Informational Issue Summary

FDA's Currently-Recommended Policies to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

Transmissible Spongiform Encephalopathies Advisory Committee

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Background

Beginning in 1978, results of experimental studies repeatedly demonstrated that the infectious agents causing the transmissible spongiform encephalopathies (TSE agents or prions) are often found in the blood of infected animals, both during the incubation period and throughout overt illness. Since 1983, the FDA, issuing a series of guidances, has periodically recommended to the blood industry steps intended to reduce the theoretical risk of transmitting the infectious agents of the transmissible spongiform encephalopathies (TSEs) causing Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) by blood and blood products. The risk of transmitting most forms of CJD by transfusions of blood components and injection of plasma derivatives, remains theoretical (see Appendices I and II), however, limited but convincing evidence strongly implicates transfusions with a blood component and injections of a human plasma-derived coagulation factor in iatrogenic transmissions of vCJD in the United Kingdom (UK). The history of FDA's policies and of the science that informed the FDA in this area is summarized in Appendices I and II, with current FDA guidance in tabular form in Appendices V and VI. (Appendices III and IV summarize certain legislation implemented in the European Union and USDA regulations relevant to FDA blood safety policies.)

In principle, when possible, several approaches are taken to reduce the risk of transmitting infectious diseases from a blood or plasma donor to a recipient:

Five "tiers" of safety for blood and components as related to CJD and vCJD

(modified from *Keeping Blood Transfusions Safe: FDA's Multi-layered Protections for Donated Blood*. US FDA Publication No. FS 02-1, February 2002

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095522.htm accessed October 2010)

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1. **Donor screening** [questionnaires]: selection of blood and plasma donors based on deferrals for medical, geographical and behavioral risk factors; deferral registries to avoid collection and use of units from identified "unsuitable" donors
2. Laboratory testing of donor blood samples for markers of blood-transmissible diseases (infectious agents)
3. **Donor Deferral Registries:** an additional control to avoid collecting blood or releasing blood from donors deferred as unsuitable
4. Quarantine: Donor blood [and plasma] quarantined until testing results available
5. **Problems and deficiencies**: manufacturing problems investigated, deficiencies corrected, FDA notified of deviations

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1, 3 and 5 are currently applicable to TSEs; laboratory testing (2 and 4) is not yet available for TSEs. In addition to protections listed, pathogen reduction techniques are currently under study for both conventional pathogens and TSE agents but are not yet validated, approved or available.

Because no validated screening tests identify TSE-agent-infected blood and there are no US-approved devices to remove TSE infectivity from blood and blood components, CJD and vCJD safety must continue to rely on precautionary deferrals of donors at increased risk for CJD and for vCJD and withdrawal of in-date components when post-donation

information reveals that a donor should have been deferred; and, additionally for vCJD, withdrawal of plasma derivatives if and when a donor is found to have vCJD or possible vCJD. The FDA continues to encourage the development of donor screening tests and devices to remove the infectious agents of TSEs from blood (see below).

The FDA, aware of the uncertainties surrounding the magnitude of the risk, the effectiveness of available risk-reducing measures, and the potential for contributing to shortages of life-sustaining blood products, has continued to review at frequent intervals its policies regarding CJD and vCJD. In particular, FDA blood safety policies regarding CJD and vCJD have periodically been reviewed publicly with the TSEAC, especially when new information suggested that risks should be reevaluated. In the appendices we provide additional current relevant information on risks of transfusion-transmitted and plasma-derivative-transmitted vCJD.

General approaches of FDA policies
to reduce risk of transmitting CJD and vCJD by blood products

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- Reduce risk that a donor was exposed to the agent of bovine spongiform encephalopathy (BSE)
  - Dietary exposure "geographic" risk-adjusted deferrals: defer some donors who resided in some BSE countries (or were potentially exposed on military bases that imported beef from UK)
  - Other exposure: defer donors who injected UK bovine insulin
- Reduce risk that donor was exposed to vCJD agent of human origin
  - Defer donors with a history of transfusion in UK after 1980
  - Defer donors with a history of transfusion in France after 1980
  - Other steps were discussed at TSEAC meetings, but FDA was not advised to consider: history of transfusion in other BSE country besides UK and France after 1980; history of surgery in high-risk BSE countries after 1980 (suggested by one TSEAC member)

There have been six general bases for FDA's recommended CJD/vCJD-related deferrals since 1983:

A. **General CJD risk reduction.** (1) CJD in a donor, (2) history of treatment with human cadaveric pituitary growth hormone or a dura mater allograft, and (3) history of CJD in a relative unless confirmed to be other than familial CJD or the donor *PRNP* genotype is found to be normal

B. **vCJD risk reduction.** (4) history of prolonged residence in most BSE countries (defined by USDA list of BSE-related import restrictions at 9) currently including UK, France or other European countries west of the Former Soviet Union (or residence/employment on a US military base in Europe during periods when beef was procured from UK), (5) history of transfusion in UK, or—more recently—history of transfusion in France, in or after 1980, and (6) injection with bovine insulin of UK origin in or after 1980

The most recent FDA CJD/vCJD-related donor deferral policies and the history of those are explained in full in FDA guidance issued on May 10, 2010 (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf), including minor modifications of the guidance of January 12, 2002. The following is a reduced summary of the essential features of the policy:

Summary of Current FDA CJD/vCJD-related Recommendations for Deferral of Blood Donors and Plasma Donors

(see FDA guidance document issued May 10, 2010 at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf)

Indefinitely defer all donors of Whole Blood and Source Plasma who

- have any form of CJD or are at increased risk of CJD (received dura mater allograft, were injected with human cadaveric pituitary growth hormone, have a relative with CJD unless familial CJD has been ruled out
- spent ≥3 mo in UK from Jan 1, 1980 to Dec 31, 1996, or
  - who ever had blood transfusion in UK or in France from 1980 to present, or
  - who ever injected UK bovine insulin prepared in or after 1980, or
- spent ≥ 5 yr in France from Jan 1, 1980 to the present
- spent ≥6 mo on US military bases from Jan 1, 1980 to end of 1990 north of Alps or end of 1996 south of Alps

Indefinitely defer all donors of Whole Blood but not donors of Source Plasma who

- spent ≥5 yr in Europe from Jan 1, 1980 to the present (including time in spent in UK 1980-1996 and France 1980-present)

Exempt from deferrals are

- Donors of Source Plasma who spent time of any duration in Europe **except** UK and France
- Donors of plasma/serum to manufacture FDA-approved non-injectable products (appropriately labeled per guidance of May 10, 2010)

The FDA-recommended CJD/vCJD-related blood safety policies are intended to reduce the risk that a blood or plasma donor might be incubating CJD of any kind while not deferring so many donors as to compromise the supply of blood products. The FDA's assessment in advance of the January 2002 guidance estimated that the recommended deferral policy would reduce donor risk of dietary exposure to BSE agent by approximately 90% while deferring some 7% of otherwise suitable blood donors. The 2010 guidance—adding a deferral of donors transfused in France from 1980 to the present, as previously recommended for donors transfused in the UK—while reducing the risk of transfusion-transmitted vCJD by only a small amount, is expected to defer very few donors who would not have been previously deferred because they resided in France for five years or more.

As always, blood and plasma establishments may implement additional more stringent requirements. If they choose to do so, FDA encourages them to assess the possibility that such actions will contribute to shortages and to undertake preemptive donor recruitment efforts to prevent shortages.

Recognition by FDA of USDA BSE-related import restrictions under 9 CFR 94.18 as a basis for FDA donor deferral policies. Since the FDA's 1999 guidance, the FDA has acknowledged the USDA's list of countries under restriction for the importation of live cattle and beef products into the US at 9 CFR 94.18 ("USDA BSE List" summarized in Appendix V) as a basis for identifying countries with increased risk of human food-

associated exposure to the BSE agent; most of the countries currently on the USDA BSE list are also listed on the current FDA donor deferral list (see Appendix IV), with three exceptions: the FDA has concluded that time spent in the UK after the end of 1996 should no longer pose an unacceptable risk of food-borne exposure to donors because of stringent food and animal feed controls implemented in the UK by that time; those measures were described at a TSEAC meeting (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf). Time spent in Israel (one case of BSE reported in 2001) and Japan (36 cases of BSE detected from 2001 through 2009) have not been taken as a reason to defer blood donors; FDA had no information to predict the number of otherwise suitable donors who would be deferred because of time spent in Israel or Japan, and FDA had concern that those numbers might be substantial in certain areas of the US.

Prospects for future modifications of FDA blood and plasma deferral policies to reduce the Possible Risk of Transmitting Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

Prospects for donor screening tests. As mentioned above, the FDA recognizes the potential value of practical blood tests to detect and defer infected donors of blood and plasma during the asymptomatic incubation periods of vCJD and CJD. FDA continues to encourage the development and validation of such tests and has several times arranged for developers of candidate tests present interim progress reports of their investigations at open meetings of TSEAC and received advice from TSEAC regarding possible pathways leading to FDA licensure of validated donor screening tests (http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4240t2.pdf). Effective testing would be a particularly attractive option for interdicting donors incubating forms of CJD other than vCJD, because no cases of transfusion-transmitted CJD or plasma-derivative-transmitted CJD have been detected in a lookback study (Dorsey, Zou et al. 2009), and many donors currently deferred because of risk factors for CJD might be re-entered if validated screening tests with high negative predictive values were not reactive. At the moment, no blood test has been validated as suitable for donor screening (http://biotuesday.ca/2010/05/31/amorfix-suspends-blood-testing-for-vcjd).

Prospects for prion-protein and infectivity removal devices. Three TSE infectivity reduction devices, in development, have targeted the RBC component of Whole Blood. Two of the devices both deplete white blood cells (leukoreduction [LR]) and reduce the content of TSE agents in pilot studies. One of these devices is a modified LR filter containing several layers of prion-protein-removing material (Sowemimo-Coker, Demczyk et al. 2010. The second manufacturer is developing a combined LR and prion removal device (Miura M, Nirasawa H et al. in Abstracts of the AABB Meeting, 2006 SP221. Evaluation of a new combination filter for prion and leukoreduction (LR) of red cell concentrates (RCC), accessible at http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2006.01023_1.x/pdf). The third filter is applied to leukoreduced RBC; the active component is a proprietary ligand claimed to adsorb both brain-derived and endogenous blood infectivity (Gregori, Gurgel et al. 2006). This filter was evaluated for safety and impact on component quality in the UK (Cahill, Murphy et al 2010; Wiltshire, Thomas et al. 2010). In April 2009 an independent UK Advisory Committee on Safety of Blood, Tissues and Organs (SaBTO recommended that " …UK blood services … prepare to enable implementation of Prion filtration as soon as

practicable, should a final recommendation to do so be made." [http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_099922.pdf]) and later, in October 2009, recommended, with reservations, that "… filtered red cells be provided to those born since 1 January 1996, subject to satisfactory completion of …[an ongoing]… clinical trial" (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_108860.pdf; http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_112477.pdf)—presumably because the risk of food-borne exposure to the BSE agent should be considerably less in younger than for older UK residents, for whom the reduced risk offered by filtration might be more difficult to justify. No "prion filter" device has been licensed for use in the US. Representatives of the sponsors developing the three devices are to describe some of their findings at the FDA TSE Advisory Committee meeting on October 29, 2010 (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/ucm225805.htm).

Implementation of measures to reduce dietary risk of exposure to the BSE agent in countries other that the UK. As presented to the 21st meeting of TSEAC on June 12, 2009 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/UCM171810.pdf), the European Commission (EC) has promulgated legislation (EC Regulation 999, 2001) obligatory throughout the European Union (EU) requiring implementation of a number of BSE-risk-reducing steps (see Appendix IV) similar to those implemented earlier in the UK (Appendix IV). The FDA has, with some exceptions, based recommendations to defer blood and plasma donors at increased risk of BSE exposure on the USDA import restriction list at 9 CFR 94.18 to determine when those steps have been adequately and uniformly implemented in various countries.

International recognition of BSE status of countries and of the declining BSE epidemics. The EC Scientific Steering Committee, in January 2000, recommended grouping countries based on their geographical BSE risk (GBR) (http://ec.europa.eu/food/fs/sc/ssc/out68_en.pdf). Four groups were recognized: GBR I: highly unlikely to have BSE; GBR II: unlikely but not excluded; GBR III: likely but not confirmed or confirmed at a low level; GBR IV: confirmed at a high level. That system for evaluating BSE risk was once widely used but is no longer supported.

The World Organisation for Animal Health (OIE) subsequently developed a system to evaluate national BSE risk based on voluntary submissions of information to an ad hoc committee for BSE status based on five main criteria used to assess the BSE risk for the cattle population of a country: risk assessment for BSE occurrence; on-going program to encourage reporting of neurological diseases in adult cattle; compulsory notification and investigation of all cattle showing BSE-like symptoms; BSE active surveillance; testing of cattle brain or other tissues. The OIE currently assigns to each country one of three BSE risk categories: negligible, controlled or undetermined (for those countries that either did not apply or failed to be classified). As of May 2010, 47 countries had been assigned a BSE risk status by the OIE: 13 countries (including three on the USDA BSE

Import Restriction List) had been assigned negligible BSE risk status, and 34 countries, including the US and Canada, were recognized as having controlled BSE risk—the same risk status assigned to most European countries including the UK and France (http://www.oie.int/eng/Status/BSE/en_BSE_free.htm). The FDA welcomes efforts to improve estimates of relative risk for exposure to the BSE agent in beef products of various national origins and to develop an international BSE risk evaluation system acceptable to US authorities and those of other countries.

Appendix I.

Selected reference chronology of important events and FDA guidances related to safety of human blood and products derived from human blood

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- 1978. Manuelidis E et al. detected CJD agent in experimentally infected guinea pig blood buffy coat (Manuelidis, Gorgacs et al. 1978).
- 1983. Kuroda, Gibbs detected GSS ("fCJD" or Fu-1) agent in mouse blood—highest concentration in buffy coat (Kuroda, Gibbs et al. 1983).
- 1983 to present. other TSE agents in other animal bloods confirmed (hamster scrapie; mice CJD, BSE; sheep BSE, scrapie; chimp GSS; monkey vCJD (Brown, Rohwer et al. 1998; Brown, Cervenakova et al. 2001))

- 1983. FDA requested withdrawal of CJD-implicated blood components (post-donation diagnosis of CJD in a donor) (http://www.fda.gov/ohrms/dockets/ac/99/backgrd/3548b1d.pdf).
- 1987. FDA recommended deferring donors treated with human cadaveric pituitary growth hormone, later other donors at increased TSE risk (dura mater allograft, family history of CJD) (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf).
- 1991. FDA recommended that in-date plasma derivatives that were manufactured from pooled plasma containing donation(s) from an individual subsequently diagnosed with CJD or from individuals at increased risk of CJD (because of history of treatment with human cadaveric pituitary growth hormone or dura mater allograft or with a family history of CJD) be withdrawn from distribution and quarantined (letter from the Director, CBER to All Establishments Engaged in Manufacturing Plasma Derivatives, 8 August 1995 [available on request from CBER])
- 1995. FDA recommended precautionary withdrawals of CJD-implicated blood components and plasma derivatives (reviewed at http://www.fda.gov/ohrms/dockets/ac/99/backgrd/3548b1d.pdf and in the transcript of the TSEAC meeting June 2, 1999 at June 2, 1999 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3518t1.rtf)

- 1996. First cases of vCJD reported from UK (Will, Ironside et al. 1996) and France (Chazot, Broussolle et al. 1996)

- 1996. FDA issued recommendations pertaining to retrieval, quarantine, destruction, and notification (reviewed at http://www.fda.gov/ohrms/dockets/ac/99/backgrd/3548b1d.pdf and in the transcript of the TSEAC meeting June 2, 1999 at June 2, 1999 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3518t1.rtf)
- 1998 (clarified in 1999). FDA recommended that 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 (December 18, 1998 TSEAC meeting transcript: http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3484t1.rtf; http://www.fda.gov/NewsEvents/Testimony/ucm115104.htm, accessed April 21, 2010; see also http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf)

  Exceptions: Derivatives of any plasma pool to which a donor with vCJD had donated would be withdrawn. (That has not happened with any US-licensed plasma derivative.) Reports of other kinds of CJD in persons younger 55 years would be evaluated on a case-by-case basis (by CDC in consultation with FDA).

- 1999. FDA recommended UK vCJD-based deferral (for ≥ 6 mo total residence in UK 1980-1996).
- 2002. FDA recommended enhanced precautionary geographic vCJD deferrals—retained in the current guidance (including donors transfused in UK since 1980).

- 2003. UK reported a case of presumptive transfusion-transmitted (TT) vCJD attributed to transfusion of non-leukoreduced RBC in one of a small cohort of recipients—Transfusion Medicine Epidemiological Review (TMER (Llewelyn, Hewitt et al. 2004)).
- Jan 2003. A risk model based on observed vCJD cases predicted a very low prevalence of preclinical infections in the [most] "susceptible" UK population (homozygous for methionine at *PRNP* codon 129 [genome present in ≅ 40% of the UK population]). Ghani AC et al. (Ghani, Ferguson et al. 2000; Ghani, Donnelly et al. 2003).
- July 2004: 2nd UK presumptive TT vCJD infection reported (in recipient heterozygous for methionine/valine [M/V] at *PRNP* codon 129 [the genotype of ≅ 50% of the UK population], the 1st infection identified in a person with that genotype) (Peden, Head et al. 2004). The recipient died of a condition unrelated to vCJD, did not fulfill the clinical case definition for vCJD, and is widely thought to have had a pre-clinical infection.
- July 2004: UK appendix (and tonsil) PrP^{TSE} survey suggested that >200 persons/million in UK might be incubating vCJD (Hilton, Ghani et al. 2004).
- Sept 2004: UK notified some recipients of plasma derivatives of an increased vCJD risk (http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/CreutzfeldtJakobDisease/VariantCJDAndBlood/cjd10VariantCJDandplasmaproducts/).
- Feb 2006: UK reported a 3rd case of presumptive transfusion-transmitted vCJD (Wroe, Pal et al. 2006).
- Apr 2006: Two of three PrP^{TSE}-positive appendices from the UK tissue survey were reported to be homozygous for valine at *PRNP* codon 129, a genome present in ≅ 10% of the UK population (Ironside, Bishop et al. 2006). (No clinical case of vCJD has been reported to date in any person with that genotype.)
- Aug 2006. FDA published draft guidance for comment to defer blood/plasma donors transfused in France after 1980 (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074083.htm)
- Jan 2007. UK reported 4th case of presumptive transfusion-transmitted vCJD (Health Protection Agency: New case of transfusion-associated variant CJD. CDR Wkly 2006; 16:50 accessed at http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3117; http://www.cjd.ed.ac.uk/TMER/reverse.htm; http://www.hpa.org.uk/hpr/archives/2007/hpr0307.pdf

  The intervals between implicated blood donation and onset of vCJD for 3 infected blood donors (to 4 recipients) were 3.5, 1.5, and 1.7, 1.4 yr.
- Jan 2009. A US lookback study of 36 blood donors later diagnosed with CJD found no evidence of CJD in any recipient (Dorsey, Zou et al. 2009).
- Feb 2009. UK reported evidence (PrP^{TSE} in spleen) of elderly man with hemophilia treated with UK plasma-derived FVIII (Peden, McCardle et al. 2010).

  One plasma donor to manufacturing pools for the product developed vCJD, but a UK risk assessment suggested that—considering possible prevalence of pre-clinical vCJD in general UK population—some other vCJD-incubating donor might have been source of infection (Bennet P, Ball J 2009 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_100337.pdf).
- June 2009. Although one plasma donor to manufacturing pools for the implicated product developed vCJD, a UK risk assessment suggested that—considering possible prevalence of pre-clinical vCJD in general UK population—some other vCJD-incubating donor might have been the source of infection (Bennet P, Ball J. Report to CJD Incidents Panel, http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_100337.pdf accessed on 27 Sept 2010)

- Dec 2009. A typical clinical case of vCJD reported from UK in a person with *PRNP*-codon-129 heterozygous M/V genotype (Kaski, Mead et al. 2009).

  Implication: A 2nd (? smaller) wave of vCJD cases with longer incubation periods may have begun. (PrP^{TSE} had previously been reported in lymphoid tissues of two persons with *PRNP*-codon-129 MV genotype without clinical evidence of neurological disease but at increased risk of vCJD and in two appendices from anonymous persons with VV genotypes (Ironside, Bishop et al. 2006).

- May 2010. CBER issued revised guidance to defer blood donors with history of transfusion after 1080 in France as well as in UK (but not donors transfused in other BSE countries, though many such donors of Whole Blood would still be deferred, because they lived there for more than 5 yr). 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. May 2010 (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf).

- FDA guidance ○ Other report related to TSE and blood safety

Appendix II.

History of TSEs as Related to Blood Safety

Most attempts to detect infectivity in blood or serum of animals with TSEs failed until 1978, when Elias Manuelidis and colleagues demonstrated the transmissible agent in crude buffy coat preparations of 13 guinea pigs injected with brain material of other guinea pigs with experimental Creutzfeldt-Jakob disease (CJD) (Manuelidis, Gorgacs et al. 1978), detected throughout most of the incubation period. Assay guinea pigs had long incubation periods (some over a year), suggesting that amounts of infectivity in donor guinea pig blood were probably very small. In 1983, NIH investigators demonstrated that the blood buffy coats of mice infected with a TSE agent derived from a patient with the Gerstmann-Sträussler-Scheinker disease (GSS)—similar to familial CJD—also contained infectivity, detectable from the middle of the incubation period through terminal illness (Kuroda, Gibbs et al. 1983). The finding of small amounts of TSE infectivity in blood was later confirmed in a variety of other animals, including sheep with naturally-acquired scrapie (Hunter, Foster et al. 2002), experimental BSE (BSE) (Houston, Foster et al. 2000), chimpanzees injected with brain material from a GSS patient (Williams, Brown et al. 2007), and macaques experimentally infected with BSE agent (Lasmézas, Fournier et al. 2001). Although much of the infectivity was associated with nucleated cells (Brown, Cervenakova et al. 1999; Brown 2000; Brown, Cervenakova et al. 2001; Holada, Vostal et al. 2002), plasma contained substantial amounts as well (Gregori, McCombie et al. 2004).

Presumptive transmissions of vCJD from blood of clinically healthy donors who later developed vCJD

In an on-going look-back study, the UK Transfusion Medicine Epidemiology Review (TMER, http://www.cjd.ed.ac.uk /TMER/TMER.htm) identified and enrolled 66 recipients of blood transfusions from 32 donors who later developed vCJD. (In addition, TMER identified nine vCJD donors who contributed plasma to 23 pools used for fractionation into plasma derivatives before 1999.) As of 2010, four instances of probable transfusion transmitted vCJD (TTvCJD) infection have been identified by the TMER, including three clinical cases of vCJD and a sub- or preclinical infection. As of 2010, 21 surviving recipients of transfusions of blood components from donors who later developed vCJD have been informed that they are at greater risk of developing vCJD. The four infections through blood transfusion identified to date (all in recipients of non-leukoreduced red blood cell concentrates) have developed in a cohort of only 32 individuals who have survived at least five years since transfusion (Chohan, Llewelyn et al. 2010).

1st presumptive vCJD infection (case). On 17 December 2003 the UK Department of Health announced that one recipient of non-leukoreduced red blood cells in the TMER cohort had died with vCJD. The case has been described in detail (Llewelyn, Hewitt et al. 2004). In March 1996, a clinically healthy young blood donor donated Whole Blood to the UK National Blood Service. Red blood cell concentrate—not leukoreduced—was transfused into an older surgical patient (later found to be homozygous for methionine at codon 129 of the prion-protein-encoding (*PRNP*) gene. Three years and four months after the transfusion, the donor became demented with other signs of neurological disease and died; the postmortem diagnosis was vCJD. In December 2003 the recipient died;

postmortem diagnosis was vCJD. UK authorities estimated the recipient's age-adjusted food-borne risk of vCJD to have been from 1:15,000 to 1:30,000.

2nd vCJD presumptive infection (in a person heterozygous for methionine at codon 129 of the *PRNP* gene). In July 2004, UK authorities announced that preclinical vCJD had been diagnosed the previous year in a second person in the TMER cohort. The case has been partially described in the medical literature (Peden, Head et al. 2004). The second recipient was transfused in 1999 with non-leukoreduced red blood cells from a clinically healthy donor who developed signs of vCJD 18 months later, confirmed at death in 2001. Five years after transfusion, the recipient died of a ruptured abdominal aortic aneurysm without signs of neurological disease. Abnormal prion protein (PrP^{TSE}) typical of vCJD was detected at autopsy in several areas of the spleen and in a cervical lymph node, suggesting that infection was present but had not yet spread to the brain. It seems highly improbable that two cases of vCJD resulting from coincidental food-borne transmission would occur by chance in the small TMER cohort during a short period of time.

This was the first report of a (presumptive) vCJD infection in a person heterozygous for methionine and valine at *PRNP* codon 129 among those tested. (As noted above, all previous vCJD patients tested were homozygous for methionine at *PRNP* codon 129.) The case was presumed to be a preclinical infection, and it seems probable that infection would eventually have progressed to involve the nervous system had the patient not died of an unrelated disease. Homozygosity for methionine or valine at *PRNP* codon 129 is known to be over-represented in persons with iatrogenic and sporadic forms of CJD (Deslys, Marce et al. 1994), however heterozygous persons have not been completely spared from those diseases. The finding of a presumptive transfusion-transmitted vCJD infection in a heterozygote implies that such individuals are unlikely to be absolutely resistant to infection with the BSE agent as well and that food-borne vCJD cases might be expected in persons of all *PRNP* codon-129 genotypes, possibly in smaller numbers and with longer incubation periods than for homozygous individuals. (One clinically typical case of vCJD—tissue not available to confirm the diagnosis—was recently described in a person with the *PRNP* codon-129 genotype (Kaski, Mead et al. 2009). In short, persons heterozygous for methionine/valine at codon 129 of the *PRNP* gene (comprising about half the population in the UK) appear to be susceptible to blood-borne infection with the human-adapted BSE agent and probably to food-borne infection with the BSE agent as well.

3rd presumptive transfusion-transmitted vCJD infection (case). In 2005, a 31-year-old male developed symptoms of vCJD 7.5 years after a vCJD-implicated transfusion of non-leukodepleted red cells. The patient was homozygous for methionine at codon 129 of the *PRNP* gene. PrP^{TSE} was detected at autopsy in the brain, tonsil and spleen (Wroe, Pal et al. 2006).

4th presumptive transfusion-transmitted vCJD infection (case). The fourth presumptive transfusion-transmitted case of vCJD was in a person homozygous for methionine at *PRNP* codon 129. The patient developed signs of illness 8.5 years after receiving a transfusion of red cells from a donor who developed vCJD about 17 months

after donation (Health Protection Agency: New case of transfusion-associated variant CJD. CDR Wkly 2006; 16:50, and Eurosurveillance, 2007;12 (3) at http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3117).

Presumptive vCJD infection in an asymptomatic UK patient with hemophilia

In the UK plasma donations from asymptomatic individuals infected with vCJD have contributed to some batches of pooled clotting factor concentrate (termed "vCJD-implicated batches"). Recently, PrP^{TSE} was detected in the spleen of a UK adult hemophilic patient who at the time of death had no neurological signs or symptoms attributable to vCJD (Peden, McCardle et al. 2010). In response to this event a risk assessment was requested by the UK CJD Incidents Panel for patients with multiple routes of exposure (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_100337.pdf). The patient had been exposed to several potential routes of vCJD infection, including multiple transfusions with blood components, repeated injections of UK-sourced fractionated plasma-derived coagulation factor VII, including some lots linked to a donor who later went on to develop clinical vCJD, several invasive biopsies, (and the general food risk present in the UK). Postmortem examination showed the presence of PrP^{TSE} in a spleen sample but no other TSE-related pathologic finding. It is important to note that the PrP^{TSE} detected in this individual would have been missed by the tests used in the UK at the time to estimate prevalence of vCJD infections. The glycoform ratio of PrP^{TSE} extracted from the spleen of in this patient resembled that described for vCJD. Genetic analysis showed that the patient was heterozygous (methionine/valine) at *PRNP* codon 129.

New cases of vCJD diagnosed each year peaked in the UK in 1999 and deaths in 2000; rates declined in the following years. The current total number of cases meeting the UK definition for confirmed or probable vCJD (as of June 2010) stood at 220 worldwide (not counting presumed preclinical infections) of which 173 were resident in the UK. The rest of the cases were 41 reported in various European countries (France 25, Republic of Ireland 4, Italy 2, Netherlands 3, Portugal 2 and Spain 5), USA 3 (two in former UK residents and one a recent arrival from Saudi Arabia and likely infected there as a child), Canada (1), Saudi Arabia (1), and Japan (1), in a person who had visited the UK for 24 days about 12 years before onset (http://www.cjd.ed.ac.uk/vcjdworld.htm).

Recently, two other cases of vCJD were described in patients with a history of blood transfusion but no evidence that a donor had vCJD. One of those patients received blood transfusions as a neonate in 1989 and died at age 18 years with pathologically confirmed vCJD. The second developed definite vCJD in 1998 at age 41 years; he had been transfused with components from a total of 103 donors in 1993. As a precaution, UK authorities have considered the donors involved as being "at risk of vCJD for public health purposes" although association may have occurred by chance (Chohan, Llewelyn et al. 2010).

Predictions of vCJD infection rates based on finding of PrP^{TSE} in lymphoid tissues of preclinical vCJD

Shortly after the first clinical and histopathological descriptions of vCJD (Will, Ironside et al. 1996), it was noted that lymphoid tissues of a person dying with vCJD (spleen, lymph nodes) contained detectable accumulations of PrP^{TSE} (Hill, Zeidler et al. 1997;

Hill, Butterworth et al. 1999)—something not seen in other forms of CJD. The appendix removed from an otherwise healthy person who developed signs of vCJD eight months later also contained PrP^{TSE} (Hilton, Fathers et al. 1998), as did another appendix removed two years before onset, although a third removed 10 years before onset was negative (Hilton, Ghani et al. 2002); those fortuitous findings suggested that a survey of archived tonsils and appendices might provide a useful estimate of the minimum number of persons with preclinical vCJD in the UK population. Two such surveys have been reported to date: the first found one positive appendix among 8318 adequate specimens saved from patients 10 to 50 years old between 1995 and 1999, yielding an estimated rate of 120/million (95% CI, 0.5 – 900/million) in that population (Hilton, Ghani et al. 2002); the second yielded three positives among 12,674 appendices for an estimated rate of 237/million (95% CI, 49 – 692/million) (Hilton, Ghani et al. 2004). All tonsils were negative, however a more recent UK survey of more than 9000 tonsil samples found one "strongly positive" result (not confirmed in another area of tissue) suggesting a possible prevalence of more than 100 pre-clinical vCJD infections per million population born between 1961 and 1985 (de Marco, Linehan et al. 2010). It is interesting to note that both tonsils and appendix of the second presumptive transfusion-transmitted case of vCJD were negative for PrP^{TSE}, plausibly attributed to that patient's non-food-borne route of infection (Peden, Head et al. 2004).

Appendix III.

BSE Surveillance and Control Measures in the European Union

Addressing the 21st TSEAC Meeting on June 12, 2009 , Dr. Martial Plantady, representing the European Commission, summarized aspects of BSE surveillance and food and feed control measures in the European Union, with emphasis on specific legislation to prevent, control and eradicate BSE; feed ban and eradication measures; and public health, animal health measures (EC Regulation 999, 2001 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/UCM171810.pdf).

The following is an FDA summary of that presentation:

- **Removal of specified risk material (SRM)**: for animals over 30 month include: brain, eyes, spinal cord, vertebral column, dorsal root ganglia. For animals of all ages tonsils and intestines from the duodenum to the rectum and the mesentery are considered SRM. SRM have to be disposed mainly by incineration.
- **Trade rules**. All bovine and caprine derived products imported into the European Union (EU) must not contain or be derived from SRM, except if the product comes from a country with negligible risk status according to the OIE.
- **Feed ban**. The first measures were taken in 1994 to prohibit the use of proteins derived from mammals to feed ruminants. In January of 2001 the EU implemented an "extended BSE ban" or "total feed ban" extending the prohibition to feed proteins of animal origin to all farm animals. This measure was intended to prevent accidental cross-contamination of ruminant feeds. Control of the feed ban is done by microscopic analysis of samples, looking for bone fragments. A "zero tolerance" rule was implemented (material is to be prohibited in feed if even a single bone fragment is detected).
- Blood meal and blood products are authorized for feeding fish and such products are labeled accordingly.
- **Export**: processed animal protein from ruminants and products containing ruminant protein are prohibited outside the EU. However, there is an exception for pet food.
- **Surveillance and eradication measures:** passive and active surveillance are implemented in the EU.
- **Passive surveillance** involves the testing of all animals suspected of being infected with the BSE agent.
- **Active surveillance** (since 1 July 2001) involves the systematic testing of selected groups of animals that do not show sign of BSE infection and includes two groups: all animals over 24 months of age must be tested if they are (i) subjected to emergency slaughtering for signs of disease or poor general condition on arrival at the slaughter house, and (ii) fallen stock or animals found dead on the farm. In addition all healthy animals over 30 months old slaughtered for human consumption are to be tested. These subgroup includes animals slaughtered during disease eradication campaigns (e.g., during foot and mouth epidemics). On discovering a BSE-positive animal an inquiry is initiated including analysis of the feed, birth, progeny and cohort history. This is followed by eradication of the herd where the infected animal was identified. Regulation 999/2001 offers two options: (i) culling the entire herd of origin, or (ii) selective culling to include all animals that might have consumed feed associated with the index case. In addition, there may be extended culling of herds where the index case resided during its lifetime.
- **Additional precautions.** If a positive animal is identified at the slaughter house, the carcass is to be destroyed. In addition, to avoid possible cross contamination, the carcasses of the preceding animal as well as those of two animals immediately following the positive animal [on the slaughter line] must also be destroyed. As described above, the cohort of the BSE-positive animal is also traced and culled.

In 2008 in the EU more than 10 million BSE tests were performed, mostly of healthy animals representing approximately 17% of the total adult cattle population. In addition, 1.5 million risk group animals were tested, representing approximately 3% of the total adult cattle population. The majority of BSE-positive cases were detected with active surveillance.

The level of BSE surveillance in the EU has remained constant for the period 2001-2008 while the number of BSE cases in EU decreased during this period. In addition, the mean age of animals positive for BSE has progressively increased since 2001 suggesting that the exposure of cattle to the BSE agent has diminished.

Appendix IV.

USDA BSE Activities Related to vCJD and Blood Safety

USDA has had a program of active BSE surveillance of cattle in place since 1990 (compared with EU testing that began in 2001) targeting high-risk animals: clinically suspect animals including animals of any age with CNS signs; cattle over 30 months of age; and animals condemned on ante-mortem inspection. USDA conducted an enhanced BSE surveillance from June 2004 to August 2006; of 830,000 animals (US origin) tested, only two were confirmed positive. (A cow imported from Canada tested positive in 2003.) USDA has estimate that, during seven years of surveillance, the prevalence of BSE in the USA has remained less than one infected animal per million based on a population of 42 million adult cattle

Two types of regulation are thought to have played a major role in reducing the risk of BSE in US cattle: prohibitions on feeding of most mammalian proteins to ruminants ("feed ban") and restrictions on importation of live cattle and beef products from most countries reporting BSE or deemed by USDA to have a substantial risk of BSE in native cattle ("BSE list"). FDA (CVM) first implemented a feed ban in 1997 that prohibited the use of most mammalian proteins in ruminant feeds; the ban was enhanced by a rule in 2008 implemented in October 2009. Since 2001, USDA has imposed import restrictions on bovine animals and beef products from countries with BSE in cattle or at increased risk for BSE (see below).

(Appendix IV continued)

USDA Categorization of countries with regard to BSE from January 1998–December 2009 at 9 CFR 94.18. See key below for explanation of symbols. If no symbol is present, the country was considered to be in the fourth category with regard to BSE at the time (courtesy of S. Kreindel, USDA, APHIS)

Country	2001	2002	2003	2004	2005	2006	2007	2008	2009
Albania	✓	✓	✓	✓	✓	✓	✓	✓	✓
Andorra		✓	✓	✓	✓	✓	✓	✓	✓
Austria	✓	✓	×	×	×	×	✓	✓	✓
Belgium	×	×	×	×	×	×	✓	✓	✓
Bosnia-Herzegovina	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bulgaria	✓	✓	✓	✓	✓	✓	✓	✓	✓
Canada				×	×	☒	☒	☒	☒
Croatia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Czech Republic	✓	×	×	×	×	×	×	×	×
Denmark	×	×	×	×	×	×	×	×	×
Federal Republic of Yugoslavia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Former Yugoslav Republic of Macedonia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Finland	✓	✓	×	×	×	×	×	×	×
France	×	×	×	×	×	×	×	×	×
Germany	✓	×	×	×	×	×	×	×	×
Greece	✓	×	×	×	×	×	×	×	×
Hungary	✓	✓	✓	✓	✓	✓	✓	✓	✓
Israel			×	×	×	×	×	×	×
Italy	✓	×	×	×	×	×	×	×	×
Japan		×	×	×	×	×	×	×	×
Liechtenstein	×	×	×	×	×	×	×	×	×
Luxembourg	×	×	×	×	×	×	×	×	×
Monaco		✓	✓	✓	✓	✓	✓	✓	✓
Norway	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oman	×	×	×	×	×	×	×	×	×
The Netherlands	×	×	×	×	×	×	×	×	×
Poland	✓	✓	×	×	×	×	×	×	×
Portugal	×	×	×	×	×	×	×	×	×
Republic of Ireland	×	×	×	×	×	×	×	×	×
Romania	✓	✓	✓	✓	✓	✓	✓	✓	✓
San Marino		✓	✓	✓	✓	✓	✓	✓	✓
Slovakia[a]	✓	✓	×	×	×	×	×	×	×
Slovenia	✓	✓	×	×	×	×	×	×	×
Spain	✓	×	×	×	×	×	×	×	×
Switzerland	×	×	×	×	×	×	×	×	×
Sweden	✓	✓	✓	✓	✓	✓	✓	✓	✓
United Kingdom[b]	×	×	×	×	×	×	×	×	×

(Appendix IV continued)

[a]Slovakia was named Slovak Republic from 1999-2002 in the CFR.
[b]Great Britain and Northern Ireland were listed as separate regions in the 1998 CFR and both were considered regions where BSE exists. The 1999 CFR listed the United Kingdom as a region that included Great Britain, Northern Ireland, and the Falklands.
Key:

- ✖ Regions where BSE exists
- ✓ Regions where import requirements are less restrictive than those of the United States or, because of inadequate surveillance, present an undue risk of introducing BSE into the country
- ☒ Regions that are minimal risk with regard to BSE

Appendix V

European country list to be used for deferral of blood and donors based on geographic risk of BSE (from [FDA] 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, May 10, 2010, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf).

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Republic of Ireland, Italy, Liechtenstein, Luxembourg, Macedonia [Former Yugoslav Republic of Macedonia], Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom (before the end of 1996), and Federal Republic of Yugoslavia [Kosovo, Montenegro, Serbia]

As per FDA guidance of May 2010, 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; and Portugal should be taken to include the Azores. In the list above, we attempted to clarify the status of several countries by listing their new common names in square brackets []; for authoritative information regarding official names of countries, please consult the US Department of State.

Appendix VI.

Tabular Summary of FDA Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products ((from [FDA] 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, May 10, 2010, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf)

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 (Biological Product Deviation Report, 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

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 (other Europe as listed on p. 23≥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

TABLE 2: DONOR DEFERRAL, PRODUCT DISPOSITION, AND RECIPIENT NOTIFICATION FOR SOURCE PLASMA (SP), RECOVERED 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 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 (other Europe as listed on p. 23 ≥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

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