Guidance for Industry

Recommendations for Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Possible Exposure to Anthrax

Final Guidance

This guidance is being distributed for immediate implementation.

FDA is issuing this guidance without initially seeking comment because the agency has determined that prior public participation is not feasible or appropriate. Comments and suggestions regarding this document should be submitted anytime to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

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For questions on the content of this guidance contact the Division of Blood Applications, Office of Blood Research and Review at (301) 827- 3524.

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This guidance document represents the agency'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 statute and regulations.

I. INTRODUCTION

This guidance document provides the current recommendations of the Food and Drug Administration (FDA) for assessment of donor suitability and product safety for donors potentially exposed to *Bacillus anthracis*, the agent of anthrax. This guidance applies to Whole Blood, blood components (including recovered plasma) and Source Plasma collections intended for use in transfusion or for further manufacturing into injectable products. FDA developed the recommendations in this guidance in consultation with other Public Health Service Agencies and with the Blood Safety Committee of the Department of Health and Human Services.

At present there are insufficient systematic human data to fully address the possible occurrence of bacteremia in an asymptomatic individual who is infected with anthrax bacilli. However, based on the current available scientific data, highly knowledgeable experts agree that such a possibility is extremely remote. There is no known risk of transmission of anthrax from blood collected from asymptomatic donors who might have been exposed to the anthrax bacterium. Moreover, current regulations provide for the deferral of any donor who is not in good health at the time of donation, and specifically require deferral of a donor with acute respiratory disease or any infectious skin disease presenting a risk of contamination of the blood. [21 CFR 640.3(b) and 21 CFR 640.63(c)] Nevertheless, FDA is issuing guidance on prudent measures that should be taken to reduce any possible risk for transmission of anthrax from blood or blood products.

II. BACKGROUND

Anthrax is caused by the bacterium *Bacillus anthracis*, a spore forming Gram-positive rod. Anthrax spores can tolerate dry conditions and stay intact for long periods of time (years), especially if they are shielded from UV light exposure. When the spores are inoculated, ingested, or inhaled they germinate to the bacterial (vegetative) form that multiply rapidly and invade tissues. There are three types of anthrax infection in humans: cutaneous, gastrointestinal, and inhalational.

Anthrax is reported annually among livestock in the United States. In areas where these animal cases occur, most human cases are the cutaneous form. Such cases occur among workers who have handled infected hoofed animals, or products from these animals. Gastrointestinal anthrax

has been reported following the ingestion of undercooked or raw meat from infected animals. Inhalational anthrax, resulting from inhalation of aerosolized spores, was associated with industrial processing of infected wool, hair or hides in the United States in the past. Prior to October 2001, no case of inhalational anthrax had been reported in the United States since 1978.

Cutaneous anthrax has an incubation period that ranges from 1 to 12 days. The skin lesions of cutaneous anthrax typically are found on the hands, arms or feet. The early infection is localized, appearing first as a papule that progresses over a few days to a 1-2 cm. vesicle that ruptures leaving a black, necrotic ulcer. The cutaneous infections usually can be cured with antibiotics.

Gastrointestinal anthrax is considered to have an incubation period that ranges from 1 to 7 days. Gastrointestinal anthrax includes anthrax of the mouth and throat ("oropharyngeal") and anthrax of the lower gastrointestinal tract ("abdominal"). Involvement of the oropharynx is characterized by lesions at the base of the tongue, sore throat, dysphagia, fever, and regional lymphadenopathy. Lower gastrointestinal tract involvement usually causes nausea, loss of appetite, vomiting and fever, followed by abdominal pain, vomiting blood, and the occurrence of bloody diarrhea.

The most serious form of anthrax occurs when someone inhales spores (inhalational anthrax), leading to a fulminant infection in the chest (necrotizing mediastinitis) and septicemia. This disease is rapidly fatal in almost all cases unless therapy is begun before the disease becomes advanced. The incubation period of inhalational anthrax among humans is unclear, but it is reported to between 1 and 7 days, and possibly sometimes as long as 60 days.

While ciprofloxacin, doxycycline and penicillin are the antibiotics most often recommended by infectious diseases experts and public health authorities, susceptibility testing is critical in guiding antibiotic therapy for anthrax, particularly for treating presumed intentional infections. Clinicians should consult the Centers for Disease Control and Prevention (CDC) or local public health authorities for further guidance.

Standard infection control precautions (handwashing, wearing gloves for handling contaminated materials) are sufficient when treating patients with anthrax. Inhalational anthrax is not contagious from person to person, obviating a need for respiratory precautions. *Bacillus anthracis* is very resistant to common environmental conditions that would destroy non-spore-forming organisms. However, household bleach, diluted 1:10 and applied for 30 minutes will eliminate the spore form as well as the bacterial form of *B. anthracis.* Steam sterilization, autoclaving, or burning may also be employed for destruction of the spores and bacteria.

Limited amounts of a vaccine for anthrax have been produced but are not currently available for general use.

Blood Donor and Blood Product Issues

The FDA has received inquiries about procedures for blood collection in reaction to reports of exposures to *B. anthracis.* To date, these reports have involved small numbers of persons either

with anthrax infection (disease) or well individuals from whom the anthrax bacillus could be cultured or otherwise detected (colonization). In these cases, anthrax apparently was acquired in circumscribed locations after direct contact with contaminated materials. Inquiries have focused on the safety of blood donation by other individuals living or working in the same general area who might also have been exposed. In response, FDA is issuing guidance on prudent measures that should be taken to reduce any possible risk for transmission of anthrax from blood or blood products.

In most cases of cutaneous anthrax, the bacteria are localized at the site of inoculation of the skin where they cause development of a necrotic ulcer. The organisms usually do not enter the bloodstream unless the individual remains untreated. Although clinical experience with gastrointestinal anthrax is extremely limited, bacteremia is known to occur in the fulminant stage of the abdominal form of gastrointestinal anthrax. In inhalational anthrax, the bacteria initially are localized to the mediastinal lymph nodes. After a generally brief incubation period, a fulminant illness develops that is characterized by necrotizing mediastinitis and bacterial sepsis.

The appearance of anthrax bacteria in the blood of an infected person is thought to coincide very closely with the onset of fever and other symptoms of a serious illness in any form of anthrax. Thus, the likelihood of anthrax bacteremia in a person who feels well enough to donate is extremely remote. For this reason, standard screening procedures that exclude sick persons from donating blood are expected to result in deferral of donors who otherwise might transmit the disease due to bacteria in their blood. In addition, the apparently limited number of individuals exposed in these recent episodes makes transfusion transmission of anthrax even less likely to occur.

After consulting with scientific experts at the CDC, the National Institutes for Health (NIH), and the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) about the possible transmission of anthrax by blood transfusion, the FDA is not recommending any changes to standard donor screening and blood collection procedures to identify or otherwise query donors who may have been exposed to anthrax. This policy is based on the assessment that there is not known or suspected to be a significant risk of transmission of anthrax from blood collected from asymptomatic donors who might have been exposed to the anthrax bacterium or its spores, and the fact that standard blood collection procedures that already are in place include deferral of any donor who is not in good health at the time of donation.

If an asymptomatic donor (other than those donors known to have proven bacterial colonization) mentions use of antibiotics to prevent anthrax, medical directors may exercise their own discretion whether to defer donors who are taking antibiotics. If an otherwise healthy and asymptomatic potential donor is taking antibiotics solely because medical or public health authorities recommended this after possible exposure to anthrax, donation is acceptable if all other criteria are met.

Nevertheless, as a prudent measure to address the possible increased risk of anthrax bacteremia in cases of active disease or proven bacterial colonization (as opposed solely to potential exposure), FDA is providing recommendations on criteria for donor deferral, and on criteria for product quarantine and retrieval related to reports of post-donation illnesses.

The FDA is continuing to consult with experts on anthrax at the CDC, NIH, and USAMRIID to ensure the greatest possible safety of the blood supply. In addition, the situation and epidemiology of this and other potential biological threats are rapidly changing. Any new data or experience related to this issue will be evaluated rapidly and further updates will be provided as appropriate.

III. RECOMMENDATIONS ON DONOR DEFERRAL

Consistent with existing regulations and applicable guidance, donors should be in good health and free of acute respiratory illnesses and of infectious skin disease presenting a risk of contamination of the blood. [21 CFR 640.3(b) and 21 CFR 640.63(c)] Standard procedures that already are in place should be adequate to defer potential donors who may have gastrointestinal or inhalational anthrax at the time of donation since such persons are expected to be symptomatic. However, additional considerations are needed to address bacterial colonization in an asymptomatic donor. Also, special consideration is needed to address confirmed or suspected cutaneous anthrax because the skin lesions usually are painless. At this time, FDA is not proposing revisions to standard donor questions. However, a donor may report such lesions, or in the performance of routine donor screening and preparation for phlebotomy, a skin lesion compatible with cutaneous anthrax may be found.

The following recommendations apply to cases of known or suspected anthrax disease or proven bacterial colonization at the time of donation.

A. Proven Anthrax Disease of Any Type or Proven Bacterial Colonization

1. FDA recommends that a potential donor with a current confirmed medical diagnosis of anthrax of any form should be deferred until the person subsequently completes a full course of an appropriate treatment and the condition is considered to be resolved.

2. Although there is no evidence that proven bacterial colonization in well persons indicates an increased risk for transmission of anthrax by transfusion, as a prudent measure FDA recommends that such persons should be deferred from donation until they have completed a full course of prophylaxis with an appropriate antibiotic.

B. Undiagnosed Skin Lesions Suspected to be Anthrax

FDA recommends that a potential donor with a skin lesion suspected to be anthrax should be deferred until either:

a) the lesion is later shown not to be due to anthrax (and is not otherwise considered to be a cause for deferral), or

b) the lesion is confirmed as cutaneous anthrax and the person subsequently completes a full course of an appropriate treatment and the infection is considered to be resolved.

IV. RECOMMENDTIONS ON PRODUCT QUARANTINE AND RETRIEVAL

The FDA is recommending that blood establishments quarantine and retrieve previously collected in-date units of blood and blood components intended for transfusion, as well as unpooled units of Source Plasma and recovered plasma intended for fractionation to make injectable products under the following circumstances:

A. Proven Anthrax Disease of Any Type

FDA recommends that the in-date blood components from prior collections should be quarantined and retrieved promptly if a donor later reports a confirmed medical diagnosis of anthrax (i.e., clinical disease of anthrax and not solely bacterial colonization). Product quarantine and retrieval should date back to the known time of potential donor exposure to *B. anthracis* or 60 days prior to the onset of illness, whichever is the shorter period.

B. Undiagnosed Post-donation Illness in Potentially Exposed Individuals

In cases of undiagnosed post-donation illnesses among donors who were in areas under investigation for anthrax exposures, FDA recommends that medical directors should exercise judgment regarding product quarantine and retrieval. Factors that may be considered include the character and severity of the illness (index of suspicion for anthrax), the likelihood of anthrax exposure for the specific individual, and whether or not the donor subsequent to an anthrax exposure received an appropriate course of antibiotic therapy recommended by public health authorities as effective prophylaxis against anthrax in the setting of likely exposure to the anthrax bacterium. In general, quarantine and retrieval would not be expected in response to undiagnosed illnesses unless there were felt to be strong epidemiologic and/or clinical evidence raising the suspicion of active anthrax disease.

If a decision is made to quarantine and retrieve prior collections, then product quarantine and retrieval should be performed promptly and should date back to the known time of potential donor exposure to anthrax or 60 days prior to the onset of illness, whichever is the shorter period.

V. RECOMMENDATIONS ON NOTIFICATION OF PRIOR TRANSFUSION RECIPIENTS

In the case that subsequent to donation, a donor is reported to have a confirmed medical diagnosis of anthrax (clinical disease of anthrax and not solely bacterial colonization), FDA recommends that medical directors consider the need for prompt record tracing and notification to the treating physicians of prior recipients of blood and blood components collected from that donor. FDA considers relevant units to be those dating back to the known time of potential donor exposure to anthrax, or 60 days from onset of illness, whichever is the shorter period.

Because the chance of anthrax transmission from transfusion is highly unlikely, FDA is not recommending lookback notification of blood and blood component recipients in cases of prior donation by a person who later reports an undiagnosed illness compatible with anthrax.

VI. IMPLEMENTATION

The recommendations in this guidance should be implemented immediately and do not require prior approval from the FDA. Under 21 CFR 601.12 licensed establishments implementing these recommendations should submit by official correspondence a statement in their annual reports indicating the date that the revised standard operating procedures, consistent with these recommendations have been established and implemented.

VII. REFERENCES

1. A.M. Friedlander, Anthrax, In: F.R. Sidell, E.T. Takafuji, D.R. Franz, eds. Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare, Washington, DC: Office of the Surgeon General, Dept. of the Army, 1997, 467-478.

2. T.V. Inglesby, D.A. Henderson, J.G. Bartlett, M.S. Ascher, E. Eitzen, A.M. Friedlander, J. Hauer, J. McDade, M.T. Osterholm, T. O'Toole, G. Parker, T.M. Perl, P.K. Russel, K. Tonat, Anthrax as a Biological Weapon; Medical and Public Health Management, JAMA (1999) 281; 1735-1745.

APPENDIX: SIGNS AND SYMPTOMS OF ANTHRAX INFECTION[1]

Inhalational anthrax: A brief prodrome resembling a viral respiratory illness followed by development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening. This, the most lethal, form of anthrax results from inspiration of 8,000-40,000 spores of *B. anthracis*. The incubation of inhalational anthrax among humans is unclear, but it is reported to range between 1 and 7 days possibly ranging up to 60 days. Host factors, dose of exposure and chemoprophylaxis may play a role. Initial symptoms include sore throat, mild fever, muscle aches and malaise. These may progress to respiratory failure and shock. Meningitis frequently develops. Case-fatality estimates for inhalational anthrax are based on incomplete information regarding exposed populations and infected populations in the few case series and studies that have been published. However, case-fatality is extremely high, even with all possible supportive care including appropriate antibiotics. Records of industrially acquired inhalational anthrax in the United Kingdom before antibiotics were available reveal that 97% of cases were fatal. With antibiotic treatment the fatality rate is estimated to be at least 75%. Estimates of the impact of the delay in post-exposure prophylaxis or treatment on survival are not known. It has been suggested that each day of delay in initiating treatment may significantly increase morbidity and mortality from anthrax infection.

Gastrointestinal anthrax: Severe abdominal distress followed by fever and signs of septicemia. This form of anthrax usually follows the consumption of raw or undercooked contaminated meat and is considered to have an incubation period of 1-7 days. An oropharyngeal and an abdominal form of the disease have been described in this category. Involvement of the pharynx is usually characterized by lesions at the base of the tongue, sore throat, dysphagia, fever, and regional lymphadenopathy. Lower bowel inflammation usually causes nausea, loss of appetite, vomiting and fever, followed by abdominal pain, vomiting blood, and bloody diarrhea. The case-fatality rate is estimated to be 25-60%, and the effect of early antibiotic treatment on that case-fatality rate is not defined.

Cutaneous anthrax: A skin lesion evolving from a papule, through a vesicular stage, to a depressed black eschar. This is the most common naturally occurring type of infection (>95%) and usually occurs after skin contact with contaminated meat, wool, hides, or leather from infected animals. Incubation period ranges from 1-12 days. Skin infection begins as a small papule, progresses to a vesicle in 1-2 days followed by a necrotic ulcer. The lesion is usually painless, but patients also may have fever, malaise, headache and regional lymphadenopathy. The case-fatality rate for cutaneous anthrax is 20% without, and less than 1% with, antibiotic treatment.

[1]See "CDC Guidelines for State Health Departments, Revised October 14, 2001."