Guidance for Industry

Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients

FINAL GUIDANCE

This guidance is being distributed for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(3) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate. FDA made this determination because vaccination programs may start soon, and blood establishments need to establish programs to clarify the suitability of donors who have been recently vaccinated or who have been infected through close contact with a recently vaccinated person. FDA invites comments on this document. Please submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that published in the *Federal Register*. FDA will review any comments we receive and revise the guidance document when appropriate.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or (301) 827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance contact the Division of Blood Applications, Office of Blood Research and Review at (301) 827-3543.

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GUIDANCE FOR INDUSTRY

Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients

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 alternate approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance document provides the current recommendations of the Food and Drug Administration (FDA) for assessment of donor suitability and quarantine and retrieval of blood and blood products in cases of donors exposed to vaccinia virus, which is the virus used in smallpox vaccines. The presence of vaccinia virus in transfused blood or plasma could be harmful to some recipients. Although the presence of vaccinia virus in blood (viremia) has rarely been documented, this possibility has not been assessed using modern laboratory techniques. Therefore, the risk of transmission of vaccinia virus by blood and blood products is uncertain.

Because of the likelihood of vaccination of many people with the smallpox vaccine, we are issuing guidance on measures to reduce any possible risk of transmission of vaccinia virus from donors of blood and blood products.

This guidance applies to collections of Whole Blood, blood components (including recovered plasma), Source Leukocytes, and Source Plasma intended for use in transfusion or for further manufacturing into injectable products. FDA developed the recommendations in this guidance in consultation with experts on vaccinia virus at the Centers for Disease Control and Prevention (CDC) and at the Department of Defense. This document is intended to provide guidance pertaining to pre-event, non-emergency, smallpox vaccination. In the event of widespread emergency vaccination due to an actual or impending smallpox outbreak, the risk-benefit evaluation may change, and these recommendations for donor deferrals, and for product quarantine and retrieval, may need to be modified according to the circumstances and available scientific information.

Throughout these recommendations, "you" refers to blood and plasma collection establishments. FDA uses mandatory language, such as "shall," "must" and "require," when referring to statutory or regulatory requirements. We use non-mandatory language, such as "should," "may," "can," and "recommend" when referring to recommendations.

II. BACKGROUND

Vaccinia virus, a virus related to cowpox virus, is a double-stranded DNA virus, which has been used to vaccinate against smallpox for more than 100 years. Because vaccinia virus and smallpox (variola virus) are closely related, the immune response to vaccinia is protective against smallpox. All modern smallpox vaccines are live virus vaccines comprised of vaccinia virus, and smallpox vaccines in the U.S. are derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus.

Smallpox vaccination was routinely performed in the U.S. until 1971. In recent years, smallpox vaccination has been recommended only for laboratory personnel working with certain orthopoxviruses, including vaccinia and smallpox. On June 20, 2002, the Advisory Committee for Immunization Practices (ACIP) of the CDC recommended that smallpox vaccine also be given to persons pre-designated to conduct investigation and follow-up of initial smallpox cases and to personnel in facilities that are pre-designated to serve as referral centers to provide care for initial smallpox cases (www.cdc.gov/nip/smallpox/supp_recs.htm). On December 13, 2002, President Bush announced his decision to begin a smallpox vaccination campaign targeted to those military and civilian personnel who have an occupational risk of contracting smallpox.

During the first stage, States will provide smallpox vaccination on a voluntary basis to those public health and health care workers who are most likely to be exposed to the first cases during a smallpox outbreak. Approximately 500,000 individuals will be eligible to receive the vaccine during this stage. During the second stage, States will provide smallpox vaccination, also on a voluntary basis, to other health care workers, emergency medical personnel, ambulance drivers, firemen, policemen, and others who may encounter smallpox cases in the course of their duties. Approximately 10 million individuals will be eligible to receive the vaccine during this stage. Although the U. S. Government does not recommend smallpox vaccination for members of the general public at this time, the President has directed the Health and Human Services (HHS) and its public health partners to develop means to accommodate those members of the general public who, despite these current recommendations, seek to obtain access to vaccination before a new licensed vaccine is available.

Smallpox vaccine is administered percutaneously. A papule forms 3-5 days after a primary vaccination (no prior vaccination) and subsequently becomes a vesicle. The vesicle then becomes pustular, reaching its maximum size at 8-10 days. The scab that forms usually separates from the skin 14-21 days after vaccination, but it may persist for up to 6 weeks (Ref. 1). Two different investigators, in 1930 and 1953, reported that vaccinia virus could sometimes be isolated from the patient's blood 3-10 days after vaccination (Ref. 2). These studies did not use the less virulent NYCBOH strain of vaccinia virus that comprises currently available vaccines in the U.S. Using the NYCBOH strain of vaccinia virus, other investigators were only able to detect virus in the blood of patients with disseminated infection, but never in patients who only had localized lesions (Refs. 3,4). All of these studies are of limited value because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination.

The consequences of transfusion-transmitted vaccinia virus could include severe complications of vaccinia infection. These would be particularly likely in transfusion recipients who are immunocompromised or who have burns, or other serious skin conditions. In addition, vaccinia virus infection rarely can cause severe complications such as encephalitis and severe generalized vaccinia in otherwise healthy people. It is possible that vaccinia infection transmitted intravenously would result in different or more severe infections than when acquired percutaneously, since the route of infection can influence the severity (Ref. 5).

III. RATIONALE FOR DONOR DEFERRAL AND PRODUCT QUARANTINE

A. Rationale for Deferral of Recipients of Smallpox Vaccine

The immune response to vaccinia includes neutralizing antibodies and a cellular immune response. Neutralizing antibodies are detected by 10 days after primary vaccination, reach peak levels around 2 weeks, and may persist for months to years (Refs. 6,7). Cell mediated immunity to vaccinia can be detected after primary vaccination, and may persist for up to 50 years (Refs. 8,9). There are no known cases of vaccinia virus persistence in the absence of a clinically recognizable infection.

Vaccinia virus is readily recovered from the vaccination site until the vaccination scab spontaneously separates from the skin. The scabs themselves contain infectious virus. Thus, although viremia is unlikely once an immune response is initiated, recipients of the vaccine could still inadvertently infect close contacts who touch the vaccination site or dressing (Ref. 10). Vaccinia virus can be recovered from the skin at the vaccination site for a mean duration of 7.8 days, with a range of 0 to 18 days (Ref. 11). Based on these considerations, and until more information is available, we recommend that you defer donors who received smallpox vaccine until after the vaccine scab has spontaneously separated (see section IV.). We will continue to evaluate our recommendations in light of evolving scientific knowledge about vaccinia virus.

B. Rationale for Deferral of Donors with Complications of Smallpox Vaccination

Viremia has been more readily detected in people with moderate or severe complications of vaccinia virus infection (Ref. 3). These complications include generalized vaccinia, eczema vaccinatum, and progressive vaccinia. The occurrence of viremia in cases of encephalitis or vaccinial keratitis has not been demonstrated. To assure a margin of safety, we recommend that you defer donors with complications of vaccinia (as defined in the Appendix), acquired by vaccination for 14 days after complete resolution of the complication, as stated in section IV., below.

C. Rationale Concerning Asymptomatic Contacts of Vaccine Recipients

Asymptomatic contacts of vaccinees are unlikely to be infected and we do not recommend that they be deferred.

D. Rationale for Deferral of Donors Who Have Contracted Symptomatic Vaccinia Virus Infection through Close Contact with a Vaccine Recipient

Persons infected by close contact with a vaccine recipient (Ref. 10) usually develop vaccinia lesions on their own skin, since the virus is transmitted to them by skin contact with the vaccination site or with other parts of the body or clothing that has been recently contaminated with vaccinia virus. As stated in section IV., below, you should defer donors who have had contact with someone else who has received the vaccine only in cases where the donors have recognizable signs or symptoms attributable to the virus. These donors present the same risks to blood recipients and collection center staff as someone who has been recently vaccinated. However, donors who have been exposed to a vaccinee, but who fail to develop signs or symptoms of infection by vaccinia, are unlikely to be infected. If infected donors have a single, localized lesion, we recommend that they be deferred until the scab has spontaneously separated. In cases where the scab was otherwise removed, we recommend deferral periods based on the date of vaccination of the vaccine recipient. As with smallpox vaccine recipients (section III. B., above), if the contacts have complications of their vaccinia virus infection, we recommend that they be deferred until 14 days after all complications have completely resolved.

E. Rationale for Product Quarantine

Vaccinia virus in blood and blood products could pose a risk to transfusion recipients of severe complications of vaccinia infection. For this reason, you should quarantine blood and blood products that were collected from donors identified as having vaccinia virus infection as stated in section IV., below. Pooled plasma for further fractionation, or products made from that pooled plasma, need not be quarantined because the manufacturing process and virus inactivation procedures applied to them are believed to be adequate to eliminate infectious vaccinia virus from the final product (Refs. 12-14).

There is no need to discard plasma that has been quarantined provided it is labeled for use in the manufacture of non-injectable products or for research use only, since such products represent minimal or no risk to the health of users.

IV. RECOMMENDATIONS FOR 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 and plasma. [21 CFR 640.3(b)(4),(5) and 21 CFR 640.63(c)(7),(8)] Furthermore, donors must be free from disease transmissible by blood transfusion, insofar as can be determined by history and examinations [21 CFR 640.3(b)(6) and 21 CFR 640.63(c)(9)]. Blood and plasma collection establishments should try to identify potential donors who have recently received smallpox vaccine; to identify such donors, we recommend that you ask the questions described below in the donor questionnaire. Standard operating procedures that are already in place should allow identification of donors who have had complications of smallpox vaccination, or who have contracted localized infection or complications of vaccinia infection from exposure to a vaccine recipient. For donors who state that they have been vaccinated

within the past two months, collection center staff should visually inspect the site of the vaccination (usually on the upper arm) to determine whether the scab has separated from the skin, and if there has been recent vaccination we recommend that they inquire whether the scab separated spontaneously. We recommend that all donors be asked the following questions:

A. Donor Deferral Questions

1. "In the past eight weeks, have you received smallpox vaccination or have you had close contact with the vaccination site of anyone else?" [Examples of close contact include physical intimacy touching the vaccination site, touching the bandages or covering of the vaccination site, or handling bedding or clothing that had been in contact with an unbandaged vaccination site.]

    a. [If the donor had smallpox vaccination:] Has the vaccination scab fallen off your skin by itself? Did you have any illness or complications due to the vaccination?
    b. [If close contacts had smallpox vaccination:] Have you had any new skin rash or skin sore since the time of contact?

B. Deferral of Recipients of Smallpox Vaccine

The following recommendations apply to donors who recently have received smallpox vaccine, as identified by donor questioning. [As noted on the first page of this guidance, in the event of widespread emergency vaccination, the deferral recommendations for vaccinated individuals may need to be modified according to the circumstances and available scientific information.]

1. Donors without vaccine complications (as defined in Appendix):

Donors without vaccine complications should be deferred until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date. Donor room staff should visually verify absence of the vaccination scab and ask if it separated spontaneously. In cases where a scab was removed prior to separating spontaneously, we recommend that you defer the donor for two months after vaccination.

2. Donors with vaccine complications (as defined in Appendix):

We recommend that you defer donors who have experienced complications of vaccination until 14 days after all vaccine complications have completely resolved.

C. Deferral of Symptomatic Contacts of Recipients of Smallpox Vaccine

The following recommendations apply to donors who acquired a clinically recognizable vaccinia virus infection by close contact with someone who received the smallpox vaccine.

1. Donors with localized skin lesions and without any other symptoms or complications:

Donor room staff should visually verify the absence of the localized skin lesion (scab) and ask if it separated spontaneously. If the localized skin lesion (scab) separated spontaneously, and is no longer present, the donor need not be deferred based on the prior exposure to a smallpox vaccine recipient. In cases where a scab was otherwise removed, we recommend that the donor be deferred for a period of three months from the date of vaccination of the vaccine recipient with whom the contact occurred. If the date is not known, but could have been within the last three months, we recommend that you defer the donor for two months from the present time.

2. Donors with vaccinia complications (as defined in Appendix):

We recommend that you defer donors who have experienced complications of vaccinia infection acquired through close contact with a vaccine recipient until 14 days after all vaccine complications have completely resolved.

V. RECOMMENDATIONS FOR PRODUCT QUARANTINE AND RETRIEVAL

We recommend that you quarantine and retrieve from consignees the relevant previously collected in-date units of blood and blood components intended for transfusion, as well as unpooled units of Source Plasma, Source Leukocytes, and recovered plasma intended to make injectable products, if you receive post-donation information that a donor had:

1) received a smallpox vaccination within 21 days before the donation,
2) a smallpox vaccination scab at the time of donation,
3) symptoms or signs of vaccinia virus infection at the time of donation resulting from close contact with a recipient of smallpox vaccine,
4) a vaccinia complication within 14 days prior to donation, or
5) a clinically apparent vaccinia virus infection during the 21 days after donation that may have resulted from contact prior to donation with a recipient of smallpox vaccine.

These units placed in quarantine should be labeled and used only for manufacture of non-injectable products or for research use; otherwise they should be destroyed.

VI. RECOMMENDATIONS FOR NOTIFICATION OF PRIOR TRANSFUSION RECIPIENTS

In the case that subsequent to donation, a donor is reported to have:

1) received a smallpox vaccination within 21 days before the donation,
2) a smallpox vaccination scab at the time of donation,
3) symptoms or signs of vaccinia virus infection at the time of donation resulting from prior contact with a recipient of smallpox vaccine,
4) a vaccinia complication within 14 days prior to donation, or
5) a clinically apparent vaccinia virus infection during the 21 days after donation that may have resulted from close contact prior to donation with a recipient of smallpox vaccine;

we recommend that medical directors consider the need for prompt record tracing and, as appropriate, notification of the treating physicians or notification of prior recipients of the affected blood and blood components previously collected from that donor.

VII. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance immediately. 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 establishment revised standard operating procedures to implement these recommendations.

VIII. REFERENCES

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IX. APPENDIX: MODERATE AND SEVERE COMPLICATIONS OF SMALLPOX VACCINATION AND INADVERTENT VACCINIA VIRUS INFECTION

Complications of smallpox vaccine or of inadvertent vaccinia virus infection, for the purpose of this guidance, are defined as the following, and are consistent with CDC definitions of moderate to severe adverse reactions to the smallpox vaccine, or to inadvertent vaccinia virus infection in contacts of vaccine recipients (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm).

1. Eczema vaccinatum
2. Generalized vaccinia
3. Progressive vaccinia
4. Postvaccinial encephalitis
5. Vaccinial keratitis

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in someone with eczema (atopic dermatitis) or a history thereof, or with other chronic or exfoliative skin conditions.

Generalized vaccinia is characterized by a vesicular rash of varying extent that can occur among persons without underlying illnesses. The rash is generally self-limited and requires minor or no therapy except in rare cases, when the vaccine recipient is systemically ill.

Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic vaccinia lesions. It has occurred almost exclusively among persons with cellular immunodeficiency.

Postvaccinial encephalitis is a rare but serious complication of vaccinia virus infection.

Vaccinial keratitis is an infection of the cornea, which can cause corneal scarring and visual impairment. This condition is usually caused by accidental self-inoculation of the eye from the vaccine site, or from self-inoculation after contact with another vaccine recipient, and is not believed to be due to hematogenous spread or associated with a secondary viremia (Ref. 15).