



American Association of Tissue Banks

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August 2, 2013

Division of Dockets Management (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

***In Re: [Docket No. FDA 2004-D-0025]***

***Final “Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products” August 2007***

Dear Madams and Sirs:

The American Association of Tissue Banks [hereinafter referred to as the “AATB” or the “Association”] submits these comments in response to the Food and Drug Administration’s (FDA) publication of the final “*Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products*” (*Final Guidance*). Since its publication six years ago, personnel at AATB-accredited tissue banks have been screening donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) following the criteria in this *Final Guidance*. It has been brought to our attention there continues to be widespread misinterpretation and other difficulties experienced surrounding a particular risk criterion with which FDA staff members have also had difficulty correctly interpreting. Our comments herein outline the issues with this outdated, problematic, HCT/P donor screening criterion and we respectfully request serious consideration of our recommendations to rectify this issue without delay. Alleviating this donor eligibility conundrum will not compromise the donor screening process or adversely affect safety for recipients of tissue allografts. As soon as possible, our recommendation should be honored to remove the criterion that identifies receipt of a human-derived clotting factor concentrate as increased risk for transmission of communicable disease, and to eliminate the need to screen for risk associated with having sex with a recipient of this product.

***I. The Interest of the AATB***

The AATB is a voluntary, professional, scientific and educational organization. The Association is nonprofit and tax-exempt under Section 501(c)(3) of the Internal Revenue Code. It was

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founded in 1976 by a group of doctors and scientists who had started in 1949 the United States Navy Tissue Bank, our nation's first tissue bank.

Like FDA, the AATB's mission is public health. The Association is dedicated to ensuring that human tissues intended for transplantation are safe and free of infectious disease, of uniform high quality, and available in quantities sufficient to meet national needs. To further that mission, the Association has, since 1984, published the only standards for tissue banks, the *Standards for Tissue Banking (Standards)*. This publication, in its 13<sup>th</sup> edition, is the recognized authoritative source for the tissue banking profession.

Beginning in 1986, the AATB initiated a voluntary Accreditation Program to ensure that tissue-banking activities are being performed in a professional manner in compliance with these *Standards*. All of the AATB's institutional members must be accredited and re-inspected and re-accredited every three years. The Association's membership currently includes nearly 1,000 individual members and more than 120 accredited tissue banks engaged in screening and testing donors and the recovery, processing, storage and/or distribution of human tissue. Annually, these tissue banks handle tissue recovered from an estimated 30,000 donors and distribute in excess of 2 million allografts for transplant.

The AATB has consistently advocated and publicly supported balanced governmental regulation aimed at safeguarding human tissues from disease transmission. With the publication of the FDA's first tissue banking regulations in 1993 [62 *Federal Register* 40,429], the AATB publicly supported establishment of interim requirements for screening tissue donors for communicable disease. The Association continues to support reasonable FDA regulation of tissue banking activities as well as evidence-based donor screening recommendations.

The AATB's *Standards* contain extensive requirements for screening donors that surpass regulations and guidance from FDA, and the *Standards* also contain more expectations than required by FDA for tissue recovery, processing, labeling, storage and distribution that promote safety and avoid disease transmission. With the exception of ocular tissue, AATB-accredited tissue establishments provide most of the commonly used structural tissues for clinical use in the United States. The Association is, therefore, extremely interested in this *Final Guidance* and the effectiveness or ineffectiveness criteria have on the safety and supply of human tissue for transplantation.

## **II. Overview of AATB's Comments and Recommendations**

Since publication in August 2007 of this FDA *Final Guidance*, members of the AATB, including Medical Directors, have expressed great concern regarding the intent of certain donor risk criteria as well as their applicability today. Definitions are lacking and publications used by FDA as references for establishing certain risk periods (i.e., "in the previous 5 years") are not

evidence-based and are now considered out of date by epidemiology experts within the U.S. Public Health Service [1].

The Association understands and appreciates the FDA's commitment to control of contamination and cross-contamination in regard to reducing the potential for communicable disease transmission from a tissue donor. Risk criteria selected for screening must be based not only on evidence-based, epidemiologically and statistically sound principles but also with consideration that, in the United States, tissue donor evaluations overwhelmingly involve a deceased donor with the donor's medical history interview (aka donor risk assessment interview) obtained from a third-party. Knowledge by a third-party is naturally limited in regard to specific medical products given to someone else (the donor) during treatment for any condition, and awareness of risky behavior can be circumstantial. It is understood by health history survey design experts that this interview process should not be influenced by questions that provide no value. Including unnecessary questions act as distractors and add to the burden of recollection for a variety of relevant risks. The interview process should be optimized to minimize response errors.

Donation professionals from tissue establishments who apply the screening guidelines to every day practice are providing notice to FDA that amendments to this guidance are overdue. More amendments can be made but we are focusing on one issue with the submission of these comments.

The AATB recommends immediate removal of the criterion that identifies receipt of a human-derived clotting factor concentrate as a risk of communicable disease. The following comments and recommendations are based on a number of facts and considerations, including the following:

- The replacement *Final Guidance* issued by FDA in August 2007 contained a previously unpublished, extremely strict risk criterion that has not been publicly debated, and it remains unexplained and unsubstantiated;
- The risk of being exposed to contaminated, human-derived clotting factor concentrates has not been formally evaluated in modern times;
- The literature references cited by FDA in this *Final Guidance* contain no information to support a rationale for a 5-year time frame or a 12-month risk period for previous exposure to a human-derived clotting factor concentrate;
- There remains widespread misinterpretation in regard to which products qualify today as "human-derived clotting factor concentrates" that could be considered to pose increased risk for communicable disease;

- FDA's inference that the medical history interview process for a deceased donor is a useful method to obtain information about "receipt of clotting factor concentrates" should be revisited; and
- To properly assess perceived risk, FDA could resolve these issues by working with experts at the Centers for Disease Control and Prevention (CDC) and utilize a risk evaluation performed by the Office of Biostatistics and Epidemiology within FDA's Center for Biologics Evaluation and Research (CBER).

The AATB is requesting that our comments and recommendations herein are taken seriously and used to properly re-evaluate this problematic criterion. This should result in FDA publishing appropriate amendments to final guidance without a lengthy delay. As these comments will demonstrate unequivocally, there is confusion surrounding this criterion, there are unanswered questions about applicability in modern times, the expectation to gather information about this therapy during the medical history interview is a major challenge, and there is a serious lack of evidence-based data to support the implicated product poses implied risks which have not been adequately examined or determined. Perhaps more importantly, the ramifications of this interpretive misunderstanding are widespread and significant, and results in decreased numbers of eligible tissue donors, which affects the supply of high quality, safe tissue grafts made available for recipients who need them.

### **III. Comments and Recommendations**

#### **Comment No. 1**

***The replacement Final Guidance issued by FDA in August 2007 contained a previously unpublished, extremely strict risk criterion that has not been publicly debated, and it remains unexplained and unsubstantiated.***

The risk criterion in question appears immediately below and was issued in August 2007 (*relevant parts only*):

#### **"IV. DONOR SCREENING (§ 1271.75)**

##### **E. What risk factors or conditions do I look for when screening a donor?**

For all donors, you must review the relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for relevant communicable disease agents and diseases, and communicable disease risks associated with xenotransplantation (§ 1271.75(a)).

Following is a list of conditions and behaviors that increase the donor's relevant communicable disease risk. Except as noted in this section, and in accordance with § 1271.75(d), you should

determine to be ineligible any potential donor who exhibits one or more of the following conditions or behaviors.

3. Persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates in the preceding 5 years (Refs. 18 and 60) (risk factor for HIV, Hepatitis B and Hepatitis C). A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate.”

The AATB first realized an unusual sequence of events related to this listing (3.) when there was an unannounced, unexpected change made to it between the publication of the *Final Guidance* issued in February 2007 and its replacement *Final Guidance* issued in August 2007. In February, the criterion was listed as follows:

- “3. Persons with hemophilia who have received human-derived clotting factor concentrates in the preceding 5 years (Refs. 18 and 60) (risk factor for HIV, Hepatitis B and Hepatitis C).”

The change issued in August (further above) was expanded without public debate or comment. The risk criterion became stricter in two ways:

- 1) It surprisingly added a risk group “persons with...other related clotting disorders” back into the criterion; and
- 2) For the first time, it expanded the possible clinical scenario coverage to be extremely restrictive by adding: “A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate.”

Without explanation this latter addition effectively reduced the risk time period from 5 years to 12 months, but the two references cited do not support that “a donor who received clotting factors once to treat an acute bleeding event” is an increased risk factor for HIV, Hepatitis B or Hepatitis C. No new references were added, there was no justification provided for this new criterion, and it has not been afforded public debate. The high-risk designation of a one-time recipient (or otherwise limited exposure) of a human-derived clotting factor concentrate during the 12 months prior to death is especially not justified today, and to support our assertion the remaining comments and recommendations that follow should be considered.

The final version of this criterion for donors of HCT/Ps added a risk group beyond hemophiliacs to “persons with...other related clotting disorders.” This appears to be obliquely related to a donor who received this product “once to treat an acute bleeding event.” A risk assessment analysis is expected to justify such a restrictive criterion that impacts the eligibility determination of many potential tissue donors who do not survive acute lifesaving measures to control bleeding. This, alone, cannot be justified and requires official, unbiased re-review without delay.

By default, a person who has had sex with a recipient of this product is “at risk” but this, too, should be removed from guidance. The risk criterion is found as part of this section’s list:

“5. Persons who have had sex in the preceding 12 months with any person described in criteria 1 through 4 of this section or with any person who has HIV infection, including a positive or reactive test for HIV virus (Refs. 17 and 18), hepatitis B infection (Ref. 64), or clinically active (symptomatic) hepatitis C infection (Refs. 65 and 66).”

Of note regarding risk to a sexual partner of a one-time recipient of a human-derived clotting factor concentrate, FDA’s Office of Blood Research and Review has already acknowledged via guidance for donors of blood and blood components [2] that “Sexual contact with a person who has received clotting factor concentrates as a one time medical use is not deferred.”

**Recommendations:** Due to these multiple reasons, a proper statistical evaluation of risk should be performed to evaluate a one-time or other limited exposure to human-derived clotting factor concentrates manufactured in modern times. The Office of Biostatistics and Epidemiology at CBER has the expertise to perform this analysis and results should be shared with all stakeholders. We believe this evaluation will result in deletion of this overly restrictive criterion. Additionally, “persons who have had sex in the preceding 12 months” with a recipient of a human-derived clotting factor concentrate should not be identified as carrying risk.

#### *Comment No. 2*

***The risk of being exposed to contaminated, human-derived clotting factor concentrates has not been formally evaluated in modern times.***

In the early days of the HIV epidemic, hemophiliacs were identified as being at higher risk of acquiring the disease. It was later shown that the virus responsible for the infection could be transmitted by human-derived clotting factor concentrates that were used to treat hemophilia. These products are manufactured by a process that involves pooling of plasma donations obtained from several thousand donors. The clotting factors are extracted and purified from these plasma pools. Before the advent of HIV screening tests and other mitigating measures, one or more infected donors could contaminate a manufacturing pool, such that all clotting factor concentrates obtained from that pool would have the ability to transmit HIV. Because of the large number of plasma donations included in a pool, a substantial proportion of clotting factor concentrates were contaminated with HIV during the 1980’s, and many hemophiliacs became infected with HIV, and also HCV [3,4,5]. Once it was recognized that hemophiliacs were at higher risk for HIV, policies were implemented to interdict blood donation by people who received human-derived clotting factor concentrates. The risk was judged to be sufficiently high that persons having sexual contact with people treated with human-derived clotting factor concentrates were also deferred from donation. These policies were rapidly and broadly adopted by most regulatory authorities in the Western hemisphere, including the FDA and Health Canada.

By analogy with risk of transmission through blood and blood-derived products, similar exclusionary criteria were adopted during the 1990's for donors of organs and donors of tissues [6, 7], however, the risk associated with human-derived clotting factor concentrates was never formally re-assessed even though two decades have passed and numerous changes were implemented surrounding the manufacture of this product. FDA is well aware of these advancements yet no re-review of risk was undertaken or published.

The following information supports that "human-derived clotting factors concentrates" have not been a "risk factor for HIV, Hepatitis B and Hepatitis C" for more than twenty (20) years. We are providing supportive evidence that this entire risk criterion has become antiquated today due to:

- 1) Technological advancements in manufacturing methods of "human-derived clotting factor concentrates" routinely used as medical therapies for acute or chronic bleeding disorders;
- 2) Improvements in development, availability and common use of improved infectious disease donor screening tests for the three viruses identified in guidance for this risk criterion;
- 3) Donor screening questionnaires used by manufacturers of plasma-derived products have been optimized to improve donor cognition and to educate the donor regarding applicable risk behaviors; and
- 4) Quality control and quality assurance measures that work to further provide safety mechanisms have widely been adopted by manufacturers of plasma products and their professional accrediting body.

Since the 1980's when viral risk associated with human-derived clotting factor concentrates was recognized, several important changes have been made that virtually eliminate the risk of contamination resulting in viral transmission by these products [8,9,10,11]. Some of these changes were already in place by 1990 and others were added a decade ago. They include the following improvements that are critical to this discussion:

- 1) Pathogen inactivation during the fractionation process: Since the mid-1980's, the manufacturing processes for human-derived clotting factor concentrates have been modified to include one or more pathogen reduction and virus inactivation steps. The most frequently used inactivation methods involve heat treatment and exposure to solvent detergent. These methods have been shown to reduce the viral load to such an extent that even if a plasma pool would inadvertently contain one or more contaminated units, the resulting plasma derived products would not contain enough virus particles to transmit

infection. FDA's review process for licensed products allows close scrutiny of these validated processes so requisite knowledge in this area is not lacking.

- 2) Advances with donor testing: At each donation, plasma donors are tested for transfusion transmissible diseases, including HIV, Hepatitis B and Hepatitis C. In addition to licensed serological tests, donations since the turn of the century are also subjected to nucleic acid amplification tests (NAT) for viral diseases. The Quality Standards in Excellence, Assurance and Leadership (QSEAL) [12] of the Plasma Protein Therapeutics Association (PPTA) has included NAT for HIV, HCV, and HBV since 2000. NAT is done primarily to identify a donor who might still be in an immune-silent phase of infection but it also has the added benefit of testing redundancy to enhance detection. In addition, by way of its International Quality Plasma Program (IQPP) the PPTA developed a National Donor Deferral Registry Standard to ensure that donors deferred in one facility for reactive test results for these diseases do not donate in other facilities [13].
- 3) Donor screening and education is greatly improved: Like blood donors, potential plasma donors are systematically evaluated for behaviours and exposures that may put them at increased risk of HIV and other blood borne infections, such as male-to-male sex, nonmedical injection drug use, sex in exchange for money or drugs, etc. For over a decade, systems have been implemented that require potential donors to read educational materials that specifically provide information and descriptions regarding high-risk behaviours, exposures, and disease transmission [14]. Potential donors who report such an activity or exposure are informed they are disqualified. Earlier this year, the FDA acknowledged the usefulness of the donor history questionnaire documents published by the PPTA by issuing them in FDA guidance [15]. Additionally, PPTA has established the "Qualified Donor Standard" [16] as part of their International Quality Plasma Program [17]. This standard establishes safeguards that substantially increase safety by further reducing the risk of undetected infectious units of plasma being manufactured. The standard works to exclude from manufacture "window units" by requiring additional testing/donations to qualify "Applicant Donors." FDA officials are familiar with these terms and processes.
- 4) Plasma quarantine/inventory hold: Moreover, plasma donated for fractionation is quarantined for a minimum period of time (i.e., at least 60 days) to allow donors to return to donate once more which provides an avenue that repeat testing of transmissible disease markers are negative again. This additional safety measure further reduces perceived risk that a contaminated donation will escape detection due to a previously negative test. This is just one standard of the QSEAL [12] established by the PPTA, whose membership covers the vast majority of plasma centers and plasma fractionators in the US and more than half of them Europe [18].

This collective knowledge has yet to be properly applied to the perception of risk attributed to receipt of these products by prospective tissue donors.

**Recommendation:** Due to all of these improvements to multiple layers of the manufacturing process, and the absence of transmission of viral disease from these products, a proper statistical evaluation of risk for exposure to human-derived clotting factor concentrates manufactured in modern times is indicated. The Office of Biostatistics and Epidemiology at CBER has the expertise to perform this analysis and share results. This evaluation should be used to remove this criterion.

**Comment No. 3**

***The literature references cited by FDA in this Final Guidance contain no information to support a rationale for a 5-year time frame or a 12-month risk period for previous exposure to a human-derived clotting factor concentrate.***

Both of the references provided in final guidance to support the need for this risk criterion are dated more than sixteen years ago and do not accurately reflect the safety state of these products today or even at the time the *Final Guidance* was first issued (February 2007). These are the two references dated from 1994 and 1996:

“18. Public Health Service. PHS Guideline for Preventing Transmission of HIV Through Transplantation of Human Tissue and Organs. *Morbidity and Mortality Weekly Report* 1994; 43(RR8):1-17. <http://www.cdc.gov/mmwr/PDF/RR/RR4308.pdf>” and

“60. Schreiber, G.B., et al., The Risk of Transfusion-Transmitted Viral Infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996; 334:1685-90.”

The latter publication concludes that: “The risk of transmitting HIV, HTLV, HCV, or HBV infection by the transfusion of screened blood is very small, and new screening tests will reduce the risk even further.” This statement was visionary and has been affirmed but this publication does not describe anything further that can be even remotely related to risk associated with “human-derived clotting factor concentrates.” This medical product is not mentioned at all.

The earlier reference from 1994 [4] was already eleven years old at the time this *Final Guidance* was issued. It contains recommendations directed at risk only for HIV and there is no description how “in the preceding 5 years” was selected as a significant risk period that requires evaluation. This time period was thought to be a compromise from longer time periods used for blood donation for the same few risk factors but it remains a mystery why “5 years” was used. This reference provides no supportive data that identifies “persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates” as risks for transmission of disease but this criterion is used in the list of “behavior/history exclusionary criteria”. Substantial risk reduction measures have been implemented since these reference articles for this risk criterion were published.

No publications exist that describe the rationale for selecting a 5-year time period for evaluating

behavioural risk for a tissue donor. FDA is well aware that the 1994 document used as a reference in *Final Guidance* has recently been updated by the U.S. Public Health Service (PHS), and use of the 5-year time period has been removed [1]. Receipt of human-derived clotting factor concentrates is also no longer listed as a risk factor that increases an organ donor's risk for HIV, HBV, or HCV. This long-awaited manuscript from PHS reports that there is **NO RISK** attributed to receipt of human derived clotting factor concentrates. They analyzed reports and data relative to risk attributed to HIV, HBV and HCV. Exhaustive evaluations of behavioural and non-behavioural risks were performed to re-establish support of previously published donor risk factors, or to remove them if evidence of risk was no longer applicable. The document describes that "given the paucity of data evaluating behavioral and nonbehavioral risk factors for HIV, HBV, and HCV in potential organ donors, we also searched for studies meeting inclusion criteria in the following populations: tissue donors; blood donors; and (the) general population." This description is important because risks applicable to the tissue donor population were considered in their evaluation. FDA guidance and PHS guidelines regarding donor screening criteria should be harmonized; disparities require thorough explanation supported by data but, historically, this has not been explained or published. It's also very important to acknowledge that disparity in collection of donor risk information during the donor screening process causes confusion in the organ, tissue and eye donation professions and promotes mistakes when differences exist. Information obtained can be used differently, however the method to collect risk information during the medical history interview process (the donor risk assessment interview) should be the same.

**Recommendation:** Without evidence of relevant references to support there is increased risk associated with receipt of human-derived clotting factor concentrates, and there is no support for use of a 5-year risk period or a 12-month risk period related to this product type, this risk criterion should be removed from the *Final Guidance* used for screening HCT/P donors.

#### ***Comment No. 4***

***There remains widespread misinterpretation in regard to which products qualify today as "human-derived clotting factor concentrates" that can be considered to pose increased risk for communicable disease.***

We are alerting FDA there is widespread misinterpretation regarding which specific products are included in the classification of "human-derived clotting factor concentrates." In December 2010, the Medical Director of an AATB-accredited tissue bank sent a written inquiry to FDA regarding the criterion surrounding "human-derived clotting factor concentrates" in the *Final Guidance* and he received a response from a Consumer Safety Officer within the Manufacturers Assistance and Technical Training Branch, Office of Communication Outreach and Development that described in the summary:

"Thus, HCT/P donors who received clotting factors within the last 12 months are unable to donate and are considered ineligible until 12 months have passed."

This general reference to “clotting factors” and not to “human-derived clotting factor concentrates” caused confusion and an inappropriate change was made to donor screening policy at this large tissue establishment where donor eligibility determinations are made.

In 2012, a written inquiry to staff at the Center for Biologics Evaluation and Research (CBER) from an eye banking professional resulted in a response containing misinformation regarding what qualifies as such a product. Specifically, a Division of Human Tissue staff member described that “cryoprecipitate” fits the description as a “clotting factor concentrate” as referenced in *Final Guidance*. Cryoprecipitate is not a “clotting factor concentrate” as intended in the *Final Guidance*.

The AATB has also learned that when personnel at tissue recovery programs are screening potential donors of HCT/Ps, and when tissue processors are reviewing a donor’s relevant medical records, decisions continue to be made to determine the donor ineligible due to receipt of any product that could be perceived to fit the therapeutic description as a “human-derived clotting factor concentrate.” Since they are a type of plasma-derived therapeutic product used to stop bleeding and are manufactured by concentrating the product via centrifugation, a confused interpretation can include single-donor platelets or cryoprecipitate, whether they are pooled from a few donors (i.e., from six is common) or not.

We are certain FDA’s intent in *Final Guidance* does not include these products as “human-derived clotting factor concentrates,” however, without a clear definition or reference to specific examples, there remains confusion and the unnecessary exclusion of otherwise suitable tissue donors. It has been reported to AATB that some of these have been donors of potentially life-saving, pediatric allograft heart valves. This is a serious matter that affects the availability of life-saving allografts for pediatric patients. This, alone, supports the urgency of our request.

It’s well known that antihemophilic factor (AHF) and factor IX complex (F IX) were considered high-risk products for the transmission of viruses during the period before and including the 1980’s [3,5], but this risk only lasted until methods were developed that would stabilize the coagulation activity of the products so virus-inactivation methods involving heating could be used [8]. By 1985, all new lots of AHF and F IX had been subjected to a validated virus-inactivation treatment method (i.e., use of heat, solvents, detergents, and/or lyophilization). Additionally, purification steps have shown to remove viruses, if any are present. Virus-removal and virus-inactivation procedures during the manufacture of plasma derivatives ensure that any residual HBV, HCV, HIV-1 or HIV-2 that might be in a pool from many donors does not result in an infectious product. It is widely recognized that, since donor screening tests were implemented and virus inactivation and removal procedures became common during manufacture [8],:

- 1) there has been no transmission of HIV by US-licensed AHF or F IX since the application of effective virus-inactivation procedures by all manufacturers in 1987;

- 2) no transmissions of HCV by these products has occurred; and,
- 3) there have been no seroconversions to anti-HIV in hemophiliacs who have received only AHF or F IX that has been manufactured from screened plasma donors and subjected to adequate virus-inactivation steps.

Improved, safe therapies are used today to control bleeding and these highly manufactured products are also being misidentified as posing increased risk for relevant communicable disease. For example, prothrombin complex concentrate and fibrinogen concentrate are relatively new products being used for rapid correction of coagulopathy especially in patients on Coumadin or for trauma patients. They primarily contain clotting factors and their use results in almost immediate correction of coagulopathy. They can also be administered in small amounts instead of a large volume of an untreated product (i.e., fresh frozen plasma). Just this year, FDA has instructed tissue recalls based on a tissue donor's receipt of one of these modern-day, highly manufactured products. That this occurs without properly defining the term, or evaluating the risk of these products today, points to serious deficiencies in guidance.

***Recommendation:*** If FDA can justify that receipt of "human-derived clotting factor concentrates" qualifies as increased risk for relevant communicable disease, the rationale must be supported by clearly defining which therapeutic products are included by this term.

#### **Comment No. 5**

***FDA's inference that the medical history interview process for a deceased donor is a useful method to obtain information about "receipt of clotting factor concentrates" should be revisited.***

In the United States, tissue donor evaluations overwhelmingly involve a deceased donor with the medical history interview (donor risk assessment interview) obtained from a third-party. Knowledge by a third-party is naturally limited in regard to specific medical products given to someone else (the donor) during treatment for an acute condition. More reliable information regarding "recent" receipt of a "human-derived clotting factor concentrate" is garnered from clinical medical records, not from the person(s) interviewed to obtain a medical history to establish communicable disease risk. Recent, qualitative work using cognitive interviewing techniques carried out by officials at the National Center for Health Statistics (NCHS) while evaluating the multi-organizational Donor Risk Assessment Interview (DRAI) form (for a donor >12 years old) revealed that interviewees "do not know what blood clotting factors are and, worse, think that they are blood thinners." FDA's inference in regard to this being a risk to look for using the interview process when obtaining a deceased donor's medical history should be closely re-evaluated and consultation with officials at NCHS is recommended. See 21 CFR Part 1271.3 (n).

***Recommendation:*** When FDA re-evaluates that receipt of “human-derived clotting factor concentrates” constitutes risk in modern times, and if it proves to be a justifiable to include, there should be consultation with health history survey design experts at NCHS to determine a logical approach to collecting risk information. Obtaining relevant information should not automatically infer this history is expected to be obtained during the medical history interview process for a deceased donor.

***Comment No. 6***

***To properly assess perceived risk, FDA could resolve these issues by working with experts at the Centers for Disease Control and Prevention (CDC) and utilize a risk evaluation performed by the Office of Biostatistics and Epidemiology within FDA’s Center for Biologics Evaluation and Research (CBER).***

Periodically, the Centers for Disease Control and Prevention (CDC) issues reports that can add to the confusion regarding the implication that “human-derived clotting factor concentrates” continue to transmit HIV disease. For example, information was discovered in “The *HIV/AIDS Surveillance Report*” (volume 19) [19] that can easily be misunderstood as representing recent transmissions of HIV related to the use of human-derived clotting factor concentrates. This report was issued by the Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Coordinating Center for Infectious Diseases. The report is dated 2007 and was issued in 2009. Via email communication in August 2010 with the Chief, HIV Incidence and Case Surveillance Branch, transmission information reported in Table 20 shows seven cases were reported to CDC in 2007, but these cases were diagnosed before 2007. In fact, these seven cases were diagnosed from June 1985 through January 1990. This important background information is not included in the surveillance report dated 2007. The seven cases of non-AIDS HIV infection included diagnosis among children whose only known risk factor for HIV was receipt of clotting factor concentrates for treatment of hemophilia. Thus, they were reported to CDC seventeen to twenty-two years after they were diagnosed, and they were no longer children. Their dates of infection (exposure to clotting factor) would have been several years earlier than when they were diagnosed. The Chief also described those seven cases were presumed to have been acquired through receipt of human-derived clotting factor concentrates because it was the only known risk factor. The CDC did not investigate those cases to confirm the presumption. The algorithm used for calculating the risk factor classification has changed with the introduction of eHARS (the Enhanced HIV/AIDS Reporting System) so that if such cases were reported to CDC now, they would no longer presume they were due to clotting factor concentrates, and would instead classify them as having no identified risk factor. Thus, CDC “agrees that it is highly unlikely that clotting factor received after 1990 would be a source of HIV infection.”

Lastly, HCT/P donors are screened for HIV-1, HBV and HCV using a battery of antigen, antibody, and nucleic acid technology assays, evaluation of the donor’s blood sample for the potential for plasma dilution occurs, and each screening test is performed on a single donor specimen; donor serum or plasma samples are not pooled for testing.

Personnel in the Office of Biostatistics and Epidemiology (OBE) within FDA's Center for Biologics Evaluation and Research (CBER) are well-informed regarding donor screening test kit capabilities and donor screening steps taken to reduce risk of communicable disease.

***Recommendation:*** Using appropriate channels, FDA could consult with experts at CDC and OBE to establish risk in the modern era in regard to receipt of human-derived clotting factor concentrates when screening deceased donors of HCT/Ps. This evaluation report should be made publicly available.

Our comments submitted via this document further expand upon the concept that "human-derived clotting factor concentrates" intended by FDA to be included as an increased risk factor actually have an outstanding safety record regarding viral transmission that spans the last twenty (20) years. Thus, receipt of "human-derived clotting factor concentrates" that fall into this category should not be considered at all when assessing increased risk for communicable disease.

***Recommendation:*** FDA should formally recognize risk identified in the distant past has not been relevant for twenty (20) years and it does not apply today. This risk criterion should be adjusted accordingly by removing it.

#### **IV. CONCLUSION**

The AATB thanks officials at FDA for the opportunity to comment on these aspects of this Final Guidance. As was described at the outset, the AATB has a long and valued history of working with government entities to develop appropriate oversight and guidelines in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit. The AATB stands ready to assist the FDA in any way you deem appropriate.

Respectfully submitted,

Frank S. Wilton  
Chief Executive Officer

References:

- [1] Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. *Public Health Rep* 2013;128:247-343.
- [2] Guidance for Industry: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components, dated October 2006, references acceptability of AABB's aDHQ and DHQ, as well as respective flowcharts and any updates (see footnotes and link at Key Resources).
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