January 21, 2014

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

ATTN: Leslie Kux, Assistant Commissioner for Policy


Dear Assistant Commissioner Kux:

On behalf of the 85 U.S. member eye bank organizations, the Eye Bank Association of America [hereinafter referred to as the “EBAA” or the “Association”] appreciates the opportunity to comment on the Food and Drug Administration’s Draft Guidance for Industry that recommends the use of an FDA-licensed nucleic acid test (NAT) for testing donors of HCT/Ps for infection with West Nile Virus (WNV).

Our U.S. member organizations provide close to 100% of all corneal tissue used for transplantation in the U.S. All EBAA eye bank members are 501(c) (3) organizations whose mission is to procure and provide donated human eye tissue for sight restoring transplantation procedures. The Association strives to ensure the superior quality of banked human eye tissue through the adoption and implementation of stringent medical standards, which are scientifically based, and specific to ocular tissue.

EBAA Background

The EBAA is the world’s oldest transplantation Association, established in 1961 by the American Academy of Ophthalmology (AAO). The EBAA first established medical standards and an accreditation program for inspection of eye banking organizations in 1980, and certification of technicians followed in the late 1980s. The Association’s standards and procedures have been used as a model for adaptation by other organizations in the United States, and other countries. They are reviewed and revised twice a year by a board of renowned corneal surgeons and certified technicians with expertise and extensive experience in eye banking and then formally considered by the American Academy of Ophthalmology (AAO), which has endorsed them each year since 1981. The EBAA standards representing “best practices” in eye banking, are based on science specific to ocular tissue, and enjoy widespread
The EBAA Accreditation Board, also established in 1980, conducts inspections of eye bank members on a regular three-year cycle or more often, as necessary. Eye banks which are accredited by the EBAA, follow EBAA medical standards, and employ EBAA procedures which closely parallel and often exceed those of the FDA Good Tissue Practice regulations.

Recommendations

The eye banking and corneal transplant community expects that any guidelines or regulations are consistent, reasonable and evidence-based. We have read and researched the draft guidance and have serious concerns that the proposed mandatory implementation of WNV NAT testing for all donors of HCT/Ps falls short on each of these criteria. Based on the comments and supporting rationales that we make in response to the draft guidance, we offer the following recommendations:

- Stay the publication of the final guidance until research demonstrates that WNV testing of donors of ocular tissue and other HCT/Ps is proven as scientifically warranted and that a true risk of WNV transmission is identified;

- Base guidance on data specific to the properties of the tissue being offered for transplant. FDA itself has provided this model in its requirement for additional testing for specific types of tissue, such as anti-HTLV I/II testing in donors of viable, leukocyte-rich cells and tissues;

- Provide a risk-based analysis based on the number of tissues likely to be discarded versus the number of recipients likely to acquire the disease; and

- The Iowa Lions Eye Bank is currently conducting a study in conjunction with Iowa State University to determine if there is a risk of transmission of WNV via corneal transplant. Allow this study to be completed, so as to provide needed evidence about the risk of WNV transmission through corneal transplant.

- If scientific evidence demonstrates that WNV can actually be transmitted via avascular corneal tissue and other processed HCT/Ps, then require WNV testing of donors of ocular and conventional tissues only when reported cases of WNV reach predetermined threshold levels in the donor’s geographic area, when and if science has demonstrated a significant benefit to testing.

The EBAA offers these comments in the spirit of cooperation and collegiality, and we look forward to working with the FDA and our other transplant partners to ensure the safety of corneas and other tissue provided for transplant. Based on our current recommendations, the EBAA cannot support the FDA’s recommendation for year-round WNV (West Nile Virus) NAT testing for HCT/P donors. We take this position for the following reasons:
1) There is no evidence that testing reduces risk of transmission of West Nile Virus from donors of corneal tissue;

2) Current donor screening is effective and sufficient for conventional tissue transplantation;

3) Implications of using the Procleix WNV or Roche TaqMan Assays are unacceptable for cadaveric blood analysis due to the sample requirements, false-positive and invalid test results and cost;

4) West Nile Virus is a seasonal disease;

5) Requiring costly tests that have not been scientifically validated to reduce risk cannot be justified in light of the current healthcare financing environment in the United States.

No evidence exists that testing reduces risk of transmission of West Nile Virus in donors of corneal tissue.

- There are no reported cases of any transmission of WNV to recipients of corneal tissue or conventional tissue allografts from deceased donors;

- No evidence exists that testing reduces risk of transmission of West Nile Virus in donors of corneal or conventional HCT/P tissues;

- There is no current or anticipated public health threat, crisis or emergency regarding WNV transmission in tissue transplantation; West Nile Virus since 1999 has become endemic to the United States where it causes seasonal outbreaks;

- There is a lack of scientific evidence regarding WNV transmission from conventional tissue allografts and/or ocular tissue;

- It is unknown if WNV infects conventional tissues, if it can survive tissue processing methods or if the virus can be transmitted from a tissue transplant, because no such cases have ever been reported.

- Even though West Nile Virus RNA was identified in skin, fat, muscle, tendon and bone marrow from a deceased donor associated with WNV transmission through solid organ transplantation, WNV could not be cultured from the RNA-positive tissues. Further studies are needed to determine if WNV can be transmitted from postmortem tissues.

In the August 2007 Final DE Guidance, the FDA determined WNV to be a “relevant communicable disease agent or disease” for HCT/Ps, based on risk of transmission, severity of consequences of transmission, and availability of appropriate screening measures or tests. There have been no reports of transmission of WNV to recipients of corneal tissue since reporting of the disease was introduced in 1999; therefore, risk of transmission is purely theoretical.
Nevertheless, eye and tissue banks implemented screening for clinical signs of WNV with the publication of the final DE Guidance. With WNV HCT/P donor screening in place, the transmission rate, equivocal to the transmission rate prior to HCT/P donor screening, remains at zero (0) occurrences.

Since the publication of the Final DE Guidance, no scientific data or information has emerged to show, or even suggest, that current screening measures are inadequate to prevent the possible transmission of WNV. Indeed, no scientific or medical evidence has emerged to confirm that a risk of WNV transmission through corneal tissue even exists. That there has been no report of WNV transmission via any conventional HCT/P to date shows instead that the risk remains theoretical and, therefore, that testing cannot further reduce such theoretical risk. In other words, testing brings no added benefit to justify the increased cost to the healthcare system and time needed to implement it.

West Nile Virus (WNV) is an arthropod-borne Flavivirus that is transmitted primarily through the bites of infected mosquitos. The virus is transiently present in blood and organs of infected persons, many of whom have no symptoms of infection. The virus has been transmitted by transfusion of infected blood products or by solid organ transplantation (SOT).

SOT transmission of WNV is reported infrequently, but is associated with a higher risk for severe neurologic disease and death, likely due to immunosuppressive therapy. In most reported cases of transmission of WNV through organ transplantation, viremia and progressive signs and symptoms associated with WNV were due to transfused red cells, platelets, and fresh-frozen plasma.

The potential for WNV transmission through hematopoietic progenitor cells (HPC) is presumably similar to blood transfusion, given the similarities in product composition and donor characteristics. However the recipients of HPC are severely immunocompromised and are more likely to experience serious outcomes as a result of WNV infection.

In 2003, there were two published cases of West Nile neuroinvasive disease (WNND) in patients receiving HPC for the treatment of acute myeloid leukemia. In one case the WNV was traced to a blood transfusion and in the other the source was not determined. The recent published report by Meny et al., described WNV transmission as a result of granulocyte transfusion to a patient with persistent neutropenia related to cancer chemotherapy. Although the donor was tested for WNV, the granulocyte apheresis product was transfused prior to obtaining the results of the WNV testing.

Recipients of ocular tissue, conventional allografts, and reproductive cells and tissues do not routinely receive immunosuppressive therapy. This treatment is normal for recipients of solid organ transplants and hematopoietic progenitor cells, and may be part of the regimen for hospitalized patients who receive blood transfusions. Such therapy puts these recipients at increased risk for WNV neuroinvasive disease. This could explain why transmission of WNV has been reported in organ transplant recipients and blood transfusion recipients, but not among tissue transplant recipients.

In contrast, WNV transmission through conventional tissue transplantation has not been identified, and the risk for transmission by this route is not known. The ability to transmit WNV via the transplantation
of any HCT/P type has not been adequately studied. To simply include all types of HCT/P donors as equal risks with blood donors and organ donors does not apply FDA’s “tiered, risk-based approach.”

Previously, FDA has required specific testing (anti-HTLV I/II) for specific types of HCT/Ps from living donors because the disease is related to risk only for viable leukocyte-rich HCT/Ps. FDA should apply this same approach to transplantation of HCT/Ps which contain red blood cells.

Ocular manifestation of WNV is limited to the vascular structures of the eye such as the retina and choroid. Corneal tissue lacks the vascularization necessary to harbor or transmit such a virus, but because it is highly innervated a potential risk exists.

There has been no direct (i.e., virus isolation) or indirect (i.e., intraocular antibodies) evidence of WNV in the eye. A review of the intraocular manifestations of WNV demonstrates a close temporal relationship between systemic WNV infection and the onset of ocular manifestations. Chorioretinitis is the most common ocular manifestation of WNV infection. Other findings include retinal vasculitis and optic nerve swelling (Garg, et al).

Eye banks are unique among HCT/P establishments, because they perform active surveillance for adverse reactions among the ocular tissue they distribute. Per EBAA Medical Standards, member eye banks are required to request postoperative outcome information between three and six months after transplant from the transplanting surgeon concerning possible adverse reactions on all corneal tissue distributed by the eye bank. (EBAA Medical Standard M1.500). Adverse reactions involving the development of systemic infectious disease in a recipient would be reportable to both the EBAA through our Online Adverse Reaction Reporting System (OARRS) and FDA through their MedWatch system. There has never been a reported WNV infection in the EBAA Online Adverse Reaction Reporting System since its inception in 2004, nor via the paper records prior to that date.

The EBAA Medical Advisory Board, which consists of experts in the fields of Ophthalmology and eye banking, regularly reviews the available data on transmission of communicable diseases associated with corneal tissues. OARRS data is presented and reviewed at each semi-annual meeting of the EBAA Medical Advisory Board. When evidence suggests a correlation between a communicable disease and corneal transplant, the Board will recommend listing the condition as a contraindication to donation. The EBAA Medical Advisory Board has not listed WNV as a contraindication, because WNV has never been reported, but will do so if and when research establishes a communicable disease risk of WNV transmission via corneal transplant.

In the absence of scientific evidence that establishes a link between transmission of WNV through corneal tissue and other conventional HCT/Ps, the EBAA recommends that the current screening regimen remains appropriate. To make such an exception for corneal tissue is consistent with other exceptions being proposed and the scientific information that is available to date. Specifically, we know that human-to-human transmission of WNV has been reported only via blood product transfusion and solid organ transplantation. The correlation between WNV transmission and red blood cells is implicit in FDA’s Draft Guidance. Under the Draft Guidance, FDA would exempt source plasma and plasma derivatives from the WNV NAT testing requirement, an exemption that appears based on a lack of red
blood cells. Because corneal tissue is non-vascularized, it too can be distinguished from blood products and organ tissue, further supporting the conclusion that the risk of WNV transmission via corneal tissue is highly unlikely. To exempt source plasma and plasma derivatives from WNV testing requirements without recognizing similar differences between corneal tissue and other human tissue is inconsistent and contrary to available scientific evidence.

In a recent article, the CDC identified WNV RNA in spleen/lymph node homogenate, skin, fat, muscle, tendon, and bone marrow samples obtained postmortem from a donor associated with transmission of WNV through solid organ transplantation. The donor’s stored serum samples were positive for WNV antibodies by serologic testing but negative for WNV RNA by nucleic acid amplification testing. Corneas, vascular tissue and heart valves were not procured. WNV was isolated from the spleen/lymph node homogenate, indicating infectious virus. However, infectious virus could not be cultured, and WNV antigens were not identified by IHC staining from any of the WNV RNA-positive tissues.

Although WNV RNA was detected in unprocessed tissues obtained from the organ donor, the absence of viral antigen by IHC staining and failure to culture infectious virus from skin, muscle, and tendon suggests that the risk for WNV transmission may be lower for transplantation of these tissues than for transplantation of solid organs. Further studies are needed to determine if infectious WNV can be recovered from and possibly transmitted by transplantation of postmortem tissues and, if so, to assess the period of risk and whether tissue processing would mitigate the risk.

RNA positivity is not equivalent with infectivity, which requires the presence of intact and live virus. There is very little data about WNV survival in cadaveric tissue. Virus survival could be different in avascular corneal tissue, minimally-processed conventional tissue, and heavily processed tissue.

**Given the absence of any reported WNV transmission in conventional tissue transplantation, current donor screening is effective and sufficient.**

There are many layers of safety employed when assessing disease risk among tissue donors. Prevention of the transmission of West Nile virus through tissue relies on the exclusion of donors with symptomatic disease. One could argue that this is ineffective since most persons infected with West Nile virus are asymptomatic (80%). However, the exclusion criteria are based on a donor’s history of recent illness obtained through the donor risk assessment interview (DRAI), review of medical records, and physical examination of the donor. It is notable that the ocular manifestations of WNV infection only occur among those with systemic and disease, who would be excluded based on their symptoms.

Current FDA Guidance for Industry: *Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products* requires tissue establishments to look for clinical evidence of WNV infection before making a donor eligibility determination. Mild symptoms include fever, headache, body aches, or eye pain, skin rash on the trunk of the body, or swollen glands. Severe illness might include encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis. Signs and symptoms of severe illness might include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors convulsions, and muscle weakness and paralysis.
EBAA Medical Standards require that a penlight or portable slit-lamp examination of the anterior segment be performed prior to enucleation or in situ corneoscleral disc excision. Any inflammation (e.g., conjunctivitis, keratitis, scleritis, iritis, uveitis) found would be considered an EBAA contraindication for transplant, and those tissues would not be offered for surgical purposes. (EBAA Medical Standards D1.110.A.9.b and E1.100). This provides a further layer of safety.

Although screening donors of HCT/P tissues may be beneficial, the sensitivity, feasibility, timeliness, and cost benefit of NAT testing has yet to be assessed. Because the risk of transmission of West Nile virus is related to the incidence of infection in the donor population, the public health benefits associated with screening will probably vary according to the year, season, and location.

**Implications of using the Procleix WNV Assay are unacceptable.**

The only screening tests available for testing cadaveric samples are the Procleix WNV Assay and Roche TaqMan, both of which can be problematic for cadaveric blood analysis. Historically molecular assays have demonstrated a high false positive rate compared to those testing positive viruses. Recommended tests must be effective, not just available.

In particular, eye banks are at the mercy of the manufacturers of test kits. If a test is approved for screening for cadaveric donors, regardless of sample requirements or false positive rates, banks are being required to use the approved test. Manufacturers do not validate tests taking into consideration whether or not their stringent sample requirements align with sample requirements of other tests required of HCT/P donors. Each time a new test is introduced, more donors are lost due to lack of adequate volumes of sample. Increasingly, available sample volume is unable to meet all required test parameters.

To run the Procleix or Roche WNV NAT test, most testing laboratories requires a minimum volume of 3.3 ml for whole blood, or 1.1 ml for serum or plasma, the highest volumes required for the current eye donor testing panel. Note: Specimen volume necessary to run repeat testing and pipette multiple times is greater than the package insert minimum volume. This is a significant increase in volume, taking into consideration the effort often required to obtain a suitable sample from a cadaveric donor. Sample volumes needed for NAT testing become problematic for deceased corneal donors, as these samples must be qualified so plasma dilution does not result in false-negative test results. Donors, whose corneas would otherwise have restored sight to vision-impaired individuals, will be lost due to stringent sample requirements, for a test which has not been proven to reduce a theoretical risk of WNV transmission, despite the fact that the disease has yet to be transmitted via corneal tissue.

Unlike blood donors, which may be re-entered into the donor pool after a 120 day deferral after a positive WNV NAT, cornea donation, coming from deceased donors, is a one-time gift and blood samples from an eye donor cannot be re-tested after the time of referral.
Unlike for blood donors, the sensitivity and specificity for detecting WNV in the blood of tissue donors is unknown. Retrospective testing of organ donor serum for WNV following identification of solid organ transplantation- transmitted WNV infections showed that WNV RNA NAT was negative in two out of six (33%) cases. Nett et al hypothesize that these negative NAT results might have occurred because of hemodilution following the administration of blood products or crystalloid during resuscitation efforts, the sensitivity or detection limit of the assay used, or residual virus remaining in the donated organs after clearance of the virus from the blood. This demonstrates a potential limitation of the use of NAT testing in plasma samples. Additionally, it is not known whether donor tissues remain infected after the apparent resolution of viremia.

To screen blood of deceased tissue donors, laboratories must possess a skilled workforce with 24/7 capabilities, perform timely confirmatory testing if borderline results occur, and rapidly communicate the results to eye banks. Most eye/tissue banks do not perform any nucleic acid testing and instead they send clinical specimens for NAT to contracted laboratories. This practice increases the turnaround time and delays corneal transplantation.

Results from one site in Alberta, Canada, suggest that screening might be accomplished without compromising organ or tissue availability, but requires substantial resources and laboratory support. From 2003 through 2005, 1531 (99%) of 1549 donor specimens submitted for NAT provided a valid negative result within a pre-determined turnaround time (i.e., 6 h for deceased organ donors, and 7 days for certain tissues). The turnaround time (TAT) was 24-48 hours for cornea and sclera, which is significant for a tissue which is transplanted within 3-5 days. Invalid results usually occurred due to hemolysis and inhibitory reactions on post-mortem specimens from tissue donors. For tissue donors, 17 out of 739 specimens (2.3%) did not receive a result due to inhibition of the control. In 2012, U.S. eye banks recovered corneas from 59,221 donors; a similar outcome would result in the loss of over 1,362 corneas for transplant. No confirmed positive or false-positive specimens were detected.

The 2013 Draft Guidance recommends that “HCT/P donors should be tested by ID-NAT using a licensed NAT donor screening test” and “any HCT/P donor whose specimen tests positive (or reactive) for WNV must be considered ineligible to donate (21 CFR 1271.50(b)(2), 1271.80(d)(1)).”

Since cadaveric samples are not allowed to be run in pools, the WNV NAT test must be run initially on individual samples, with no confirmatory step or test. The donation will have already occurred, as test results are not received until post-recovery; the one time gift of eye tissue must be discarded per the recommendations made in the Draft Guidance. This would be a needless loss.

Additionally, there are concerns that universal NAT testing of low-risk donors may lead to increased false-positive results and the unnecessary exclusion of suitable donors. There needs to be a balance between tissue supply and risk reduction. The relevancy of a positive WNV NAT test, with its known high false-positive rate, will be subject to challenge by recipients of organs in those instances where the corneal donor was also an organ donor. The transplanting organ surgeon will be faced with the dilemma of the knowledge that the shared donor has been deemed ineligible by the eye/tissue bank for WNV risk. Implementation of WNV NAT testing becomes not just an issue of safety, but of vulnerability,
placing an organ recipient in jeopardy of unnecessary treatment for a perceived risk of communicable
disease, based on a screening test with a known high false positive rate.

The FDA needs to communicate and coordinate its testing requirements with HRSA, OPTN and UNOS.
The FDA and HRSA need to provide guidance on how to treat shared donors with initially reactive WNV
NAT tests, when those tests are performed by the other tissue organization. When a shared donor’s
WNV test is positive and that report is received by the OPO or transplant center, the organs may be
rejected for transplant. In a recent model described by Kibert and Forward, NAT screening was predicted
to be detrimental to the transplant community as a whole, assuming a prevalence of 0.005 in donors
and a test specificity of 99.5%. The current waiting list for life-saving organs is >121,000 people. The
results of a medical decision analysis examining the effectiveness of screening organ donors in 2002
with WNV NAT estimates that it would have resulted in a loss of 452 life-years among potential organ
recipients.

The cost/benefit of a screening program is highly dependent on the specificity of the test and the
prevalence of viremia in the population screened. NAT testing which yields a borderline, non-repeatable
test result will be reported as indeterminate, and the donor will be lost. Tilley et al reported that invalid
results usually occurred on postmortem hemolyzed tissue donor samples due to inhibitory reactions.
There were no confirmed positive donors, so the direct benefit of WNV screening to patients could not
be demonstrated and Tilley et al was unable to estimate the cost effectiveness of the donor screening
program.

**West Nile Virus is a seasonal disease.**

The potential for WNV transmission by blood transfusion was first recognized in 2002. However, routine
individual donation nucleic acid testing (ID-NAT) screening is not feasible for many blood centers
because of the resulting logistic and financial burdens. Therefore, most blood centers use WNV minipool
nucleic acid testing (MP-NAT) screening until a trigger threshold of one or more positive MP-NAT results
is reached over a specific period and then switch to ID-NAT. Each blood center has its own triggering
threshold, developed within the constraints of FDA guidance and updated guidance of AABB (formerly
known as the American Association of Blood Banks).

The blood industry requirement to test with ID-NAT is limited to periods of high WNV activity, using
established criteria to define high WNV activity in particular geographic regions. In the non-seasonal
periods, blood banks may test in mini-pools, which allows for repeat testing of individual samples if the
pool is positive, a built-in confirmatory step. The FDA acknowledges the lowered risk of WNV in the
donor population during the non-seasonal period by allowing less stringent testing of blood donors,
by mini-pools. The seasonality of WNV, which does not reach threshold levels at all during the year in
several states, is not taken into account for HCT/P donor testing. ID NAT testing is being recommended
year-round for donors of HCT/P’s, even in states that report no occurrences of human WNV cases.
This blanket method of testing is not justified. The final DE Guidance allows HCT/P donors to be tested for HIV-1 group O, or screened for travel to/certain activity in the region endemic to the disease. Testing is not required when the donor did not visit the HIV-1 group O endemic region. Likewise, WNV testing of all HCT/P donors should not be required when a donor did not reside in or travel to a region that has not reached threshold levels for human cases of WNV, especially when the risk of transmission via HCT/P’s is only theoretical. The eye banking community asks for consistency and clarity in the guidance that is published for HCT/Ps, particularly when no scientific data exist to warrant that the disease being tested transmits from cornea donor to recipient.

If scientific evidence demonstrates that WNV can actually be transmitted via avascular corneal tissue and other processed HCT/Ps, then require WNV testing of donors of ocular tissue only when reported cases of WNV reach predetermined threshold levels in the donor’s geographic area when and if science has demonstrated a significant benefit to testing.

FDA should allow the option to discontinue WNV NAT during low incidence months (December 1 through April 30) defined by targeted ID-NAT triggering criteria that has been adopted and refined by the blood community. Similarly, eye/tissue banks should utilize the reported WNV activity for the blood donors in the geographic region, reports of WNV activity in mosquitoes or animals (equine or avian), and human clinical cases reported to county/state health departments or the U.S. Centers for Disease Control for triggering decisions to implement ID-NAT testing, if warranted.

The AABB WNV Biovigilance Network uses the donor’s residential/postal zip code as their location for reporting. Although mosquito exposure may occur at any location, it is most likely that exposure occurred while the donor was at his or her residence (dawn or dusk, when mosquito activity is highest). In the event of extended travel/vacation of the donor during the incubation period, the zip code that more likely represents the location of the exposure should be utilized to determine WNV risk.

**Increasing costs are absorbed by the health care system and eye banks.**

The cost of the Alberta, Canada WNV NAT screening program for organ, hematopoietic stem cell and tissue donors was approximately $109,000 per season (June to October, inclusive), including reagents, labor, callbacks and overtime, repeat and confirmatory testing, and proficiency testing. This represented a cost of approximately $233 per donor (Tilley et al).

Each additional required test adds to the cost of providing tissue for transplant. As more tests are developed and made available, each test should demonstrate tangible benefit to the screening of donors to justify the increased costs before being added to the list of required tests. Not every test developed should be required for every type of tissue donation simply because it is available. For each new test, scientific data must demonstrate that it will contribute to the safety of the tissue being transplanted. The addition of the Procleix WNV Assay raises the price of the eye donor testing panel as high as $100 per donor, a significant cost for one test among many. Such an increase in cost is justifiable...
when a test can indeed reduce a real risk that a serious communicable disease can be transmitted. It is not justifiable, when there is nothing more than a theoretical risk of transmission.

Payers are extremely sensitive to cost issues in today’s environment. CMS, (the Centers for Medicare and Medicaid Services), under the U.S. Department of Health and Human Services (HHS), is the single largest payer for corneal tissue, and currently reimburses facilities at the eye bank’s invoice cost for processing. This processing cost “pass-through” strikes a delicate balance in an era of capitation, and, eye bank’s ability to recoup their costs in ensuring the safety of tissue could be jeopardized by increased processing fees. The EBAA has struggled on behalf of all member non-profit banks to avoid a cap on reimbursement of corneal tissue processing fees. Such a cap would devastate the not-for-profit eye banking community and severely reduce the availability of ocular tissue provided for transplantation in the U.S. In short, it would needlessly handicap both the citizens of the United States who could not get a transplant and a historically successful system. Additional costs assigned, but lacking proper scientific support, place this very system in jeopardy by challenging the necessary costs of assessing donor eligibility.

Additional research is needed to determine the relevance for various cell and tissue types before FDA makes a determination regarding the use of WNV NAT for all HCT/P donors.

The Iowa Lions Eye Bank has allocated research funds to determine whether corneal tissue is susceptible to WNV infection in vitro and in vivo. Their lead researcher is Bradley Blitvitch, PhD, from Iowa State University. Dr Blitvitch is well published and performed some of the initial animal WNV transmission work. Since the cornea is a privileged, avascular tissue, we speculate that if WNV is transmitted to the cornea, it moves along the nerve track. This study has been undertaken to test for the presence of West Nile viremia in corneal tissue and to determine if WNV can be transmitted from postmortem corneas.

To date, they have obtained [unpublished] evidence that human corneal epithelial (HCE) cells are susceptible to WNV infection in vitro. WNV RNA was detected in RT-PCR in virus-inoculated human corneal epithelial cells and the WNV envelope protein can be detected by western blot analysis in lysates prepared from WNV-infected corneal cell cultures.

Additionally, Dr. Blitvitch was able to detect WNV by RT-PCR and western blot in human corneas cultured in the presence of virus. Titers are higher when corneas are pre-incubated in media for three days before virus challenge, because a number of cells detach from the cornea and it is easier for the virus to attach to individual cells floating in the media. When corneas are not incubated in cell media prior to WNV challenge, the titers are extremely low because the virus has trouble attaching itself to intact corneas.

We recognize that these experiments do not replicate the normal corneal environment. Further studies are needed to determine if human corneas from individuals naturally infected with WNV support viral replication and contain infectious viral particles at the time of the graft. The Iowa Lions Eye Bank is
committed to further studies and at this time is actively seeking cornea tissue from other eye banks who have a higher incidence of WNV related deaths.

We request that the FDA delay finalization of this guidance to allow us to complete our studies on corneas from donors who test positive for WNV. We have been in communication with scientists and medical epidemiologists from the Arboviral Diseases Branch of the CDC, but have been unable to date to obtain corneal specimens from donors who were WNV positive at the time of death to perform experiments to determine viral presence and viral load.

We ask the FDA to join the Association in this endeavor and partner with us in this important study. The hypothesis is that the gathered data will support the safety of avascular corneal tissue and provide information to explain the lack of occurrences of WNV transmission via transplantation of corneal tissue. Obviously, if the data proves a risk of viral transmission through corneal transplants, the EBAA will mandate WNV NAT testing for ocular donors in our Medical Standards to ensure the safety of ocular tissue for transplant.

Additional research is also needed on factors affecting donor-derived WNV transmission, NAT performance in the tissue donor population, and the economics associated with universal screening and possible tissue wastage due to false-positive tests.

Again, the EBAA requests that until scientific data are produced that prove testing for WNV reduces the risk of WNV transmission via corneal transplantation, the final guidance requiring ID NAT testing for HCT/P donors should not be issued.

Closing Remarks

The EBAA thanks the FDA for the opportunity to comment on the draft guidance document. The Association understands and appreciates the FDA’s efforts to help ensure the safety of human tissues for transplant and prevent the transmission of communicable disease by HCT/Ps. We appreciate the opportunity to work with you to ensure the safety of ocular tissue offered for transplant.

For 70 years, since the first eye bank was established in the U.S., corneal transplantation has enjoyed a long and enviable history of success and safety in our country; eye banking standards, first promulgated by the EBAA’s Medical Advisory Board in 1980, have provided a model on which other transplant standards are based. On behalf of our active and committed eye banking community, we implore the FDA to reinforce the positive contributions that corneal transplantation effects to its citizenry and to recognize the system for the safety and efficacy that it provides.

As was said at the outset, the EBAA has a long and valued history of working with the FDA and our other transplant partners to develop an appropriate regulatory scheme to address emerging infectious agents. These comments are intended to continue that collegial and cooperative spirit.
Sincerely,

[Signature]

Kevin P. Corcoran, CAE
President & CEO

**References:**


