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

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Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

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

Guidance for Industry

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I. INTRODUCTION

This guidance is the latest in a series of guidances addressing the risk of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD)[1] transmission by blood and blood products.

- In 1999, we, FDA, issued a document entitled "Guidance for Industry: 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" dated November 1999 (1999 guidance).[2]
- In 2002, we issued a document entitled "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" dated January 2002 (2002 guidance).[3]
- In 2006, we issued a draft document entitled "Draft Guidance for Industry: Amendment (Donor Deferral for Transfusion in France Since 1980) to 'Guidance for Industry: Revised Preventive Measures to Reduce the Possible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Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products'" dated August 2006 (2006 draft guidance).

[1] We have retained the same nomenclature used in previous guidance documents for the new variant of CJD (originally abbreviated "nvCJD," but later as "vCJD"). We refer to all other forms of CJD (sporadic, familial and iatrogenic) as "CJD."

[2] The 1999 guidance addressed the theoretical possibility that a new variant of CJD that had been plausibly attributed to human infection with the agent of bovine spongiform encephalopathy might be transmissible from human to human through blood and blood products.

[3] The 2002 guidance superseded the 1999 guidance and recommended new deferrals for certain donors at risk of exposure to BSE.

- In 2010, we issued a document entitled "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" dated May 2010 (2010 guidance).[4]
- Finally, in 2012, we issued a draft guidance entitled "Draft Guidance for Industry: Amendment to 'Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products,'" dated June 2012 (2012 draft guidance), which recommended revised labeling of plasma-derived products to reflect current understanding of vCJD transmission through blood and blood products.

This guidance amends the 2010 guidance and finalizes the 2012 draft guidance. This guidance incorporates the recommendations from the 2012 draft guidance for revised labeling for plasma-derived products, including albumin and products containing plasma-derived albumin. This guidance also provides manufacturers of plasma-derived products with recommendations on how to report the labeling changes to FDA under 21 CFR 601.12. All other recommendations in the 2010 guidance are unchanged.[5]

In addition, this guidance amends the 2010 guidance by: a) including information relevant to the new labeling recommendations; b) providing updated information on the global vCJD and Bovine Spongiform Encephalopathy (BSE) epidemics in Section II; c) clarifying the reentry criteria for a donor with a family history of CJD in Section IV.C.; d) clarifying the requirements related to biological product deviation reporting in Section V. and in Tables 1 and 2 of the Appendix; and e) updating, adding, and removing certain footnotes and references.

Tests are being developed to detect CJD and vCJD infections in blood and plasma donors. However, until suitable donor screening tests become available, FDA continues to recommend interim preventive measures based on the available scientific data and the evolving state of knowledge regarding these diseases.

We expect that additional epidemiological information will become available as the epidemics of vCJD and BSE continue to 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.

This guidance applies to Whole Blood and blood components intended for transfusion, and blood components intended for use in further manufacturing into injectable and non-injectable products,

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[4] The 2010 guidance finalized the donor deferral recommendation from the 2006 draft guidance (for donors who have received a transfusion of blood or blood components in France since 1980); provided updated scientific information; and revised labeling recommendations for Whole Blood and blood components intended for transfusion.

[5] FDA discussed potential changes to the geographic exposure based deferrals for risk of vCJD with its Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) in June 2015. Available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/ucm444810.htm. FDA intends to address revised recommendations for geographic donor deferrals in future guidance documents.

including recovered plasma, Source Leukocytes and Source Plasma, and plasma derivatives. Within this document, "donors" refers to donors of Whole Blood and blood components and "you" refers to blood collecting establishments or manufacturers of plasma derivatives.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. CJD and vCJD

CJD is a rare but invariably fatal degenerative disease of the central nervous system, one of a group of transmissible diseases called transmissible spongiform encephalopathies (TSEs) or prion diseases. TSEs are associated with a poorly understood transmissible agent (Refs. 1-6), now designated TSE agents or prions (Ref. 7). Cases of sporadic CJD—the most common human TSE—occur at low frequency by an unknown mechanism. CJD may be acquired by an identified exogenous (usually iatrogenic) exposure to infectious material; or it may be familial, associated with one of a number of mutations in the prion-protein-encoding (*PRNP*) gene. Clinical latency for iatrogenic CJD, following point exposures to contaminated materials, has sometimes exceeded 30 years (Ref. 8); incubation periods of kuru—another human TSE—appear to have sometimes exceeded 50 years (Ref. 9).

In 1996, a previously unrecognized variant of CJD, now designated vCJD, was reported in the United Kingdom (U.K.) (Ref. 10). vCJD is distinguished from CJD by differences in clinical presentation, cerebral imaging and neuropathologic changes, summarized in Table 1 (Refs. 10-14).

Table 1. vCJD compared with CJD[6]

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	No diagnostic EEG changes	Diagnostic EEG changes commonly seen
Median duration of illness (Ref. 15)	13 months	4 months
MRI abnormalities (Refs. 16-17)	Hyperintensity in pulvinar; little atrophy in cerebral cortical gray matter	Hyperintensity in putamen and caudate nucleus; atrophy of cerebral cortical gray matter
Neuropathologic features	Florid prion protein plaques, surrounded by spongiform changes	Florid prion plaques uncommon
Immunohistochemistry (Ref. 18)	Abnormal accumulations of prion protein detectable in lymphoid tissues	Abnormal accumulations of prion protein not detected in lymphoid tissues

The unique accumulation of abnormal prion protein seen in vCJD lymphoid tissues led to concerns that transmission of vCJD by blood might be a greater risk than for CJD (Ref. 19). Presumptive transmissions of vCJD by transfusions and possible transmission of vCJD by plasma-derived Factor VIII were subsequently reported in the U.K. (see Section II.C. below). 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

[6] See Centers for Disease Control and Prevention (CDC) fact sheet at http://www.cdc.gov/prions/vcjd/index.html for more information.

3. High-density accumulations of abnormal prion protein, particularly in the cerebrum and cerebellum as shown by immunohistochemistry and other techniques (Ref. 20).

However, a clinical diagnosis of "suspected" vCJD can be made based upon certain clinical features, if adequate neuropathological specimens are unavailable. Although recommended diagnostic evaluations and criteria for vCJD are evolving, the Centers for Disease Control and Prevention (CDC) classifies cases in the United States (U.S.) with all of the following features as suspected vCJD:

1. Current age (if alive) or age at death less than 55 years;
2. Persistent painful sensory symptoms and/or psychiatric symptoms at clinical presentation;
3. Dementia, and delayed development (≥four 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 electroencephalogram (EEG) but not the diagnostic EEG changes often seen in classic CJD;
5. Duration of illness of at least six months;
6. Routine investigations do not suggest an alternative non-CJD diagnosis;
7. A history of possible exposure to BSE (e.g., residence or travel in a BSE-affected country from 1980 to the present);
8. No history of iatrogenic exposure to CJD, such as receipt of a dura mater allograft or injection of human cadaveric pituitary-derived hormones; and
9. Absence of a mutation in the *PRNP* gene, or, if this has not been determined, no history of CJD in a first-degree relative.

As of May 2015, 228 patients, including 177 in the U.K., 27 in France and 25 in ten other countries (including four in the U.S. and two in Canada), have been diagnosed with clinical vCJD (definite and probable cases).[7] The size of the vCJD epidemic has not yet been determined with certainty. (Refs. 21-24). Deaths from vCJD in the U.K. appeared to have peaked in 2000 and have subsequently decreased.[8] However, additional "waves" of cases in the U.K. and elsewhere have been predicted by some experts and the possibility of an increased incidence of cases in the future cannot be dismissed (Refs. 22-25).[9] Of the four cases of vCJD identified in the U.S., two were in former residents of the U.K., one in a former resident of Saudi Arabia and one in a former resident of Kuwait

[7] The European and Allied Countries Collaborative Study Group of CJD (EUROCJD) plus the Extended European Collaborative Study Group of CJD (NEUROCJD) at http://www.eurocjd.ed.ac.uk/surveillance%20data%201.html.
[8] NCJDSU at http://www.cjd.ed.ac.uk.
[9] See also, McKie, R. "Warning over second wave of CJD cases. Scientists say that threat of brain illness returning will persist for decades," Observer, Aug. 3, 2008 at 11; Collinge, J. et al. (2006) "Kuru in the 21st century—an acquired human prion disease with very long incubation periods." Lancet **376**: 2068-74.

and the former Soviet Union.[10] Cases of vCJD have also been reported from the Republic of Ireland (4), Japan (1), Italy (2), the Netherlands (3), Portugal (2), Saudi Arabia (1), Taiwan (1) and Spain (5). Most of these cases occurred in persons who had never resided in the U.K. Laboratory and epidemiologic studies have linked vCJD to human infection with the agent of BSE, probably acquired from contaminated beef products (Refs. 25-26).

B. Evolution of the Global BSE Epidemic

The vCJD and BSE epidemics have continued to evolve. BSE cases have been reported in over 20 countries of Europe, including Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, the Republic of Ireland, Italy, Liechtenstein, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the U.K. BSE has also been identified in Japan (36 cases) and Israel (1 case).[11]

1. BSE in Europe

In the U.K., BSE infections probably first occurred in cattle in about 1980, although the disease was not recognized there until 1985. Cases of BSE in the U.K. peaked in 1992. That year, over 37,000 confirmed cases were reported to the World Organization for Animal Health (OIE), with reports falling to low levels by 1996 as a result of control measures. U.K. authorities reported 114 confirmed cases to the OIE in 2006.[12] While the current prevalence of BSE is much lower a few cases continue to be reported yearly in Europe.[13]

2. BSE in Asia and the Middle East

Following the first recognized case of BSE in Japan in 2001, a total of 36 cattle with the disease have been reported to OIE.[14] Israel reported a single case of BSE in 2002 but no additional cases have been reported.[15]

3. BSE in North America

BSE was first confirmed in Canada in 1993 in a cow imported from the U.K. The first reported case of BSE in a native-born Canadian cow occurred ten years later. As of February 2015, 21 cases of BSE in Canada have been detected, 20 of which

[10] See CDC fact sheet at http://www.cdc.gov/prions/vcjd/vcjd-reported.html and http://www.cdc.gov/prions/vcjd/news.html; also see Maheshwari A, et.al. Recent US case of variant Creutzfeldt-Jakob disease—global implications. Emerging Infectious Diseases 2015;21:750-9.
[11] World Organization for Animal Health (OIE) at http://www.oie.int/en/anial-health-in-the-world/bse-specific-data/.
[12] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/.
[13] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/.
[14] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/.
[15] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/.

are in native-born Canadian cattle.[16] The first case of BSE in the U.S. was confirmed in 2003 in a Canadian-born cow. Three cases were later detected in U.S.-born cows.[17] The overall prevalence of BSE in U.S. cattle was estimated by the United States Department of Agriculture (USDA), based on the results of a temporarily enhanced active surveillance program, to be very low—less than one case per million cattle at the 95 percent confidence level, based on an adult cattle population of 42 million animals.[18]

C. TSE Agents and Blood

1. Potential Risk of Transmitting CJD by Transfusion

In 1978, blood of guinea pigs experimentally infected with the CJD agent was found to transmit infection to normal guinea pigs (Ref. 27). Subsequently, blood of mice with experimentally induced TSE was also found to contain the transmissible agent (Ref. 28). Transmission of BSE has been repeatedly achieved by blood transfusions from experimentally infected sheep to normal sheep (Refs. 29-30), and infection has also been transmitted by transfusions of blood from scrapie-infected sheep (Refs. 30-31). In blood of hamsters infected with scrapie—the most thoroughly studied model of TSE—infectivity, although detectable in all components, appeared to be mainly associated with both nucleated cells and plasma (Ref. 32).

Based on repeated demonstrations that the blood of animals infected with a variety of TSE agents sometimes contained infectivity (Ref. 33) and the recognition that iatrogenic CJD had been transmitted by human cadaveric pituitary growth hormones (Ref. 34), FDA recommended in 1987[19] that persons identified by history to be at increased risk for CJD because they had received human cadaveric pituitary growth hormone injections be deferred from donating blood. These recommendations were later broadened in August 1995 and slightly revised in December 1996[20] to include deferral of donors who had been treated with human dura mater allografts, also implicated in iatrogenic transmission of CJD (Ref. 35), and donors who had a family history of CJD, because of its association with a transmissible agent similar to those found in sporadic and

[16] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data and the Canadian Food Inspection Agency at http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/bse/fact-sheet/eng/1363892691907/1363893176627.
[17] OIE at http://www.oie.int/eng/info/en_esbmonde.htm and USDA at http://www.ars.usda.gov/research/publications/publications.htm?seq_no_115=197033.
[18] USDA at http://www.usda.gov/wps/portal/usda/usdahome?contentid=BSE_Ongoing_Surveillance_Information_Center.html&contentidonly=true.
[19] See FDA memo at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063012.pdf.
[20] June 2, 1999 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3518t1.rtf.

iatrogenic CJD (Refs. 2 and 36). Subsequently, a number of published epidemiological studies failed to suggest that CJD (sporadic, familial, and iatrogenic forms) had been transmitted by blood and blood products. This evidence included five case-control studies of over 600 CJD cases, two lookback studies tracing recipients of components from blood of donors later found to have CJD, and two autopsy studies of patients with hemophilia (Refs. 37-43). None of these studies linked CJD to receipt of blood or blood products. Nonetheless, FDA continues to recommend (1) deferrals for donors at increased risk for CJD; and (2) market withdrawal and retrieval of labile blood components from donors when post-donation information reveals an increased risk of CJD.

In 1998, FDA recommended that—with the exceptions discussed below—plasma derivatives no longer be withdrawn when post-donation information reveals that a plasma donor had been diagnosed with CJD or was at increased risk for CJD.[21] That change in policy was based mainly on the following information: (1) the CDC reviewed 3,642 reported CJD deaths over a period of 16 years (later increased to 4,468 reports) and concluded that no reported CJD case had any other diagnosis of a condition associated with frequent receipt of blood or blood products (hemophilia, thalassemia, or sickle cell disease (Ref. 44)); and (2) experimental studies with animal models suggested that procedures used in manufacture consistently and substantially lowered the amounts of infectious material present in most plasma derivatives (Ref. 45).

Also in 1998, the U.S. Surgeon General[22], in collaboration with NIH, CDC and FDA, concluded that previous withdrawals of plasma derivatives from donors who were later determined to have CJD or have been at increased risk for CJD did not improve the safety of plasma derivatives. In addition, the U.S. Surgeon General concluded that the withdrawal of plasma derivatives from such donors contributed to serious shortages of immunoglobulin products. Further withdrawals of "CJD-implicated" plasma derivatives would be indicated only if a plasma donor was later found to have vCJD (or CJD with onset before age 55 where vCJD could not be excluded on a case-by-case basis). Since then, accumulating evidence has repeatedly confirmed that several manufacturing processes commonly used to manufacture plasma derivatives are effective in removing from plasma both abnormal forms of the prion protein and infectivity spiked into blood (Refs. 46-52).[23] However, as detailed below in Section II.C.2, there has been one case of transmission of vCJD in the U.K. that may be due to

[21] December 18, 1998 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3484t1.rtf.
[22] FDA website at http://www.fda.gov/NewsEvents/Testimony/ucm115104.htm.
[23] February 20, 2003 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3923t1.htm.

treatment of a patient with a plasma derivative product.[24] Recipients of plasma derivatives are the subject of a continuing lookback study in the U.K. as part of the Transfusion Medicine Epidemiology Review.[25]

2. Evidence that vCJD Has Been Transmitted by Blood Products

Soon after the first description in the U.K. of vCJD affecting 10 young patients in 1996 (Ref. 10), vCJD was recognized to be an emerging infectious disease with several unique clinical and pathological characteristics differing from those of previously known forms of CJD. It was uncertain whether human blood might transmit the vCJD agent. FDA therefore recommended in the 1999 guidance a donor deferral policy more stringent for donors at increased risk of vCJD than for those at increased risk of the "classical" forms of the disease (see Section IV below), including a recommendation to withdraw plasma derivatives should a plasma donor later be diagnosed with vCJD (a situation never recognized in the U.S. to date) and a case-by-case review when a plasma donor is suspected of having vCJD (including all donors with onset of CJD before the age of 55 years) instead of a more common form of CJD.

In December 2003, U.K. authorities reported a case of vCJD in a recipient of non-leukoreduced red blood cell concentrate obtained from a clinically healthy donor who later developed typical vCJD (Ref. 53). In July 2004, a second recipient of non-leukoreduced red blood cell concentrate from another such donor in the U.K. was reported to have died of other causes without clinical or neuropathological evidence of vCJD, but at autopsy the recipient had abnormal accumulations of prion protein in lymphoid tissues (Ref. 54). This finding is typical of vCJD, although the recipient had a *PRNP* genotype (heterozygous for the sequences encoding methionine and valine at *PRNP* codon 129 [129 MV]) not previously found in cases of vCJD (all of which have been 129 MM homozygous). Two additional recipients of non-leukoreduced red blood cell concentrates from a donor incubating vCJD were subsequently reported by U.K. authorities in February 2006 (Refs. 55-56) and January 2007[26] to have died with confirmed vCJD. These four cases provided convincing epidemiological evidence that vCJD infections have been transmitted by non-leukoreduced red blood cell concentrates. Although no other blood components have been associated with transfusion-transmitted vCJD, experience is still too limited to allow a conclusion that other blood components cannot transmit the infection.

[24] U.K. Health Protection Agency (HPA), "vCJD abnormal prion protein found in a patient with haemophilia at post mortem," dated February 17, 2009, and "Variant CJD and plasma products," dated July 27, 2009 at http://www.hpa.org.uk.
[25] Transfusion Medicine Epidemiology Review: http://www.cjd.ed.ac.uk/TMER/TMER.htm.
[26] Transfusion Medicine Epidemiology Review: http://www.cjd.ed.ac.uk/TMER/TMER.htm.

In February 2009, the United Kingdom Health Protection Agency announced evidence of vCJD infection in a patient with type-A hemophilia at postmortem.[27] The patient had been treated with human plasma-derived Factor VIII clotting factor manufactured using plasma from U.K. donors, including one batch that was manufactured using plasma from a donor who later developed typical vCJD. This is the first report that vCJD abnormal protein has been found in a patient with hemophilia or any patient treated with plasma products. The patient, who was over 70 years old, died of other causes and may have been exposed to other risk factors for vCJD. A risk assessment performed by U.K. health authorities concluded that, assuming that the abnormal prion protein finding was a marker for asymptomatic vCJD infection, the most likely source of such an infection was plasma-derived Factor VIII, rather than dietary exposure, endoscopy procedures, or red blood cell transfusions.

At this time, plasma derivatives have not been implicated in vCJD transmission in any country other than the U.K. To date, no U.S.-licensed plasma-derived products have been manufactured from a donor known to have developed vCJD and no cases of vCJD have been reported from use of a U.S.-licensed plasma derivative. In addition, published studies and information submitted to FDA show that certain plasma derivative manufacturing steps can remove TSE infectivity, although such experiments have inherent limitations (Refs. 51, 57). Based on animal studies as well as on FDA risk assessments, the possibility of vCJD transmission by a U.S.-licensed plasma derivative is extremely small.

D. FDA Regulatory History

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 manufacturers 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 that demonstrated absence of a familial-CJD-associated abnormality (mutation) of the prion protein gene—generally requiring complete nucleotide sequencing of both *PRNP* genes. We made no specific recommendations regarding vCJD in that document. Changes to

[27] U.K. Health Protection Agency (HPA), "vCJD abnormal prion protein found in a patient with haemophilia at postmortem," dated February 17, 2009, and "Variant CJD and plasma products," dated July 27, 2009, at http://www.hpa.org.uk.

those recommendations were announced on September 8, 1998, and were incorporated into an August 1999 guidance that was revised and updated in November 1999. Those changes were as follows:

- that you no longer withdraw plasma derivatives containing plasma from donors with CJD or CJD risk factors;
- that you withdraw all material collected from donors diagnosed with vCJD or suspected vCJD; and
- 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.

Because the potential for transmission was unknown, in August 1999, we recommended that, as a preventive measure, 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 have resided in the U.K. for a total of six months or more, between the beginning of 1980 and the end of 1996. We estimated that this policy would result in deferral of donors accounting for approximately 87% of total days of potential dietary exposure to the BSE agent in the U.K. ("donor exposure days").

The period from 1980 through 1996 reflects the peak years of the U.K. BSE epidemic. In 1998, FDA, advised by the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), concluded that measures implemented in the U.K. since 1996 have been adequate to keep the BSE agent out of the human food chain there.[28] As other countries institute similar food chain protections against BSE and the prevalence of BSE in their national cattle herds declines, we expect to reconsider this and other geographic donor deferral policies for other countries.

At its meeting, on June 1, 2000, the TSEAC discussed the possible deferral of donors from other countries known or suspected to be affected by BSE.[29] The TSEAC voted not to recommend new donor deferrals for potential exposures in European countries outside the U.K. at that time. This decision was based on conclusions that: (1) the extent of the BSE epidemic in Europe was undetermined; and (2) U.S. donor deferrals for U.K. residence had only recently been fully implemented so that the potential for adverse impact on the availability of blood and blood products had not yet been fully appreciated. The TSEAC also recommended against changing the U.K. donor deferral period to one shorter than six months.

At its meeting on January 18, 2001,[30] the TSEAC reviewed more recent epidemiological information on exposure to BSE in European countries, and again discussed possible changes to 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 had resided or traveled in the U.K. The TSEAC did recommend

[28] December 18, 1998 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3484t1.rtf.
[29] June 1, 2000 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t1.rtf.
[30] January 18, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t1.rtf.

that deferrals be considered for donors potentially exposed to beef products exported from the U.K. to U.S. military bases in Europe, and for donors potentially exposed to BSE since 1980 in France, Portugal, and the Republic of Ireland. In response to advice from the TSEAC that FDA should consider recommending deferral of donors for residence or travel in Portugal and the Republic of Ireland (i.e., countries where BSE exposure was not related to human consumption of British beef *per se*), we decided to re-examine the issue publicly with the TSEAC on June 28-29, 2001.[31] At this meeting, the TSEAC considered the estimated potential human exposures to the BSE agent in the U.K. and other parts of Europe, as well as estimates of risk reduction and donor loss expected to result from tightened geographic donor deferrals. Specifically, the TSEAC considered three deferral options (including the option proposed by the TSEAC at its January 2001 meeting) and voted (10 for and 7 against) to endorse instead a revised set of recommendations proposed by FDA.

The main features of the recommendation were: (1) deferral of donors for any cumulative travel or residence for a period of five years or more in any European country except the U.K. from 1980 through the present; (2) deferral of donors who spent three months or more in the U.K. from 1980 through the end of 1996; (3) deferral of donors who spent more than six months in Europe on a base of the U.S. Department of Defense (DoD) from 1980 through the end of 1996 (or 1980 through 1990 if all exposure after 1990 was on bases in Northern Europe); and (4) deferral of any recipient of a blood transfusion in the U.K. from 1980 to the present. Deferrals were to be recommended for implementation in two stages within six months of publication by FDA of a final guidance. FDA estimated that the new policy might lead to a loss of 4.6% to 5.3% of blood donors with a 72% reduction in existing vCJD risk, for a total reduction of 90% relative to the risk that had existed prior to implementation of the 1999 recommendations. The TSEAC also evaluated information suggesting that measures taken in the U.K. to prevent human exposure to food-borne BSE agents were adequate to reduce the risk there markedly after the end of 1996. The proposed deferral policy was endorsed by a majority of TSEAC members and used by FDA as the basis for the 2002 guidance.

At its meeting, held jointly with the Blood Products Advisory Committee on January 17, 2002, the TSEAC reviewed the FDA guidance of January 2002 and agreed again - by unanimous vote - that the combination of measures implemented in the U.K. by the end of 1996 to protect the human food chain from BSE contamination were sufficient to obviate the need for donor deferrals based on subsequent travel or residence in the U.K.[32] However, TSEAC members stressed that U.K. authorities must assure vigorous, sustained, and consistent application of aggressive food-protective measures with active BSE surveillance and monitoring of BSE-safety-related efforts.

In December 2003, as noted in Section II.C.2 above, the first case of presumptive transfusion-transmitted vCJD was reported from the U.K. and the first U.S. case of BSE

[31] June 28-29, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3762t1.rtf and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3762t2.rtf.
[32] January 17, 2002 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3834t2.rtf.

was diagnosed postmortem in a Canadian-born cow slaughtered in Washington State (seven months after the first native-born cow was diagnosed with BSE in the Canadian Province of Alberta). At its meeting on February 12-13, 2004, the TSEAC discussed those two events and their possible implications for U.S. blood safety.[33] The TSEAC expressed confidence that the deferral policies already in place were likely to be effective and were concerned that additional restrictions on blood donor eligibility, while probably adding little to safety, might seriously reduce supply. The TSEAC discussed the possible benefit of leukoreduction, which had been introduced in several BSE countries in the hope of reducing the risk of transfusion-transmitted vCJD (Ref. 58).[34] Experimental studies using blood of rodents infected with scrapie agent as a model for human TSE (Ref. 59) subsequently confirmed previous findings, suggesting that a substantial portion of blood-borne infectivity was in plasma and not removed by leukoreduction filtration (Ref. 32). The TSEAC concluded that, whatever its other benefits, leukoreduction remains of unproven value in reducing the risk of transfusion-transmitted vCJD and should not be relied upon to replace a donor deferral policy. At its meeting, on October 14, 2004, the TSEAC discussed: (1) whether the policies recommended by FDA in the guidance of January 2002 were still justified; and (2) whether additional preventive measures were indicated to enhance blood safety.[35] The TSEAC voted unanimously that the measures FDA had recommended in the 2002 guidance were still justified. The TSEAC voted (13 for and 1 against) that FDA should continue to recommend those deferral policies without enhancements and also should follow the situation closely and consider adding risk-reducing measures if indicated. One TSEAC member expressed the opinion that FDA should seriously consider recommending deferral of donors transfused in some BSE countries besides the U.K.

At its meeting, on February 8, 2005, the TSEAC discussed available information and recommendations for deferral of U.S. donors transfused in France and in other European countries since 1980.[36] The TSEAC voted (12 in favor, 3 against, with one abstention) to recommend deferral of blood donors with a history of transfusion in France since 1980. However, the TSEAC voted unanimously against advising deferral of both blood donors and Source Plasma donors transfused in other European countries besides France and the U.K., reasoning that many more cases of vCJD had occurred in France than in any other country except the U.K. In a closely divided vote, the TSEAC advised FDA not to recommend deferral of Source Plasma donors with a history of transfusion in France (five members favored deferral of Source Plasma donors while seven members opposed it and one abstained), based on information presented at the October 14, 2004 TSEAC meeting showing that the processes used to manufacture plasma derivatives had the capacity to

[33] February 12-13, 2004 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4019t1.htm and http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4019t2.htm.
[34] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1621089/pdf/pmed.0030342.htm.
[35] October 14, 2004 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4075T1.htm.
[36] February 8, 2005 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4088t1_01.pdf.

remove substantial amounts of TSE infectivity (Refs. 47-49 and 51-52).[37] Subsequent presentations on the capacity of processes used to manufacture plasma derivatives to remove TSE infectivity were made to the TSEAC on September 18, 2006,[38] and December 15, 2006.[39]

In the 2006 draft guidance, FDA summarized interim events, including advice from the TSEAC, and proposed to amend the 2002 guidance to include a recommendation that blood establishments indefinitely defer blood donors who have received transfusions of blood or blood components in France since 1980. In the 2006 draft guidance, FDA, while again relying on laboratory studies showing that steps used in certain processes used to manufacture fractionated plasma products reduce TSE infectivity, cautioned that " … not all products have been thoroughly studied [and] … it remains uncertain whether the models accurately reflect the form of infectivity in blood." Therefore, we also recommended in the 2006 draft guidance that Source Plasma donors who have received a transfusion of blood or blood components in France since 1980 be indefinitely deferred, and stated that we will continue to monitor the BSE epidemic and re-evaluate the necessity of deferring donors transfused in other European countries.

After the 2006 draft guidance was issued for comment, FDA received additional information concerning the risk of transmitting vCJD by plasma derivatives (uncertain but small in most although not all scenarios analyzed by probabilistic computer models[40]) and remains concerned about the increasing number of vCJD cases reported from France. The 2010 guidance recognized new information and incorporated advice we received from the TSEAC since the 2002 guidance was issued, and included revisions made in response to comments received on the 2006 draft guidance.

In October 2010, we sought the advice of the TSEAC on our proposed labeling recommendations to reflect potential risk of vCJD in plasma-derived products. We proposed recommendations for labeling for plasma-derivatives that included mention of vCJD for the first time, and the potential risk for its transmission.

Similarly, we proposed revisions to the labeling for plasma-derived albumin and products containing plasma-derived albumin. In addition to its indications for direct infusion into patients, albumin may be used in the manufacture of other biological products. For example, it is used in the culture media of certain licensed vaccines or as a stabilizer in certain recombinant clotting factor products. Licensed albumin and albumin contained in other licensed products have never been known to transmit viruses, CJD or vCJD, and laboratory experimental evidence suggests albumin is less likely to contain CJD-like agents when compared with other fractionated products (Refs. 45, 60-61). There is no

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[37] Presentation slides at: http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4075S1_05_files/frame.htm.
[38] Presentation slides at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1-index.htm.
[39] Presentation slides at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4271S1_00-index.htm.
[40] September 18, 2006 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1-index.htm and December 15, 2006 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4271S1_00-index.htm.

epidemiological evidence for transmission of CJD or vCJD in the U.S., U.K., or elsewhere by products containing plasma-derived albumin. Therefore, our recommendations for revised warning statements for vCJD risk for plasma-derived albumin and products containing plasma-derived albumin contained additional language to reflect the extremely low likelihood of vCJD and CJD transmission through these products.

TSEAC agreed unanimously that labeling for the potential risk of vCJD is warranted for plasma derivatives, including albumin and products containing albumin.[41] The revised recommendations for labeling plasma-derived products, including albumin and products containing plasma-derived albumin in this guidance are based upon current knowledge and the advice from TSEAC.

We are not recommending changes to the elements of the warning label for CJD. The transmission of CJD is currently described as a theoretical risk, given that there is no evidence that CJD is transmitted by blood (Refs. 56, 62-64).

E. Rationale for Geographic Donor Deferrals

This guidance document contains 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, we distinguish donors with vCJD from those with CJD or with CJD risk factors because of differences in the demonstrated risk of transfusion transmission. While no case of classical CJD has been attributed to transfusion, vCJD has several times been transmitted by blood transfusion (Ref. 65).[42]

These recommendations reflect a continuing effort to minimize the possible risk of transmitting vCJD by blood and blood products while maintaining their availability. We have previously estimated that vCJD-related donor deferrals might result in a 90% reduction in total person-days of risk-weighted (relative to U.K. risk 1980-1996) donor exposure to the agent of vCJD. We calculated risk as the sum of relative risk-weighted person-days exposure in the U.K. (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).[43] We later estimated that deferring donors transfused in France after 1980 might result in the loss of fewer than 2 in 10,000 otherwise suitable blood donors.[44] Donor loss, under the policy recommendations in the 2002 guidance, was projected to be

[41] October 28, 2010 TSEAC meeting transcript: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/ucm244061.htm.
[42] October 14, 2004 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4075t1_01.pdf.
[43] January 18, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/slides/3681s1.htm.
[44] October 14, 2004 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4075T1.htm.

approximately 5%, based upon analysis of data from a 1999 multi-center blood donor travel survey,[45] which was conducted using methodology described for Retrovirus Epidemiology Donor Studies (Ref. 66). We recognized that these deferrals might adversely affect the available supply of blood and plasma derivatives and warned that supplies needed to be monitored closely. The impact was expected to vary locally and regionally depending upon the dynamics of supply and demand and other characteristics such as demographics of the donor populations. More specifically, we were concerned that donors with a history of travel to the U.K. and other parts of Europe might be as much as 50% higher in urban coastal cities than in central and rural areas of the U.S.[46] As noted above BSE has been found in 36 Japanese cattle, one cow in Israel, 19 cattle in Canada and three in the U.S.[47] Residence in those countries, and residence in the U.K. after the end of 1996, has not been considered by FDA as cause to recommend donor deferral. The news media reported that other countries also received U.K. meat-and-bone meal,[48] implying that those countries might also have introduced the BSE infection into their cattle herds but have no recognized cases. We considered additional deferrals based upon possible donor exposure to BSE in Asian and other countries after the recommended deferrals were fully implemented in the fall of 2002, their impact assessed, and additional information about the potential level of BSE exposure and food chain controls in various countries sought. Following the recognition of BSE in North American cattle in 2003, the entire worldwide situation was considered by FDA and implications discussed publicly at meetings of TSEAC. We reasoned that additional deferrals would probably yield only a negligible benefit in reducing risk while compromising, to some uncertain but potentially significant degree, the continued supply of Whole Blood and blood components. The question whether additional geographically based donor deferrals should be considered for exposure in the Kingdom of Saudi Arabia was discussed with TSEAC in April 2011. Geographic deferrals were more broadly discussed with TSEAC in June 2015 in consideration of the results of a new FDA-developed quantitative assessment model for vCJD global geographic risk and the estimated risk reduction achieved by voluntary implementation of leukocyte reduction for red blood cells. We will reconsider our recommendations as appropriate based on the impact of expanded or reduced donor deferrals on the safety and availability of blood products.

[45] June 28, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3762t1.rtf.
[46] January 18-19, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t1.rtf and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t2.rtf.
[47] OIE at http://www.oie.int/eng/info/en_esb.htm.
[48] "Japan's Beef Scandal." Nature **413** (6854): 333.

III. EXPLANATION OF CURRENT vCJD RECOMMENDATIONS

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

The vCJD epidemic in the U.K., while markedly reduced since deaths peaked in 2000[49] (Ref. 21), continues. Furthermore, it has not been excluded that additional "waves" of cases may occur and that some uncertain but potentially substantial number of persons in the U.K. may have pre-clinical or sub-clinical infections (Refs. 67-70).[50]

To increase protection of the U.S. blood supply, we continue to recommend that you defer blood and plasma donors who have traveled or resided in the U.K. for a cumulative period of three or more months from the beginning of 1980 through the end of 1996.

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

In January 2001, the TSEAC recognized two types of risk outside the U.K.: (1) exposure to BSE from infected cows in the country of residence ("indigenous" BSE exposure); and (2) 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 ("imported" BSE exposure).

Available data suggest that France imported a substantial amount of beef from the U.K. during the peak years of the BSE epidemic;[51] at least 5% of beef consumed in France is estimated to have come from the U.K. during the late 1980s. The number of French vCJD cases (23) is currently about 13% of those in the U.K.[52] It has been speculated that many French vCJD cases might have been infected by consumption of British beef in France, since only one of the 23 individuals had lived in the U.K. for six or more months, and the indigenous French BSE epidemic has been much 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 apparently then exported from the Netherlands to a variety of other countries.[53]

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.[54] The suggested 10-year (120-month) deferral period for France reflected an estimated 5% risk of exposure to BSE, compared

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[49] CJD Statistics from the British Department of Health at www.doh.gov.uk.
[50] See also, McKie, R. "Warning over second wave of CJD cases. Scientists say that threat of brain illness returning will persist for decades," Observer, Aug. 3, 2008 at 11; Collinge, J. et al. (2006) "Kuru in the 21st century—an acquired human prion disease with very long incubation periods." Lancet 376: 2068-74.
[51] June 1-2, 2000 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t1.rtf and http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t2.rtf.
[52] Chart at: www.invs.sante.fr/publications/mcj/donnees_mcj.html.
[53] June 1-2, 2000 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t1.rtf and http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t2.rtf.
[54] January 18-19, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t1.rtf and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t2.rtf.

to exposure of donors who resided in the U.K. for at least six months. However, in our 2002 guidance, FDA recommended a more stringent deferral for exposure of five or more years in Europe (see Section III.C. below) consistent with a revised recommendation of deferral for three months exposure in the U.K. Although more recent data suggest that the relative risk of BSE exposure in France compared with the U.K. may have exceeded 5%, we continue to recommend deferral of blood and plasma donors with a history of five 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 were also potentially exposed to British beef procured for consumption or sale on U.S. military bases between 1980 and 1996. British beef was distributed to U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) between 1980 and 1990, and to U.S. military bases elsewhere in Europe (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 U.K.[55] In January 2001, 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 a history of potential consumption of U.K. beef by persons on U.S. military bases in Europe, we continue to recommend that current and former U.S. military personnel, civilian military personnel, and their dependents stationed at European bases for six months or more during the timeframes outlined in the preceding paragraph be deferred indefinitely. Based upon information provided by the DoD, we estimated that approximately 1.8% of U.S. blood donors might be deferred by this recommendation. Since as of 1996, DoD no longer procures U.K. beef for any U.S. military bases, such deferred donors now constitute a smaller percentage of otherwise suitable donors.

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 implementation of control measures to prevent the BSE agent from entering the human food chain. Control measures have included some of the following:

- prohibition of air injection stunning methods for cattle;
- active surveillance through testing of slaughtered cattle more than 30 months old for BSE;
- prohibitions on the use of carcasses from disabled cattle (so-called “downer” cattle not inspected and passed for human consumption);

[55] January 18-19, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t1.rtf and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t2.rtf.

- holding of all carcasses from cattle tested for cause until non-positive results have been received;
- exclusion of high-risk material (e.g., brain, other neural tissues, lymphoid tissues, and many parts of the 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.[56]

BSE has been detected in many European countries.[57] Food chain control measures (and their enforcement) have varied in Europe 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 have not been practical. Therefore, FDA 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 U.K. between 1980 and 1996. Also, as noted in Section III.B above, residents in France may have consumed at least 5% of their total beef as imported British beef during the epidemic period, while other Europeans almost certainly consumed less. Therefore, the estimated maximum risk of BSE exposure in Europe was taken to be approximately 1.5-5% of that in the U.K. Assuming a "worst-case" relative risk of 5% per day of exposure, a European donor deferral of five years (60 months) was equivalent to a three-month deferral for cumulative travel or residence in the U.K. This remains the basis for our current recommendation to defer donors of Whole Blood and blood components intended for transfusion and Source Leukocytes who have a history of five or more years of residence or travel in Europe outside of the U.K.

As discussed in Section II.C.2., there has been one case of transmission of vCJD in the U.K. that may be due to the use of human plasma. In 2006, the TSEAC discussed risk assessments for potential exposure to vCJD risk from certain plasma-derived products.[58] The risk of transmitting vCJD by plasma derivatives was estimated based upon the probable infectivity of plasma from pre-symptomatic or asymptomatic donors with vCJD infections, the prevalence of vCJD in the donor population (mainly dependent on the

[56] European Commission Scientific Steering Committee opinions on the Geographical Risk of BSE: http://ec.europa.eu/food/fs/bse/scientific_advice01_en.html.
[57] January 18-19, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t1.rtf and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3681t2.rtf, and June 1-2, 2000 TSEAC Meeting Transcript: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t1.rtf and http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3617t2.rtf.
[58] Risk assessments for plasma-derived factors VIII and XI presented to the TSEAC on December 15, 2006: http://www.fda.gov/ohrms/dockets/ac/cber06.html#TransmissibleSpongiform and draft risk assessments presented to the TSEAC on October 15, 2006: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4271b1-index.htm.

number infected in the U.K., not all of whom are deferred by recommended policies), the size of the plasma pool used for fractionation, and the removal of vCJD infectivity during the manufacturing process. In experimental studies, model TSE agents were removed from plasma products by a number of manufacturing steps, including precipitation, depth filtration, and column chromatography (Refs. 48-49, 57-60). Other unpublished data provided to FDA also suggested that the vCJD agent was similarly removed from most plasma derivatives by the same manufacturing steps.

The relative risks and benefits of excluding plasma donors who have lived or traveled in Europe for five 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.[59] However, the implementation in October 2002, of the previous enhanced vCJD deferral policies for donors of Source Plasma was not followed by reported shortages of plasma-derived products in the U.S. Furthermore, in contrast to blood, plasma derivatives are highly processed materials. Considering the estimated low prevalence of vCJD infections in most countries of Europe compared to the U.K. and France, the likelihood that plasma fractionation processes reduce TSE infectivity, and the uncertain effect of additional deferrals upon the supply of plasma derivatives, we have not recommended that you defer Source Plasma donors who lived or traveled in other countries of Europe, although we are recommending that donors who lived in France for five or more years from 1980 to the present should be deferred from donating Source Plasma. Moreover, we are recommending, in consideration of the relatively greater risk of vCJD in persons with exposure to beef products from the U.K. that you should not collect Source 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 B. of this document.

Blood donors who are deferred for history of European travel or residence (except as stated for the U.K., France, and U.S. military bases in Europe) remain eligible to donate Source Plasma in a Center for Biologics Evaluation and Research (CBER) approved program. 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 the countries of Europe listed in the Appendix to this document for a cumulative period of five years or more, between the beginning of 1980 and the present. We recommend that donors of Source Plasma who resided in the U.K., France, and U.S. military bases in Europe, be deferred as noted in the previous sections of this guidance.[60]

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[59] June 28, 2001 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3762t1.rtf.

[60] We continue to refer to donor deferrals both for risk of exposure to BSE due to residence in BSE countries, consumption of British beef products, injection of U.K. bovine insulin, and history of transfusion in the U.K. or in France after 1980 as "geographic risk deferrals."

D. Potential Infection with vCJD Agent Acquired by Transfusion

As discussed in Section II.C., there have been four reports of presumptive transmissions of vCJD to humans by blood transfusions, three resulting in clinical cases of vCJD and one in an infection with typical abnormal accumulations of prion protein in lymphoid tissues. FDA has little doubt that vCJD has been efficiently transmitted by non-leukoreduced Red Blood Cells from clinically healthy donors who later became ill with vCJD. Other components, while not implicated in transfusion transmissions of vCJD to date, cannot be considered safe. In addition, there has been one reported case of vCJD transmission in the U.K. that may be due to use of plasma-derived Factor VIII. Therefore, as a preventive measure, donors who have received transfusions of blood or blood components in the U.K. and in France since 1980 should be indefinitely deferred.

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.[61] We are aware that some diabetic patients have imported bovine insulin for personal use.[62] Additionally, some insulin products legally distributed in the U.S. since 1980 were manufactured from cattle in the U.K. Therefore, as a preventive measure, you should indefinitely defer blood donors who have injected bovine insulin since the beginning of 1980, unless you can confirm that the product was not manufactured after 1980 from cattle in the U.K. We are not aware that bovine insulin has been imported into the U.S. from France or any other European BSE country.

F. Reports of Biological Product Deviations

The biological product deviation regulation[63] requires blood establishments to submit a biological product deviation report (BPDR) when the event meets the standard set out in 21 CFR 606.171. The regulation requires an establishment to report to FDA events that:

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

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

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[61] 59 FR 44591, Aug. 29, 1994.
[62] For examples, see: http://www.fda.gov/OHRMS/DOCKETS/dailys/02/Dec02/122302/80042e34.txt and http://www.gopetition.co.uk/petitions/restore-beef-insulins-to-the-united-states.html.
[63] 65 FR 6635, Nov. 7, 2000, as amended at 70 FR 14984, March 24, 2005.

Example #1: On the first day after implementing new donor criteria, a repeat donor provided information of living for seven years in France between 1981 and 1988. The donor was deferred at this donation. Must the establishment submit a BPDR with respect to units previously collected from that donor, if those units were distributed?

The regulation does not require the establishment to submit a BPDR. At the time of prior donations, collection from that donor did not represent a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications, and the donor would not have been deferred. Nor was the collection an unexpected or unforeseeable event.

Example #2: One year after implementing new donor criteria, the establishment discovers that one of its repeat donors provided information of living 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. Must the establishment submit a BPDR with respect to those units, if those units were distributed?

The establishment must submit a BPDR (21 CFR 606.171). 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: The establishment discovers 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. Must the establishment submit a BPDR with respect to units previously collected from that donor, if those units were distributed?

The establishment must submit a BPDR (21 CFR 606.171). Collection from that donor represented an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product. Neither the blood establishment nor the agency expected or foresaw that the establishment would collect donations from individuals with CJD or vCJD.

Example #4: Six months after implementing new donor criteria, a repeat donor provided information of receiving a blood transfusion to treat a bleeding ulcer during a vacation in France 20 years ago. The donor donated Whole Blood three months earlier, at which time the donor provided the same information. Must the establishment submit a BPDR with respect to units previously collected from that donor, if those units were distributed?

The establishment must submit a BPDR (21 CFR 606.171). At the time of the donation, collection from that donor represented a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications.

G. Definitions

Audio CASI: computer assisted interactive donor questioning program that is accompanied by an audio component. The donor reads the questions on a computer display screen 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: An individual who is or was a member of 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., a spouse, child, parent, other) of a member of one of the U.S. military services or a civilian employee of one of the U.S. military services.

Recovered Plasma: the fluid portion of human blood obtained from Whole Blood or as a byproduct of apheresis procedures (e.g., plateletperesis) in conjunction with the preparation of blood components for transfusion and Source Leukocytes. Recovered plasma, an unlicensed product, is intended for further manufacturing into injectable and non-injectable products.

Source Leukocytes: a blood component derived from human blood collected by either manual or automated apheresis techniques and intended for further manufacturing into injectable products, like interferon. Source Leukocyte donors may donate once every eight weeks or more frequently and must meet Whole Blood or Source Plasma donor suitability criteria depending on the type and frequency of donation.[64]

Source Plasma: the fluid portion of human blood collected by plasmapheresis and intended for use as a source material for further manufacturing. Source Plasma may be manufactured into products intended for either injectable or non-injectable uses (21 CFR 640.60).

Source Plasma Donors:

- **Frequent Source Plasma Donor:** a donor who donates more frequently than once every four weeks. These donors are subject to the requirements in 21 CFR 630.15 and 21 CFR 640.65(b)(1)).[65]
- **Infrequent Source Plasma Donor:** a donor who has 1) not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks and 2) not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 pounds) in the past year. (See 21 CFR 630.3(e) and 21 CFR 630.25).[65]

[64] See 21 CFR 630.10 and 630.15. See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015). The rule is effective May 23, 2016. Current requirements are in 21 CFR 640.3 and 640.63.

[65] See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015). The rule is effective May 23, 2016.

IV. RECOMMENDATIONS FOR DONOR DEFERRAL

A. Donor Deferral Criteria

Donor deferral criteria 1-7 apply to all donors. Donor deferral criterion 8 (residence in Europe for 5 years or more between 1980 and the present) applies to 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.[66]

2. You should permanently defer donors at increased risk for CJD (as identified by questions 2 and 3 in Section IV.B. Donors are considered to have an increased risk for CJD if they have received a dura mater transplant or an injection of human cadaveric pituitary-derived growth hormone. Donors with one or more blood relatives diagnosed with CJD (as identified in Section IV.B., Question 1 below) 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 five years or more cumulatively in France from the beginning of 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 six 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 six 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. or in France between the beginning of 1980 and the present.

[66] For the purposes of this document, FDA considers the less common TSEs, Gerstmann-Sträussler-Scheinker syndrome and fatal insomnia syndromes, to be equivalent in risk to familial and sporadic CJD. The blood establishment need not name these rare syndromes in the questionnaire but might consider them as equivalent in risk to CJD if, in response to a question about CJD, the donor offers information that a family member has been diagnosed with one of them.

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 five years or more in Europe from the beginning of 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 (for example, because they lived in the U.K. or France or on U.S. military bases for the periods of time noted previously), these donors remain eligible for Source Plasma donation.

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

B. 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. 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 1999 and 2002 guidances. 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 ever had Creutzfeldt-Jakob Disease?[67]

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 needs to be asked only once, since human cadaveric pituitary growth hormone is no longer available.

[67] See footnote 66.

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

NOTE: This question may be preceded by the more general question "Have you ever had brain surgery?" Ask the specific question only if the donor responds "yes" to the general question.

C. 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. Note that gene sequencing of the donor is not necessary to demonstrate that the donor is not at risk for familial CJD. Sequencing of the family member with CJD or the appropriate parent of the donor, if the CJD-affected family member was a second-degree relative, may be sufficient to demonstrate that the donor does not have a mutation associated with familial CJD.

D. 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 blood establishment's standard operating procedures (SOP)). Instead of face-to-face interviews, you may use a computerized interactive donor interview program that includes an audio component (audio-CASI) as described in the FDA guidance entitled "Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires," dated July 2003.[68] You should submit 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.

[68] Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm075086.htm.

2. Donor Questions

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

To identify donors with geographic risk of BSE exposure.

Since the beginning of 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," then ask the following questions:

    1) Between 1980 through 1996 did you spend time that adds up to three 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) or in France?[69]
    3) Between 1980 through 1996, were you a member of the 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 six months or more associated with a military base in any of the following countries:

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

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

[69] 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; France should be taken to include its overseas departments (e.g., Martinique and others).

To identify donors of Source Plasma who have additional geographic risk of BSE exposure, you should ask the following questions:

4) Since 1980, have you spent time that adds up to five years or more in France?

For donors of Whole Blood, components intended for transfusion, and Source Leukocytes**,** you should **substitute** the following for question 4):

Question 4 (alternative): Since 1980, have you spent time that adds up to five years or more in Europe (including time spent in the U.K. from 1980 through 1996)?

Donors deferred from donating Whole Blood based on this question remain eligible to donate Source Plasma in a CBER-approved program, unless they are otherwise unsuitable.

For Donors of Source Plasma, however, you should **continue to ask** the **original** version of **Question 4**, as described above, rather than the alternative. 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. FDA does not currently consider those European and non-European countries that are not listed in the Appendix to this document to pose a BSE-exposure risk warranting deferral of donors who have spent any period of time there, even if these countries have reported cases of BSE to the OIE.[70]

To identify donors who have been injected with bovine insulin since 1980, you should ask donors with diabetes the following 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" in response to the question, you should indefinitely defer that donor, unless it can be documented that the product was not manufactured from cattle in the U.K. after 1980.

NOTE: Donors of Source Plasma who otherwise should be indefinitely deferred based on their responses to the questions specified in Sections IV.D.2.(b)(3) and IV.D.2.(b)(4), may continue to donate if they are participating in a CBER-

[70] OIE at http://www.oie.int/en/animal-health-in-the-world/bse-specific-data.

approved program that allows collection of Source Plasma 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-date cellular blood components intended for manufacturing into injectable products, and all recovered plasma that are under your control. We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the implicated components. Such notification should occur within one week of receiving the post-donation information.

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

If you received post-donation information about a donor with CJD, you must submit a BPDR (21 CFR 606.171) for any distributed components. The regulation requires you to submit a BPDR as soon as possible but not to exceed 45 calendar days after you discover the event (21 CFR 606.171(c)). If you received post-donation information about a donor with CJD risk factors, you must submit a BPDR (21 CFR 606.171) for any distributed components collected after the implementation of donor deferral. A BPDR is not required if components were collected prior to the implementation of donor deferral.

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

Donors with Geographic Risk Deferrals

1. Product Disposition

If you receive post-donation information about a donor with 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-date cellular blood components intended for manufacturing into injectable products, that are under your control. We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the implicated components. Such notification should occur within one week of receiving the post-donation information.

2. Biological Product Deviation Reports

If you received post-donation information about a donor with geographic risk factors, you must submit a BPDR (21 CFR 606.171) for any distributed components collected after the implementation of donor deferral. A BPDR is not required if components were collected prior to the implementation of donor deferral.

Donors with Exposure to Bovine Insulin Made in the U.K. since 1980

1. 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, and Source Leukocytes), and all in-date cellular blood components intended for manufacturing into injectable products, that are under your control. We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the implicated components. Such notification should occur within one week of receiving the post-donation information.

2. Biological Product Deviation Reports

If you received post-donation information about a donor exposure to bovine insulin made in the U.K. since 1980, you must submit a BPDR (21 CFR 606.171) for any distributed components collected after the implementation of donor deferral. A BPDR is not required if components were collected prior to the implementation of donor deferral.

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

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. We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the Source Plasma and recovered plasma. Such notification should occur within one week of receiving the post-donation information.

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

If you received post-donation information about a donor with geographic risk factors or exposure to bovine insulin made in the U.K. since 1980, you must submit a BPDR (21 CFR 606.171) for any distributed components collected after the implementation of donor deferral. A BPDR is not required if components were collected prior to the implementation of donor deferral.

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 and Age Less Than 55 Years

1. Product Disposition

We recommend you contact the Office of Blood Research and Review (OBRR), CBER at 240-402-8360 as soon as possible upon receiving post-donation information about a donor with vCJD, suspected vCJD, or CJD and age less than 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-date cellular blood components intended for manufacturing into injectable products that are under your control. We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the implicated components. Such notification should occur within one week of receiving the post-donation information.

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

If you received post-donation information about a donor with vCJD, suspected vCJD, or CJD and age less than 55 years, you must submit a BPDR (21 CFR 606.171) for any distributed components. The regulations require you to submit a BPDR as soon as possible but not to exceed 45 calendar days after you discover the event (21 CFR 606.171(c)).

E. Plasma Derivatives

1. Plasma derivatives manufactured using plasma 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 manufactured using plasma from donors diagnosed with vCJD or suspected vCJD

    a. Product Disposition

    We recommend you contact OBRR, CBER at 240-402-8360 as soon as possible upon receiving 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.

    We also recommend that you follow your SOPs or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the pooled plasma,

intermediates, and derivatives, and any other materials containing plasma from the vCJD donor. Such notification should occur within one week of receiving the post-donation information.

b. Biological Product Deviation Reports

You must submit a BPDR (21 CFR 600.14) if a plasma derivative product is manufactured using plasma collected from a donor who was diagnosed with vCJD or suspected vCJD and the product was distributed. The regulations require you to submit a BPDR as soon as possible but not to exceed 45 calendar days after you discover the event (21 CFR 606.171(c)).

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

a. Product Disposition

We recommend you contact OBRR, CBER at 240-402-8360 as soon as possible upon receiving information about a donor's diagnosis of CJD when less than 55 years old. 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

You must submit a BPDR (21 CFR 600.14) if a plasma derivative product is manufactured using plasma collected from a donor with a physician's clinical or pathological diagnosis of CJD and age less than 55 years, and the product was distributed.

The regulations require you to submit a BPDR as soon as possible but not to exceed 45 calendar days after you discover the event (21 CFR 600.14(c)).

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 or 2 N NaOH or concentrated

sodium hypochlorite for at least 1 hour. These treatments are known to diminish (but may not completely eliminate) infectivity (Refs. 71-72).[71] 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 less than 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 transfusible 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. or in France 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 less than 55 years). 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, as appropriate:

- "Biohazard";

[71] World Health Organization (WHO) Infection Control Guidelines for Transmissible Spongiform Encephalopathies at http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/.

- "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
- "Caution: For laboratory research use only"; or "Caution: For use in manufacturing non-injectable products only."[72]

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:

- "Biohazard";
- "Collected from a donor with variant CJD"; and
- "Caution: Only for laboratory research on variant CJD."

B. Labeling of Non-Implicated Products

As a prudent notice, we recommend that all blood, blood components, and plasma-derived products include labeling to address the possible risk of transmission of vCJD and CJD. 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 instruction circular should include the following warning statement:

   "Because Whole Blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents (e.g., viruses, bacteria, parasites, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent."[73]

[72] Donors who are otherwise deferred based upon donor deferral criteria 2 through 8 of this guidance, may continue to donate if they are participating in a CBER approved program that allows collection of Source Plasma solely for use in manufacturing of non-injectable products (see Section IV.A.).

[73] This language is included in the AABB "Circular of Information for the Use of Human Blood and Blood Components," dated November 2013, which FDA has recognized as an acceptable mechanism that is consistent with FDA requirements and recommendations for the labeling of Whole Blood and blood components intended for transfusion. If you do not utilize the AABB Circular of Information, you may attach the recommended labeling statement to your current circular until it is revised.

2. For plasma-derived products other than albumin, you should revise the statement in the Warnings and Precautions section of your labeling 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, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

3. For plasma-derived albumin, you should revise the statement in the Warning and Precautions section of your labeling 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin."

4. For products containing plasma-derived albumin, you should revise the statement in the Warnings and Precautions section of your labeling 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products."

VIII. IMPLEMENTATION OF RECOMMENDATIONS

We recommend that you implement the new recommendations contained in this guidance, (i.e., those recommendations related to labeling of plasma-derived products, including albumin and products containing plasma-derived albumin), within six months of publication of this guidance.[74] Manufacturers must submit the labeling change to FDA in accordance with 21 CFR 601.12(f)(2).

[74] As stated in the 2010 guidance, all recommendations contained therein should have been implemented no later than November 2010.

IX. 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 six months or more in Europe since 1980 or a cumulative period of three months or more in the U.K. 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 in 2001, both the industry-proposed and FDA-proposed deferrals resulted in an estimated one-log reduction of theoretical risk. Importantly, the donor loss for the industry proposal, if implemented on a national basis, was estimated by FDA to be at least 8-9% (3-4% higher than the FDA-recommended policy announced in January 2002). Some countries have recommended deferring donors who received transfusions in countries other than the U.K. and France (Ref. 58). Some authorities have noted that potential exposure of some U.S. military personnel residing in certain bases in Europe to the BSE agent between 1980-1996 might have exceeded that in France and suggested that persons transfused with their blood also be deferred as blood donors.

FDA's recommendations for donor deferral related to risk of CJD and vCJD are based on our current consideration of the relative benefits of risk reduction compared with the potential adverse effects of a decrease in availability of the blood supply, and may be updated in the future as better scientific information becomes available. Nevertheless, we recognize that 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 periods of deferral more stringent than those outlined by this guidance. If you wish to implement donor deferrals other than those recommended in this guidance, consider strategies for offsetting projected donor losses and maintaining an adequate blood supply to meet hospital demands for blood products.

X. SOURCES OF ADDITIONAL INFORMATION

Subject	Contact
FDA policies on CJD, vCJD and BSE exposure	Division of Emerging and Transfusion-Transmitted Diseases, OBRR, CBER at 240-402-8360
This guidance and FDA policies for implementing acceptable DHQ documents	Division of Blood Components and Devices, OBRR, CBER at 301-402-8360
Receipt of post-donation information about a donor with vCJD, suspected vCJD or CJD and under age 55.	Division of Blood Components and Devices, OBRR, CBER at 240-402-8360
The vDHQ-1.3 or other AABB DHQ documents	AABB at 301-907-6977, attention of the AABB Donor History Task Force
DHQ documents that FDA has recognized as acceptable	http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/ucm164185.htm.
Biological product deviation reporting	Division of Inspections and Surveillance, OCBQ, CBER, at 240-402-9160 or by email at http://www.accessdata.fda.gov/scripts/email/cber/bpdrcontact.cfm.

XI. REFERENCES

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APPENDIX: List of European Countries with BSE or at Risk of BSE Applicable to Donor Deferral

European Countries List to be Used for Deferral of Donors Based on Geographic Risk of BSE[75]

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 Kingdom, and Federal Republic of Yugoslavia.

[75] 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; France should be taken to include its overseas departments (e.g., Martinique and others); Spain should be taken to include the Canary Islands and Spanish North African territories; Portugal should be taken to include the Azores.

APPENDIX 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 And Consignee Notification**	**BPDR** (21 CFR 606.171) for previously distributed product	**Recipient Tracing/ Notification**
Diagnosed with vCJD or CJD, or suspected vCJD	Permanent	Immediately retrieve, quarantine, and follow /update SOPs regarding notifying consignees for all in-date products and 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, and follow/update SOPs regarding notifying consignees for all in-date products and 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, and follow/update SOPs regarding notifying consignees for all in-date products and cellular blood components intended for manufacturing into injectable products.	Yes*	No

* As stated in Section V. of this guidance, a BPDR is not required if components were collected prior to the implementation of donor deferral.
** Note that gene sequencing of the donor is not necessary to demonstrate that the donor is not at risk for familial CJD. Sequencing of the family member with CJD or the appropriate parent of the donor, if the CJD-affected family member was a second-degree relative, may be sufficient to demonstrate that the donor does not have a mutation associated with familial CJD.

Risk	**Deferral**	**Disposition of Product And Consignee Notification**	**BPDR** (21 CFR 606.171) for previously distributed product	**Recipient Tracing/ Notification**
Geographic donor deferrals (U.K. ≥3 months 1980-1996; France ≥5 years 1980-present; military in Europe as specified)	Indefinite	Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for all in-date products and cellular blood components intended for manufacturing into injectable products.	Yes*	No
Geographic donor deferrals (Europe other than U.K. ≥5 years 1980-present)	Indefinite	Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for all in-date products and cellular blood components intended for manufacturing into injectable products.	Yes*	No
Bovine insulin injection	Indefinite, donor may be re-entered after proof of non-U.K. insulin source	Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for all in-date products and cellular blood components intended for manufacturing into injectable products.	Yes*	No
Transfusion in U.K. or in France from Jan 1, 1980 to the present	Indefinite	Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for all in-date products and cellular blood components intended for manufacturing into injectable products.	Yes*	No

APPENDIX TABLE 2: DONOR DEFERRAL, PRODUCT DISPOSTION, AND RECIPIENT NOTIFICATION FOR SOURCE PLASMA (SP), RECOVER PLASMA (RP) AND PLASMA DERIVATIVES (PD)

Risk	**Deferral**	**Disposition of Product** **And Consignee Notification**	**BPDR** (21 CFR 606.171 or 600.14) for previously distributed product	**Recipient Tracing/ Notification**
Diagnosed with vCJD, suspected vCJD	Permanent	SP and RP: Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for in-date SP and all RP PD: Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees	SP and RP: Yes PD: Yes	Consignee notified, consignee informs responsible caretaker for discretionary recipient notification, counseling
Diagnosed with CJD (and age <55)	Permanent	SP and RP: Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for in-date SP and all RP PD: Disposition decided case-by-case depending upon investigation results	SP and RP: Yes PD: 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, and follow/update SOPs regarding notifying consignees for in-date SP and all RP unless plasma known to be previously pooled PD: No retrieval, quarantine, consignee notification	SP and RP: Yes PD: No	SP and RP: N/A PD: No

Risk	**Deferral**	**Disposition of Product And Consignee Notification**	**BPDR** (21 CFR 606.171, 600.14) for previously distributed product	**Recipient Tracing/ Notification**
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, and follow/update SOPs regarding notifying consignees for in-date SP and all RP unless plasma known to be previously pooled PD: No retrieval, quarantine, consignee notification	SP and RP: Yes* PD: No	SP and RP: N/A PD: 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, and follow/update SOPs regarding notifying consignees for in-date SP and all RP unless plasma known to be previously pooled PD: No retrieval, quarantine, consignee notification	SP and RP: Yes* PD: No	SP and RP: N/A PD: No
Geographic donor deferrals (U.K. ≥3 months 1980-1996; France ≥5 years 1980-present; military in Europe as specified, transfusion in U.K. or France since 1980)	Indefinite	SP and RP: Immediately retrieve, quarantine, and follow/update SOPs regarding notifying consignees for in-date SP and all RP unless plasma known to be previously pooled PD: No retrieval, quarantine, consignee notification	SP and RP: Yes* PD: No	SP and RP: N/A PD: No

Risk	Deferral	Disposition of Product	BPDR (21 CFR 606.171, 600.14) for previously distributed product	Consignee Notification
Geographic donor deferrals (Europe other than U.K.. ≥5 years 1980-present)	RP: Indefinite SP: No deferral	RP: Immediately retrieve, quarantine, and update/follow SOPs regarding notifying consignees unless plasma known to be previously pooled SP: N/A PD: No retrieval, quarantine, notification of consignee	RP: Yes* SP: N/A PD: No	RP: N/A SP: N/A PD: No
Bovine insulin injection	Indefinite	SP and RP: Immediately retrieve, quarantine, and update/follow SOPs regarding notifying consignees for all RP and for in-date SP unless plasma known to be previously pooled PD: No retrieval, quarantine, notification of consignee	SP and RP: Yes* PD: No	SP and RP:N/A PD: No

* As stated in Section V. of this guidance, a BPDR is not required if components were collected prior to the implementation of donor deferral.
** Note that gene sequencing of the donor is not necessary to demonstrate that the donor is not at risk for familial CJD. Sequencing of the family member with CJD or the appropriate parent of the donor, if the CJD-affected family member was a second-degree relative, may be sufficient to demonstrate that the donor does not have a mutation associated with familial CJD.