Recommendations for Assessment of Blood Donor Eligibility, Donor Deferral and Blood Product Management in Response to an Ebola Disease Outbreak

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at anytime. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2014-D-2175.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2017
Updated June 2026

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Contains Nonbinding Recommendations

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Guidance for Industry

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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are notifying you, blood establishments that collect blood and blood components for transfusion or further manufacture, including Source Plasma, that we have determined Ebola disease to be a transfusion-transmitted infection (TTI) under Title 21 of the Code of Federal Regulations (CFR) 630.3(*l*). We are also providing you with recommendations for assessing blood donor eligibility, donor deferral and blood product management in the event of an Ebola disease outbreak in at least one country. This guidance document was developed in response to the 2014 Ebola virus (species Orthoebolavirus zairense) outbreak in West Africa. However, FDA expects the recommendations to apply to all Orthoebolaviruses that cause Ebola disease in humans (e.g., Bundibugyo virus, Tai Forest virus, Sudan virus) should an Ebola disease outbreak occur.

The recommendations in section III. of this guidance document apply to the routine collection of blood and blood components for transfusion or further manufacture, including Source Plasma. The collection of convalescent plasma from Ebola disease survivors is addressed in section V. of this guidance document.

This guidance updates the final guidance titled, "Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus," dated January 2017. The January 2017 guidance finalized the draft guidance of the same title dated December 2015. We have updated the guidance with minor changes. For example, we revised the terms used to describe Ebola disease and removed links to inactive websites and withdrawn guidance documents. We have also clarified that FDA will communicate when the recommendations in sections III.A.2. and III.B of the guidance should be implemented and specify the countries for which donor residency and travel history should be assessed.

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viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Ebola disease, caused by viruses from the Orthoebolavirus genus of the family *Filoviridae,* can present as severe hemorrhagic fever in humans and non-human primates (NHPs) with historically high morbidity and mortality rates of up to 90% (Refs. 1 and 2). However, in the 2014 outbreak in West Africa, the mortality rate was lower, with 28,652 suspected, probable, and confirmed cases, including 15,261 laboratory-confirmed cases, and 11,325 deaths reported as of April 2016.[1] Ebola virus is a lipid-enveloped zoonotic pathogen that, when studied in the laboratory, requires the highest level of biosafety containment (BSL-4). The Centers for Disease Control and Prevention (CDC) has classified it as a "Category A" bioterrorism agent/disease. Ebola virus is reported to be inactivated by heating at 60 C for 60 minutes, and also following incubation at pH 2.5 (Ref. 3). Solvent-detergent treatment and pathogen inactivation technologies are also known to inactivate lipid-enveloped viruses (Refs. 4 through 8).

In humans, Ebola disease is typically characterized at onset by fever, severe headache, muscle pain and weakness, followed by diarrhea, vomiting, abdominal pain and sometimes diffuse hemorrhage (bleeding or bruising). In previous outbreaks of Ebola disease, symptoms generally appeared within 21 days and most often within 4-10 days following infection (Refs. 9 and 10). Based on mathematical models, symptom onset later than 21 days is estimated as possible in 0.1 to 12% of cases (Refs. 10 and 11). In a retrospective study in which 500 patients diagnosed with Ebola disease in 2014 recalled their likely source of infection, 5% reported symptom onset > 21 days (up to a maximum of 43 days) post-exposure (Ref. 10).

Viremia and virus shedding escalate rapidly after onset of symptoms and infectivity appears to correlate with severity and stage of disease. Although viremia in survivors typically resolves within 21 days of disease onset, infectious virus and viral RNA have been detected in other body components or fluids (e.g., aqueous humor, semen and vaginal fluids) for longer periods. For instance, viable Ebola virus was detected in aqueous humor obtained from the eye 14 weeks after the onset of the initial symptoms of Ebola disease and 9 weeks after the clearance of viremia (Ref. 12). Infectious virus and viral RNA have been detected in semen up to 82 and 272 days post Ebola disease onset, respectively (Refs. 13 through 17). Further, a case of sexual transmission of Ebola virus was reported in which the patient was exposed to Ebola virus through sexual contact with a survivor 179 days after likely disease onset (Refs. 18 and 19). These findings raise the theoretical possibility, which has not been documented in humans or animal models, of an intermittent low-level viremia after recovery from illness. In addition, there have been isolated reports of apparently asymptomatic Ebola virus infection in individuals who had contact with Ebola disease patients (Ref. 18), and of antibody to Ebola virus in rural African populations reportedly unassociated with acute illness (Ref. 19). These reports raise the possibility that there may be an asymptomatic infection or mild disease in some individuals; if

[1] See CDC website: Outbreak History | Ebola | CDC

this condition exists, the infectivity of these individuals is uncertain but likely to be less than that of severely ill persons.

Ebola disease is transmitted from human to human by direct contact with body fluids (such as blood, urine, stool, saliva, semen, vaginal fluids or vomit) of symptomatic infected individuals. Therefore, blood and blood products from symptomatic individuals, if they were to donate, would have the potential of transmitting Ebola disease to recipients. The theoretical possibility of pre-symptomatic viremia has not been extensively investigated. If this condition exists the infectivity is uncertain, but likely to be less than of symptomatic persons. Healthcare providers caring for symptomatic Ebola disease patients, and family and friends in close contact with symptomatic Ebola disease patients, are at the highest risk of becoming infected because they may come in direct contact with infected blood or other body fluids of sick patients. Because of the severity of the disease and the risk of transmission by blood and blood products, we have determined that Ebola disease meets the definition of TTI in 21 CFR 630.3(*l*).[2]

III. RECOMMENDATIONS

Under 21 CFR 630.10(a), a donor must be in good health and free from TTIs. A donor must also have a normal temperature at the time of donation (21 CFR 630.10(f)(1)). Additionally, under 21 CFR 630.10(a) a donor is not eligible if you identify any factor(s) that may cause the donation to adversely affect the safety, purity, or potency of the blood or blood component. Such factors include symptoms of a recent or current illness, as well as travel to, or residence in, an area endemic for a TTI (21 CFR 630.10(e)(2)(i) and (iii)).

Standard procedures that are already in place to ensure that the donor is healthy at the time of donation serve as an effective safeguard against collecting blood or blood components from a donor who seeks to donate after the onset of clinical symptoms of Ebola disease. The following recommendations are intended to reduce the risks of collecting blood and blood components from potentially infected persons during the asymptomatic incubation period before the onset of clinical symptoms, as well as from individuals with a history of Ebola disease.

This guidance contains a recommendation for updating your donor educational materials in section III.A.1. During an Ebola disease outbreak, FDA, in consultation with CDC, will communicate when the recommendations in section III.A.2 and III.B. should be implemented and specify the countries for which donor residency and travel history should be assessed.

A. Donor Educational Material and Donor History Questionnaire

1. Donor Educational Material

We expect very few individuals with a history of Ebola disease to present as blood donors. When there are no countries with an Ebola disease outbreak, self-

[2] We have determined that Ebola disease does not meet the definition of a relevant transfusion-transmitted infection because it may not have sufficient incidence and/or prevalence to affect the potential donor population (see 21 CFR 630.3(h)(2)(ii)(A)).

deferral of donors with a history of Ebola disease should provide sufficient protection. We recommend that you update your donor educational materials to instruct donors with a history of Ebola disease to not donate blood or blood components.

2. Donor History Questionnaire

In the event of an Ebola disease outbreak, and when communicated by FDA, your donor history questionnaire (DHQ), including your full-length and abbreviated DHQ, and accompanying materials, must incorporate elements to assess prospective donors for symptoms of recent or current illness with Ebola disease, and travel to, or residence in, an area endemic for Ebola in accordance with 21 CFR 630.10(e)(2). We recommend that your DHQ assess donors for:

a. A history of Ebola disease.

b. A history of residence in or travel in the past 8 weeks to a country with an Ebola disease outbreak, as specified by FDA

In addition, we also recommend that the updated DHQ includes the following elements to further assess prospective donors for risk of Ebola disease:

a. A history of close contact in the past 8 weeks with a person confirmed to have Ebola disease or a person under investigation (PUI) for Ebola disease in whom diagnosis is pending. For the purposes of this guidance, close contact is defined as contact that could have resulted in direct exposure to body fluids. Individuals falling into this close contact category include healthcare workers and other persons who care for, have lived with, or have otherwise been in contact with a PUI or a person confirmed to have Ebola disease.[3]

    - Additionally, this close contact category includes individuals with a history of sexual contact in the past 8 weeks with a person known to have recovered from Ebola disease prior to that instance of sexual contact, regardless of the time since the person's recovery.

b. A history of notification by a public health authority that they may have been exposed in the past 8 weeks to a person with Ebola disease.

We note that educational material may assist donors in assessing their risk factors for Ebola disease as described above. Relevant information on risk factors can be found on CDC's website at Ebola Disease Basics | Ebola | CDC.

[3] For additional information on epidemiologic risk factors to consider when evaluating a person for exposure to Orthoebolavirus see: Ebola Disease Basics | Ebola | CDC

B. Donor Deferral

You must defer a donor found to be ineligible because of symptoms of a recent or current illness, as well as travel to, or residence in an area endemic for a TTI, including Ebola disease (21 CFR 630.10(e)(2) and (h)). We recommend the following deferral periods for such donors:

1. Indefinite[4] deferral of a donor with a history of Ebola disease.

   Note: This recommendation excludes the collection of convalescent plasma for treatment of Ebola disease as described in section V. of this guidance.

2. Eight week[5] deferral from the date of their departure a donor who has been a resident of or has travelled to a country with an Ebola disease outbreak, as specified by FDA.

In addition, we recommend the following additional deferral periods:

1. Eight week[8] deferral after the last contact a donor who has had close contact with a person confirmed to have Ebola disease or a PUI in whom the diagnosis is pending. Individuals falling into this category include healthcare workers and other persons who care for, or have lived with, or person confirmed to have Ebola disease or a PUI.[5]

   - In addition, we recommend that you defer for 8 weeks[8] after the last sexual contact a donor who has had sexual contact with a person known to have recovered from Ebola disease regardless of the time since the person's recovery.[6]

2. Eight week deferral after exposure[8] a donor who has been notified by a federal, state, or local public health authority that they may have been exposed to a person with Ebola disease.

[4] Until more data regarding the persistence of Ebola disease in survivors becomes available, we recommend you defer such donors indefinitely.

[5] Although symptoms generally appear within 21 days of infection, we recommend an extended deferral period of 8 weeks to prevent blood and blood component collection from an individual who could be infected and have an extended incubation period. In addition, 8 weeks is consistent with the inter-donation interval for Whole Blood donations.

[6] Until additional data regarding the length of time semen could be infectious post Ebola disease becomes available, we recommend that you defer for 8 weeks after the last sexual contact a donor who has had sexual contact with a person known to have recovered from Ebola disease.

C. Product Retrieval, Quarantine, and Notification

1. Blood and Blood Components Collected from Donors at Risk for Ebola Disease Because of Risk Factors Related to Residency, Travel or Close Contact

If you collected blood or blood components intended for transfusion or further manufacture into injectable and non-injectable products from a donor who should have been deferred for risk factors for Ebola disease related to residency, travel, or close contact, according to the recommendations in section III.B. of this document, we recommend that you quarantine and destroy all undistributed in-date blood and blood components from that donor.

a. If you distributed blood or blood components intended for transfusion or for further manufacture into injectable and non-injectable products from a donor who should have been deferred for risk factors for Ebola disease related to residency, travel or close contact according to the recommendations in section III.B. of this document, we recommend that you notify consignees to retrieve, quarantine and destroy the in-date blood and blood components collected from that donor.

b. We do not recommend retrieval or quarantine of plasma pooled for further manufacturing into products that are manufactured under processes that include multiple validated viral inactivation and clearance steps, which have been shown to be robust in the inactivation and clearance of lipid-enveloped viruses.

2. Blood and Blood Components Collected from Donors Later Determined to Have Ebola Disease

We recommend you contact FDA[7] as soon as possible upon learning that you collected blood or blood components from a donor later determined to have Ebola disease. This recommendation applies to the collection of blood components in the 8 weeks prior to disease onset or any time after disease onset. In addition, blood establishments should consider the need to notify state and local public health authorities.

a. If you collected blood or blood components within a recommended deferral period as specified in section III.B. of this document from a donor later determined to have Ebola disease, you should promptly retrieve and quarantine the blood and blood components collected in the 8 weeks prior to disease onset and any time after disease onset.

[7] Contact CBER's Office of Blood Research and Review at cberobrrbpbinquiries@fda.hhs.gov.

- If such blood components were transfused, we recommend that consignees notify the transfusion recipient's physician of record regarding the need for notification and monitoring of the recipient for possible Ebola disease.

Manufacturers should contact the appropriate FDA review division to discuss their conduct of an adequate risk analysis if plasma collected from a donor later determined to have Ebola disease has been pooled for further manufacturing or manufactured into a finished product. Finished products manufactured from such plasma pools should not be released prior to completion of an adequate risk analysis demonstrating that the product will not place patients at risk of Ebola disease. Finished products manufactured from such plasma pools that have already been released should also undergo a risk analysis.

IV. REPORTING A BIOLOGICAL PRODUCT DEVIATION (BPD)

If you have distributed blood or blood components for transfusion or further manufacture collected from a donor at risk for or known to have Ebola disease according to section III.B. of this document, you should report a BPD as soon as possible but you must report at a date not to exceed 45 calendar days from the date you acquire the information reasonably suggesting that a reportable event has occurred (21 CFR 606.171).

If you have distributed finished products manufactured from blood or blood components collected from a donor later determined to have Ebola disease according to section III.B. of this guidance, you should report a BPD as soon as possible but you must report at a date not to exceed 45 calendar days from the date you acquire the information reasonably suggesting that a reportable event has occurred (21 CFR 600.14).

V. CONVALESCENT PLASMA

Serum and plasma therapies have been used to treat many infectious diseases, including Junin Virus, a virus that also causes hemorrhagic fever (Ref. 22). There is similar interest in whether convalescent serum or plasma collected from Ebola disease survivors may be an effective therapy in Ebola virus outbreaks. Neutralizing antibodies are generated during filovirus infection in humans (Ref. 23). Ebola virus-infected individuals develop humoral immune responses (Ref. 24) that include neutralizing antibodies in some survivors. In previous studies conducted using non-human primates, passive transfer of certain neutralizing monoclonal antibodies (Refs. 25 and 26) and convalescent immunoglobulin concentrate prepared from non-human primates that were vaccinated and virus challenged (Ref. 27) have resulted in protection against lethal challenge with Ebola virus. However, whole blood from Ebola virus vaccinated and challenged monkeys did not protect against Ebola virus challenge in non-human primates (Ref. 28).

Treatment of Ebola disease patients with convalescent human sera has been used in uncontrolled studies (Refs. 29 through 31). Based on the available scientific evidence, the World Health Organization (WHO) has developed interim guidance for national health authorities and blood transfusion services, entitled, "Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks," dated September 2014, http://www.who.int/csr/resources/publications/ebola/convalescent-treatment/en/.

As noted above, this investigational treatment has not been proven to be effective and results of one clinical trial in Guinea were negative (Ref. 32). However, the effectiveness of convalescent plasma or immune globulin concentrates made from convalescent plasma remains biologically plausible and further studies may still be considered. Convalescent plasma or serum collected from donors who have recovered from Ebola disease is an investigational product, and controlled studies with an adequate number of patients are needed to assess safety and effectiveness. Blood establishments wishing to collect or distribute convalescent plasma intended for transfusion in the United States must submit an investigational new drug application in accordance with 21 CFR Part 312, and sponsors seeking to develop devices containing convalescent plasma are subject to the investigational device regulations in 21 CFR Part 812 (see 21 CFR 601.21). Such sponsors should contact FDA to discuss the submission.[8]

VI. IMPLEMENTATION

We recommend that you revise your donor education materials consistent with recommendations in section III.A.1 no later than 12 weeks after the guidance issue date. The revisions to the donor history questionnaire and accompanying materials described in section III.A.2 and III.B should be implemented as soon as feasible and no later than 4 weeks from the date FDA communicates that the recommendations should be implemented and specifies the countries for which donor residency and travel history should be assessed.

Licensed manufacturers must report the implementation of the recommendations in this guidance to FDA under 21 CFR 601.12 as follows:

1. Revision of your donor educational materials must be reported in an Annual Report under 21 CFR 601.12(d), noting the date the process was implemented. See 21 CFR 601.12(a)(3).

2. Revision of your own DHQ and accompanying materials must be reported in an Annual Report under 21 CFR 601.12(d), noting the date the process was implemented. See 21 CFR 601.12(a)(3).

[8] Please contact the appropriate review division in CBER in accordance with CBER SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. See http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm.

3. Revision of an FDA accepted DHQ and accompanying materials according to the directions in the User Brochure or Directions for Use must be reported in an Annual Report under 21 CFR 601.12(d), noting the date the process was implemented. See 21 CFR 601.12(a)(3).

4. Revision of an FDA accepted DHQ and accompanying materials other than as described in section VI.2 of this guidance is considered a major change. If you wish to implement the acceptable DHQ documents modified in a manner other than as described in section VI.3 of this guidance, you must report such changes as a Prior Approval Supplement (PAS) under 21 CFR 601.12(b).

   We recommend that you include the following in the PAS submission:

   a. Form FDA 356h "Application to Market a New or Abbreviated New Drug, or Biologic for Human Use" which may be obtained at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm;
   b. A cover letter describing the request and the contents of the submission;
   c. A written standard operating procedure (SOP) describing the donor questions and questionnaire process; and
   d. The donor history questionnaires and accompanying document(s). Please highlight the modifications.

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