UNOFFICIAL SUMMARY
for the
Transmissible Spongiform Encephalopathies Advisory Committee Meeting on
Monday, October 31, 2005

This summary provides an unofficial overview of the October 31, 2005 TSEAC meeting.

The Committee received an update from Dr. Lisa Ferguson, APHIS, USDA on, US and worldwide bovine spongiform encephalopathy (BSE) status and a summary of the discussions of a recent FDA Device Panel Scientific regarding issues in evaluating products intended to decontaminate surgical instruments exposed to TSE agents from Dr Sheila Murphey.

Topic 1: Progress Report on FDA's Risk Assessment for Potential Exposure to Variant Creutzfeldt-Jakob disease in Human Plasma-Derived Antihemophilic Factor (FVIII) Products

Issue: FDA is developing a risk assessment for vCJD exposure in U.S. licensed plasma-derived FVIII products. FDA asked for the Committee's advice on how best to refine the input parameters that are used in the risk assessment model. Additionally, FDA requested the Committee's opinion on the value of the model as a basis for risk communication in view of the large uncertainties

Dr. Dorothy Scott of FDA introduced this discussion topic. Dr. Steven Anderson, FDA, presented an overview of the FDA risk assessment model, including model input parameters. The Committee received an update on vCJD in the UK and other countries from Azra C. Ghani, PhD, London School of Hygiene and Tropical Medicine and from Richard Knight, MD UK, Director, CJD Surveillance Unit, Edinburgh. Dr. Alan Williams, FDA, discussed how to model the risk of vCJD in US donors. Dr. David Asher, FDA, reviewed experimental models of vCJD infectivity and their use to estimate the amount of infectivity in human plasma, and Dr. Scott presented an overview of publicly available information on potential TSE clearance in Factor VIII product manufacturing. Dr. Mark Weinstein summarized Factor VIII use by different patient groups in the U.S.

The following speakers addressed the Committee during the Open Public Session of the meeting:

1. Dr. Peter Ostrow, Professor, University of Buffalo Medical School spoke on behalf of the CJD Foundation Medical Education Program informing the Committee of a new DVD they were producing on CJD and other prion diseases

2. Mr. Mark Skinner, President of the World Federation of Hemophilia (WFH) spoke on behalf of the WFH and National Hemophilia Foundation (NHF) presenting their organizations recommendations on FDA's risk assessment model, and on the importance of hemophilia community involvement in communication

when the risk assessment for FVIII is finished. He expressed concerns that the risk assessment could affect product supply, as well as health care for people with hemophilia.

3. David Cavenaugh on behalf of the Committee of Ten Thousand expressed his organizations concerns regarding the safety of blood and blood products based on the predicted number of individuals with preclinical vCJD and their infectivity.

The Committee then discussed the following questions:

1. What estimate(s) should be used to reflect the prevalence of vCJD in the U.K.?

FDA Proposal: We propose using the surgical tissue surveillance data as the assumed prevalence of vCJD in the U.K. to provide a more conservative estimate for possible exposure in the risk assessment than those from epidemiological models based on observed clinical cases of vCJD. However, we propose that the risk assessment also be done using epidemiogical predictions based on diagnosed clinical vCJD cases as an alternative assumption of prevalence (with adjustments for possible latent infections during the incubation period).

Committee members agreed with the above stated FDA proposal that both sets of data should be used.

2. How effective are current donor deferrals for geographic risk of vCJD?

FDA Proposal: Based on the currently available surveys of unreported risk for other conditions (and allowing for a margin of error), we propose to estimate that the FDA-recommended deferral policy has a 90% - 99% efficiency for deferring donors with the specified increased vCJD risk.

Committee members expressed concern regarding the number of recently reported vCJD cases in France and the possible need to adjust the relative risk of vCJD in France upwards for the risk assessment model. Committee members requested the lower limit of donor deferral efficiency be dropped from 90 to 85 % in order to take into account numbers presented by Dr. Williams for other deferral, and to address their concern over the accuracy of screening of some paid donors. The Committee members requested a study be conducted based on survey data to better determine the efficiency of the geographical deferrals and the reliability of the answers to some of the donor deferral questions.

3. What intravenous infectivity range (in ID_{50}) should be selected for plasma, based on animal studies?

FDA Proposal: The FDA FVIII model will use a statistical distribution of infectivity, with a minimum value of 0.1 IC ID50, a most likely value of 10 IC

ID50, and a maximum value of 310 ID ID50. Since the BSE agent in primates may more closely reflect the human situation than rodent models, we propose to model the IC/IV ratio for infectivity over a range of 1 to 5.

Committee members expressed concern that the maximum intravenous infectivity range value proposed for use in FDA's proposal was obtained from a study that had not been reproduced. Other published studies reported a maximum of about a log and a half. Committee members stated that a lower infectivity maximum of 100 ID50/ml is more consistent with the majority of available data. Committee members reached a consensus that the model should use an IC/IV ratio of a range from 1 to 1 to 1 to 10.

4. Is there sufficient evidence to estimate when during the incubation period human plasma is infectious?

FDA Proposal: Because of uncertainties about incubation periods of food-borne vCJD and the time during the incubation period at which infectivity appears, FDA proposes to adopt a conservative approach, and assumes plasma to be potentially infectious throughout the incubation period.

The Committee wanted the model to be based on published data, rather than selecting the most conservative value of infectivity throughout the incubation period. The members agreed that the model be run first only using infectivity in the last half of the incubation period to obtain an estimate, and that this parameter would also be run for the full incubation period as part of the sensitivity analysis.

5. Does the Committee agree with FDA's proposed approach for estimating clearance of vCJD infectivity from FVIII by manufacturing processes?

FDA Proposal: FDA proposes to model three clearance ranges, to represent likely minimum (2-3), mid-range (4-6) and maximum (7-9) Log_{10} clearance of the vCJD agent from products manufactured using a variety of methods.

The Committee was informed that these clearance values are "above" any dilution effect. Committee members concurred that the model uses the above three clearance ranges.

6. What experiments might enable refinement of these clearance estimates and allow comparison of clearance offered by various steps in the methods used to manufacture plasma-derived FVIII?

Committee members requested both spiked and endogenous experiments be conducted with multiple animal models.

7. What data should be used to estimate how much FVIII is used by typical patients?

FDA Proposal:

•We plan to analyze data from the ongoing UDC survey (1998-present) to estimate the numbers of patients using specific product brands, and the distribution of disease types, e.g. HA severe, moderate, mild; Type III vowed.

•We also plan to extrapolate data from the 1993-1998 survey in six states to estimate the total number of U.S. patients, and product consumption per patient, with stratification by clinical setting.

•If there is inconsistent information from these two analyses it will be reconciled using patient based medical record data.

The Committee agreed with FDA's proposal. Members also requested that FDA explore the use of alternate sources of information such as health care insurance records, home care distribution companies and patient records.

8. What is the effect of plasma pool size (i.e. number of donors per final product) for FVIII recipients?

FDA Proposal: FDA proposes to estimate plasma pool size as a range, between 20,000 and 60,000 donations, with a bimodal distribution to reflect expected source and recovered plasma pool numbers. FDA will seek additional data from plasma fractionators.

Committee members stated that FDA proposal was acceptable. Pool sizes of 20,000 to 60,000 donations should be considered.

9. Can a cumulative effect from repeated exposures to low doses of the vCJD agent be incorporated into the risk model?
Proposal: to allow for the theoretical possibility of cumulative effects, the model will provide the cumulative risk for a 1-year period.

Members stated a cumulative risk for a one year period (risk per annum) must be included in the model. The model should not be based on a "per dose" basis since in animal models using different dosing schedules and amounts provide different results than would have been extrapolated from a single dose exposure.

10. Given the present scientific uncertainties in the underlying assumptions of the FVIII risk assessment, does the Committee believe that the risk assessment model could provide a useful basis for risk communication to patients, their families, and health care providers?

Committee members expressed concern over how well the message is articulated to the patients. They suggested that such a communication

include that there are currently no vCJD cases in this country and that the model is based on a theoretical risk. The Committee stated that in the UK there are not any known cases of vCJD as a result of receiving plasma products. They also suggested that the uncertainties of the model inputs and the sensitivity analysis be conveyed as part of the risk communication. FDA needs to move forward with the model, the results should be communicated in a manner to make them useful and educational, rather than frightening. The Committee commented that the risk assessment could result in preferential use of recombinant FVIII over plasma-derived FVIII. It was noted by FDA that patients with Von Willebrand's disease are obligate users of plasma-derived FVIII, and that plasma-derived product might be advantageous in immune tolerance induction. Members expressed concern over how the results may affect health care of those at risk. Committee members encouraged FDA to work with HHS to make sure that plasma product recipients at risk will continue to receive proper access to health care. FDA should work with hemophilia organizations to optimize risk communication, and to minimize the impact on patients of the risk assessment.

The Committee voted: 17 yes, 0 No and 0 abstained.

Topic 2: Labeling Claims for Filters Intended to Remove TSE Infectivity from Blood Components

Issue: FDA seeks the advice of the Committee on the minimal scientific criteria for validation of a claim for reducing TSE infectivity in blood products by filtration
The Committee listened to the following presentations:

Dr. Jaroslav Vostal introduced this topic to the Committee. Dr. Mark Turner from the University of Edinburgh, described the UK regulatory plan for an independent evaluation of blood product filters to establish a claim of reduction of TSE infectivity. Then three product manufacturers described their company's products. These included: Dr. Sam Coker from the Pall Corporation, Dr. Robert Rohwer from Pathogen Removal and Diagnostic Technologies Inc. and Dr. Ralph Zahn from Alicon AG.
There were no requests to speak at the afternoon open public hearing session.

After the presentations Committee members made the following individual comments:

Bioassays need to be done although concern was expressed over the time required for such validation studies. A Western Blot study can be used to demonstrate reproducibility. For spiked experiments the investigator should start with 6 logs of spike in order to use the Western Blot. Other tests could also be considered. At this time the Committee did not recommend biomarkers for establishing labeling claims, but concurred that they could be used on a routine basis to confirm that the device was working properly.

For spiked experiments plasma product manufacturers should demonstrate 2 to 4 logs reduction. For endogenous experiments sterility is mandatory.

Committee members suggested that two animal models be considered and 301V mouse adapted model was recommended. While the blood should come from a model using larger animals some members recommended using the transgenic mouse model as the most reliable and sensitive test for infectivity in blood. Other suggestions were the use of the transgenic hamster. The members stated that FDA should express their concerns regarding studies for claims but that some flexibility in conducting these studies should be left up to the sponsor. The 301 V mouse was suggested for endogenous claims. Members recommended that methodologies include a large animal model (cow, sheep or primate {when available}) and the clinical equipment and filters (not scaled down versions) used to process this blood. In addition to clearance the blood needs to be tested for functionality.

Clearance studies performed at two separate sites was suggested to insure reproducibility, but members stated concerns regarding contamination could also be addressed by well controlled studies. Depending on the claim a whole unit of blood should be processed but only small aliquots would need to be tested. For levels of clearance some members suggested one log for endogenous experiments could be considered. Other members stated that any transmission of endogenous studies should be considered a failure. Members stated that for spiked experiments two logs could be considered based on evidence presented, but three logs would give a better margin of error. Members expressed concern that the manufacture be sure to guarantee absolute reproducibility

Members then changed FDA's proposal to read:

Proposal for validating a claim of reducing TSE infectivity in human blood products

- Demonstrate elimination of endogenous TSE infectivity and reduction of spiked TSE infectivity by three logs using two animal models, two strains and two hosts.
- Use full scale blood unit and leukoreduction filter
- TSE infectivity from BSE or vCJD strain
- Reduction of PrPsc in blood product will be considered supportive but not sufficient for a claim
- Study performed consistently and reproducibly
- Study size sufficient to support statistically valid conclusion

Question 1: Are the revised proposed minimal criteria for validation of TSE infectivity reduction by filtration adequate and appropriate?

The Committee voted: 10 yes, 0 no, and 0 abstained.

Question 2: Does the FDA's proposed labeling for a filter meet the appropriate criteria for a claim of reduction of TSE infectivity in blood or blood components?

A) This filter (device) has been shown to reduce TSE infectivity in blood from an infected animal model.

or

B) This filter (device) has been shown to reduce transmission of TSE infectivity by transfusion in an animal model.

and (A+C or B+C)

C) Due to lack of feasibility, studies have not been performed to validate this claim in a human population.

The Committee stated that a label could include either A+C or B+C depending on the experiments preformed.

The Committee voted: 9 yes, 0 no and 0 abstained.