

**SUMMARY OF TRANSMISSIBLE  
SPONGIFORM ENCEPHALOPATHIES  
ADVISORY COMMITTEE MEETING,  
JUNE 1-2, 2000**

**Committee Update**

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66<sup>th</sup> Meeting  
June 15-16, 2000  
Holiday Inn, Silver Spring  
8777 Georgia Avenue  
Silver Spring, MD

**DRAFT "Quick Summary"**  
For the June 1 & 2, 2000  
**Transmissible Spongiform encephalopathy Advisory Committee Meeting**

**JUNE 1, 2000, DONOR DEFERRAL**

**CHARGE**

The FDA asked the TSEAC to evaluate new information that has become available concerning new variant CJD and BSE in France and BSE in European countries besides France and the UK. The committee was asked to consider the risk that donors traveling or resident in France and other BSE countries outside the UK might have been exposed to and infected by the BSE agent and that their blood, blood components and plasma derivatives might transmit infection to recipients.

The Committee was also asked to consider, in the context of a risk-benefit estimate, any effects that recent changes in blood-donor deferral policy may have had on the blood supply in the United States as well as effects reasonably to be anticipated if additional deferrals of donors are recommended.

**QUESTIONS**

1. Do the Committee members believe that available scientific data on the risk of vCJD warrant a change in the current FDA policy regarding deferrals of blood and plasma donors based on a history of travel or residence in the UK? Please comment.

**The committee voted: 3 Yes votes, 15 No votes, and 0 abstentions.**

**The committee stated that there was not strong data to support changing the UK position from what was recommended last year. Also there was not sufficient time to understand the impact of the current policy on availability. Therefore, the committee voted not to change FDA's newly implemented policy on deferral of UK donors.**

2. Considering the current scientific data on the risk of vCJD and the potential impact on the blood supply, should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in France?

**The Committee voted: 1 Yes vote, 17 No votes, and 0 abstentions.**

**The data presented clearly revealed less risk of nvCJD in France as compared to the UK. While the committee encouraged all countries to work to eliminate BSE and thus to reduce vCJD and the theoretical risk of transfusion transmitted vCJD, they voted against deferral of blood or plasma from persons with a history of travel or residence in France .**

3. Should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in BSE countries other than the UK and France (without reported vCJD)?

**The committee voted: 1 yes vote, 17 no votes, and 0 abstained.**

**This vote reflected the conclusion of a lower risk in these other countries . The committee emphasized that FDA deferral policy needs a periodic reassessment as more information is obtained.**

**TSEAC Draft summary (page 2)**

**JUNE 1, 2000, – Leukoreduction**

**CHARGE:**

TSEAC was asked to consider whether leukoreduction of blood and blood components might be expected to reduce substantially the theoretical risk of transmitting the CJD or nvCJD agent, and if they would recommend universal leukoreduction of blood and blood components as a risk reduction measure for CJD and nvCJD.

**QUESTION:**

Can leukoreduction significantly reduce the infectivity of CJD and vCJD? For what blood components?

**The Committee commented that available data were insufficient to make a scientific decision. With that clarification, the vote was: 2 yes votes, 12 no votes, and 1 abstention.**

# Transmissible Spongiform Encephalopathies Advisory Committee

June 1, 2000

Issue 1.

## Donors in BSE Countries besides UK: Introduction, Charge and Questions

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# Epidemiological Studies of Exposure to Blood from Donors Who Later Got CJD

(Adapted from Schonberger L [CDC]. Presentation to PHS ACBSA Jan 1998)

- Case reports of CJD attributable to blood: none
- Case-control studies:
  - 6 negative (several large; used different methods to reduce bias)
  - None positive
- National mortality surveillance:

(CDC: 4,164 cases of CJD during 18 yr from 1979-96)

  - No increasing incidence ( $\sim 1/10^6$ /yr age-adjusted)
  - No Dx hemophilia, thalassemia, sickle cell
  - No CJD Dx in persons < 19 yr old

# Epidemiological Studies of Exposure to Blood from Donors Incubating CJD

(Adapted from Schonberger L [CDC]. Presentation to PHS ACBSA Jan 1998)

- Recipients of blood components from CJD donors

(ARC-CDC-Nat'l Blood Donor Resource Center)

- No CJD Dx in 196 recipients of blood components from 15 CJD donors
- 42 recipients lived > 5 yr after transfusion
- In a similar European study, 13 recipients lived >10 yr and 8 lived > 15 yr after transfusion

- Hemophilia survey

(CDC-Hemophilia Treatment Centers)

- No clinical Dx of CJD in >12,000 patients through 1998
- No histopathol Dx CJD 30 autopsies (mean age 39 yr)

## Epidemiological Studies of Exposure to Blood from Donors Incubating CJD

- Recipients of vaccines containing excipient albumin (followed through 1996):
  - >38 million children aged  $\leq 5$  yr. received a vaccine containing excipient albumin at some time between 1967 and 1986.
  - By end of 1996 they had lived to ages 11 to 19 yr.
  - No CJD was diagnosed in any recipient.

# Conflicting Evidence that Blood of Humans or Animals with TSE May be Infectious

Human epidemiological studies: all negative

Experimental studies: not completely reassuring

- **Human CJD blood**
  - into primates: all negative
  - into rodents: a few positive ( $\pm$ )
  - (spleen, liver, nodes into primates: some positive)
- **Animal natural TSE blood**
  - BSE cow, scrapie sheep, goat into rodents: negative
  - mink encephalopathy into mink: negative
  - Rodent experimental CJD/scrapie blood into rodents:  
several models positive ( low titers  $\leq 100$  icLD<sub>50</sub>/ml)

# Distribution of Scrapie Infectivity Spiked into Human Blood

(Brown P et al. Transfusion 1998;38:810)

<u>Product</u>	Total Infectivity <u>icLD50</u>	% Infectivity <u>Recovered</u>
Whole Blood	10.0	100%
RBC	9.9	22%
WBC, platelets	8.8	7%
Plasma	8.5	3%
Plasma	8.2	100%
Cryoprecipitate	6.8	0.7%
IgG	3.9	0.006%
Albumin	2.7	0.0004%

US Public Health Service Advisory Committee  
on Blood Safety and Availability  
(Concerns Expressed to PHS Jan 1998)

- There is no demonstrated risk to recipients of CJD-implicated plasma derivatives--theoretical only.
- CJD withdrawals do not substantially reduce theoretical risk. ( $\geq 25\%$  of large plasma pools used to produce derivatives are likely to contain contribution from a donor who will ultimately get sporadic CJD.)
- No screening question can defer or pre-morbid laboratory test detect those donors.
- Withdrawals fail to retrieve most CJD-implicated product.
- CJD withdrawals contribute significantly to shortages of some plasma derivatives.

# US Public Health Service TSE Policies Concerning Blood Safety and Availability

## Advice to PHS (PHS ACBSA Jan 1998)

- “[FDA should] work with industry and appropriate consumer groups to relax current CJD guidelines [FDA, CBER 11 Dec 1996] on retrieval and withdrawal of blood products to the extent necessary to relieve shortages [of affected plasma derivatives] ...”

## Response from PHS: revised policy

(Announcement Aug 1998; interim FDA guidance Sept 1998; unified guidance Aug 1999)

- Withdraw plasma derivatives only for vCJD in a donor.
- Stop withdrawals of derivative for sCJD and increased risk of CJD.
- Consider revised labeling of plasma derivatives.
- Continue epidemiological surveillance, laboratory studies of TSE.
- Policies for deferral of sCJD donors, retrieval of whole blood and components remain unchanged.

## Guidance for Industry:

Revised Precautionary Measures to Reduce Possible Risk of  
Transmission of CJD & nvCJD by Blood & Blood Products  
(CBER Sept 98, rev Aug 1999 recommended for immediate implementation)

- Continued deferral of donors with CJD or increased risk of CJD
- Continued quarantine of blood and components (including plasma) from donors with CJD or increased risk of CJD
- **No withdrawal of plasma derivatives prepared from pools to which donors with classical CJD or increased risk of classical CJD contributed**
- **Withdrawal of plasma derivatives and quarantine of intermediates prepared from pools to which any donor who develops new-variant CJD contributed**

(Risk factors for CJD=PRNP mutation associated with fCJD or GSS, recipient of dura graft or of human pituitary hormone.)

[Full document available at [www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)]

## Reasons for Increased Concern about Blood Donors During Incubation Period of vCJD

- Less is known about pathogenesis of vCJD than sporadic CJD (sCJD).
- vCJD is an emerging infection not found in USA.
- Lymphoid tissues in vCJ contain detectable protease-resistant prion protein while in sCJD do not.

Infectivity of those tissues is not yet clear. (Note: Lymphoid tissues of some patients with conventional forms of CJD have been infectious [Brown P et al. Ann Neurol 1994;35:513].)

Implication: Blood, which contains lymphoid cells, might be more infectious in vCJD than in other forms of CJD.

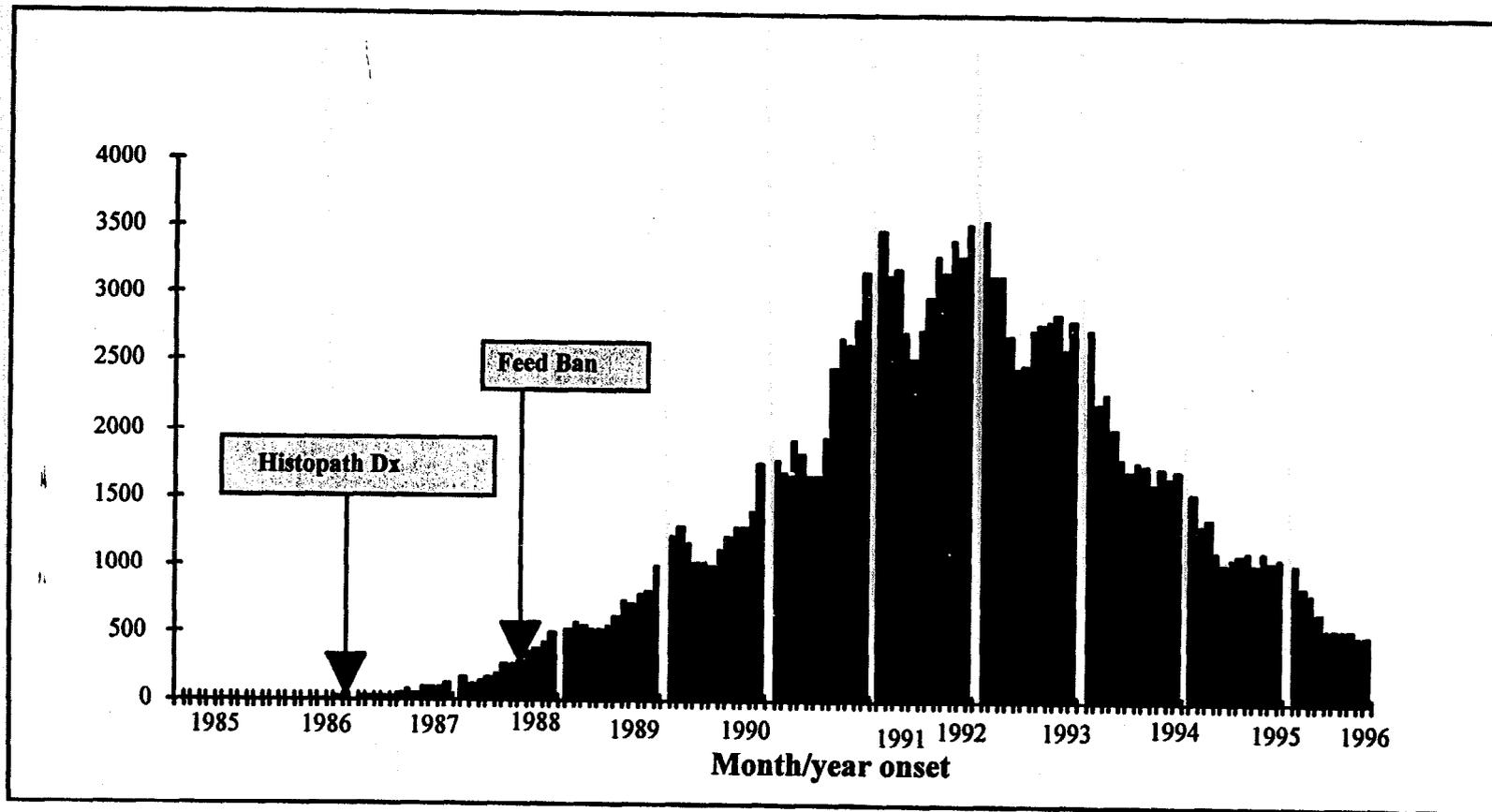
- UK authorities decided not to source plasma for fractionation from UK donors (which implies lack of confidence).

**FDA Guidance for Industry:**  
**Revised Precautionary Measures to Reduce Possible Risk of**  
**Transmission of CJD & vCJD by Blood & Blood Products (cont.):**  
**Response to TSEAC Advice of 18 Dec 1998, 2 June 1999**  
**(CBER Nov 1999, recommended for implementation by Apr 17, 2000)**

- **Deferral of donors who resided in UK for  $\geq 6$  mo (cumulative) between 1 Jan 1980 and 31 Dec 1996**
- **Deferral of donors who received injected UK bovine insulin**
- **Retrieval of blood and blood components (including plasma) from donors deferred because of UK residence or exposure to injected UK bovine insulin**
- **No withdrawal of plasma derivatives for UK residence or exposure to injectable bovine products from BSE countries**
- **Monitor effect of revised blood policy on blood supply and reevaluate policy frequently.**

(UK=England, Northern Ireland, Scotland, Wales, Isle of Man, Channel Islands)

# Cases of BSE Registered in UK through 1996



# USDA (APHIS) Interim Regulation Regarding BSE and European Ruminant Products

- Jan 6, 1998: Pending clarification of the status of European countries, as a preventive step, the USDA prohibited importation of all live ruminants and most ruminant products (excluding gelatin [for human consumption], milk and milk products) from all countries of Europe due to potential risk of BSE.

# Concerns about BSE and vCJD Outside UK

- Diagnosed BSE cases have increased in several European countries.
- Substantial exports of UK cattle, beef and beef products to several European countries continued during high-BSE years.
- Cases of vCJD in France have increased to three.

# Evaluating Risk of Accidental Transmission of a Spongiform Encephalopathy: Elements of Risk

(modified from WHO/CDS/CSR/APH/000.3\*)

- Probability that source is infected with a TSE agent
  - Overt disease, incubation period
  - High risk, lower risk, minimal risk
- Amount of infectious agent in material (tissue, fluid)
- Type of exposure to materials containing TSE agent
  - Route of exposure
    - » Sharp (invasive)
      - ★ Nervous system
      - ★ Other: iv, im, subq, lesional
    - » Other
      - ★ Oculo-conjunctival
      - ★ Oral
      - ★ Aerosol
  - Intensity of exposure: volume, frequency

\* available at [www.who.int/emc-documents/tse](http://www.who.int/emc-documents/tse)

# CJD: Infectivity in Human Body

(modified from WHO/CDS/CSR/APH/000.3)

- High

Brain

Spinal cord

Eye

- Lower

CSF

Kidney

Liver

Lung

Lymph node

Placenta (?)

CJD: No Infectivity Reliably Detected in  
Tissue, Fluid, Secretion, Excretion (minimal risk)  
(modified from WHO/CDS/CSR/APH/000.3)

Adrenal

Blood (?)

Fat

Feces

Gingiva

Intestine

Milk

Mucus

Muscle, skeletal

Muscle, heart

Nerve

Prostate

Saliva

Semen

Serous exudate

Sweat

Tears

Testis

Thyroid

Urine

# Precautionary Principle

European Commission COM (2000)1

(European concept--no status in US law)

- “Where there is uncertainty as to the existence or extent of risks to human health...institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent.”

[EC Court ruling of 5 May 1998 on EC decision to ban export of UK beef.]

# Place of the European “Precautionary Principle” in Decisions about Risks

European Commission COM (2000)1

- Society has the right to establish a level of protection against risk that it deems appropriate.
- Risk must be assessed, managed, and communicated to the public.
- The “Precautionary Principle” describes an approach to managing a risk that cannot be accurately and confidently assessed.
- Decisions on acceptable level of risk are political, based on science and public concern.

# Any Risk-Management Measure Based on the European Precautionary Principle Should be ...

European Commission COM (2000)1

- Proportional to the level of protection chosen
- Non-discriminatory in application
- Consistent with similar measures taken previously
- Based on risk-benefit analysis (not necessarily quantitative)
- Subject to review when new scientific information becomes available
- Explicit in assigning responsibility for producing scientific information to improve the assessment of risk

Issue 1.

## Blood & Plasma Donors in BSE Countries Other Than UK

### CHARGE

Evaluate new information concerning new-variant CJD and BSE in the UK and France and BSE in other European countries besides France and the UK. Recognizing remaining uncertainties about BSE and vCJD, consider the risk that donors traveling or resident in France and other BSE countries outside the UK might have been exposed to and infected by the BSE agent and that their blood, blood components and plasma derivatives might transmit infection to recipients; risk should be compared with that for donors in the UK.

Issue 1.  
Blood & Plasma Donors in BSE Countries  
Other Than UK

**CHARGE** (continued)

The Committee should also consider, in the context of a risk-benefit estimate, any effects that recent changes in blood-donor deferral policy may have had on the supply of blood and blood products in the United States as well as effects to be anticipated if additional deferrals of donors are recommended.

# TSEAC Meeting

June 1, 2000

## Program

1. Recent events concerning vCJD and BSE in the UK
2. Projections of potential exposure to BSE agent and cases of vCJD recognized and to be expected in France and the Republic of Ireland
3. CJD and BSE surveillance in Switzerland
4. USDA estimates of BSE in various countries and USDA policies intended to prevent the importation of materials potentially contaminated with the BSE agent in order to protect health of animals

## **Program (continued)**

5. Estimates of possible human exposures to BSE agent throughout the European Union and BSE and CJD surveillance activities and policies of the European Commission and of European national authorities
6. Assessment by Canadian authorities of vCJD risk to Canadians traveling to the UK and France
7. Effects of recent deferral policies on the supply of blood and blood products in the USA and estimates of further reduction to be expected if additional deferral criteria are recommended

Issue 1.

# Blood & Plasma Donors in BSE Countries Other Than UK

## QUESTIONS

1. Do the Committee members believe that available scientific data on the risk of transmitting CJD and vCJD warrant a change in the current FDA policy regarding deferrals of blood and plasma donors and product retrievals? Please comment.

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Blood & Plasma Donors in BSE Countries  
Other Than UK

**QUESTIONS (continued)**

2. Considering the current scientific data on the risk of vCJD and the potential impact on the blood supply, should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in France?
  - a. If so, what time period (years during which there was greatest potential exposure) and what aggregate duration of exposure should be considered as a basis for deferral?
  - b. If so, should deferral be based on the combined duration of travel or residence in the UK and France?

Issue 1.

## Blood & Plasma Donors in BSE Countries Other Than UK

### QUESTIONS (continued)

2. [continued] Considering the current scientific data on the risk of vCJD and the potential impact on the blood supply, should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in France?

c. If so, should the recommendation apply to whole blood and blood components?

d. Should the recommendation apply to plasma for fractionation?

Issue 1.

## Blood & Plasma Donors in BSE Countries Other Than UK

### QUESTIONS (continued)

3. Should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in BSE countries other than the UK and France?
  - a. If so, for which countries, during what time period and for what aggregate duration of exposure should donor deferral be recommended?
  - b. If so, should deferral be based on the combined duration of travel or residence in BSE countries?

Issue 1.

Blood & Plasma Donors in BSE Countries  
Other Than UK

**QUESTIONS (continued)**

3. [continued] Should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in BSE countries other than the UK and France?
  - c. If so, should the recommendation apply to whole blood and blood components?
  - d. If so, should the recommendation apply to plasma for fractionation?

Transmissible Spongiform Encephalopathies  
Advisory Committee  
June 2, 2000

Issue 2.

Possible Effects of Leukoreduction on CJD Risk

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# Possible Effects of Leukoreduction on CJD Risk

## Charge

Please discuss the scientific evidence suggesting that leukoreduction might be expected to reduce the theoretical risk of transmitting CJD and vCJD by human blood, blood components and plasma derivatives. Consider whether the reduction in risk is likely to be substantial enough to have practical value and, consequently, whether universal leukoreduction of blood and blood components should be recommended by the FDA for that purpose.

# Possible Effects of Leukoreduction on CJD Risk

## Program

1. Background, recent recommendations and prospects for implementation of leukoreduction
2. Techniques and theoretical applications of leukoreduction to remove TSE agents from blood
3. Possible role of leukocytes in experimental pathogenesis of TSEs in rodents and implications for human blood
4. TSE infectivity in blood of experimentally infected rodents and implications for CJD and vCJD

# Possible Effects of Leukoreduction on CJD Risk

## Questions

1. Can leukoreduction be expected to reduce significantly the infectivity theoretically present in blood of persons during the course of CJD and vCJD? If so, for which components?

# Possible Effects of Leukoreduction on CJD Risk

## Questions

2. If the answer to Question 1 was yes :
  - Should the FDA recommend leukoreduction for blood components for transfusion?
  - Should the FDA recommend leukoreduction for plasma for further manufacture?