January 27, 2000

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Suitability Determination for Donors of Human Cellular and Tissue-Based Products, [Docket No. 97N-484S]

Dear Sir/Madam:

The Eye Bank Association of America recently commissioned a committee to provide an independent report on the occurrence and transmissibility of Creutzfeldt-Jakob Disease (CJD) as it relates to cornea transplantation and to comment on the proposed rule concerning "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." The committee includes members with expertise in prion disease, cornea transplantation, eye banking, neurology, and epidemiology. We have considered various approaches to minimize the risk of CJD development among cornea recipients and have reached the following conclusions:

1. Collection of information on signs and symptoms suggestive of CJD would not be a useful method of screening potential donors. At best, the possible reduction in risk of CJD transmission would likely be very small in relation to the associated costs, particularly due to decreased supply of useable tissue.
2. Current laboratory methods of testing for CJD are not adequate to screen potential donors within the short time before corneas must be used.
3. The death rates of CJD, though quite low, are highest in the older age groups. For purposes of minimizing the overall risk of CJD transmission, each Eye Bank should encourage policies and procedures that ensure maximum use of young donors even as the supply of older donors continues to expand.
4. The available medical information on potential donors should be reviewed for any evidence of a diagnosis or family history of CJD and for evidence that human pituitary-derived growth hormone had been received. Any with positive findings should be eliminated from further consideration for cornea donation. We are not aware of any Eye Bank in the United States that does not already adhere to this recommendation.

Collection of information on signs and symptoms suggestive of CJD: This issue was approached by evaluating epidemiological information on age-specific death rates of CJD, age-specific all cause death rates, the current age distribution of cornea donors, and estimates of the incubation period of CJD in humans. We estimated the levels of risk posed by potential donors who might have been symptomatic from CJD at the time of death (approximately 9% of total risk) as well as by those who might have been incubating CJD (assuming a 10-year incubation period) even though symptoms had not yet developed (approximately 91% of total risk). These estimates suggest that much of the potential risk could not be eliminated because donors with preclinical (not yet symptomatic) CJD could not be identified.

Among the annual total of approximately 45,000 cornea donors in the United States, we estimate that 1.3 donors might be expected to have either preclinical or symptomatic CJD. However, the

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risk of CJD occurring in a cornea recipient is much lower than the estimate of the likelihood of CJD occurring in a cornea donor. In the United States, a single case was reported in 1974, before guidelines were used to specifically exclude potential donors with known CJD. No additional cases of CJD have been reported among recipients of the more than 500,000 donor corneas that have been transplanted in the United States since that time. Because of the low frequency of CJD among potential donors, any screening program would need to have very high specificity (i.e., correctly identify those who do not have CJD) in order to avoid significant losses of useable tissue. Several factors would limit the specificity of questioning about symptoms of CJD including: 1) the symptoms of CJD overlap with common age-related findings among the elderly (e.g., mental deterioration); and 2) the information would be obtained by technicians with limited medical training from family members and others who may have considerable difficulty in judging and agreeing on whether a potential donor had a particular symptom.

Our estimates indicate that because of the combination of low occurrence of symptomatic CJD at the time of death of cornea donors (approximately 1 case every 8 years) and limited specificity of questioning about signs and symptoms, screening would likely result in many thousands of otherwise useable corneas being discarded in order to exclude even a single donor who had symptomatic CJD. For example, if the specificity of screening were as high as 90% and screening were applied only to donors 50 to 69 years of age (the group at highest risk), more than 15,000 donors (30,000 corneas) would be excluded during the same eight-year period. Although sufficient donor corneas are available to meet current demand in the United States, worldwide demand will far exceed supply for the foreseeable future. Consequently, restriction of the supply of donor corneas would have a direct impact on the number of patients who could have their vision restored by cornea transplantation.

Laboratory testing of potential cornea donors for CJD: Potential screening tests would be limited to immunohistopathological examination of either brain or retina. Neither test satisfies criteria necessary for testing to be performed on a routine basis. The criteria would include: 1) reasonable cost in relation to expected improvements in safety; 2) high sensitivity and specificity; 3) completion of testing within the short period of time before a donor cornea must be used; and 4) accessibility and availability of tissue for testing. Screening of blood for the presence of diagnostic prion protein might meet these criteria, but no sufficiently sensitive methodology has yet been discovered (several laboratories are currently working on the problem, and a blood test may become available within the next two years).

Encourage maximum use of young donors: The risk of CJD among donors less than 40 years of age at the time of death is approximately 40 times lower than the already low risk among older donors. This suggests that efforts to maximize the supply of young donors would help to keep the overall level of risk of CJD transmission as low as possible. However, exclusion of potential donors because of older age would not be an appropriate screening strategy because even among older donors the risk of CJD occurrence is quite low, more than half of all cornea donors are older than 60 years, and demand for donor corneas exceeds the available supply. If donors age 60 to 69 years were not selected, more than 19,000 donors (38,000 corneas) would be excluded for each case of preclinical or symptomatic CJD eliminated from the donor pool.

New variant CJD: Although no cases of new variant CJD have been identified in the United States, the possibility exists that new variant CJD could occur in the future. We believe that any screening or restriction of the supply of younger donors before a first case of new variant CJD has

been reported would not be beneficial because the risk of CJD is currently far lower (about 40 times lower) among donors less than 40 years of age than among older donors.

The risk of developing CJD following cornea transplantation is remarkably low with use of current practices for screening potential donors. Our analyses indicate that screening based on signs and symptoms suggestive of CJD would likely lead to minimal additional improvement in safety, but would reduce the supply of donor corneas and result in many patients not receiving needed treatment. Consequently, we would not recommend such screening. If you so desire, we would be pleased to discuss our analyses and recommendations in greater detail. Thank you for your consideration of this information.

Sincerely,

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