Unofficial Summary
For the
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE MEETING
September 18 & 19, 2006
Gaithersburg, MD

This quick summary is provided as an unofficial overview of the September 18 & 19, 2006 TSEAC meeting until the official transcripts become available.

The Committee received updates on the following topics:

- US and worldwide BSE by Dr. Lisa Ferguson, USDA

- vCJD epidemiology and transfusion-transmission by Dr. Dorothy Scott, FDA

- Draft Guidance for Industry: Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" by Dr. Alan Williams, FDA

- Critical factors influencing prion decontamination using sodium hydroxide – PPTA collaborative study by Dr. Kang Cai, PPTA, Talecris Biotherapeutics

- Human prions: clearance and plasma lipoproteins by Dr. Jiri Safar, University of California, San Francisco

- Status of FDA's initiative on communication of the potential exposure to vCJD risk from an investigational product, plasma derived Factor XI that was manufactured from UK donor plasma by Dr. Mark Weinstein, FDA

- Summary of World Health Organization consultation on distribution of infectivity in tissues of animals and humans with transmissible spongiform encephalopathies by Dr. David Asher, FDA

Topic I: Experimental Clearance of Transmissible Spongiform Encephalopathy Infectivity in Plasma-derived Factor VIII Products

FDA asked the Committee to discuss whether standardized methods and assessment criteria are feasible and appropriate for determining clearance of TSE agents by the manufacturing processes for plasma-derived FVIII (pdFVIII) products.

Dr. Dorothy Scott introduced the topic summarizing TSE safety concerns, the importance of TSE clearance, upstream pdFVIII manufacturing processes, and methodological and logistical challenges of TSE clearance studies using exogenous spiking materials or

endogenously infected blood. She also discussed the question of whether a minimum TSE agent reduction factor might serve as an appropriate standard for demonstrating vCJD safety, similar to analogous precedents from viral validation studies. Then Dr. Thomas Kreil, PPTA, discussed specific TSE clearance study challenges with regard to scale-down and conditioning. Dr. Kreil also presented data from industry-sponsored TSE clearance studies for pdFVIII.

Questions for the Committee

1. **a. Please comment on the feasibility and scientific value of adopting standardized exogenous (spiking) study methods to assess TSE clearance in manufacturing of pdFVIII including the following:**

I) Optimal spiking material and its preparation from the standpoint of relevance to blood infectivity

The committee discussed several possibilities, including TSE-infected brain-derived spiking materials, such as hamster 263K brain homogenate which is frequently used, is partially characterized with regard to partitioning during fractionation, and provides sufficiently high titers of infectivity and PrP^{TSE} to allow demonstration of a broad range of clearance in studies. Spleen-derived spikes have lower titers, and there is no guarantee that they represent the physical form of TSE agent in blood better than do brain spikes. It was suggested that, since VLDL fractions of blood may preferentially contain TSE infectivity (based on data from Dr. Safar), such fractions might usefully represent endogenous infectivity. Committee members felt that current experiments might begin with brain homogenate preparations, and that more definitively blood-relevant spikes or endogenous infectivity needed further study. It was widely acknowledged that the physical form of TSE agents in endogenously infected blood must be better understood before the most relevant spiking materials can be selected.

II) Selection of a TSE strain and animal model

Several models were discussed (e.g., PrP-bovinized transgenic mice, sheep, and chimeric transgenic mice). Bovinized mice are very susceptible to infection with vCJD agent, and conventional RIII mice can be used to model vCJD as well. It was suggested that, in theory, TSE-infected sheep blood could be assayed with RIII mice, enabling titration of large amounts of plasma or product intermediates. Mice lacking the PrP GPI anchor were also suggested as a possible model, since their blood titers of infectivity have been very high (although it is not known whether the form of infectious TSE agent and its associations in such deficient mice would faithfully model more typical infections). Some members of the committee felt that the most relevant strains of TSE agent to be studied would be derived from humans with vCJD or cows with BSE.

III) TSE immunoassays for PrP^{TSE} and bioassays for infectivity

Members commented that conformation-dependent immunoassay (CDI) or protein misfolding cyclic amplification (PMCA) technique showed preliminary promising

results. However, the committee discussed the need to compare and carefully validate CDI, PMCA, and other binding assays with bioassays, and some members felt that infectivity still should be demonstrated by bioassay.

IV) Identification of manufacturing processes that might alter TSE agent properties

The Committee members commented that the manufacturing process itself is not standardized and varies from product to product and manufacturer to manufacturer so that developing a standard method for validation will require further consideration.

Overall, efforts at standardization were felt by some to be premature, since characteristics of endogenous infectivity are still not well understood, and therefore difficult to model; standardization might even impede research to address remaining challenges in TSE clearance studies. A second viewpoint was expressed, that some standardization now might be useful, because as better methods are discovered they are inevitably adopted.

1. b. Please comment on the feasibility and scientific value of adopting standardized endogenous study methods to assess TSE clearance in manufacturing of pdFVIII.

The Committee discussed the merits of various models including the use of transgenic mice (e.g., PrP-cervidized mice for CWD, PrP-bovinized mice for BSE, and PrP GPI-deficient mice) and sheep models of infectivity. Dr. Kreil warned that a potential limitation of endogenous infectivity studies is that animal plasma is known to have characteristics somewhat different from those of human plasma when fractionated, so that manufacturing processes might not be comparable and results with animal models not predictive of those with human plasma. While data were not presented to support or refute this contention, the committee agreed that it might pose an additional limitation of studies using endogenous TSE infectivity in animal plasma.

2. Based on available scientific knowledge, please discuss whether a minimum TSE agent reduction factor, demonstrated using an exogenous (spiking) model in scaled-down manufacturing experiments, might serve as an appropriate standard for demonstrating vCJD safety of the products.

A detailed discussion of this question was postponed until the next meeting when risk assessment results will be discussed. One member reminded the Committee of the need for a clear definition for “log reduction” of infectivity, recognizing that the 50-percent infectious dose (ID50) is a continuous rather than a discrete variable and that estimated reductions to less than a single ID50 do not guarantee safety.

3. Considering the outcome of the discussion on Item 2, in cases where a lower reduction factor is demonstrated for a pdFVIII, should FDA consider the following:

a. Labeling that would differentiate the lower clearance products from other products with sufficient TSE clearance;

b. **Recommending addition of TSE clearance steps to the manufacturing method;**
c. **Performance of TSE clearance experiments using endogenous infectivity models;**
d. **Any other actions?**

This answer depends on the answer to the previous questions, thus definitive discussions were deferred until more information is available. In limited discussion, some members felt that labeling of a product as having less clearance might unfavorably dispose consumers or physicians against certain products even though no vCJD infection has ever been attributed to any plasma derivative. A member felt that the patient community might favor adding effective clearance steps to a manufacturing process but that labeling of products with low clearance values is not indicated now and would not be helpful.

Open Public Hearing:

During the morning Open Public Hearing, Mr. David Cavenaugh, representing the Committee of Ten Thousand, requested that FDA recommend deferral of Source Plasma donors that have resided in Europe for five years or more since 1980.

During the afternoon Open Public Hearing, two speakers addressed the committee.

Dr. Charles A. Sims, Medical Director of California Cryobank, Inc., requested that FDA consider more specific risk based criteria for human sperm and egg donors than those currently in the FDA guidelines.

Dr. Paul Brown, speaking for Nordic Cryobank, stated that sperm from European donors does not pose a risk of vCJD transmission and that its exclusion from use in the U.S. should be reconsidered by the FDA.

Topic II: Potential screening assays to detect blood and plasma donors infected with agents of transmissible spongiform encephalopathies (TSE agents or prions): Possible FDA review criteria and related issues

FDA sought the advice of the Committee regarding potential approaches and issues to consider when validating candidate screening tests for vCJD and other TSE infections in donors of blood, plasma and human cells, tissues and cellular and tissue-based products.

Dr. Pedro Piccardo introduced the topic and discussed donor TSE screening test issues of concern to FDA including test sensitivity, specificity, and confirmatory testing. Next, Dr. Marc Turner, University of Edinburgh, presented an algorithm for eventual approval of human TSE blood donor screening tests in Europe. Dr. Philip Minor**,** NIBSC, presented a review of TSE reference materials available through the WHO and official UK sources to assist in development and validation of TSE screening tests. The Committee then received research updates on the current status of test development from the following speakers:

Alex Raeber, Ph.D., Prionics AG
Claudio Soto, Ph.D., University of Texas
Stuart Wilson, Ph.D., Microsens Biotechnologies
Peter van Driessche, BioMerieux
Kent Lohman, Ph.D., Adlyfe
David Peretz, MSc., DSc., Chiron
Jiri Safar, M.D., University of California San Francisco

Questions for the Committee

1. Please comment on pre-clinical analytical studies needed to evaluate candidate donor screening tests for vCJD and other TSEs.

2. Please comment on clinical studies needed to evaluate candidate donor screening tests for vCJD and other TSEs.

3. Please discuss the relative merits of technical options that might be feasible to confirm screening test results for vCJD and other TSEs, e.g., bioassays, alternate immunoassays, prion protein amplification, etc.

Committee members offered individual comments regarding the above three questions. No votes were taken or consensus attempted. Some of the more important comments were the following:

Caution must be used when using data from tests with animal samples to predict infectivity of various tissues and body fluids from humans with TSEs. However, due to the shortage of samples of infected human blood, early development of tests should begin using animal models. A recommendation was made that animal models used should include mouse-adapted vCJD or BSE models.

To evaluate candidate TSE tests, developers must establish both analytical sensitivity and clinical diagnostic sensitivity. In order to do that, Committee members encouraged the identification, and follow-up of high-risk populations, such as individuals receiving blood transfusion from donors who later developed vCJD and to obtain adequate blood samples from such blood recipients when possible.

Due to the shortage of suitable blood samples from living subjects, the Committee discussed a suggestion to use cadaveric blood from autopsies of persons with vCJD. However, members suggested caution in using such samples, due to the multiple differences between blood samples collected ante mortem and post mortem.

The Committee agreed that a supplementary test should be developed to confirm results of screening tests, because many false-positive results are expected when screening a large low-risk population and those would probably be unacceptable in the setting of blood programs. The Committee noted that, although bioassay (transmission of disease to animals) remains the "gold standard" to assess the presence of infectivity in biological materials, for practical reasons, bioassays will probably be used mainly to compare the performance of various tests. In addition, the Committee indicated that characterization of TSE reference materials should include estimates of infectivity by bioassays.

Open Public Hearing

During the Open Public Hearing session, Allene Carr-Greer of the American Association of Blood Banks encouraged FDA to use tools available through the Critical Path Initiative to consider several issues, e.g., (i) prognostic significance of repeatedly reactive TSE screening test results in a low risk population, (ii) information provided to individuals with a repeatedly reactive screening test results, and (iii) the need for a confirmatory test.