependent mechanisms of bacterial killing.
- The route of administration should be designated and should be the same in both monkeys and humans.
- Each of at least 10 monkeys should have both peak and trough plasma concentrations determined at least 5 times during the study.
- Because it is anticipated that the drug to be tested already will be on the market, adequate pharmacokinetic data should already be available in package labeling or in the literature. If such information is not available, the sponsor should provide pharmacokinetic data after single-dose and repeat-dose administration from an adequate number of male and female subjects for the purpose of providing descriptive statistics and to show comparable systemic drug exposure to that in the animal models used to study the drug for inhalational anthrax (post-exposure).
- Pharmacokinetic data for special populations, including pediatric patients, elderly subjects (≥65 years), and subjects with renal and hepatic impairment should be provided.
- Available pharmacokinetic data in pregnant women should be submitted.
- Available data for drug excretion into human breast milk should be submitted.

- Available pharmacokinetic data in the animals chosen for study of the drug for inhalational anthrax (post-exposure) and comparison of the pharmacokinetic and/or systemic exposure between the animals and humans should be submitted.

- Full characterization of the metabolic profile (in vitro and in vivo) in humans and in the animals chosen to study the drug for inhalational anthrax (post-exposure) should be provided.

- Information regarding the potential for pharmacokinetic drug interactions in humans should be submitted.

- Information comparing the plasma protein binding of the drug in the chosen animals and in humans should be submitted.

G. Efficacy in Humans for Other Indications

It is expected that in the event of a large-scale exposure to anthrax, large numbers of people would be administered antimicrobials to prevent symptomatic infection by *B. anthracis*. As a result, the Agency recommends that drugs to be developed for this use already be on the market and already show their effectiveness in the treatment of a range of infectious diseases, which may include, but need not be limited to, respiratory, mediastinal, intra-abdominal, bone, or meningeal infections.

In summary, we recommend the following:

- The drug to be evaluated should already be an approved ***and marketed*** drug.

- The drug should be safe and effective in the treatment of a range of infectious diseases due to a variety of pathogens.

H. Evidence of Long-Term Safety in Humans

Because the anticipated duration of therapy for patients exposed to inhaled anthrax spores is at least 60 days, there should be sufficient data on prolonged use of the drug in large numbers of patients. The drug should have shown few and self-limited, or reversible, adverse events. For example, ciprofloxacin was initially approved in 1987. By the time of approval for inhalational anthrax (post-exposure) in 2000, the drug had been prescribed to at least 100 million patients for the treatment of other infections. Doxycycline and penicillin G procaine both have been on the worldwide market for more than 30 and 50 years, respectively.

The sponsor should provide any data on adverse events that may be unique or more common with longer duration of dosing compared to shorter courses of therapy. In addition to long-term safety data, sponsors should provide marketing information on all applicable formulations, including solid oral dosage forms, pediatric oral dosage forms, and parenteral dosing forms.

Finally, the Agency is interested in reviewing all available data on the safety of the drug in relevant subpopulations, including geriatric patients, adults, the pediatric population, and pregnant women. Information on patients with kidney or renal impairment, as appropriate, also should be submitted.

I. Statistics

In the animal model to support approval, the antimicrobial drug must demonstrate efficacy, that is, it must be shown to be statistically superior to placebo (21 CFR 314.510 and 314.126).

J. Regulatory Issues

Unless it already carries an anthrax indication (e.g., tetracycline class agents, aqueous penicillin G), the drug would be approved under § 314.500, Subpart H, accelerated approval. This approval would be based on the surrogate endpoint of the relationship between serum concentrations in humans and animals, in the context of the animal model of efficacy, as was the case for ciprofloxacin.

K. Labeling

Once the supplement has been approved, labeling should:

- List the organism in the in vitro microbiology subsection

  Note: The Agency does not believe including this particular organism in the in vitro section of the labeling in the absence of data supporting approval of the indication is appropriate.

- List the indication (e.g., inhalational anthrax (post exposure))
- Provide the appropriate dosing regimen
- Provide the regulatory information forming the basis of approval
- Provide a summary of the data that served as the basis of approval

L. Postapproval Commitments and/or Requirements

Because it is anticipated that these drugs would be approved for inhalational anthrax (post-exposure) under Subpart H regulations (§ 314.500), the approval letter would request that confirmatory clinical data be provided in the event of an accidental or intentional exposure to aerosolized *B. anthracis* (§ 314.510). Applicants should include as part of their application a plan or approach to obtaining such confirmatory data in the event such studies become ethical and feasible as a result of such an exposure. Among other information, relevant data would include patient identifying information, a listing of the drugs that were used, and data on compliance, adverse reactions, and outcomes. Sponsors may wish to consult with the division about the contents of their postmarketing study plan before submission to the Agency. In addition, the company would agree to cooperate with relevant U.S.-based public health agencies in the collection and evaluation

of data on the use of the drug product in a large U.S. population exposed to *B. anthracis*, should such an exposure occur.

Under Subpart H regulations, the company also would have to have any advertising or promotional material for this indication cleared by the Agency before use (§ 314.550).

VI. SUMMARY

In summary, we recommend that the applicant provide information on the following:

- In vitro antimicrobial sensitivity data on an adequate number of isolates, reflecting the spectrum of available isolates and taking into consideration the possibility of engineered resistant strains
- Clinical pharmacology data on the proposed dosing regimen of the product
- Safety data, including preclinical and clinical dose and duration data that support the use of this product for long durations up to at least 60 days
- Evidence of extensive use of the product including use in geriatric patients, adults, the pediatric population, pregnant women, and any other special populations
- Efficacy data in humans. Priority will be given to drugs that have been approved for a variety of indications and have a fairly substantial marketing history.
- Efficacy, pharmacokinetic and histopathology data from nonhuman primate models of inhalational anthrax. Efficacy data should be submitted based on a study of the antimicrobial in a nonhuman primate model of inhalational anthrax that replicates the Friedlander study. Other animal models may be used once the Friedlander study has been replicated successfully with studies of other antimicrobials for inhalational anthrax (post-exposure) and those animal models have been validated. Other animal models could include nonhuman primates other than rhesus monkeys and smaller animals. The ultimate goal of such studies is to find a small animal model with more readily available animals to replace the rhesus monkey model so that more specific and detailed testing of dosing, duration, and combinations can be done.

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