

ISSUE SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE MEETING
February 8, 2005
Silver Spring, MD

Topic # 2: Risk Assessment Model for Potential Risk of Exposure to Variant Creutzfeldt-Jakob Disease (vCJD) Agent in Plasma Products

Issue: FDA seeks the advice of the Committee on the design and input parameters of a risk assessment model for potential vCJD exposures from products made with U.S. plasma.

Background and Rationale

Two cases of presumed transfusion transmission of vCJD were reported in the United Kingdom, respectively in December 2003 and July 2004. The U.K. commissioned – through Det Norske Veritas - an updated risk assessment based upon these new vCJD transmissions.¹ As a result of this assessment, U.K. authorities have informed U.K. recipients of FVIII, through their physicians, that they may be at increased risk for vCJD.² Some recipients of other products were also informed.³ Correspondingly, FDA seeks to understand the vCJD risk from U.S. licensed products that are made with U.S., as compared with U.K. sourced plasma. Such estimates may serve as a basis for reexamination of the adequacy of current measures to protect blood and plasma derived products. Towards that end, FDA staff have developed a risk assessment model for CJD and vCJD for discussion.

In the setting of uncertainties, risk assessments cannot predict risk precisely, but rather supply a range of possible risks. These ranges are refined over time as more scientific and epidemiologic information become known. This risk assessment estimates the likelihood of potential exposure to the vCJD agent, not the likelihood of developing a clinical infection.

The risk assessment approaches used by the FDA generally follow the four-part framework and guidelines of the National Academies of Science.⁴ An assessment of vCJD exposure risk in U.S. products is expected to provide:

- ?? A framework for more precise risk assessments in the future
- ?? Ranking of product classes that may have greater or lesser margins of safety
- ?? Estimation of likely, best-case, and worst-case risk of exposure to vCJD via products

¹ Det Norske Veritas Risk Assessment 2003, at http://www.dnv.com/consulting/news_consulting/RiskofInfectionfromvariantCJDinBlood.asp

² Health Protection Agency website, at http://www.hpa.org.uk/infections/topics_az/cjd/blood_products.htm

³ See attachment 1, vCJD and plasma products: who may be affected? Ibid, under “Further Information.”

⁴ Risk Assessment in the Federal Government: Managing the Process. 1983. Washington DC, National Academy Press

- ?? Estimation of the need for additional risk reduction measures
- ?? Estimation of levels of TSE clearance in manufacturing that are likely to be meaningful
- ?? Risk communication to the public

Variant CJD risk assessments are limited because some of the needed information is not available. In these cases, the approach is to use a range of estimates based upon current knowledge and expert opinion. In the case of vCJD, the prevalence of infection is not known among blood donors in the U.S., but is estimated to be very low. The amounts of infectivity in blood of people incubating vCJD is not known, but have been estimated based upon observations in animal models. The TSE clearance capacity of manufacturing processes is based upon animal model studies, using spiking material that may not entirely reproduce the form of the TSE agent in plasma. The susceptibility of recipients to infection is also an unknown factor, although people that are heterozygous for methionine/valine or homozygous for valine at prion protein codon 129 may be at lower risk. Transfusion transmission of vCJD occurred in a person heterozygous for methionine/valine at that locus suggesting that no genotype may protect absolutely against infection.

Elements of vCJD Risk Assessment for Plasma Products

A risk assessment usually consists of a mathematical model and a document detailing the scope of the assessment, the data and information used, the assumptions, methods, results and conclusions. Three main categories of information are needed to perform a vCJD risk assessment: the amount of infectivity in starting material, the amount of clearance during manufacturing, and the amount of product given to a recipient. Because of the uncertainties associated with these components a probabilistic model using statistical distributions to represent the information for each variable is used. The likelihood of an infected donor of U.S. plasma is difficult to estimate, but is likely to be extremely low due to geographic blood donor deferrals to reduce possible exposure to BSE. The quantity of infectivity is estimated based upon experiments in animals, as approximately 0.5 – 500 intracerebral (ic) ID₅₀/ml of plasma. The ID₅₀ is defined as the dose that is necessary to initiate infection in 50 % of those exposed. Thus exposure to 1 ID₅₀ would suggest a 50% probability of infection, and 0.1 ID₅₀ would suggest a 5% probability of infection. In this model, an ID₅₀ is based on data from animal studies, and the relevance to humans of an ID₅₀ derived from animal studies is unknown. The amount of TSE clearance in products is estimated based upon steps in manufacturing that have been shown to result in clearance of spiked or endogenous infectivity in pilot studies with animal models. Since such studies have not been performed for all plasma derivatives, and there is biological variability associated with TSE animal models and manufacturing pilot studies, the logs of clearance used for the purpose of this model are defined as ranges. Each plasma derivative product is unique in its manufacturing processes, so that identical levels of clearance cannot be assumed for different products. Published data from animal studies in model TSE's are used to define the upper and lower vCJD clearance estimates for manufacturing processes.

Results in the risk characterization portion of the risk assessment will be expressed using a measure of central tendency (e.g. mean, median, etc.) and a confidence interval (usually 95% CI) to express the uncertainty associated with the resulting risk estimate. A

sensitivity analysis in which parameters are varied by a preset percentage of the value (10%, 25%, 50%, etc.) is conducted to determine the parameters that have the greatest influence on the final risk estimate and identifies areas where additional information may improve the risk estimate. Finally, a discussion of uncertainties and data gaps provides useful information for data needs and research priorities.

Several specific parameters are critical to generating a U.S. risk assessment:

- ?? Prevalence of vCJD in screened blood donors, modified to allow for effectiveness of blood donor deferral, and possible exposures of short duration to the BSE agent, for which blood and plasma donors are not deferred.
- ?? Infectivity of plasma from persons incubating vCJD, based upon animal studies. The assigned numbers may be viewed as maximum, because it may be that some infected donors would not have infectivity in blood.
- ?? Plasma manufacturing pool size (number of donors contributing, volume of donations).
- ?? TSE clearance by manufacturing processes, based upon published clearance studies with animal-adapted TSE agents. Since many products have not fully undergone such studies, a range of clearances is selected.
- ?? The amount of infectivity that might be contained in a single dose of product.
- ?? The amount of product given to a typical recipient per course of treatment or per year.

Interpretation of even the worst-case scenario must take into account the many uncertainties inherent in underlying assumptions.

Question and scope addressed by risk assessment: Given the recent transmission of vCJD via transfusion of whole blood and component products in the United Kingdom, what is the risk of potential exposure to the vCJD agent to U.S. plasma derivative recipients? In drafting a risk assessment model, many input variables must be considered.

Exposure Assessment

The exposure assessment component of a risk assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses the probability of exposure, and if present, the quantity of vCJD agent that may potentially be present in plasma derived products manufactured in the United States. The route of exposure is defined, since plasma derivatives are usually administered to patients either intravenously or intramuscularly.

The assessment assumes that plasma pools consisting of 20,000 or more donations collected from U.S. plasma donors are used, from which a number of plasma-derived products are purified. Because of the relatively large number of donations per plasma pool there is a small probability that even in the United States some plasma pools may contain a donation from a donor that is unknowingly infected with vCJD. Manufacturing processes may remove

and reduce a certain percentage of the vCJD agent in the product. Ultimately exposure can potentially occur through use of plasma-derived products. The overview and text that follows describes the components that contribute to potential exposure to the vCJD agent and the model in more detail.

Overview of Model

Module 1 – Estimation of potential vCJD incidence in the U.S. This portion of the model estimates the annual number of both symptomatic and asymptomatic vCJD cases in the United States. To date, there have been no reported cases of domestically acquired BSE or vCJD in the U.S. Theoretically, cases of vCJD in the U.S. might be expected to arise from two potential sources: (1) dietary exposures to the BSE agent to in U.S. residents with extended travel to or residence in the U.K. or other parts of Europe, or (2) dietary exposure to the BSE agent via infected cattle in the U.S. Based upon current USDA surveillance data, the potential for dietary exposure to BSE in the U.S. donors is estimated to be negligible. For any potential vCJD-incubating donors, it is assumed that the level and infectivity of vCJD agent present in blood and plasma remain at a constant level in the blood during the entire incubation period. Therefore, any plasma donation from a vCJD-infected person is assumed capable of transmitting the disease to a recipient.

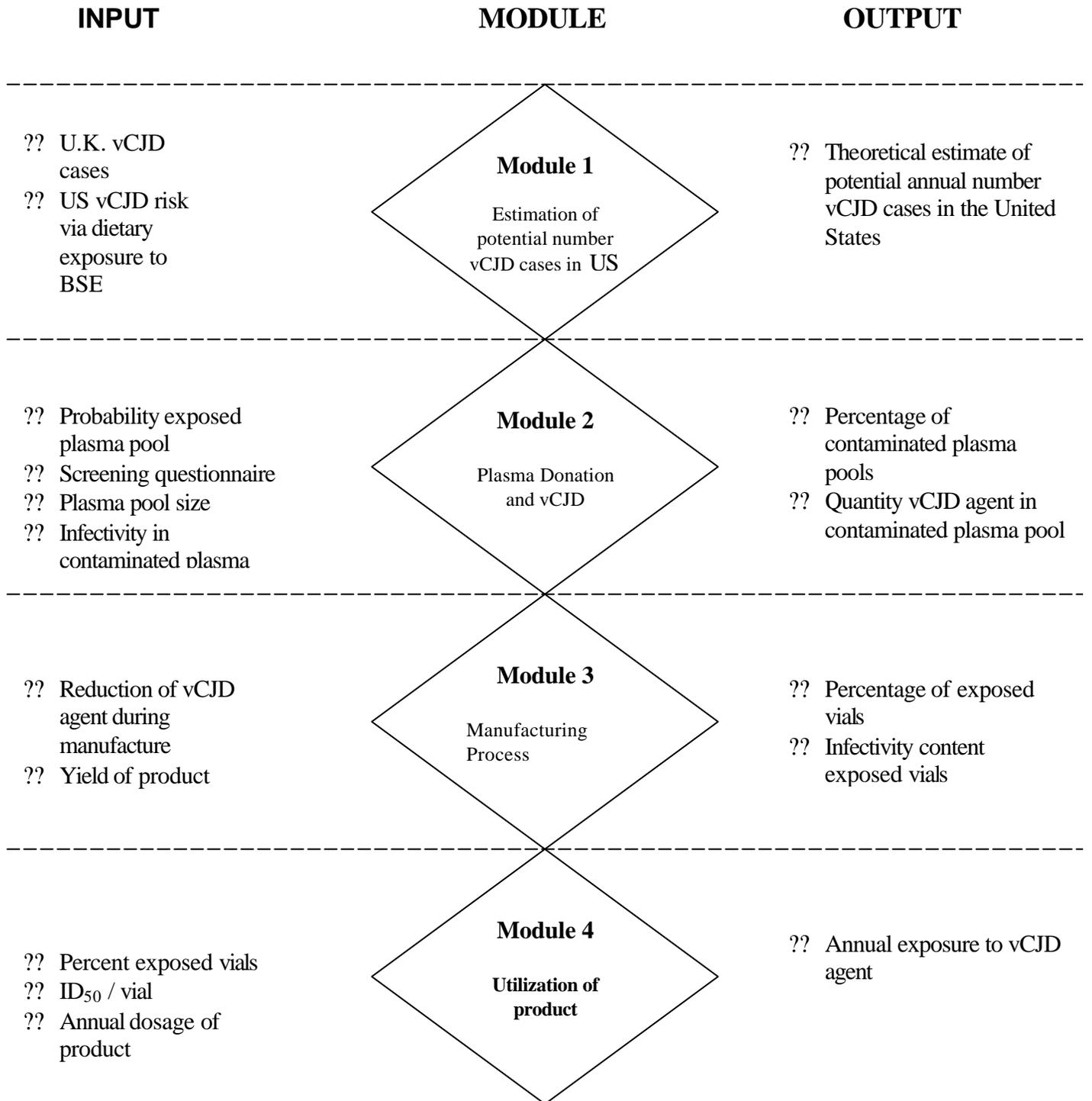
Module 2 - Plasma Donation and vCJD. This module estimates the percentage of potential vCJD contaminated plasma pools based on the predicted potential annual number of people incubating vCJD among the U.S. population, the rate and frequency of plasma donations, and the total number of plasma pools produced. The model also considers the level of effectiveness of the donor deferral policies in screening and eliminating potentially infected donors. Potential exposure to the vCJD agent is estimated in the model by considering the probability of a vCJD donation being present in a plasma pool and the amount of infectivity that might be present in the contaminated donation. Given the low prevalence of possible donations from vCJD-infected individuals, the model assumes that if vCJD agent were present at all in a plasma pool, there would likely be only one such donation per pool.

Module 3 – Manufacturing Process. The quantity of vCJD potentially present in product vials made from vCJD-exposed plasma pools may be estimated based on the possible infectivity present in an entire plasma pool, and the total yield of product from plasma. As material from a plasma pool is fractionated during manufacture it is assumed that the amount of vCJD agent present is reduced through clearance mechanisms. The degree of reduction varies depending on the type of specific fractionation and purification steps used.

Module 4 - Utilization of Products. Potential exposure of an individual patient to the vCJD agent can be estimated in the model based on the total quantity of product used per year, and the estimated quantity of vCJD agent predicted to be present in the product. The quantity of product utilized by an individual patient is dependent on the severity of the disease and the treatment regimen of choice. Our model can estimate the annual potential exposure of individual patients to the vCJD agent.

Model of Exposure Assessment

Figure 3-1 Exposure assessment diagram



Sensitivity Analysis

Sensitivity (or importance) analysis is a process of varying the value of variables in the model to identify those with the greatest influence on the estimated risk outcome(s). Such variables include the estimated incidence of vCJD in the U.S., which is dependent on factors such as the incidence of vCJD in the U.K., and the effectiveness of donor deferrals for vCJD risk. Other important variables include the total number of donations in a pool, and the log reduction of vCJD agent during processing and manufacture of products.

Uncertainty and Data Gaps

Uncertainty arises from the absence of information or availability of limited information. In our probabilistic model statistical distributions can be used to represent the uncertainty of the information used in the model. Uncertainty of final risk estimates from the model can be expressed as a mathematical mean (average) of exposure in ID₅₀ units and the 5% and 95% confidence intervals for each estimate. In the future, additional research and information may be substituted for assumptions or used to improve estimates for the individual parameters and ultimately improve the precision of the final risk estimates generated by the model.

Even considering the associated uncertainty of estimated risks, risk assessment provides a best estimate of risk based on the current and known information. It is still a useful tool that informs the science-based decision making process. It can identify data gaps and research priorities where additional research and information would have the greatest impact on enhancing the final risk estimates.

No data are available on the level of infectious units or ID₅₀ units present in the bloodstream of vCJD infected individuals at the time of blood donation. The model extrapolates an estimate of the level of vCJD agent that might be present in human blood based on data from several animal models. However, the level of agent present in an infected individual at the time of blood donation could differ from our assumption and this adds to the uncertainty of the risk assessment outcomes.

The model estimates exposure to the vCJD agent in the form of intravenous ID₅₀ units. Data are not available to estimate the probability of various clinical outcomes, such as infection or illness that might be predicted to arise from exposure to a particular level of agent. *Therefore, the model will not estimate a probability of infection or illness..* A meaningful dose-response model will need to be generated for vCJD exposure in humans to estimate the probability of adverse clinical outcomes for humans. Until then, estimates of the probability of vCJD infection or illness arising from exposure to the agent remain uncertain.

Conclusions

Potential exposure to the vCJD agent present in plasma derivatives manufactured from U.S. plasma can be modeled. The selection of parameters for the model is likely to strongly influence results.

Because of manufacturing steps and variation in the quantity of product utilized, the potential vCJD exposure risk for various plasma derivatives may differ significantly. In general, products manufactured by processes that afford limited clearance of the vCJD agent and that are used in larger quantities pose a larger potential for exposure to the vCJD agent.

Questions to the Committee

FDA requests the committee's consideration and comment on the U.S. risk model.

Please comment with regard to:

- a. The model per se; and
- b. Any additional information that is needed to improve risk estimates for the various plasma derivative