

Guidance for Industry

Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

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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

On November 11, 1999, the Food and Drug Administration (FDA) issued a final guidance document for implementation entitled, "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products." We, FDA, have continued to monitor epidemiological findings and other scientific data regarding new variant CJD. On August 29, 2001, we issued a draft guidance for comment, entitled "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," which recommended new donor deferrals for risk of exposure to bovine spongiform encephalopathy (BSE). This guidance finalizes the August 29, 2001, draft guidance, and supersedes the November 11, 1999, guidance. In keeping with current usage, the nomenclature used in previous guidances for new variant CJD, "nvCJD," has now been changed to variant CJD, or "vCJD." We refer to all other forms of CJD as "CJD." This final guidance provides comprehensive current recommendations, including new recommendations for deferral of donors with possible exposure to the agent of vCJD. We based these recommendations upon current knowledge, and advice from the FDA's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC). Recommendations for all other forms of CJD (sporadic, familial, and iatrogenic) are unchanged.

Tests are being developed to detect CJD and vCJD infections in blood and plasma donors. However, until suitable donor screening tests are available, FDA is recommending interim preventive measures that we deem to be prudent based on the available scientific data and the evolving state of knowledge regarding these diseases. We also expect that additional epidemiological information will become available as the vCJD and Bovine Spongiform Encephalopathy (BSE) epidemics evolve. We may update this guidance in the future, in light of developments in testing technology, epidemiological information, and the impact of these recommendations on the supply of blood and blood-derived products.

FDA uses mandatory language, such as “shall,” “must,” and “require,” when referring to statutory or regulatory requirements. The FDA uses non-mandatory language, such as “should,” “may,” “can,” and “recommend” when referring to recommendations.

II. BACKGROUND

CJD is a rare but invariably fatal degenerative disease of the central nervous system, associated with a poorly understood transmissible agent (Refs. 1, 2). Sporadic CJD cases occur at low frequency by an unknown mechanism. CJD may also be acquired by exogenous (usually iatrogenic) exposure to infectious material; or may be familial, caused by a genetic mutation of the prion protein gene. Clinical latency for iatrogenic CJD may exceed 30 years, based upon observations following point exposures to contaminated materials.

In 1996, a previously unrecognized variant of CJD, vCJD, was identified in the United Kingdom (U.K.) (Ref. 3). vCJD is distinguished from CJD by differences in clinical presentation and neuropathologic changes, summarized below (Refs. 3-8).

Differences in clinical presentation	vCJD	CJD
Age of onset	Earlier	Later
Median age at death	28 years	68 years
Psychiatric and sensory symptoms	Frequent in early course of illness	Appear later in course of illness
EEG changes	Absence of diagnostic EEG changes	Diagnostic EEG changes commonly seen
Duration of illness (median) (Ref. 7)	13 months	4 months
Neuropathologic features	Florid prion protein plaques, surrounded by spongiform changes	Florid plaques uncommon
Immunohistochemistry (Ref. 8)	Abnormal prion protein detectable in lymphoid tissues	Abnormal prion protein not detected in lymphoid tissues

The concentration of abnormal prion protein seen in vCJD lymphoid tissues has led to concerns that transmission of vCJD by blood might be a greater risk than for CJD (Ref. 9).

Neuropathologic examination of brain tissue is required to confirm a diagnosis of vCJD. A confirmed (or definite) case of vCJD is currently defined by the following neuropathologic findings:

- 1) numerous widespread kuru-type amyloid plaques, surrounded by vacuoles, in both the cerebellum and cerebrum (“florid plaques”);

- 2) spongiform change most evident in the basal ganglia and thalamus, with sparse distribution in the cerebral cortex; and
- 3) high density accumulation of abnormal prion protein, particularly in the cerebrum and cerebellum as shown by immunohistochemistry.

A clinical diagnosis of “suspected” vCJD can be made based upon certain clinical features, if adequate neuropathology specimens are unavailable. Although recommended diagnostic evaluations and criteria for vCJD are evolving, at present the Centers for Disease Control and Prevention (CDC) classifies cases in the U.S. with all of the following features as suspected vCJD:

1. Current age (if alive) or age at death <55.
2. Persistent painful sensory symptoms and/or psychiatric symptoms at clinical presentation.
3. Dementia, and delayed development (≥ 4 months after illness onset) of ataxia, plus at least one of the following three neurologic signs: myoclonus, chorea, or dystonia.
4. A normal or abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.
5. Duration of illness of at least 6 months.
6. Routine investigations do not suggest an alternative, non-CJD diagnosis.
7. A history of possible exposure to BSE, e.g., having been a resident or traveler to a BSE-affected country from 1980 to the present.
8. No history of iatrogenic exposure to CJD, such as receipt of a dura mater graft, or human pituitary-derived hormones.
9. Absence of a prion protein gene mutation, or, if this has not been determined, no history of CJD in a first degree relative.

To date more than 100 patients, mostly in the United Kingdom (U.K.), as well as five patients in France, have been diagnosed with vCJD. The size of the vCJD epidemic cannot yet be determined, but is believed to be increasing in the U.K. (Refs. 10-11). No cases of vCJD have been identified in the U.S., except for one U.K. resident with vCJD who traveled to California in 2001 for medical care. Laboratory and epidemiologic studies have linked vCJD to the epidemic of BSE in the U.K. (Refs. 12-13). In the U.K., BSE probably first occurred in cattle in 1980, peaked in 1992, and fell to low levels by 1996, as a result of control measures. BSE prevalence, while lower than in the U.K., appears to be increasing in some European countries, and the peak levels of those epidemics cannot yet be ascertained (Refs. 14-15). In September 2001, the first case of BSE was reported in Asia (Ref. 16). BSE has not been reported, to date, in U.S. cattle.

On December 11, 1996, we issued a memorandum to all registered blood and plasma establishments and all establishments engaged in manufacturing plasma derivatives entitled “Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products.” We recommended, as a preventive measure, that you, the manufacturer, should quarantine and destroy in-date Source Plasma and plasma derivatives, and in-date transfusion products prepared from donors who were at increased risk for developing CJD or who were subsequently diagnosed with CJD. We also recommended

permanent deferral of donors with CJD or CJD risks, unless, in cases of a family member with CJD, the donor underwent genetic testing which demonstrated absence of a familial-CJD associated abnormality of the prion protein gene. We did not make specific recommendations for vCJD in that document. Changes to those recommendations were announced on September 8, 1998, and were incorporated into the August 1999 guidance, which was revised and updated in November 1999. These changes were:

- 1) that you no longer withdraw plasma derivatives containing plasma from donors with CJD or CJD risk factors;
- 2) that you withdraw all material collected from donors diagnosed with vCJD or suspected vCJD; and
- 3) that you defer donors based on their potential exposure to BSE in the U.K., or injection of insulin made from bovine sources in the U.K.

We changed the 1996 recommendation to withdraw plasma derivatives containing plasma from donors with CJD or CJD risk, because of recently published epidemiological and laboratory data which provided additional assurance that transmission of CJD by blood and blood products is unlikely. This evidence included five case-control studies of over 600 CJD cases, two lookback studies of recipients of products from CJD patients, and two autopsy studies of patients with hemophilia (Refs. 17-23). None of these studies linked CJD to receipt of blood or blood products. In addition, mortality surveillance by the CDC of 3,642 CJD deaths over 16 years (later updated to 4,468 reports), showed that none of these cases were reported to have conditions associated with frequent receipt of blood and blood products (hemophilia, thalassemia, or sickle cell disease) (Ref. 24). Finally, experimental studies in animal models for CJD suggested that manufacturing procedures used for plasma derivatives could lower the amount of infectious material present in plasma derivatives compared with whatever levels may be present in blood (Refs. 25-26).

In contrast to CJD, vCJD is an emerging disease with unique clinical and pathological characteristics. Few experimental or epidemiological studies of vCJD transmissibility by blood components or plasma derivatives have been published, and it is uncertain whether human blood can transmit the vCJD agent. Because the potential for transmission is unknown, as a preventive measure, we recommended, in August 1999, that you withdraw blood components and derivatives collected from donors diagnosed with vCJD. As a further preventive measure, we also recommended that you defer donors who resided in the U.K. for a total of 6 months or more, between 1980 and 1996. Approximately 87% of donor exposure-days to BSE in the U.K. were eliminated by this donor deferral. The period from 1980 through 1996 reflects the peak years of the U.K. BSE epidemic, and recognizes the measures implemented in the U.K. since 1996, that are designed to keep BSE out of the human food chain (Ref. 27). As other countries institute similar food chain protections against BSE, we will reconsider the current donor deferrals.

Since we published the November 1999 guidance, the vCJD and BSE epidemics have continued to evolve. More BSE cases have been reported in Europe, including new reports of BSE in Spain, Italy, Germany, the Czech Republic, Greece, Slovakia, Slovenia, Austria, and Finland. BSE was recently identified in Japan (Ref. 16). Furthermore, transmission of BSE appears to have been experimentally achieved by transfusion in a single sheep (Ref. 28), heightening concerns about possible transmissibility of the vCJD agent by human blood. On June 6-7, 2000,

the TSEAC met to discuss deferral of donors from countries affected by BSE. The TSEAC voted not to recommend new donor deferrals for European exposures outside of the U.K. at that time. This decision was based on observations that 1) the extent of the BSE epidemic in Europe was undetermined and 2) donor deferrals for U.K. residence had only recently been fully implemented, and the potential for adverse impact on the availability of blood and blood products had not been fully appreciated. The TSEAC also recommended against changing the U.K. donor deferral period to one more stringent than 6 months.

At its meeting on January 18-19, 2001, the TSEAC reviewed more recent epidemiological information on exposure to BSE in European countries, and again considered donor deferrals for vCJD risk. The TSEAC again voted that epidemiological and other currently available scientific information did not support changing the current deferral for donors who resided in the U.K. The TSEAC did recommend that deferrals be considered for donors who were exposed to beef products exported from the U.K. to U.S. military bases in Europe, and to France; and for donors potentially exposed to BSE since 1980 in France, Portugal, or the Republic of Ireland. In response to advice from the TSEAC that FDA should consider a donor deferral recommendation for residence or travel in Portugal and Republic of Ireland (i.e., countries where BSE exposure was not related to human consumption of British beef per se), we decided to reexamine the issue with the TSEAC. Therefore, the TSEAC met again June 28-29, 2001, to consider the estimated potential human exposures to the BSE agent in the U.K. and other parts of Europe, as well as risk reduction and donor loss estimates that would be associated with tightened geographic donor deferrals. At this meeting, the TSEAC considered three deferral options (including the option proposed by the TSEAC at its January 2001 meeting) and voted to recommend the deferral policies which form the basis of these recommendations (Ref. 29).

Rationale for New Geographic Donor Deferrals

This guidance document contains comprehensive revised recommendations based upon advisory committee discussions, public comments to the docket and at advisory committee meetings, and internal Public Health Service and FDA deliberations. We have developed recommendations for donor deferral, product retrieval, and quarantine and disposition based upon consideration of risk in the donor and product, and the effect that withdrawals and deferrals might have on the supply of life- and health-sustaining blood, blood components and plasma derivatives. In particular, donors with vCJD are distinguished from those with CJD or CJD risk factors, because of very limited historical and epidemiological experience with vCJD, known pathological differences between CJD and vCJD, and uncertainty about the potential for vCJD transmission by blood transfusion.

The new recommendations reflect an attempt to minimize the possible risk of vCJD transmission from blood and blood products consistent with maintaining their availability. We estimated that the recommended new donor deferrals will result in a 90% reduction in total person-days of risk-weighted donor exposure to the agent of vCJD. We calculated risk as the sum of relative risk-weighted person-days exposure in the United Kingdom (weight = 1.0), France (weight = 0.05), other European countries (weight = 0.015), and members of the U.S. military and their dependents (weight = 0.35).

Donor loss under this policy is projected to be approximately 5%, based upon our recent analysis of data from the 1999 multi-center blood donor travel survey (Ref. 29), which was conducted using methodology described for Retrovirus Epidemiology Donor Studies (Ref. 30). We recognize that these deferrals may adversely affect the available supply of blood and plasma derivatives and that supplies need to be monitored closely. This impact will vary locally and regionally depending upon the dynamics of supply and demand and other characteristics such as demographics of the donor populations. More specifically, travel prevalence to the U.K. and other parts of Europe may be as much as 50% higher in urban coastal cities with corresponding lower travel in central and rural areas of the U.S. (Ref. 14).

Since the publication of draft guidance in August 2001, BSE has been diagnosed in Japan. The source of this outbreak is likely to have been meat-and-bone meal, imported from the U.K. The news media has reported that other countries may also have received U.K. meat-and-bone meal (Ref. 31). We may consider additional deferrals based upon possible exposure to BSE in Asia or elsewhere after the currently recommended deferrals have been implemented, their impact is assessed, and additional information about the potential level of BSE exposure and food chain controls is acquired.

In anticipation of the new geographic deferral recommendation, we strongly encourage proactive planning to ensure blood supply adequacy before, during, and after implementation. Steps to moderate supply impact may include assertively increasing collection volume before implementation, and careful monitoring of the blood supply and demand factors before, during, and after implementation. To moderate the impact on the blood supply, we recommend that you implement donor deferrals in two separate phases (sections IV. D. 2., IV. D. 3., and VIII.). Considering the importance of an adequate blood supply, we will reconsider our recommendations as appropriate based on the impact of the expanded donor deferrals on the availability of blood products.

III. EXPLANATION OF CURRENT vCJD RECOMMENDATIONS

A. Exposure to British Beef in the U.K.

The vCJD epidemic in the U.K. continues to increase (Ref. 11, and CJD Statistics from the British Department of Health, at www.doh.gov.uk). To increase protection of the U.S. blood supply, we now recommend that you defer blood and plasma donors who have traveled or resided in the U.K. for a cumulative period of 3 or more months between 1980 and the end of 1996.

B. Exposure to British Beef Products Distributed Outside of the U.K.

The TSEAC recognized two types of risk outside of the U.K. These include: exposure to BSE from infected cows in the country of residence (“indigenous”), and exposure to BSE from bovine products exported from the U.K. during the BSE epidemic (prior to full implementation of food control measures in 1996).

Available data suggest that France imported a substantial amount of beef from the U.K. during the peak years of the BSE epidemic (Ref. 32). Approximately 5% of beef consumed in France is estimated to have come from the U.K., and the number of French vCJD cases (three confirmed and two probable) is approximately 4.4% of those in the U.K. (Ref. 33). It is currently speculated that the French vCJD cases were infected by consumption of British beef in France, since none of the individuals had lived in the U.K., and the indigenous French BSE epidemic is relatively smaller and more recent than that in the U.K. Substantial amounts of British beef also were exported to the Netherlands, but it appears that much of this meat was exported from the Netherlands to a variety of other countries (Ref. 32).

On January 18, 2001, the TSEAC voted to defer potential donors who resided in France for 10 years or more, from 1980 until the present. The suggested 10 year (120 month) deferral period for France reflected an estimated 5% risk of exposure to BSE, compared to exposure of donors who resided in the U.K. for at least 6 months. Based upon a revised deferral criterion of 3 months for exposure in the U.K., we now recommend deferral of blood and plasma donors with a history of 5 or more years of cumulative residence or travel in France since 1980.

Some U.S. military personnel, civilian military personnel, and their dependents in Europe also potentially were exposed to British beef procured for use on U.S. military bases between 1980 and 1996. British beef was distributed to U.S. military bases North of the Alps (Germany, United Kingdom, Belgium, and the Netherlands) between 1980 and 1990, and South of the Alps (Greece, Turkey, Spain, Portugal, and Italy), between 1980 and 1996. While exposure varied widely, it is estimated that in some areas, up to 35% of beef consumed on U.S. military bases in Europe came from the United Kingdom (Ref. 14). The TSEAC recommended deferring such donors, but advised that more information was needed to assess the impact of deferral for various time periods in Europe on the supply of blood products.

Due to the potential exposure to U.K. beef on U.S. military bases in Europe, we recommend that you should indefinitely defer current and former U.S. military personnel, civilian military personnel, and their dependents who were stationed at European bases for 6 months or more during the time periods outlined above. Based upon information provided by the Department of Defense, we estimate that approximately 1.8% of current U.S. blood donors may be deferred by this recommendation.

C. Indigenous BSE Exposure Outside the U.K.

BSE in Europe is likely to have originated from infected cattle and cattle feed that were exported from the U.K. to other parts of Europe. The risk of human exposure to the BSE agent in any country is based upon several factors, including the prevalence of BSE and the presence of control measures to prevent the BSE agent from entering the human food chain. Control measures include:

- active surveillance through testing of slaughtered cattle more than 30 months old for BSE,
- exclusion of high-risk material e.g., brain, other neural tissue, lymphoid tissues, intestines from human food,
- a ban on human consumption of slaughtered cattle more than 30 months old,
- prohibition of mechanically recovered meat,
- a ban on mammalian-derived feed for ruminants,
- use of certain rendering processes, and
- additional herd control and surveillance (Ref. 15).

The timing and degree to which the European countries have implemented such controls has varied (Refs. 15, 32). The current prevalence of BSE in each country is uncertain because active surveillance of the epidemic has not been completely implemented. (Refs. 14, 15, 29, 32). The Scientific Steering Committee on the Geographical Risk of BSE (SSC GBR) reported that in the United Kingdom and Portugal, the prevalence of BSE is greater than 100 cows/million in cattle over 24 months of age (Ref. 15). These countries have been categorized as “Level IV.” Because of the comparatively high BSE prevalence in Portugal, the TSEAC recommended in January 2001 that donors who have resided in Portugal for 10 years or more between 1980 and the present should be deferred. The BSE epidemic in Ireland was estimated to be nearly as large in absolute numbers as that in Portugal, although Ireland was classified as “Level III” by the SSC GBR. After limited discussion, the TSEAC, by a narrow margin, recommended deferral of donors who resided in the Republic of Ireland for 10 years or more since 1980.

BSE has been detected in many, but not all, European countries, and the increase or decrease of BSE in many countries is not predictable (Refs. 14, 32). In addition, food chain control measures (and their enforcement) also vary, and cannot be assured for all time periods in question. Because of these uncertainties, and the evolving BSE epidemic, donor deferrals on a country-by-country basis are not practical at this time. FDA therefore has developed a uniform recommendation for donor deferral based on exposure in Europe outside of the U.K. The highest prevalence of BSE that has been observed in a European country with a strong surveillance program (Switzerland) is approximately 1.5% of the BSE prevalence that was observed for the United Kingdom between 1980 and 1996. Also, residents in France consumed up to 5% British beef during the epidemic period, and other Europeans, less. Therefore, the current estimated maximum risk of BSE exposure in Europe is approximately 1.5-5% of that in the United Kingdom. Assuming a “worst-case” relative risk of 5% per day of exposure, a European donor deferral of 5 years (60 months) is equivalent to the new 3-month deferral for cumulative travel or residence in the United Kingdom. This is the basis for our current recommendation to exclude from transfusion use, blood and blood components from donors with a history of 5 or more years of residence or travel in Europe outside of the U.K.

To date, transmission of vCJD by human blood or plasma has not been demonstrated, and no laboratory or epidemiological studies have demonstrated infectivity of blood from vCJD donors (Ref. 29). Experimental assays of blood samples from small numbers of

vCJD patients showed that abnormal vCJD-associated prion proteins and infectivity could not be detected, but the tests used were not sensitive enough to detect very low levels of infectious material, if present (Refs. 34, 35). However, blood from animals experimentally infected with transmissible spongiform encephalopathy (TSE) agents contains low levels of infectivity, and TSE infection, including BSE, has been transmitted by blood in some experiments (Refs. 25, 28, 32, 36-38). For this reason, the transmission of vCJD by blood components and plasma derivatives is considered a theoretical possibility. The risk of vCJD transmission by plasma derivatives is based upon the infectivity, if any, of plasma during vCJD infection, the prevalence of vCJD in the donor population, the size of the plasma pool for fractionation, and the removal of vCJD infectivity during the manufacturing process. Model TSE agents are removed from plasma products by manufacturing steps such as precipitation, depth filtration, and column chromatography (Refs. 36, 39-41). Additionally, unpublished data provided to FDA suggest that the vCJD agent is similarly reduced by some manufacturing steps.

The relative risks and benefits of excluding plasma donors who have lived or traveled in Europe for 5 years or more have not been established. In particular, the effect of such a donor deferral upon the supply of life and health-sustaining plasma derivatives has not been determined, but could be significant (Ref. 29).

In contrast to blood, plasma derivatives are highly processed materials. Considering the estimated low prevalence of vCJD infections in Europe compared to the U.K., the likely ability of plasma fractionation processes to reduce TSE infectivity, and the uncertain effect of a deferral upon the supply of plasma derivatives, we do not recommend that you defer Source Plasma donors who have lived or traveled in Europe for 5 or more years. However, in consideration of the relatively greater risk of vCJD in persons with exposure to beef products from the U.K., you should not collect Source Plasma and recovered plasma from donors with a history of travel or residence in the U.K., U.S. military bases in Europe, and in France, as described in sections III.A. and III.B.

Consistent with this recommendation, recovered plasma collected prior to deferral, from donors with 5 years or more travel or residence in Europe, is still acceptable for manufacturing of plasma derivatives. However, in order to prevent possible accidental use of blood and blood components for transfusion, you should not continue to collect recovered plasma from Whole Blood donors who have been deferred for history of European residence. You may make an exception in the case of plasma or serum donors if they are participating in a CBER approved program that allows collection of plasma or serum solely for use in manufacturing of non-injectable products. Blood donors who are deferred for history of European travel or residence remain eligible to donate Source Plasma because there is no possibility that such collections will generate blood components for transfusion. However, we believe that recovered plasma collected from these donors after deferral implementation becomes unsuitable, because of the risk that blood and blood components from such donors may inadvertently be transfused. We will continue to evaluate this recommendation in light of evolving experimental and epidemiological information.

Given these considerations, we recommend that you defer donors of Whole Blood and blood components intended for transfusion, Source Leukocytes, and recovered plasma, but not donors of Source Plasma, who have resided in Europe for a cumulative period of 5 years or more, between 1980 and the present.

NOTE: We will refer to donor deferrals both for risk of exposure to BSE due to residence in BSE countries, or consumption of British beef products, as “geographic risk deferrals.”

D. Theoretical Exposure to vCJD by Transfusion

There are no known cases of vCJD transmission by blood transfusion to humans. In the U.K., at least 20 people are known to have received blood or blood components from donors who later developed vCJD. To date, none of these recipients has been diagnosed with vCJD (Ref. 14). However, BSE has apparently been transmitted from one sheep to another by transfusion (Ref. 28). Another study suggests that the BSE agent can adapt to primate hosts, thus potentially enhancing the possibility of transfusion transmission of vCJD from a vCJD-incubating donor (Ref. 42). Therefore, as a preventive measure, you should defer donors who have received transfusions of blood or blood components in the U.K. from 1980 to the present.

E. Exposure to Bovine Insulin

No cases of transmission of vCJD have been reported in recipients of bovine insulin or other injectable products manufactured in BSE-affected countries. However, as a safeguard, most material from cattle in BSE countries should not be used in the manufacture of FDA regulated products (59 FR 44591, August 29, 1994). We are aware that some diabetic patients have imported bovine insulin for personal use. Additionally, some insulin products legally distributed in the U.S. since 1980 were manufactured from cattle in the United Kingdom. Therefore, as a preventive measure, you should indefinitely defer blood donors who have injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from cattle in the United Kingdom.

F. Filing Reports of Biological Product Deviations

The biological products deviations rule requires blood establishments to file a report of biological product deviation (BPDR) when the deviation meets the standard set out in 21 CFR 606.171. If product was distributed, the regulation requires an establishment to report to FDA events that

- Occurred while the product was in the establishment's control; and
- EITHER represent a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications; OR represent an unexpected or unforeseeable event; and
- may affect the safety, purity or potency of that product.

Some establishments have asked questions about BPDR reporting in the context of these donor deferral recommendations.

Example #1: On the first day after implementing new donor criteria, the establishment learns that one of its repeat donors lived for seven years in France between 1981 and 1988. Should the establishment file a BPDR with respect to units previously collected from that donor, if those units were distributed?

The regulation does not require the establishment to file a BPDR. At the time of donation, collection from that donor did not represent a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications. Nor was the collection an unexpected or unforeseeable event. The agency foresees that establishments will collect donations from such donors until establishments implement the new deferral recommendations.

Example #2: One year after implementing new donor criteria, the establishment learns that one of its repeat donors lived in France between 1981 and 1988. The donor donated Source Plasma eight weeks earlier, and whole blood five months earlier. Despite the donor's unsuitability under the new donor criteria, the establishment accepted those donations. Should the establishment file a BPDR with respect to those units, if those units were distributed?

The establishment should file a BPDR. At the time of the donations, collection from that donor represented a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications.

Example #3: Before implementing new donor criteria, the establishment learns that one of its repeat donors has developed CJD or vCJD. The donor donated whole blood three months earlier, and has a long history of donating. Should the establishment file a BPDR with respect to units previously collected from that donor, if those units were distributed?

The establishment should file a BPDR. Collection from that donor represented an unexpected or unforeseeable event that may affect the safety, purity, and potency of the product. Neither blood establishments nor the agency expect and foresee that establishments will collect donations from individuals with CJD or vCJD.

G. Definitions

Audio CASI - computer assisted interactive donor questioning program that is accompanied by an audio component. The donor reads the questions on the computer and hears the questions through a speaker or headphones.

Blood components intended for transfusion - Red Blood Cells, Platelets, Plasma, Cryoprecipitate, or Granulocytes derived from human blood collected by either manual whole blood collection or automated apheresis techniques and intended to be transfused to human recipients.

Military employee or dependent - individual is a member of the one of the U.S. military services (Army, Air Force, Navy, Marines, Coast Guard), a civilian employee of one of the U.S. military services or a dependent (e.g., spouse, child, parent, etc.) of a member of the one of the U.S. services or of a civilian employee of the one of the U.S. services.

Recovered Plasma - unlicensed raw material obtained from Whole Blood or as a by-product of apheresis procedures (e.g., plateletpheresis), in conjunction with preparing transfusion blood components and Source Leukocytes intended for further manufacturing into injectable and non-injectable products.

Source Leukocytes - blood component derived from human blood that is collected by either manual or automated apheresis techniques and is intended for further manufacturing into injectable products, like interferon. Source Leukocyte donors may donate once every 8 weeks or more frequently and must meet Whole Blood or Source Plasma donor suitability criteria depending on the type and frequency of donation.

Source Plasma Donors

- Frequent Source Plasma donor - donor who donates more frequently than once every 4 weeks. These donors must undergo an annual physical examination (21 CFR 640.63(b)) and a Serum Protein Electrophoresis measurement at least every 4 months (21 CFR 640.65(b)(1)).
- Infrequent Source Plasma donor - donor who donates less frequently than once every 4 weeks. These donors meet the Whole Blood donor suitability criteria described in 21 CFR 640.3 and do not need to undergo an annual physical examination or a Serum Protein Electrophoresis measurement.

IV. RECOMMENDATIONS FOR DONOR DEFERRAL

A. Recommended Donor Deferral Criteria

Donor deferrals 1-7 are for all donors. Donor deferral 8 (residence in Europe for 5 years or more between 1980 and the present), is for all donors *with the exception of* donors of Source Plasma.

1. You should permanently defer donors who have been diagnosed with vCJD or any other form of CJD.
2. You should permanently defer donors at increased risk for CJD (as identified by questions in section IV.B, Questions 2 and 3). Donors are considered to have an increased risk for CJD if they have received a dura mater transplant, or human pituitary-derived growth hormone. Donors with one or more blood relatives diagnosed with CJD (as identified in section IV.B., Question 1) are also considered to be at increased risk of CJD, and should be indefinitely deferred (see section IV.C. for donor reentry recommendations).

3. You should indefinitely defer donors who have spent three months or more cumulatively in the U.K. from the beginning of 1980 through the end of 1996.
4. You should indefinitely defer donors who have spent 5 years or more cumulatively in France from 1980 to the present.
5. You should indefinitely defer former or current U.S. military personnel, civilian military personnel, and their dependents as follows:
 - a. individuals who resided at U.S. military bases in Northern Europe (Germany, United Kingdom, Belgium, and the Netherlands) for 6 months or more, from 1980 through 1990 or,
 - b. individuals who resided at U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more, from 1980 through 1996.
6. You should indefinitely defer donors who have received a transfusion of blood or blood components in the U.K. between 1980 and the present.
7. You should indefinitely defer donors who have injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from U.K. cattle.
8. You should indefinitely defer donors of Whole Blood, blood components for transfusion, and Source Leukocytes, who have lived cumulatively for 5 years or more in Europe from 1980 until the present. (Note this criterion includes time spent in the U.K. from 1980 through 1996 and time spent in France from 1980 to the present.) Unless otherwise unsuitable, these donors remain eligible for Source Plasma donation.

NOTE: Donors who are otherwise deferred based upon the above recommendations 2-8, may continue to donate if they are participating in a CBER-approved program that allows collection of blood components solely for use in manufacturing of non-injectable products. We recommend special labeling for products obtained from such donors (see section VII.A.).

B. Recommended Questions to Identify Donors at an Increased Risk for CJD

You should question frequent Source Plasma donors at the first donation following implementation of the recommendations in this guidance, and annually thereafter. You should question donors of Whole Blood and blood components, infrequent Source Plasma donors and Source Leukocyte donors at each donation. Question 2 may be asked only once, since pituitary-derived growth hormone is no longer being manufactured or administered. If the donor is not familiar with the term “Creutzfeldt-Jakob Disease,” you may take that as a negative response. These questions are similar to those in the

November 11, 1999, guidance. We consider donors who answer “Yes” to any of the questions below to have an increased risk for developing CJD.

Question 1) Have any of your blood relatives had Creutzfeldt-Jakob Disease?

Question 2) Have you ever received growth hormone made from human pituitary glands?

NOTE: If the donor is uncertain about his or her treatment, the following question describing human pituitary-derived growth hormone injections may be asked: “Was the hormone treatment given repeatedly by injection?” This question only needs to be asked once, since human pituitary growth hormone is no longer available.

Question 3) Have you received a dura mater (or brain covering) graft?

This question may be preceded by the more general, “Have you ever had brain surgery?” You need to ask the specific question only if the donor responds “yes,” to the general question.

C. Recommendations for Donor Reentry After Donor Deferral for Risk of Familial CJD

If you defer a donor because of family history of CJD, you may reenter that donor if:

- 1) The diagnosis of CJD in the family member(s) is confidently excluded, or CJD in the family member(s) is iatrogenic, or the family member(s) is(are) not a blood relative(s); or
- 2) Laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

D. Recommended Questions for Identifying Donors at Risk for Exposure to BSE

1. Method of Donor Questioning

Due to the added complexity of screening donors for cumulative periods of potential exposure to BSE, a trained staff member should administer the revised geographic donor deferral criteria by face-to-face interview to each new donor (as defined in your SOP). Instead of face-to-face interviews, you may use a computerized interactive donor interview program that includes an audio component (audio-CASI) (Refs. 43, 44). You should submit your changes to your donor interview procedure according to 21 CFR 601.12. For repeat donors, you may use alternative methods for introducing and emphasizing the new questions. Your alternative method should provide the repeat donor with a detailed

description of the changes to the donor questionnaire, to highlight any new questions and modifications.

2. Timing of Implementation

In order to attenuate the impact of deferrals on the blood supply, you may implement deferrals in two separate phases. Phase I comprises deferral for cumulative time spent in the U.K. and France, deferral for military employees, and their dependents, and for recipients of transfusion in the U.K. Phase II comprises deferral of donors of Whole Blood and blood components for transfusion, Source Leukocytes, and other cellular blood components for manufacture into injectable products (but not Source Plasma) who have traveled to, or lived in, Europe for 5 years or more, between 1980 and the present. We recommend that you implement Phase I by May 31, 2002, and Phase II by October 31, 2002.

3. Donor Questions

You should indefinitely defer donors who answer “Yes” to the following questions:

Phase I: To identify donors with geographic risk of BSE exposure.

Since 1980, have you ever lived in, or traveled to Europe?

- a. If the donor answers no, you need not take any further action.
- b. If the donor answers yes, ask the following questions:
 - 1) Between 1980 through 1996 did you spend time that adds up to 3 months or more in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands)?
 - 2) Since 1980 have you received a transfusion of blood, platelets, plasma, cryoprecipitate, or granulocytes in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands)?
 - 3) Since 1980 have you spent time that adds up to 5 years or more in France?
 - 4) Between 1980 through 1996, were you a member of U.S. military, a civilian military employee or a dependent of a member of the U.S. military?

If the donor answers no, you need not take any further action.

If the donor answers yes, ask the following question:

Did you spend a total time of 6 months or more associated with a military base in any of the following countries:

- From 1980 through 1990 in Belgium, the Netherlands, or Germany.
- From 1980 through 1996 in Spain, Portugal, Turkey, Italy, or Greece.

NOTE: For Questions 1) and 4), you only need to question donors once, because these questions encompass a discrete time frame. You should administer Questions 2) and 3) to frequent Source Plasma donors at intervals of no greater than 4 months, and to all other donors, at each donation.

Phase II: To identify donors who have additional geographic risk of BSE exposure.

For donors of Whole Blood, components intended for transfusion, and Source Leukocytes, you should *substitute* the following for question 3) in Phase I (section IV.D.3.):

Question) Since 1980 have you spent time that adds up to 5 years or more in Europe (including time spent in the U.K. from 1980 through 1996)?

Donors deferred based on this question remain eligible to donate Source Plasma, unless they are otherwise unsuitable.

For Donors of Source Plasma, however, you should *continue to ask* Question 3) from Phase I (section IV.D.3.):

Question 3) Since 1980 have you spent time that adds up to 5 years or more in France?

European countries with BSE risk that FDA has identified as a basis for donor deferral are listed in the Appendix to this document. We will periodically issue new guidance to update the list of countries with BSE risk, to be used as a basis for donor deferral.

4. To identify donors who have been injected with bovine insulin since 1980, you should ask donors with diabetes the following question:

Question 5) Since 1980, have you ever injected bovine (beef) insulin?

Since the above question applies to a subset of potential donors, you may ask it as a secondary question to a general medication question if a donor responds that they have taken insulin. If the donor answers “yes” or “I don’t know” to the question, you should indefinitely defer that donor, unless it can be documented that the product was not manufactured from cattle in the United Kingdom after 1980.

NOTE: Donors of Whole Blood, blood components, Source Leukocytes, and Source Plasma who otherwise should be indefinitely deferred based on their response to the questions specified in sections IV.D.3., and IV.D.4. may continue to donate if they are participating in a CBER-approved program that allows collection of blood components solely for use in manufacturing of non-injectable products. We recommend special labeling for products obtained from such donors. (See section VII.A.)

V. POST-DONATION INFORMATION: RECOMMENDATIONS FOR PRODUCT RETRIEVAL AND QUARANTINE, CONSIGNEE NOTIFICATION, AND BIOLOGICAL PRODUCT DEVIATION REPORTING

A. Whole Blood and Blood Components Intended For Transfusion, Cellular Blood Components Intended For Further Manufacture Into Injectable Products, and Source Plasma From Donors With CJD Or CJD Risk Factors

1. Product Disposition

If you receive post-donation information about a donor with CJD or CJD risk factors, you should immediately retrieve and quarantine for subsequent destruction all in-date blood components (including Whole Blood, blood components intended for transfusion, Source Leukocytes, and Source Plasma), all in and out-of-date cellular blood components intended for manufacturing into injectable products, and all recovered plasma that are under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components for subsequent destruction.

NOTE: If you have sent Source Plasma or recovered plasma to a consignee and receive post donation information about a donor with CJD or CJD risk factors, at a time when you know the plasma units have been pooled, you should not conduct product retrieval or consignee notification for those units.

2. Biological Product Deviation Reports

You should file a BPDR (21 CFR 606.171) if the product was distributed.

B. Whole Blood and Blood Components Intended For Transfusion, Source Leukocytes and Other Cellular Blood Components Intended For Further Manufacture Into Injectable Products, From Donors With Geographic Risk Deferrals and/or Exposure to Bovine Insulin Made in the U.K. Since 1980

1. Phase I deferrals

a. Product Disposition

If you receive post donation information about a donor with Phase I geographic risk factors, you should immediately retrieve and quarantine for subsequent destruction all in-date blood components (including Whole Blood, blood components intended for transfusion, and Source Leukocytes), and all in and out-of-date cellular blood components intended for manufacturing into injectable products, that are under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components for subsequent destruction.

b. Biological Product Deviation Reports

i) Components collected before implementation of donor deferral:

A BPDR is not required.

ii) Components collected after implementation of donor deferral:

You should file a BPDR (21 CFR 606.171) if the product has been distributed.

2. Phase II deferrals

a. Product Disposition

i) Products collected before implementation of donor deferral:

If you receive post donation information about a donor with Phase II geographic risk factors, we do not recommend that you conduct quarantine, retrieval, or consignee notification for products collected before implementation of Phase II donor deferrals. We make this recommendation based on the low amount of BSE exposure in non-U.K. Europe as a whole, and to mitigate the expected impact upon supply of donor deferrals for 5 years or

more residence in Europe.

ii) Products collected after implementation of donor deferral:

If you receive post-donation information about a donor with Phase II geographic deferrals, you should immediately retrieve and quarantine for subsequent destruction all in-date blood components (including Whole Blood, blood components intended for transfusion, and Source Leukocytes), and all in and out-of-date cellular blood components intended for manufacturing into injectable products, that are under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components for subsequent destruction.

b. Biological Product Deviation Reports

i) Components collected before implementation of donor deferral:

A BPDR is not required.

ii) Components collected after implementation of donor deferral:

You should file a BPDR (21 CFR 606.171) if the product has been distributed.

3. Donors with exposure to bovine insulin made in the U.K. since 1980

a. Product Disposition

If you receive post-donation information about a donor exposure to bovine insulin made in the U.K. since 1980, you should immediately retrieve and quarantine for subsequent destruction all in-date blood components (including Whole Blood, blood components intended for transfusion, Source Leukocytes), and all in and out-of-date cellular blood components intended for manufacturing into injectable products, that are under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components for subsequent destruction.

b. Biological Product Deviation Reports

You should file a BPDR (21 CFR 606.171) if the product has been distributed.

C. Source Plasma and Recovered Plasma from Donors with Geographic Risk Deferrals and/or Exposure to Bovine Insulin Made in the U.K. Since 1980

1. Product Disposition

- a. Products collected prior to implementation of donor deferral:

We do not recommend quarantine, retrieval, or consignee notification if components were collected before donor deferral implementation.

- b. Products collected after implementation of donor deferral:

If you receive post-donation information about a donor with geographic risk factors, or exposure to bovine insulin made in the U.K. since 1980, you should immediately retrieve and quarantine for subsequent destruction all in-date Source Plasma and all recovered plasma under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components for subsequent destruction.

NOTE: If you have sent Source Plasma or recovered plasma to a consignee and receive post donation information about a donor with geographic risk factors, or exposure to bovine insulin from the U.K. at a time when you know the plasma units have been pooled, you should not conduct product retrieval or consignee notification for those units.

2. Biological Product Deviation Reports

- a. Components collected prior to implementation of donor deferral:

A BPDR is not required.

- b. Components collected after implementation of donor deferral

You should file a BPDR (21 CFR 606.171) if the product has been distributed.

D. Whole Blood and Blood Components Intended For Transfusion, Recovered Plasma, Source Leukocytes, Other Cellular Blood Components Intended For Manufacturing Into Injectable Products, and Source Plasma From Donors With vCJD, Suspected vCJD, or CJD Diagnosis and Age <55 Years

1. Product Disposition

If you receive post-donation information about a donor with vCJD, suspected

vCJD, or CJD diagnosis and age <55 years, you should immediately retrieve and quarantine for subsequent destruction, all in-date blood components (including Whole Blood, blood components intended for transfusion, Source Leukocytes, and Source Plasma), all recovered plasma, and all in and out-of-date cellular blood components intended for manufacturing into injectable products, that are under your control. You should, within one week of receiving post-donation information, notify all consignees to immediately retrieve and quarantine implicated components, for subsequent destruction.

You may save the collected material for use in research on vCJD by qualified laboratories (see section VII.A. for labeling recommendations).

2. Biological Product Deviation Reports

The regulations require you to file a BPDR as soon as possible and in no event later than 45 calendar days after you discover the event (21 CFR 606.171(c)). We request that you notify the FDA as soon as possible, and do not wait 45 days, about events involving the collection of donations from donors later diagnosed with vCJD or suspected vCJD. FDA will respond to telephone inquiries (301) 827-6190, in order to facilitate speedy notifications. We intend to consult with the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the CDC, (404) 639-3091, in the event that we receive a report of a donor with vCJD or suspected vCJD.

E. Plasma Derivatives

1. Plasma derivatives from donors with CJD or CJD risk factors, or geographic risk deferrals (as defined in section IV.D.):

We are not recommending that you withdraw pooled plasma, intermediates, and plasma derivatives manufactured from these donors.

2. Plasma derivatives from donors diagnosed with vCJD, or suspected vCJD

a. Product Disposition

If you receive post-donation information about a donor with vCJD or suspected vCJD, you should immediately retrieve and quarantine for subsequent destruction any pooled plasma, intermediates, derivatives, and any other material containing plasma from such a donor. Alternatively, you may save the material for use in research on vCJD by qualified laboratories (see section VII.A. for labeling recommendations). You should not use such material for non-injectable products.

You should, within a week of receiving a post-donation report of vCJD or suspected vCJD diagnosis, notify all consignees to immediately retrieve

and quarantine for subsequent destruction pooled plasma, intermediates, and derivatives, and any other materials containing plasma from the vCJD donor.

b. Biological Product Deviation Reports

The regulations require you to file a BPDR as soon as possible and in no event later than 45 calendar days after you discover the event (21 CFR 606.171(c)). We request that you notify the FDA as soon as possible, and do not wait 45 days, about events involving the collection of donations from donors later diagnosed with vCJD or suspected vCJD. FDA will respond to telephone inquiries (301) 827-6190, in order to facilitate speedy notifications. We intend to consult with the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the CDC, (404) 639-3091, in the event that we receive a report of a donor with vCJD or suspected vCJD.

3. Plasma derivatives from donors with a physician's clinical or pathological diagnosis of CJD and age less than 55 years:

a. Product Disposition

We will make recommendations to quarantine and withdraw plasma derivatives from such donors on a case-by-case basis, depending upon results of the investigation. We may recommend quarantine and withdrawal of products if available information is ambiguous, and does not clearly eliminate the possibility of vCJD. You should treat quarantined and withdrawn material from such donors in the same manner as for vCJD (see section V.D.).

b. Biological Product Deviation Reports

The regulations require you to file a BPDR as soon as possible and in no event later than 45 calendar days after you discover the event (21 CFR 606.171(c)). We request that you notify the FDA as soon as possible, and do not wait 45 days, about events involving the use of material from donors with CJD diagnosis and age <55. FDA will respond to telephone inquiries (301) 827-6190, in order to facilitate speedy notifications. We intend to consult with the CJD Surveillance Unit of the Division of Viral and Rickettsial Diseases of the CDC, (404) 639-3091, in the event that we receive a report of a donor with CJD diagnosis and age <55.

F. Disposal of Retrieved and Quarantined Products

TSE agents are quite resistant to most disinfecting regimens. There is no current consensus on specific details of decontamination requirements for blood products.

However, methods of destruction of TSE-implicated material include steam autoclaving at 132°C for 1-4 hours, incineration, or treatment with 1 N NaOH or concentrated sodium hypochlorite for at least 1 hour. These treatments are known to diminish (but may not completely eliminate) infectivity (Refs. 45-49).

You may save blood components and plasma derivatives from donors with vCJD, or which have been withdrawn because the donor might have vCJD, to use in research on vCJD by qualified laboratories (see section VII.A. for labeling recommendations).

VI. RECOMMENDATIONS FOR RECIPIENT TRACING AND NOTIFICATION

It may be appropriate to identify blood components for transfusion prepared from prior collections from any donor found to have CJD, vCJD, suspected vCJD, risk factors for CJD, or if withdrawal is recommended in cases under investigation for vCJD (CJD diagnosis and age <55). In those situations, consignee notification could enable the consignee to inform the physician, or other qualified personnel responsible for the care of the recipients, so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of health care providers.

For transfusable components from a donor with one family member diagnosed with CJD, or with risk factors for vCJD (due to geographic risk deferral, transfusion in the U.K. between 1980 and the present, or due to injection of bovine insulin), we believe it is not appropriate to conduct tracing and notification of recipients of prior donations.

It may be appropriate to identify plasma derivatives prepared from prior collections from any donor found to have vCJD, suspected vCJD, or if withdrawal is recommended in cases under investigation for vCJD (CJD diagnosis and age <55). In those situations, consignee notification could enable the consignee to inform the physician, or other qualified personnel responsible for the care of the recipients, so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of health care providers.

VII. LABELING RECOMMENDATIONS

A. Labeling of Blood and Blood Components from Deferred Donors for Research, or Intended for Further Manufacture into Non-Injectable Products

You should label blood and blood components from donors with CJD, who are at increased risk for CJD, or who have potential exposure to the agent of vCJD with the following statements:

1. “Biohazard”;

2. “Collected from a donor determined to be at risk for CJD”; or “Collected from a donor diagnosed with CJD”; or “Collected from a donor with potential risk of exposure to variant CJD”; and
3. “Caution: For laboratory research use only”; or “Caution: For use in manufacturing non-injectable products only.”

You should not use blood or blood components from donors diagnosed with vCJD for further manufacture into non-injectable products. However blood components and plasma derivatives from donors with vCJD, suspected vCJD, or which have been withdrawn on a case-by-case basis for suspicion of vCJD, may be used in laboratory research on vCJD by qualified laboratories. You should label these products with the following statements:

1. “Biohazard”;
2. “Collected from a donor with variant CJD”; and
3. “Caution: Only for laboratory research on variant CJD”.

B. Labeling of Non-Implicated Products

No transmission of CJD or vCJD by human blood, blood components or plasma derivatives has been documented to date. However, as a prudent notice, we recommend that all blood, blood components and plasma-derived products include labeling to address the theoretical risk. Because albumin has never been known to transmit viral diseases, and because laboratory experiments suggest that albumin is less likely to contain CJD-like agents than other plasma fractions, the package insert for albumin, and products containing albumin, may contain a more specific statement.

1. For Whole Blood and blood components intended for transfusion, the Circular of Information should be revised to include under “Side Effects and Hazards,” the following statement:

“Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

Until the circular is revised, you may insert or attach this statement to the current circular.

2. For plasma-derived products other than albumin, you should revise the package insert warning section to include the following statement:

“Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

3. For plasma-derived albumin, you should revise the package insert warning section to include the following statement:

“Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.”

4. For products containing plasma-derived albumin, you should revise the package insert warning section to include the following statement:

“This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.”

VIII. IMPLEMENTATION OF RECOMMENDATIONS

We recommend that you implement, by May 31, 2002, all recommendations contained in this guidance including labeling, with the exception of the Phase II deferral, described in section IV.D.3. (deferral of donors who have lived in Europe for five years or more, 1980 - present).

We recommend that you implement, by October 31, 2002, the Phase II deferral (section IV.D.3.).

You may implement these changes without prior approval from the agency. Licensed blood establishments should report the changes to FDA in the following manner:

- Report changes in your donor questionnaire in your annual report (21 CFR 601.12(d)).
- Submit labeling changes as a Changes Being Effected supplement (21 CFR 601.12(f)(2)).

IX. PILOT PROGRAMS TO ASSESS THE IMPACT OF GEOGRAPHIC DONOR DEFERRALS THAT ARE MORE STRINGENT THAN THOSE RECOMMENDED BY THIS GUIDANCE

A more stringent geographic donor deferral policy (deferral for a cumulative period of 6 months or more in Europe since 1980 or a cumulative period of 3 months or more in the United

Kingdom since 1980) was proposed as an initiative in early 2001 by a member of the blood industry. Based upon the BSE geographic relative risk model proposed by the FDA and CDC and reviewed by the TSEAC (Ref. 30), both the industry-proposed and FDA-proposed deferrals result in an estimated one-log reduction of theoretical risk (Ref. 30). Importantly, the donor loss for the industry proposal, if implemented on a national basis, is estimated by FDA to be at least 8-9% (3-4% higher than the FDA-recommended policy).

In response to this industry initiative, some blood establishments may wish to implement geographic donor deferrals that are more stringent than the FDA-recommended policy. We are concerned that blood availability may be more severely affected by more stringent periods of deferral than those outlined by this draft guidance. If you wish to implement donor deferrals other than those recommended in this guidance, you should undertake such pilot programs only as a part of a carefully structured plan that includes the following elements:

Prior to implementation:

- ◆ Demonstrate an augmented donor recruitment program sufficient to offset projected donor losses,
- ◆ Define an endpoint (or stopping rules) for the pilot program at which time deferral policy will be determined or an additional pilot period will be implemented,
- ◆ Define a contingency plan for maintaining blood supplies in the event that local recruitment efforts are insufficient to meet patient demand, and

During the pilot period:

- ◆ Monitor the loss of donors, the nature and effectiveness of donor recruitment efforts, and fluctuations in hospital demand for blood products.

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APPENDIX: LIST OF EUROPEAN COUNTRIES WITH BSE, OR AT RISK OF BSE APPLICABLE TO DONOR DEFERRAL

The list below includes all European countries on the current U.S. Department of Agriculture (USDA) BSE list (January 6, 1998). The current USDA list of countries with BSE or at risk of BSE may be found at 9 CFR 94.18(a).

European Countries List to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Republic of Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom¹, and Federal Republic of Yugoslavia.

¹ For purposes of this guidance, the United Kingdom should be taken to include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

TABLE 1: DONOR DEFERRAL, PRODUCT DISPOSITION, RECIPIENT NOTIFICATION FOR WHOLE BLOOD, BLOOD COMPONENTS INTENDED FOR TRANSFUSION, SOURCE LEUKOCYTES, AND OTHER CELLULAR BLOOD COMPONENTS INTENDED FOR FURTHER MANUFACTURE

Risk	Deferral	Disposition of Product	BPDR (21 CFR 606.171) for previously distributed product	Recipient Tracing/Notification
Diagnosed with vCJD, or suspected vCJD, CJD, or CJD and age <55	Permanent	Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	Yes	Consignee notified, consignee informs responsible caretaker for discretionary recipient notification, counseling
Risk factors for CJD: Receipt of pituitary-derived growth hormone, or dura mater transplant Family history of CJD in >1 family member	Permanent Indefinite; reentry if genetic testing does not reveal CJD- associated prion protein allele	Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	Yes	Consignee notified, consignee informs responsible caretaker for discretionary recipient notification, counseling
CJD in only 1 family member	Indefinite; reentry if genetic testing does not reveal CJD- associated prion protein allele	Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	Yes	No
Phase I Geographic donor deferrals (U.K. ≥3 months 1980- 1996; France ≥5 years 1980- present; military in Europe as specified, transfusion in U.K. since 1980)	Indefinite	Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	No – if prior to deferral implementation	No
			Yes - if after deferral implementation	

TABLE 1 : Continued

Risk	Deferral	Disposition of Product	BPDR (21 CFR 606.171) for previously distributed product	Recipient Tracing/Notification
Phase II Geographic donor deferrals (Europe ≥5 years 1980- present)	Indefinite	Collected prior to deferral implementation - No retrieval, quarantine, consignee notification	No – if prior to deferral implementation	No
		Collected after deferral implemented – Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	Yes - if after deferral implementation	
Bovine insulin injection	Indefinite, donor reentry if proof of non-U.K. insulin source	Immediately retrieve, quarantine/notify consignees for all in-date products and all out-of-date cellular blood components intended for manufacturing into injectable products.	Yes	No

TABLE 2: DONOR DEFERRAL, PRODUCT DISPOSITION, AND RECIPIENT NOTIFICATION FOR PLASMA AND PLASMA DERIVATIVES¹

Risk	Deferral	Disposition of Product	BPDR (21 CFR 606.171) for previously distributed product	Recipient Tracing/ Notification
Phase I Geographic donor deferrals (U.K. ≥ 3 months 1980-1996; France ≥ 5 years 1980-present; military in Europe as specified, transfusion in U.K. since 1980)	Indefinite	SP and RP: Collected prior to deferral implementation- No retrieval, quarantine, consignee notification	No – if prior to deferral implementation	No
		SP and RP: Collected after deferral implementation – Immediately retrieve, quarantine, notify consignees of in-date SP and all RP unless known to be previously pooled	Yes- if after deferral implementation	
		PD: No retrieval, quarantine, consignee notification	No	
Phase II Geographic donor deferrals (Europe ≥ 5 years 1980-present) SP	No deferral	SP: <i>All phase I deferrals remain in place</i> , e.g., U.K. ≥ 3 months 1980-1996; France ≥ 5 years 1980-present; military in Europe as specified; transfusion in the U.K. since 1980. There is no Phase II deferral for SP.	Not applicable	No
Phase II Geographic donor deferrals (Europe ≥ 5 years 1980-present) RP	Indefinite	RP: Collected prior to deferral implementation- No retrieval, quarantine, consignee notification	No- if collected prior to deferral implementation	
		RP: Collected after deferral implementation: Immediately retrieve, quarantine, notify consignees for all RP unless known to be previously pooled	Yes – if collected after deferral implementation	
		PD: No retrieval, quarantine, consignee notification	No	
Bovine insulin injection	Indefinite, donor reentry if proof of non-U.K. insulin source	SP and RP: Immediately retrieve, quarantine/notify consignees for in-date SP and all RP unless plasma known to be previously pooled	Yes	No
		PD: No retrieval, quarantine, consignee notification	No	No

¹ Abbreviations: SP, Source Plasma; RP, recovered plasma; PD, plasma derivatives; BPDR, Biological Products Deviation Report

TABLE 2: Continued

Risk	Deferral	Disposition of Product	BPDR (21 CFR 606.171) for previously distributed product	Recipient Tracing/Notification
Diagnosed with vCJD, suspected vCJD	Permanent	SP and RP: Immediately retrieve, quarantine/notify consignees for in-date SP and all RP PD: Immediately retrieve, quarantine, notify consignees	Yes Yes	Consignee notified, consignee informs responsible caretaker for discretionary recipient notification, counseling
Diagnosed with CJD and age <55	Permanent	SP and RP: Disposition decided case-by-case depending upon investigation results PD: Disposition decided case-by-case depending upon investigation results	Yes Decided upon case-by-case	Case-by-case recommendation, depending upon investigation results
Diagnosed CJD (and age ≥ 55)	Permanent	SP and RP: Immediately retrieve, quarantine/notify consignees for in-date SP and all RP unless known to be previously pooled PD: No retrieval, quarantine, consignee notification	Yes No	No No
Risk factors for CJD: Receipt of pituitary-derived growth hormone, or dura mater transplant Family history of CJD in >1 family member	Permanent Indefinite	SP and RP: Immediately retrieve, quarantine/notify consignees for in-date SP and all RP unless known to be previously pooled PD: No retrieval, quarantine, consignee notification	Yes No	No No
CJD in only 1 family member	Indefinite; reentry if genetic testing does not reveal CJD-associated prion protein allele	SP and RP: Immediately retrieve, quarantine/notify consignees in-date SP and all RP unless known to be previously pooled PD: No retrieval, quarantine, consignee notification	Yes No	No No