Issue Summary
Transmissible Spongiform Encephalopathies
Advisory Committee Meeting
February 8, 2005
Silver Spring, Maryland

Topic 1: Possible vCJD Risk from Investigational Coagulation Factor XI Manufactured in the 1990's from Plasma of Donors Residing in the United Kingdom (UK)

Issue: In the 1990's, under an IND, a number of U.S. residents received investigational coagulation Factor XI manufactured in the UK from plasma donated in the UK. The FDA seeks the advice of the Committee on a risk assessment model for potential vCJD exposure from these products.

Background

The UK issued a precautionary notice on Sept. 21, 2004, advising that patients with bleeding disorders and congenital antithrombin III deficiency in the U.K. who had infused plasma-derived concentrates (including Factors VIII, IX, XI, and antithrombin III) between 1980 and 2001, were at an increased risk of developing variant Creutzfeldt-Jakob Disease (vCJD). These products were manufactured from plasma obtained from UK donors, who are at risk of vCJD infection from consumption of BSE-infected meat. The notification was issued because of an increased concern about the probable transmission of vCJD through blood products, in light of the recent finding that vCJD was transmitted to recipients of labile blood components from donors that later developed vCJD.

Patients that received such notification were advised:

- ?? Not to donate blood, organs or tissues
- ?? To inform their surgeons and dentists of their increased risk, so that special arrangements can be made for surgical and dental instruments to control potential infection.
- ?? To inform their families so that surgeons could be informed in case of emergency surgery

In the US, no licensed product was made from UK plasma. However, a small number of patients, estimated to be around 50, received a FXI derivative manufactured from UK plasma between 1989 and 1997, under Investigational New Drug (IND) protocols. None of the product used in the US was derived from a donor with known vCJD, although potentially such lots might be identified in the future.
FXI deficiency is a very rare bleeding disorder, with an estimated prevalence of the homozygous form to be 1 per million. The frequency is much higher in certain populations including Ashkenazi Jews, Iranians, and French Canadians. The disease may be associated with bleeding, but is less severe than hemophilia. Physical manifestations of the disease are rare, and it may go unrecognized until bleeding occurs associated with

surgery, trauma, dental procedures, or menses. Most FXI product studied under IND was used to prevent excessive surgical or dental bleeding, in contrast to the frequent use of plasma derivatives for hemophilia.

Summary of the FDA Draft Risk Assessment: "Potential Exposure to the vCJD agent in United States recipients of Factor XI coagulation product manufactured in the United Kingdom"

The probable transmission of vCJD via whole blood or blood components in the UK raised the possibility that plasma derivatives from donors incubating vCJD could pose a risk of vCJD transmission. The probable transfusion transmission of vCJD, results of the U.K. (Det Norske Veritas) risk assessment, prompted UK authorities to notify recipients of some U.K.-manufactured plasma derivatives of their increased risk. Since Factor XI made from UK plasma was used investigationally in the U.S. the FDA has drafted a risk assessment for this product.

Estimates used to generate exposure assessment

A number of factors were used as part of the assessment of possible exposure to vCJD via U.K.-manufactured FXI. These included:

- ?? Estimates of infectivity in plasma (ranges modeled)
- ?? Estimates of vCJD incidence in the U.K., based on a surveillance data
- ?? Plasma pool size
- ?? Likelihood that a plasma pool would contain donation(s) from a vCJD-incubating donor (ranges modeled)
- ?? Estimated reduction of vCJD agent during manufacturing, based upon the manufacturing process (range modeled)
- ?? Adjustment for i.v. route of exposure
- ?? Manufacturing yield of FXI from plasma
- ?? Amount of product received by patients

Results

Results from the model are presented below in Table I. The intravenous (i.v.) ID_{50} per single unit and per vial of Factor XI was estimated by the model. Additionally, results that predict exposure for 3 scenarios depicting various levels of utilization that approximate clinical treatment with FXI were generated. Scenario 1 estimates the potential exposure to the vCJD agent that might occur during the treatment of a 60 kg individual prior to surgery with 15 to 30 units/kg given to restore FXI levels to normal. It was further assumed that the patient received two post-operative treatments at 2 to 3 days intervals at a level of 10-15 units/kg. Scenario 2 and Scenario 3 assume a treatment regimen consisting of 10,000 units, and 15,000 units of FXI, respectively.

Table I – Exposure to vCJD agent i.v. ID_{50} via Factor XI. Results are expressed as per unit or vial of FXI. Hypothetical scenarios provide an estimate of the magnitude of exposure to vCJD agent i.v. ID_{50} that might occur per surgery incident. A surgical incident includes prophylactic treatment prior to surgery and possibly several post-operative treatments with FXI.

Scenario	Quantity Factor XI Utilized	Mean vCJD i.v. ID_{50}	5th percentile	95th percentile
A single unit FXI	1 u	1.87×10^{-5}	7.44×10^{-8}	2.71×10^{-5}
One vial FXI	1,000 u	0.020	7.44×10^{-5}	2.6×10^{-2}
Scenario 1: Treatment 60 Kg person	~3,500 u	0.063	0.00025	0.092
Scenario 2: Treatment 10,000 u	10,000 u	0.187	0.00074	0.271
Scenario 3: Treatment 15,000 u	15,000 u	0.281	0.0011	0.406

Uncertainties and limitations

Risk assessment is a science-based tool for informing the decision making process when uncertainty is high. The uncertainties and limitations of any risk assessment for transmissible spongiform encephalopathies (TSE), including BSE and vCJD, are considerable. Perhaps the greatest source of uncertainty in TSE risk assessments arises from the use of animal data, which is assumed to reflect the level of TSE infectivity in human blood. Although human blood can likely transmit the vCJD agent – the actual levels of infectivity in blood, the time of appearance of infectivity in the blood during the incubation period, the amount of infectivity needed to establish infection, and other factors remain unknown and highly uncertain. Uncertainties arise from our lack of knowledge about the incidence of vCJD in human populations and estimating the number of donations that may contain infectivity. Additional uncertainty arises from the limited

amount of information and data concerning the levels of reduction and clearance of TSE agents from plasma that occurs during the manufacturing process. In total these and other uncertainties are inherent in the final risk estimates and should be carefully considered when interpreting the results of any risk assessment.

Conclusions

Potential exposure to vCJD agent present in Factor XI manufactured in the UK in the 1990s was estimated in this risk assessment.

None of the UK-manufactured FXI products used in the US were made from plasma pools that contained donations from an individual later diagnosed with vCJD. To date, no recipients of plasma derivatives have been diagnosed with vCJD in the U.K. or elsewhere. However, given the potentially prolonged incubation times for human TSEs, it is still theoretically possible that such transmissions could occur, and are yet to be identified.

Questions for the Committee:

Please comment on the FDA vCJD risk assessment for FXI manufactured from U.K. plasma, with regard to

a. The model as applied to FXI; and
b. Any additional information that is needed to improve risk estimates for this FXI product.