

ATTACHMENT 11

**ISSUE PAPERS WITH QUESTIONS
TO THE COMMITTEE
TOPICS 1 AND 2**

ISSUE 1: SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

JUNE 1, 2000
HOLIDAY INN GAITHERSBURG
GAITHERSBURG, MARYLAND

ISSUE

In November 1999 the Center for Biologics Evaluation and Research (CBER) issued a guidance document for industry entitled "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products" and recommended its implementation by April 17, 2000. The document, a revision of guidance of August 1999 that incorporated advice offered by the Committee in meetings on December 18, 1998 and June 2, 1999, recommended, among other things, that blood donors who spent six months or more cumulatively in the United Kingdom from 1980 through 1996 be indefinitely deferred in order to reduce the risk of obtaining blood from donors who might have been infected with the agent of bovine spongiform encephalopathy (BSE). Recent information suggests that BSE may be more common in several other European countries than was previously thought and that significant amounts of beef and beef products imported from the UK may have been consumed in other countries during the years of concern. Should deferral of donors resident in other BSE countries besides the UK be considered? If so, what cumulative periods of residence and years of residence in which countries—if any—might be recommended as additional criteria for deferral? Should deferral criteria apply both to whole blood and to plasma for fractionation?

BACKGROUND

Consideration of this issue follows issuance in November 1999 of the guidance document described above, which can be reached at www.fda.gov/cber/gdlns/cidnvcjd.pdf.

The scheduled presentations will review the following information: (1) Recent events concerning new-variant CJD (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 to prevent the importation of materials potentially contaminated with the BSE agent; (5) Estimates of possible human exposures to the BSE agent throughout the European Union and BSE and CJD surveillance activities and policies of the European Commission and 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 any additional deferral criteria are recommended.

DISCUSSION

One year ago the TSEAC considered available evidence suggesting that blood of persons with the new variant of Creutzfeldt-Jakob disease (now designated in the UK as "variant" CJD or vCJD) or in the asymptomatic incubation period of vCJD might contain the infectious agent and pose a theoretical risk of transmitting disease to recipients of blood, blood components and plasma. The TSEAC considered information on potential food-borne and other exposure to the agent of bovine spongiform encephalopathy (BSE)—the probable source of vCJD in humans—in various countries where BSE has either been recognized in native cattle or where United States Department of Agriculture (USDA) has been unable to determine that BSE is not present, including projections of the possible time course and extent of the outbreak of vCJD in the UK. The Committee also considered the reduction in the blood supply that might be expected to result from deferral of donors. The TSEAC voted to recommend deferring both blood and plasma donors based on food-borne exposure to the BSE agent, to withdraw whole blood and blood components from deferred donors based on their exposure but not to withdraw plasma derivatives. The TSEAC was also polled to suggest a duration of residence or travel in the UK on which to base deferral. A majority of TSEAC members agreed that it would be prudent to defer blood donors resident in the UK for any aggregate period of six months or more (several members favored deferral for shorter periods of residence) between the beginning of 1980 and the end of 1996. Deferral for travel or residence of six months or more would reduce the total risk—taken as the total number of "donor-exposure days" in the UK—by an estimated 87%, with an estimated 2.2% reduction in donated units of blood expected to result.

Following the TSEAC meeting, FDA staff met with members of the Public Health Service Blood Safety Committee (BSC), which includes participants from both the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) as well as from the FDA. The BSC recommended to Dr. David Satcher, Surgeon General and Assistant Secretary for Health, the six-month UK-deferral period. Dr. Satcher accepted the BSC recommendation. He asked the Public Health Agencies to increase efforts to ensure the continued adequacy of the blood supply and to review the scientific basis for the new deferral policy every six months.

Since the last meeting of the TSEAC a year ago, some new information has accumulated concerning BSE and vCJD. Diagnosed cases of BSE continue to increase in cattle of several European countries, and a new country has found BSE in its cattle. In addition to a greater risk of human exposure to the BSE agent in beef and beef products originating within BSE countries on the European continent, it has also been recognized that importation of such products from the UK into at least one of those countries before 1997 was greater than previously thought.

Cases of vCJD continue to be confirmed in the UK, although not at an increasing rate; a study of tonsils and appendices of young normal subjects also failed to suggest that a marked increase in occurrence of vCJD was to be expected in the near future. However, the number of reported cases of vCJD in France has increased from one to three in the past year. Finally, attempts to detect agent in the blood of persons with vCJD, while not far advanced, have thus far not suggested that large amounts of agent are likely to be present in that tissue.

The following questions may assist the committee in its discussion of the issue:

- Do members of the Committee still believe that existing information supports FDA's recent conclusion that food-borne exposure to the BSE agent should be considered a risk factor for vCJD, that persons with a history of substantial exposure may be at increased risk of getting vCJD, and that, until the magnitude of that risk is better understood, people with a history of substantial exposure should not donate blood?
- In comparison to risk of exposure to the BSE agent in the UK, is the risk for donors resident in any other European country or countries sufficient to justify considering their deferral?
- Do any recent events in the UK or other BSE countries alter predictions for the course of the BSE epidemics in those countries or estimates of the possible number of vCJD cases to be expected?
- Are ongoing studies attempting to detect infectivity in blood of patients with vCJD sufficiently advanced to help with decisions concerning blood-donor deferral policies?
- Are preliminary results of recent surveys failing to find protease-resistant prion protein in lymphoid tissues of young normal subjects in the UK sufficiently reassuring to alter risk assessments?
- Is it possible to estimate the impact that additional deferrals of donors resident in various BSE countries for certain periods of time would have on the supply of blood and blood products in the USA?

REFERENCES

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CHARGE

The FDA is asking 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. Recognizing the remaining uncertainties about BSE and vCJD, the TSEAC should 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; that risk should be compared with the risk that donors resident in the UK were infected.

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 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.
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?

If yes,

- a. 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. should deferral be based on some form of combined duration of travel or residence in the UK and France? Please comment how the exposure periods should be combined.
 - c. should the recommendation apply to whole blood and blood components for transfusion?
 - d. should the recommendation apply to plasma for fractionation?
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)?

If yes,

- a. for which countries, during what time period and for what aggregate duration of exposure should donor deferral be recommended?
- b. should deferral be based on the combined duration of travel or residence in BSE countries?
- c. should the recommendation apply to whole blood and blood components for transfusion?
- d. should the recommendation apply to plasma for fractionation?

ISSUE 2 SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY
COMMITTEE
JUNE 2, 2000 GAITHERSBURG, MARYLAND

ISSUE: On September 18, 1998, the Blood Products Advisory Committee (BPAC) voted (13 yes, 0 no, 3 abstentions), that the benefit-to-risk ratio associated with leukoreduction was sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte blood components for transfusion, irrespective of the theoretical considerations for transfusion-transmitted CJD. In addition, several European countries have responded to the potential threat that blood donors infected with the BSE agent might transmit the disease to recipients of blood or blood components by instituting universal leukoreduction.

Now TSEAC is being 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 whether the committee recommends universal leukoreduction of blood and blood components as a risk reduction measure for CJD and nvCJD. TSEAC is also being asked whether leukoreduction is unnecessary for plasma for further manufacture as a risk reduction measure for CJD and nvCJD.

BACKGROUND: Consideration of this issue follows the September 18, 1998 BPAC meeting. The questions to the committee, agenda, and summary of committee votes are included in the background material. The complete transcript of the meeting is at www.fda.gov/ohrms/dockets/ac/cber98t.htm. Note, however, that BPAC did not consider CJD or nvCJD risk.

Transfusion therapy is becoming more product-specific in that only particular blood products, such as red blood cells or platelets, are transfused for specific clinical indications instead of whole blood. Physical methods are used to separate the cellular components (red cells, platelets, and mononuclear cells) from each other and from plasma. Even though separation technology has improved greatly there is still a significant amount of cross contamination between cellular blood fractions, particularly with leukocytes. To improve the quality of transfused cellular products, leukoreduction, by filtration or by improved collection technology, has been recommended for the reduction of transfusion associated 1) febrile nonhemolytic reactions, 2) alloimmunization and 3) transmission of leukocyte-associated viruses. Acellular blood products, such as plasma, are not completely free of leukocytes, however they are not currently being leukoreduced.

DISCUSSION: Recent reports indicate that TSE infected rodents carry infectivity in blood. The majority of infectivity is distributed between cellular fractions that concentrate leukocytes (buffy coat) and plasma. Thus leukocytes appear to be closely tied to the presence of infectivity in blood. Leukocytes may be involved in

transporting and/or propagating infectivity in the blood of TSE infected animals. Certain leukocytes have also been shown to be required in the propagation of peripherally inoculated infectivity and its transfer to the CNS.

The scheduled presentations will review (1) the background, recent recommendations, and prospects for implementation for leukoreduction; (2) techniques, results, theoretical applications to TSE agents in blood; (3) infectivity of nucleated blood cells from experimentally infected rodents and implications for blood; and (4) experimental studies with blood and possible implications for safety of human blood with regard to CJD and nvCJD.

Some specific concerns, which can be addressed in the context of answering questions to the committee, are:

- Based on available scientific knowledge, will leukoreduction reduce the theoretical risk of transmission of CJD and nvCJD?
- Based on available scientific knowledge, is the risk reduction substantial?
- Should universal leukoreduction of blood and blood components be recommended as a risk reduction measure for CJD and nvCJD?

QUESTIONS: The questions to be considered by the committee at the conclusions of these presentations and discussions follow.

- 1. Can leukoreduction significantly reduce the infectivity of CJD and vCJD? For what blood components?**
- 2. If yes, should leukoreduction be recommended for blood components for transfusion? Plasma for further manufacture?**