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Guidance for Industry

Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

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For questions on the content of this draft document, contact the Human Tissue Staff at 301/827-0967

U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY

Preventive Measures To Reduce The Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

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I. INTRODUCTION

We, the Food and Drug Administration (FDA), currently regulate human tissue under 21 CFR Part 1270 (Human Tissue Intended for Transplantation) and under 21 CFR Part 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Products) (HCT/Ps). Section 1271.3(j) identifies those tissues that we currently regulate under Part 1270. Section 1271.3(d)1) describes tissues currently subject to registration and listing under Part 1271, and §1271.3(d)(2) describes the broader category of tissues scheduled to become subject to registration and listing on January 21, 2003. Under §1270.21, we require you, manufacturers of human tissue intended for transplantation, to screen donors for clinical evidence of and risk factors for human immunodefiency virus (HIV), Hepatitis B virus (HBV), and Hepatitis C virus (HCV), and to test them for evidence of infection by any of these agents. In February 1997, we proposed a risk-based approach to the regulation of human cellular and tissue-based products that would have a broader scope and additional requirements (Ref. 1). To implement the proposed approach, we have published three proposed rules. One of them, "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule" has been finalized (Ref. 2). Work on the other two proposed rules, "Suitability of Donors of Human Cellular and Tissue-Based Products;" (Ref. 3), and "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement;" (Ref. 4), is underway.

We are concerned about the potential for transmission of classic Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) by transplantation, implantation, infusion, or transfer of human cells, tissues, and cellular and tissue-based products (HCT/Ps). Before writing this guidance, we sought advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) at its meeting held on January 18-19, 2001 (Ref. 5), regarding prevention of vCJD transmission by HCT/Ps. The committee voted 14-0, agreeing that compared to the risk of transmission of vCJD by blood transfusion, there is an equal or greater risk of transmission of vCJD from HCT/Ps that are transplanted, implanted, infused, or transferred. The committee voted 9-6 in favor of FDA making recommendations regarding donor deferral criteria for HCT/P donors potentially exposed to the Bovine Spongiform Encephalopathy (BSE) agent. The committee discussed the deferral criteria. However, the committee did not recommend specific deferral criteria because of the paucity of information available about the transmission of vCJD in tissues. The committee noted that a validated test for PrP^{res} (protease resistant prion protein, i.e., the form of prion protein associated with infectivity) would be an invaluable tool for use in donor screening, when such a test becomes available.

We believe that, as for blood and blood products, there are concerns about potential transmission of prion disease through HCT/Ps. There are greater risks for CJD/vCJD transmission through some HCT/Ps (for example, dura mater and cornea) as compared to blood and blood products. We sought advice from the TSEAC on January 18-19, June 28-29, and October 25-26, 2001, (Ref. 6) regarding deferral of blood donors from countries affected by BSE. We issued for public comment a draft guidance document "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" in August 2001, and issued a final guidance in January 2002 (Ref. 7).

Scientists are developing tests to detect abnormal prion proteins in blood. These tests would be a useful addition to screening donors of HCT/Ps. However, we believe that pending the availability of such tests, the interim preventive measures contained in this guidance are prudent. The recommendations in the guidance are based upon current knowledge, advice from FDA's TSEAC, and input from the Public Health Service (PHS) ad hoc Working Group on Transmissible Spongiform Encephalopathies/Bovine

Spongiform Encephalopathy (TSE/BSE). We expect that additional scientific and epidemiological information will become available as the vCJD and BSE epidemics evolve.

We recognize that we may need to revise this draft guidance in the future in light of developments in testing technology, epidemiological information, and the impact of these recommendations on the HCT/P supply.

CJD is a rare but invariably fatal degenerative disease of the central nervous system, associated with a poorly understood transmissible agent (Refs. 8, 9). Sporadic CJD cases occur at a low frequency by an unknown mechanism. CJD may also be acquired by exogenous (usually iatrogenic) exposure to infectious material, including transplantation of certain tissues. CJD also may be familial, associated with a genetic mutation of the prion protein gene. Clinical latency for iatrogenic CJD may exceed 30 years, based upon observations following point exposures to contaminated materials.

In 1996, a previously unrecognized variant of CJD, vCJD, was identified in the United Kingdom (U.K.) (Ref. 10). vCJD is distinguished from CJD by differences in clinical presentation and neuropathologic changes, summarized below (Refs. 10-15).

Differences in clinical presentation	vCJD	CJD
Age of onset	Earlier	Later
Median age at death	28 years	68 years
Psychiatric and sensory symptoms	Frequent in early course of illness	Appear later in course of illness
EEG changes	Absence of diagnostic EEG changes	Diagnostic EEG changes commonly seen
Duration of illness (Median survival) (Ref. 14)	13 months	4 months
Neuropathologic features	Florid prion protein plaques, surrounded by spongiform changes	Florid plaques uncommon
Immunohistochemistry (Ref. 15)	Abnormal prion protein detectable in lymphoid tissues	Abnormal prion protein not detected in lymphoid tissues

As of January 2002, over 120 vCJD cases have been diagnosed world-wide. To date, indigenous cases have occurred only in the U.K. and France. The size of the vCJD epidemic cannot yet be determined, but is believed to be increasing in the U.K. (Refs. 16, 17). No cases of vCJD have been identified in the United States (U.S.), except for one U.K. resident with vCJD who traveled to California in 2001 for medical care and one U.K. resident who migrated to Florida prior to onset of her illness (http://www.cdc.gov/od/oc/media/pressrel/r020418.htm). Laboratory and epidemiological studies have linked vCJD to the epidemic of BSE in the U.K. (Refs. 18, 19). In the U.K., BSE probably first occurred in cattle in about 1980, peaked at the end of 1992, and fell to much lower levels by 1996 as a result of control measures. In contrast to the U.K., the numbers of reported cases of BSE in some other European countries are increasing, though each of these countries is reporting fewer new

cases than the U.K. The peak levels of the BSE epidemics in European countries cannot yet be ascertained (Refs. 5, 20). No BSE has been reported to date in U.S. cattle.

vCJD is an emerging disease with unique clinical and pathological characteristics. To date, transmission of vCJD by human blood, plasma, or HCT/Ps has not been demonstrated. Few experimental or epidemiological studies of vCJD transmissibility by blood components or plasma derivatives have been published. There are also no published studies regarding the transmissibility of vCJD by HCT/Ps. However, blood from some animals experimentally infected with transmissible spongiform encephalopathy (TSE) agents, including the BSE agent, contains low levels of infectivity. Several TSE infections, including BSE, have been transmitted by transfusion in experiments (Refs. 21-26). For this reason, the transmission of vCJD by blood and blood products, and by most HCT/Ps, is considered a theoretical possibility. Furthermore, the possibility for transmission of vCJD from certain tissues (i.e., cornea and processed dura mater allograft) seems especially likely, since these tissues are already known to have transmitted CJD.

Since 1996 the vCJD and BSE epidemics have continued to evolve. More BSE cases have been reported in Europe, including new reports of BSE in Spain, Italy, Germany, the Czech Republic, Greece, Slovenia, Slovakia, Austria, and Finland. Japan and Israel have also reported BSE, and many other countries, which also imported meat and bone meal from the UK from 1980 to 1996, may also have BSE. Furthermore, apparent transmission of BSE to a single transfused sheep has been reported (Ref. 22), heightening concerns about possible transmissibility of the vCJD agent by human blood. [FDA has received an unpublished update to the latter report, which appears to confirm the finding].

We have included in the guidance comprehensive recommendations for deferral of HCT/P donors, based upon advisory committee discussions and internal PHS and FDA deliberations. We cannot confidently predict the effect of such deferrals on the supply of HCT/Ps, because much less is known about HCT/P donors than about donors of blood and plasma. In the guidance, we make recommendations to minimize the risk of vCJD transmission from HCT/Ps and ask you for your comments. We are especially interested in receiving information about the effect that these

recommendations might have on availability of HCT/Ps.

We recognize that implementing these deferrals for HCT/P donors might reduce the available supply of HCT/Ps. The effect would probably vary locally and regionally depending upon the dynamics of supply and demand and other characteristics such as demographics of the donor populations. For example, when compared with blood donors from central and rural areas of the central U.S., almost twice as many blood donors from some coastal urban cities have a history of foreign travel (Ref. 5). Before recommending specific deferrals for blood and plasma donors, we worked with outside organizations to compare the estimated effects on the blood supply with various reductions in risk of exposure to the BSE agent to be expected from various proposed policies. We estimated that the currently recommended blood donor deferral policy would result in a 90% reduction in total person-days of risk-weighted donor exposure to the agent of vCJD, with an estimated 5% reduction in supply (Ref. 7). We calculated risk as the sum of relative-risk-weighted person-days exposure in the United Kingdom (weight = 1.0), France (weight = 0.05), other European countries (weight = 0.015), and members of the U.S. military and their dependents (weight = 0.35).

We based these donor deferral recommendations for HCT/P donors on our recommendations for blood donor deferral because we believe that HCT/P transplantation poses similar, and in some cases greater, risks. Under our Good Guidance Practices (GGPs), we may reconsider our recommendations after reviewing comments and information submitted to the docket, and the effect of donor deferrals on the availability of HCT/Ps or other relevant information.

Diagnosis of CJD and vCJD:

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

1. multifocal spongiform changes, astrogliosis, neuronal loss and absence of inflammatory response;
2. demonstration of protease-resistant prion protein (PrP^{res}); and

3. relative lack of florid amyloid plaques (as compared to vCJD) – Rare amyloid plaques without surrounding vacuolation, usually in the cerebral cortex, can be demonstrated in 5% to 15% of CJD cases (Ref. 27).

A confirmed case of vCJD is currently defined by the following neuropathologic findings:

1. spongiform change most evident in the basal ganglia and thalamus, with sparse distribution in the cerebral cortex;
2. dense accumulations of abnormal prion protein, particularly in the cerebrum and cerebellum as shown by immunohistochemistry; and
3. numerous widespread kuru-type amyloid plaques, surrounded by vacuoles, in both the cerebellum and cerebrum ("florid plaques").

One can make a clinical diagnosis of "suspected" CJD based upon certain clinical features, if adequate neuropathology specimens are unavailable. The clinical features are:

1. progressive dementia;
2. typical EEG (generalized triphasic periodic complexes at approximately one per second); and
3. at least two of the following: myoclonus; visual impairment or cerebellar signs; pyramidal or extrapyramidal signs; akinetic mutism (Ref. 28).

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

1. Current age or age at death <55 years (a brain autopsy is recommended, however, for all physician-diagnosed CJD cases).
2. Persistent painful sensory symptoms and/or psychiatric symptoms at clinical presentation.
3. Dementia and development ≥4 months after illness onset of ataxia and at least one of the following three neurologic signs: myoclonus, chorea, or dystonia.
4. A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.

5. Duration of illness of over 6 months.
6. Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis.
7. No history of receipt of cadaveric human pituitary growth hormone or a human dura mater graft.
8. No history of CJD in a first degree relative or prion protein gene mutation in the patient.

NOTE:

1. If a patient has the typical bilateral pulvinar high signal on MRI scan, a suspected diagnosis of variant CJD requires the presence of a progressive neuropsychiatric disorder, 4, 5, 6 and 7 of the above criteria, and four of the following five criteria: a) early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal); b) persistent painful sensory symptoms (frank pain and/or dysesthesia); c) ataxia; d) myoclonus or chorea or dystonia; and e) dementia.

2. A history of possible exposure to bovine spongiform encephalopathy (BSE) such as residence or travel to a BSE-affected country after 1980 increases the index of suspicion for a variant CJD diagnosis.

II. BASIS FOR CJD RECOMMENDATIONS

In our July 1997, "Guidance for Industry - Screening and Testing of Donors of Human Tissue Intended for Transplantation" (Ref. 29), we recommended screening tissue donors for increased risk of CJD. We cited the following relevant CJD-related factors:

1. persons with a diagnosis of CJD or known family history (blood relative) of a person with non-iatrogenic CJD;
2. persons who have received injections of human pituitary-derived growth hormone (pit-hGH); and
3. persons who are known to have received transplants of dura mater.

Iatrogenic transmission of CJD through transplantation of dura mater allograft and cornea has been

reported. There have been more than 114 cases of transmission of CJD by dura mater allograft worldwide, including three in the U.S. The mean interval between receipt of dura mater and occurrence of disease was 8.6 years, with the longest latent period being 18.2 years (Ref. 30). The first case was reported in 1987, in a 28-year-old woman who had received a lyophilized, irradiated human cadaveric dura mater graft (a product never cleared by FDA), imported into the U.S. from Canada (Ref. 31). This patient died 22 months after receiving the graft. A case in New Zealand and four cases in Spain, all involving the same brand of dura mater grafts, were subsequently reported. A second U.S. case associated with a dura mater graft in a 28-year-old
woman was reported in 1994 (Ref. 32). Before 1987, the involved dura mater had been commingled from many cadaveric donors in the same container during processing. A third U.S. case of a 39-year-old woman that occurred in 1998 was reported in the literature in 2001 (Ref. 33). This case involved dura mater from a different manufacturer wherein the dura mater had not been commingled. The donor had been inadequately screened and the dura had been subjected to 0.1 N sodium hydroxide, rather than 1.0 N sodium hydroxide recommended by FDA, for one hour. The majority of CJD transmissions from dura mater have occurred in Japan since 1985. Japan has had at least 67 cases – almost all of these patients were believed to have received dura mater made in a commingled process (Ref. 34).

At the present time, we regulate dura mater as a medical device. However, we published our intention to regulate it as an HCT/P in the future in the final rule on "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" (Ref. 2).

On October 14, 1999, we published a guidance document entitled "Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater" (Ref. 35). In this guidance document, we incorporate advice given by TSEAC on October 6, 1997, and April 16, 1998, and recommend donor deferral based on risk of CJD, pathological examination of the donor's brain, archiving of specimens, processing methods, and manufacturing controls.

Transmissions of CJD by ocular tissue have included one definitive case in the United States (Ref. 36), one possible case in Japan (Ref. 37), and one possible case in Germany (Ref. 38). There was concern

for the potential for transmission of CJD with the transplantation, and subsequent explantation, of two corneas and sclera donated by a Scottish woman who was later determined to have CJD (Ref. 39). The United States case published in 1974 was that of a 55-year-old woman who received a cornea from a donor who had died of a neurological illness. The donor's illness consisted of ataxia, memory deficit, myoclonus, and involuntary movements. After the cornea was transplanted, the donor's autopsy revealed spongiform changes consistent with CJD. The transplant recipient first became ill within 18 months of transplantation, and died 26 months after transplantation. The transplant recipient's autopsy revealed spongiform encephalopathy consistent with CJD. The Japanese report in 1994 was that of a 63-year-old woman who developed neurological symptoms 15 months after receiving a cornea. She died 40 months later and had typical CJD histological changes at autopsy. The article did not present details about the patient's medical history, but stated that there was a link between her disease and a previous corneal transplant. The German case published in 1997 was that of a 45-year-old woman who developed neurological symptoms and EEG signs of CJD. An autopsy was refused. She had no family history of CJD, no genetic markers of familial CJD, and was homozygous for methionine at codon 129 on chromosome 20. This patient had received a corneal transplant thirty years earlier. Though the pathology slides from the donor were no longer available for review, the original medical records and necropsy reports indicated the donor had died of CJD.

III. BASIS FOR vCJD RECOMMENDATIONS

Five currently recognized risks of exposure to the BSE agent are:

- exposure to BSE agent from British beef in the U.K.;
- exposure to BSE agent from British beef products distributed outside of the U.K. during the BSE epidemic (prior to full implementation of food control measures in 1996);
- exposure to BSE agent from beef products of infected cows in the country of residence ("indigenous" BSE) outside the U.K.;
- theoretical exposure to vCJD agent by transfusion of blood or blood products from U.K. donors; and
- theoretical exposure to BSE agent through bovine insulin produced from cattle in the U.K.

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

A link has been established between consumption of beef products from cows infected with the BSE agent and development of vCJD (Ref. 18, 19). The vCJD epidemic in the U.K. continues to increase (Ref. 17, and CJD Statistics from the British Department of Health, at www.doh.gov.uk). To increase protection of the U.S. supply of HCT/Ps, we now recommend that you defer donors of HCT/Ps who have traveled or resided in the U.K. for a cumulative period of 3 or more months between the beginning of 1980 and the end of 1996.

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

Available data suggest that France imported a substantial amount of beef from the U.K. during the peak years of the BSE epidemic (Ref. 23). As of April 2002, the number of French vCJD cases (four confirmed and two probable) is approximately 5% of vCJD cases in the U.K.(117 definite or probable cases). Current speculation is that the people who developed vCJD in France were infected after consuming British beef in France. None of the individuals for whom information has been reported had lived in the U.K., and the indigenous French BSE epidemic is relatively smaller and more recent than that in the U.K. Substantial amounts of British beef also were exported to the Netherlands, but it is believed that much of this meat was subsequently exported from the Netherlands to other countries (Ref. 23).

On January 18, 2001, the TSEAC recommended expanding the geographic deferral of potential blood donors. The recommendation was to include potential blood donors who resided in France for any cumulative period of 10 years or more from 1980 until the present. The suggested deferral for any 10-year (120 month) period of residence or travel in France reflected an estimated 5% risk of exposure to the BSE agent in France,

compared to exposure of donors who resided in the U.K. for at least 6 months. A 5-year exposure period would reflect a 5% exposure risk compared with donors who resided in the U.K for 3 months.

Some U.S. military personnel, civilian military employees, and their dependents in Europe were also potentially exposed to British beef procured for use on U.S. military bases between 1980 and 1996. British beef was distributed to U.S. military bases north of the Alps (Germany, United Kingdom, Belgium, and the Netherlands) between 1980 and 1990, and south of the Alps (Greece, Turkey, Spain, Portugal, and Italy), between 1980 and 1996. While exposure varied widely, up to 35% of beef consumed on some U.S. military bases in Europe came from the United Kingdom (Ref. 5).

Due to the potential exposure to U.K. beef on U.S. military bases in Europe, we recommend that, if you manufacture HCT/Ps, you indefinitely defer current and former U.S. military personnel, civilian military employees, and their dependents who were stationed at European bases for 6 months or more during the time periods outlined in the preceding paragraph.

C. Exposure to Indigenous BSE Agent Outside the U.K.

BSE in Europe probably 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 include:

- active surveillance through testing for BSE in any slaughtered cattle more than 30 months old;
- exclusion of high-risk material (for example – brain, other neural tissue, lymphoid tissues, intestines) from human food;

- a ban on human consumption of slaughtered cattle more than 30 months old;
- prohibition of mechanically recovered meat;
- a ban on mammalian-derived feed for ruminants;
- use of certain rendering processes; and
- additional herd control and surveillance (Ref. 20).

The timing and degree to which the European countries have implemented such controls has varied (Refs. 20, 23). The current prevalence of BSE in each country is uncertain because active surveillance of the epidemic has not been completely implemented (Refs. 5, 6, 20, 23).

BSE has been detected in many, but not all, European countries, and the increase or decrease of BSE in many countries is not predictable (Refs. 5, 23). Food chain control measures (and their enforcement) vary, and cannot be assured for all time periods in question. Because of these uncertainties, and the evolving BSE epidemic, donor deferrals on a country-by-country basis are not practical at this time. FDA, therefore, has developed a uniform recommendation for donor deferral based on exposure in Europe outside of the U.K. The highest prevalence of BSE that has been observed in a European country with a strong surveillance program (Switzerland) is approximately 1.5% of the BSE prevalence that was observed for the United Kingdom between 1980 and 1996. Also, residents in France consumed an estimated 5% British beef during the epidemic period, and other Europeans probably ate less. Therefore, the current estimated maximum risk of BSE exposure in Europe is approximately 1.5-5% of that in the United Kingdom. Assuming a "worst-case" relative risk of 5% per day of exposure, a deferral of donors resident in Europe for 5 years (60 months) is equivalent to the currently recommended deferral for donors with a history of three months of cumulative travel or residence in the U.K. This is the basis for our recommendation to exclude HCT/Ps from donors with a history of 5 or more years of residence or travel in Europe outside of the U.K. from 1980 to the present.

D. Theoretical Exposure to vCJD Agent by Transfusion

There are no known cases of vCJD transmission to humans by blood transfusion. In the U.K., at least 20 people are known to have received blood or blood components from donors who later developed vCJD. To date, none of these recipients has been diagnosed with vCJD (Ref. 5). However, BSE has apparently been transmitted from one sheep to another by transfusion (Ref. 22). Another study also suggests that the BSE agent can adapt to primate hosts, thus potentially enhancing the possibility of transfusion transmission of vCJD from a vCJD-incubating donor (Ref. 40). Therefore, as a preventive measure, we recommend that you defer HCT/P donors who have received transfusions of blood or blood components in the U.K. from 1980 to the present.

E. Exposure to Bovine Insulin

No cases of transmission of vCJD have been reported in recipients of bovine insulin or other injectable products manufactured in BSE- countries. However, as a safeguard, we have recommended that material from cattle in BSE- countries should not be used in the manufacture of FDA regulated products (Ref. 41). Some diabetic patients may have imported bovine insulin for personal use. Additionally, some insulin products distributed in the U.S. since 1980 were manufactured from cattle in the U.K. Therefore, as a preventive measure, you should indefinitely defer HCT/P donors who have injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from cattle in the U.K.

IV. RECOMMENDATIONS FOR DONOR ELIGIBILITY

You should determine to be ineligible any donor who:

1. has been diagnosed with vCJD or any other form of CJD;
2. has been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system (CNS) or other neurological disease of unknown etiology; (HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident, brain tumor, head trauma, or toxic/metabolic dementia and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director.)
3. is at increased risk for CJD; (Donors are considered to have an increased risk for CJD if they have received a dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD [see following Note].)
4. spent three months or more cumulatively in the U.K. (see Appendix) from the beginning of 1980 through the end of 1996;
5. is a current or former U.S. military member, civilian military employee, or dependent of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996;
6. lived cumulatively for 5 years or more in Europe from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996);
7. received any transfusion of blood or blood components in the U.K. between 1980 and the present; or
8. has injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from cattle in the U.K.

NOTE: We recognize that if an establishment applied these recommendations to hematopoietic stem cells, the exclusion of potential donors based upon recommendations 3-8 could reduce the availability of HLA-matched hematopoietic stem cells. Unlike other HCT/Ps, hematopoietic stem cells require close HLA matching between donor and recipient. However, recommendations 3-8 may work to screen out some close matches (for example, if the genetic match for a patient in need of hematopoietic stem cells

can be obtained only from a donor who resides in a country listed in the Appendix.) To mitigate this potential effect, we believe that hematopoietic stem cells from a donor who would otherwise be determined ineligible by one or more of the recommendations 3-8 may be collected and stored. Use of such hematopoietic stem cells could be appropriate to address an urgent medical need if necessary to achieve an appropriate match with a recipient and if the benefits of such use outweigh the risks.

You should include this information in the donor's medical history, which is part of the relevant medical records. If the living donor or the individual knowledgeable about the donor's medical and travel history is not familiar with the term "Creutzfeldt-Jakob Disease," you may take that as a negative response. You may perform an abbreviated donor screening for a living donor on repeat donations, if a complete donor screening has been performed within the previous 6 months. The abbreviated screening procedure should determine and document any changes in the donor's medical history, including relevant travel, since the previous donation that would make the donor ineligible (Ref. 3).

You should exclude a donor with a history of CJD in a blood relative unless:

1. the diagnosis of CJD was subsequently found to be an incorrect diagnosis;
2. the CJD was iatrogenic; or
3. laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

We have listed the countries that FDA uses as a basis for donor deferral in the Appendix to this document. FDA is aware that BSE has been diagnosed in Japan. The source is likely to have been meat-and-bone meal imported from the U.K. We may consider additional deferrals based upon exposure to BSE in Asia or elsewhere after the currently recommended deferrals have been implemented, their impact is assessed, and additional information about the potential level of BSE exposure and food chain controls is acquired.

V. NONCLINICAL SCIENTIFIC OR EDUCATIONAL USE

If the product is not destroyed, you should label an HCT/P from an ineligible donor as follows:

1. With a Biohazard legend;
2. "For nonclinical use only"; and
3. "Collected from a donor diagnosed with CJD," "Collected from a donor determined to be at risk of CJD," or "Collected from a donor with a potential risk of vCJD," whichever is applicable.

VI. ASSESSING THE IMPACT OF THESE RECOMMENDATIONS ON THE HCT/P SUPPLY

We have incorporated recommendations from the July 1997 guidance into this guidance. However, we lack adequate information about how these recommendations, when implemented, would affect the supply of HCT/Ps. Unlike blood and blood products, there is no readily available demographic information about the HCT/P donor population. Therefore, as we announced in the Federal Register notice of availability related to this draft guidance, we encourage you to submit with your comments study data concerning the effect that implementation of these recommendations could have on the HCT/P supply.

VII. IMPLEMENTATION OF RECOMMENDATIONS

We are publishing this draft guidance for public comment to present our current thinking about preventing the transmission of CJD/vCJD by HCT/Ps through deferral of donors with possible exposure to the agents of CJD and vCJD. When the final rule on donor suitability is published, we intend to issue another draft guidance document for public comment that would include recommendations to screen and test donors for relevant communicable diseases other than CJD and vCJD. We intend to combine both draft guidance documents into one final guidance, issued at the time that the final rule is implemented. When implemented, this final guidance will supersede the July 1997 guidance (Ref. 29).

IX. REFERENCES

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2. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule (66 FR 5447) January 19, 2001. http://www.fda.gov/cber/rules/frtisreg011901.htm.
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APPENDIX:

List of BSE-affected Countries Applicable to Donor Deferral

The list below includes all European countries on the current U.S. Department of Agriculture (USDA) BSE list. The most current USDA list of countries with BSE or at undue risk of introducing BSE into the United States may be found at 9 CFR 94.18(a) (http://www.access.gpo.gov/su_docs/aces/aces140.html).

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

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

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