ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD (ADVISORY BOARD) MEETING

Date: Friday, June 8, 2012
Time: 1:30 p.m. – 4:30 p.m.
Location: TELECONFERENCE CALL ONLY
Dial In Number: 1(888)808-6959
Conference Code: 8509227761
** This meeting is open to the public.*
*** This meeting is being recorded.*

AGENDA

I. Call to Order/Roll
II. Opening Comments
III. Approval of Minutes from the December 16, 2011 Meeting
IV. Old Business
  a. Adverse Reactions
    i. Review of activity at December 16th meeting
    ii. Discussion
    iii. Develop Advisory Board's recommended language
  b. Medical Director Qualifications
    i. Review of activity at December 16th meeting
    ii. Report from Dr. Temple
    iii. Discussion
    iv. Develop Advisory Board's recommended language
V. New Business
  a. Plasma Dilution Criteria
  b. HIV and Other Communicable Disease Testing Methodologies
VI. Planning for Future Meetings and Calendar
VII. Announcements and Public Comment
  *Public comment will be included if time permits.
VIII. Adjournment

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD

JUNE 8, 2012 MEETING

MATERIALS FOR AGENDA ITEM III: DECEMBER 16, 2011 MEETING MINUTES

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD (ADVISORY BOARD) MEETING MINUTES - DRAFT

Date: **Friday, December 16, 2011**
Time: **1:00 p.m. – 4:00 p.m.**
Location: **TELECONFERENCE CALL ONLY**
Dial In Number: 1(888)808-6959
Conference Code: 8509227761

Advisory Board Members present: (alphabetically arranged)

Beth Fetter
Susan S. Ganz, M.D.
Caroline A. Hartill
Joseph A. Hegleh, M.D., F.A.C.S. – Chair
Lesley Lang
David M. Levi, M.D., F.A.C.S.
Vijay Reddy, M.D., Ph.D.
H. Thomas Temple, M.D.
Jason K. Woody, C.E.B.T.

Advisory Board Members absent: (alphabetically arranged)

Michael Angelis, M.D., F.A.C.S. – Vice Chair
Janice B. McCall, M.D., F.C.A.P.
Stephen J. Nelson, M.D., F.C.A.P.
Pamela M. Schuler, M.D.

Agency for Health Care Administration (Agency) Staff present (alphabetically arranged):

Jamie Jackson
Bill McCort
Dayle D. Mooney
Karen Rivera

Note: This meeting was open to and attended by members of the public.

AGENDA

I. Call to Order
- The meeting was called to order by the Chair at 1:05 p.m..
- A quorum was established.

II. Opening Comments
- The Chair welcomed the Advisory Board members and members of the public.
- Members of the public were asked to withhold comments until the end of the meeting.
- Advisory Board members were asked to limit comments to 2-5 minutes with allowances for response.

III. Old Business
- Section 4(c), First Bullet, page 3 of 12, Petition to Initiate Rulemaking regarding organ donation by a potential donor whose blood tests positive for hepatitis or HIV
  - Prior to this meeting, Advisory Board members were provided with a method of accessing the "Draft 2011 Public Health Service (PHS) Guideline for Reducing the Transmission of HIV, HBV, and HCV through Solid Organ Transplantation". Additionally, the Department of Health, Bureau of HIV/AIDS provided the Advisory Board with a copy of draft language for Section

64D-2.005, Florida Administrative Code and its incorporated document entitled "The Model Protocol for Counseling Blood, Tissue or Organ Donors" for review and comment.

- Robbie Bouplon, Senior Human Services Program Specialist and Sherry Riley, Program Administrator from the Florida Department of Health, Bureau of HIV/AIDS, Operations and Management Section were present to report on recent activities regarding Section 64D-2.005, Florida Administrative Code. Ms. Bouplon advised that the Bureau of HIV/AIDS has reviewed this section of rule and is considering revisions as indicated in draft language provided. They are seeking comment and recommendations from the Advisory Board before proceeding with rule promulgation activities.
- There was significant member discussion regarding both the Draft PHS Guideline and the draft language for 64D-2.005, F.A.C..
- Dr. Hegleh, Dr. Ganz, Beth Fetter, Jason Woody, Carrie Hartill, and Dr. Levi represented areas of concern with the Draft PHS Guideline such as:
    - The additional testing requirements proposed commonly cannot be performed in a timely manner. This lack of access may result in a "loss" of transplantable organs.
    - Proposed Guideline appears to disallow transplants in patients who have false positive initial test results.
    - Extensive donor history screening would significantly enlarge the "high risk donor pool" i.e. a potential donor who has had two or more sexual partners within the previous 12 months would be considered a high risk donor. High risk donors must be reported to potential recipients as such. Advisory Board members expressed the belief that this designation without supporting clinical indications may result in patients inappropriately refusing a potential organ for transplant.
    - More than 50% of the original workgroup assigned to collaborate on the document abjured the process before completion citing a lack of evidence based medicine. Public comment indicates strong opposition from the scientific and medical community.
- Ms. Fetter, Dr. Ganz and Dr. Levi represented areas of concern with draft language for Section 64D-2.005, Florida Administrative Code which continues to require organs donated by Hepatitis positive individuals to be discarded. Current OPO practice, notwithstanding Florida's regulatory restrictions, is to transplant organs procured from patients with certain types of viral Hepatitis based on established clinical considerations. Dr. Hegleh expressed concern with a complete removal of "Hepatitis" from the proposed language as other body substances i.e. blood, plasma, semen would be impacted.
- MOTION made to recommend that DOH Bureau of HIV/AIDS strike the word Hepatitis from the draft document, seconded, and passed without objection.

- Section 4(a), page 2 of 12, Petition to Initiate Rulemaking related to the definition of adverse reaction
    - In response to specific request made at the September 23, 2011 meeting, Dayle Mooney reported that the terms "adverse reaction" and "adverse incident" are not defined elsewhere in Florida Statute or Florida Administrative Code. Research indicated that subsection 395.0197(5), Florida Statute's definition of "adverse incident" is the most approximate terminology.
    - There was discussion among the members regarding mechanisms and procedure for reporting adverse events and adverse reactions. Ms. Hartill noted that the FDA allowed tissue banks up to 15 days from receiving notification to determine if a reported event is allograft related. Current Florida regulation requires the Agency to be notified immediately of a potential adverse reaction and follow-up reporting once a final outcome is made. Mr. Woody, Dr. Reddy and Ms. Hartill confirmed that issues such as primary graft failures are not reported as adverse reactions.
    - There was discussion about the possibility of eliminating duplicative reporting requirements. Ms. Mooney indicated that the Agency has a statutory responsibility to monitor certified programs for program compliance and a confirmed adverse reaction is a possible indicator for deficient practice.

- When asked by Ms. Fetter, Ms. Mooney indicated that the Agency reviews and monitors received reports of adverse reactions to 1.) ensure compliance with reporting requirements, 2.) conduct epidemiological surveillance, 3.) evaluate certified programs' quality assurance procedures, and 4.) verify indicated allografts were eliminated as a causal agent.
- Ms. Mooney informed the Advisory Board that the only identifiable trend in adverse reactions has been inconsistent reporting. When asked by Dr. Levi, Ms. Mooney informed the Advisory Board that there is not a suggested listing of reportable events.
- There was extensive discussion on various occurrences that are federally reportable, occurrences that should be considered as meeting Florida reporting requirement, and possible mechanisms for complying with the statutory requirement to monitor Florida facilities for program compliance without exceeding federal reporting guidelines.
- Ms. Mooney advised that while no formal position has been taken at this time, the Agency's goal in any changes proposed for Chapter 765, Part V, Florida Statutes or any made to Chapter 59A-1, Florida Administrative Code will be to act in the best interest of Florida's transplant recipients. It was further indicated that proposals may include changes that exceed current federal requirements should they be deemed necessary to meet this goal.
- MOTION made to recommend amending the definition of adverse reaction to an event where there is potential for the unanticipated transmission of communicable disease or malignancy and to require adverse reactions be reported to the Agency within 15 days of notification, seconded, and passed without objection.

- Section 4(c), page 3 of 12, Petition to Initiate Rulemaking regarding the maintenance of the original consent for donation.
  - Ms. Mooney reported on research conducted since the September 23, 2011 meeting:
    - Request for CMS guidance indicated that "legally reproduced copy" was not defined in federal regulations.
    - Agency General Counsel's research found no instance of "legally reproduced copy" being defined elsewhere in Florida Statute or Administrative Code.
    - A definition of "legally reproduced copy" was found in Texas Administrative Code and appears to exclude Xerox copy.
    - Agency staff contacted Bill Bell, General Counsel for the Florida Hospital Association to ascertain its opinion. It was communicated that hospitals generally maintain responsibility for a patient even after death and as organ and tissue procurement is routinely performed on hospital premises the original consent for donation should be maintained in the hospital's medical record. Exception was indicated in instances where consent maintenance was specifically stipulated in agreements between the hospital and designated procurement organization(s).
  - There was discussion among the Advisory Board members regarding various barriers to obtaining original consent forms for inclusion in the hospital record.
  - Advisory Board members representing organ, tissue and eye procurement organizations were unaware of any instance of a hospital resisting or objecting to maintaining a copy of the donation consent.
  - MOTION made to recommend amending sub-paragraph 59A-1.005(7)(a)4., Florida Administrative Code to require that a copy of the consent be maintained in the hospital record, seconded, passed without objection.
- Section 4(c), page 4 of 12, Petition to Initiate Rulemaking regarding incorporation of accreditation organization standards
  - Ms. Mooney reported on the findings of 2010's reported Florida tissue distribution.
  - Ms. Hartill refuted allegations, which have been represented to the Agency, that secondary tissue distributors are not eligible for accreditation and indicated that accreditation standards are applied based on services performed. She further reported that tissue processors, accredited by the American Association of Tissue Banks (AATB) have a responsibility to ensure that their tissue distribution intermediary partners employ systems meeting AATB standards.
    - Accredited tissue processors satisfy this responsibility through inspection.

- It was noted with concern, that they only inspect the next level of consignee and as there are multiple layers of distribution there may be distributors who are not visible to the processing bank or the Agency.

- Mr. Woody indicated that the Eye Bank of America's accreditation process is applied in the same manner as AATB's.
- There was discussion supporting the requirement of accreditation by the Association of Organ Procurement Organization, AATB, and EBAA for Florida certified facilities.
- Advisory Board members generally agreed that all certified facilities should be required to comply with the requirement but, specific language should be included that allowed sufficient time for currently non-accredited certified entities to obtain accreditation.
- Ms. Mooney indicated that the maximum timeframe which could be allowed would be 12 months from the effective date of the Rule.
- It was noted that separate conversations with the accepted accreditation organizations should be held to determine impact and feasibility before specifying time requirements.
- MOTION made recommending the Agency move to require accreditation by the appropriate organization for distribution within a timeframe determined by the Agency, seconded, passed without objection.

II. New Business

- Medical Director Qualifications
  - Ms. Hartill expressed concern with current Florida requirement for a Medical Director to be licensed to practice medicine and surgery.
  - Ms. Mooney explained that this item was included in the meeting agenda based on an increasing number of tissue bank applicants' Medical Directors not being in compliance with Florida's medical licensure requirements while appearing to have adequate experience or training within their fields to function in the designated capacity.
  - There was significant discussion between the Advisory Board members.
  - It was agreed that active medical licensure, not limited by a specific state requirement, be required.
  - Dr. Temple volunteered to obtain information regarding medical director qualification requirements from various governmental or accreditation bodies.
  - Item TABLED to a future meeting.

III. Planning for Future Meetings and Calendar

- Next meeting date proposed for late February or March.
- Ms. Mooney will contact Advisory Board members to schedule.

IV. Announcements and Public Comment

- Scott Brubaker with the American Association of Tissue Banks thanked Ms. Hartill for her expertise, encouraged Advisory Board members and any member of the public to submit comments to the CDC on the Draft PHS Guideline before the deadline of December 23, 2011, and he encouraged the Advisory Board to adapt terminology that will be harmonious with global definitions such as those developed by the European Union (EU) and World Health Organization (WHO).
  - When requested by Ms. Mooney, Mr. Brubaker agreed to forward a document containing the EU directives, the FDA's definition, and AATB's definitions with the understanding that AATB is currently considering updates to their language to correlate with the newest global versions.
  - Liz Lehr with Lifelink OPO reported that Florida is a "net importer" of organs and indicated that the Advisory Board's current proposal placed an unfair burden on Florida's OPOs. She stated that statistics obtained through federal reporting entities would allow global tracking and better serve Floridians and suggested that the Agency satisfy its statutory responsibility to ensure program compliance by monitoring OPOs' compliance with federal reporting requirements.
- Dan Shultz from Lifelink Tissue Bank expressed concern that requiring distributorships to obtain AATB accreditation would 1.) be onerous for AATB to handle the influx of applicants, 2.) significantly increase the cost of tissue placement, and 3.) potentially harm the industry as facilities, such as medical device manufacturers that are also involved in tissue distribution, would shift their

focus away from tissue. Mr. Schultz encouraged the Advisory Board to discuss the matters with AATB further before implementing changes.

- Mark Strong with Lifelink Tissue Bank expressed reservations regarding requiring accreditation for tissue distribution. He believes that tissue availability would be impacted, at least in the short term, for certain specialized tissue types. Mr. Strong also stated that none of the tissue banks that obtain telephonic consents for donation are actually providing copies of that consent to the hospital. He encouraged the Advisory Board to only require a copy of consent to be included in the hospital record when the procedure occurs at the hospital.
- Dr. Wayne Daniels with Cryolife thanked the Advisory Board for inclusion in the meeting and encouraged consideration of AATBs comments regarding the Draft PHS Guideline.

V. Other Action

- Point of Order: Approval of Minutes from the September 23, 2011 Meeting
- MOTION made to approve minutes as written, seconded, passed without objection.

VI. Adjournment

Minutes submitted by: Dayle D. Mooney

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD

JUNE 8, 2012 MEETING

MATERIALS FOR AGENDA ITEM IV, a. ~ ADVERSE REACTIONS

Relevant Definitions

EU for cells and tissues (Directive 2004/23/EC)

Serious adverse event
any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity

Serious adverse reaction
an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity

---

US FDA for HCT/Ps (GTP Final Rule)

1271.3 (y) *Adverse reaction* means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.

AATB's *Standards for Tissue Banking* 12th edition 2008

A2.000 Definitions of Terms
ADVERSE OUTCOME—An undesirable effect or untoward complication in a recipient consequent to or reasonably related to tissue transplantation.

SAB Note: Discussion with AATB membership will occur during early 2012 regarding adoption of new terminology being considered for use on a global scale as this would enhance the ability to collect and trend useful data that could lead to process improvements. See the EUSTITE Project's definitions; these are essentially the same as published in Directive 2004/23/EC, and refer to WHO's Guiding Principle #10.
EUSTITE documents can be found at this link:
http://www.iss.it/ecet/aler/cont.php?id=771&lang=3&tipo=117
Directive 2004/23/EC is here:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004L0023:EN:HTML

WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation

Sixty-third World Health Assembly Resolution WHA63.22
May 2010
(relevant part only – also see attachment)

Guiding Principle 10
High-quality, safe and efficacious procedures are essential for donors and recipients alike. The longterm outcomes of cell, tissue and organ donation and transplantation should be assessed for the living donor as well as the recipient in order to document benefit and harm. The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported, both nationally and for exported human products.

Commentary on Guiding Principle 10
Optimizing the outcome of cell, tissue and organ transplantation entails a rules-based process that encompasses clinical interventions and ex vivo procedures from donor selection through long-term follow-up. Under the oversight of national health authorities, transplant programmes should monitor both donors and recipients to ensure that they receive appropriate care, including information regarding the transplantation team responsible for their care. Evaluation of information regarding the long-term risks and benefits is essential to the consent process and for adequately balancing the interests of donors as well as recipients. The benefits to both must outweigh the risks associated with the donation and transplantation. Donors should not be permitted to donate in clinically hopeless situations. Donation and transplant programmes are encouraged to participate in national and/or international transplant registries. All deviations from accepted processes that could elevate the risk to recipients or donors, as well as any untoward consequences of donation or transplantation, should be reported to and analysed by responsible health authorities. Transplantation of human material which does not involve maintenance treatment may not require active, long-term follow-up, though traceability should be ensured for the anticipated lifetime of the donor and the recipient. Internationally agreed means of coding to identify tissues and cells used in transplantation are essential for full traceability.

The United States is a Member of the WHO.

Cell Tissue Bank
DOI 10.1007/s10561-010-9226-0

World Health Organization

WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation

Sixty-Third World Health Assembly

Received: 5 July 2010 / Accepted: 5 July 2010

Abstract In May 2010, the Sixty-third World Health Assembly Resolution WHA63.22 endorsed the WHO Guiding Principles, updated in the light of changes in practices and attitudes regarding organ and tissue transplantation. The Guiding Principles are intended to provide an orderly, ethical and acceptable framework for the procurement and transplantation of human cells, tissues and organs for therapeutic purposes. Each jurisdiction will determine the means of implementing these WHO Guiding Principles. They preserve the essential points of the 1991 version while incorporating new provisions in response to current trends in transplantation, particularly the protection of the living donor, and the increasing use of human cells and tissues. The Guiding Principles stress the necessity of documentation and transparency, both for quality management purposes and to justify the confidence of patients, clinicians and the community at large in donation and transplantation services.

Keywords Living donors · Deceased donors · Live donations · Donation from deceased persons · Explicit consent · Presumed consent · Opting in · Opting out · Altruistic donation · Prohibition of commercialization · Allocation criteria · Follow-up · Quality systems · Traceability

As endorsed by the sixty-third World Health Assembly in May 2010, in Resolution WHA63.22.

Address correspondence to: Luc Noel, M.D., World Health Organization. E-mail: noell@who.int

Preamble

1. As the Director-General's report to the Executive Board at its Seventy-ninth session pointed out, human organ transplantation began with a series of experimental studies at the beginning of the twentieth century. The report drew attention to some of the major clinical and scientific advances in the field since Alexis Carrel was awarded the Nobel Prize in 1912 for his pioneering work. Surgical transplantation of human organs from deceased, as well as living, donors to sick and dying patients began after the Second World War. Over the past 50 years, the transplantation of human organs, tissues and cells has become a worldwide practice which has extended, and greatly enhanced the quality of, hundreds of thousands of lives. Continuous improvements in medical technology, particularly in relation to organ and tissue rejection, have led to an increase in the demand for organs and tissues, which has always exceeded supply despite substantial expansion in deceased organ donation as well as greater reliance on donation from living persons in recent years.

Published online: 04 December 2010

2. The shortage of available organs has not only prompted many countries to develop procedures and systems to increase supply but has also stimulated commercial traffic in human organs, particularly from living donors who are unrelated to recipients. The evidence of such commerce, along with the related traffic in human beings, has become clearer in recent decades. Moreover, the growing ease of international communication and travel has led many patients to travel abroad to medical centres that advertise their ability to perform transplants and to supply donor organs for a single, inclusive charge.
3. Resolutions WHA40.13 and WHA42.5 first expressed the Health Assembly's concern over commercial trade in organs and the need for global standards for transplantation. Based on a process of consultation undertaken by the Secretariat, the Health Assembly then endorsed the WHO Guiding Principles on Human Organ Transplantation in resolution WHA44.25. Over the past 17 years the Guiding Principles have greatly influenced professional codes and practices as well as legislation around the world. In the light of changes in practices and attitudes regarding organ and tissue transplantation, the Fifty-seventh World Health Assembly in resolution WHA57.18 requested the Director-General, inter alia, "to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogeneic transplantation and on ethical issues, including living donation, in order to update the Guiding Principles on Human Organ Transplantation".
4. The following Guiding Principles are intended to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes. Each jurisdiction will determine the means of implementing the Guiding Principles. They preserve the essential points of the 1991 version while incorporating new provisions in response to current trends in transplantation, particularly organ transplants from living donors and the increasing use of human cells and tissues. The Guiding Principles do not apply to transplantation of gametes, ovarian or testicular tissue, or embryos for reproductive purposes, or to blood or blood constituents collected for transfusion purposes.

Cells, tissues and organs may be removed from deceased and living persons for the purpose of transplantation, only in accordance with the following Guiding Principles.

Guiding Principle 1

Cells, tissues and organs may be removed from the bodies of deceased persons for the purpose of transplantation if:

(a) any consent required by law is obtained, and
(b) there is no reason to believe that the deceased person objected to such removal.

Commentary on Guiding Principle 1

Consent is the ethical cornerstone of all medical interventions. National authorities are responsible for defining the process of obtaining and recording consent for cell, tissue and organ donation in the light of international ethical standards, the manner in which organ procurement is organized in their country, and the practical role of consent as a safeguard against abuses and safety breaches.

Whether consent to procure organs and tissues from deceased persons is "explicit" or "presumed" depends upon each country's social, medical and cultural traditions, including the manner in which families are involved in decision-making about health care generally. Under both systems any valid indication of deceased persons' opposition to posthumous removal of their cells, tissues or organs will prevent such removal.

Under a regime of explicit consent – sometimes referred to as "opting in" – cells, tissues or organs may be removed from a deceased person if the person had expressly consented to such removal during his or her lifetime; depending upon domestic law, such consent may be made orally or recorded on a donor card, driver's license or identity card or in the medical record or a donor registry. When the deceased has neither consented nor clearly expressed opposition to organ removal, permission should be obtained from a legally specified surrogate, usually a family member.

The alternative, presumed consent system – termed "opting (or contracting) out" – permits material to be removed from the body of a deceased

person for transplantation and, in some countries, for anatomical study or research, unless the person had expressed his or her opposition before death by filing an objection with an identified office, or an informed party reports that the deceased definitely voiced an objection to donation. Given the ethical importance of consent, such a system should ensure that people are fully informed about the policy and are provided with an easy means to opt out.

Although expressed consent is not required in an opting-out system before removal of the cells, tissues or organs of a deceased person who had not objected while still alive, procurement programmes may be reluctant to proceed if the relatives personally oppose the donation; likewise, in opting-in systems, programmes typically seek permission from the family even when the deceased gave pre-mortem consent. Programmes are more able to rely on the deceased's explicit or presumed consent, without seeking further permission from family members, when the public's understanding and acceptance of the process of donating cells, tissues and organs is deep-seated and unambiguous. Even when permission is not sought from relatives, donor programmes need to review the deceased's medical and behavioural history with family members who knew him or her well, since accurate information about donors helps to increase the safety of transplantation.

For tissue donation, which entails slightly less challenging time constraints, it is recommended always to seek the approval of the next of kin. An important point to be addressed is the manner in which the appearance of the deceased's body will be restored after the tissues are removed.

Guiding Principle 2

Physicians determining that a potential donor has died should not be directly involved in cell, tissue or organ removal from the donor or subsequent transplantation procedures; nor should they be responsible for the care of any intended recipient of such cells, tissues and organs.

Commentary on Guiding Principle 2

This Principle is designed to avoid the conflict of interest that would arise were the physician or physicians determining the death of a potential donor to be responsible in addition for the care of other patients whose welfare depended on cells, tissues or organs transplanted from that donor.

National authorities will set out the legal standards for determining that death has occurred and specify how the criteria and process for determining death will be formulated and applied.

Guiding Principle 3

Donation from deceased persons should be developed to its maximum therapeutic potential, but adult living persons may donate organs as permitted by domestic regulations. In general living donors should be genetically, legally or emotionally related to their recipients.

Live donations are acceptable when the donor's informed and voluntary consent is obtained, when professional care of donors is ensured and follow-up is well organized, and when selection criteria for donors are scrupulously applied and monitored. Live donors should be informed of the probable risks, benefits and consequences of donation in a complete and understandable fashion; they should be legally competent and capable of weighing the information; and they should be acting willingly, free of any undue influence or coercion.

Commentary on Guiding Principle 3

The Principle emphasizes the importance both of taking the legal and logistical steps needed to develop deceased donor programmes where these do not exist and of making existing programmes as effective and efficient as possible.

While favouring the maximal development of transplant programmes that avoid the inherent risks to live donors, the Principle also sets forth basic conditions for live donation. A genetic relationship between donor and recipient may be therapeutically advantageous and can provide reassurance that the donor is motivated by genuine concern for the recipient, as can a legal relationship (such as that between spouses). Many altruistic donations also originate from emotionally related donors, though the strength of a claimed connection may be difficult to evaluate. Donations by unrelated donors have been a

source of concern, though some such cases are unexceptionable, such as in hematopoietic stem cell transplantation (where a wide donor pool is therapeutically advisable) or when an exchange of kidneys is made because the donors are not immunologically well matched with the recipients to whom they are related.

With live donation, particularly by unrelated donors, psychosocial evaluation is needed to guard against coercion of the donor or the commercialism banned by Principle 5. The national health authority should ensure that the evaluation is carried out by an appropriately qualified, independent party. By assessing the donor's motivation and the donor's and recipient's expectations regarding outcomes, such evaluations may help identify – and avert – donations that are forced or are actually paid transactions.

The Principle underscores the necessity of genuine and well-informed choice, which requires full, objective, and locally relevant information and excludes vulnerable persons who are incapable of fulfilling the requirements for voluntary and knowledgeable consent. Voluntary consent also implies that adequate provisions exist for withdrawal of consent up until medical interventions on the recipient have reached the point where the recipient would be in acute danger if the transplant did not proceed. This should be communicated at the time of consent.

Finally, this Principle stresses the importance of protecting the health of living donors during the process of selection, donation, and necessary aftercare to ensure that the potential untoward consequences of the donation are unlikely to disadvantage the remainder of the donor's life. Care for the donor should match care for the recipient, and health authorities have the same responsibility for the welfare of both.

Guiding Principle 4

No cells, tissues or organs should be removed from the body of a living minor for the purpose of transplantation other than narrow exceptions allowed under national law. Specific measures should be in place to protect the minor and, wherever possible the minor's assent should be obtained before donation. What is applicable to minors also applies to any legally incompetent person.

Commentary on Guiding Principle 4

This Principle states a general prohibition on the removal of cells, tissues or organs from legal minors for transplantation. The major exceptions that may be authorized are familial donation of regenerative cells (when a therapeutically comparable adult donor is not available) and kidney transplants between identical twins (where avoiding immunosuppression represents a benefit to the recipient adequate to justify the exception, in the absence of a genetic disorder that could adversely affect the donor in the future).

While the permission of the parent(s) or the legal guardian for organ removal is usually sufficient, they may have a conflict of interest if they are responsible for the welfare of the intended recipient. In such cases, review and approval by an independent body, such as a court or other competent authority, should be required. In any event, a minor's objection to making a donation should prevail over the permission provided by any other party. The professional counselling provided to potential living donors in order to assess, and when needed, address any pressure in the decision to donate, is especially important for minor donors.

Guiding Principle 5

Cells, tissues and organs should only be donated freely, without any monetary payment or other reward of monetary value. Purchasing, or offering to purchase, cells, tissues or organs for transplantation, or their sale by living persons or by the next of kin for deceased persons, should be banned.

The prohibition on sale or purchase of cells, tissues and organs does not preclude reimbursing reasonable and verifiable expenses incurred by the donor, including loss of income, or paying the costs of recovering, processing, preserving and supplying human cells, tissues or organs for transplantation.

Commentary on Guiding Principle 5

Payment for cells, tissues and organs is likely to take unfair advantage of the poorest and most vulnerable groups, undermines altruistic donation, and leads to profiteering and human trafficking. Such payment

conveys the idea that some persons lack dignity, that they are mere objects to be used by others.

Besides preventing trafficking in human materials, this Principle aims to affirm the special merit of donating human materials to save and enhance life. However, it allows for circumstances where it is customary to provide donors with tokens of gratitude that cannot be assigned a value in monetary terms. National law should ensure that any gifts or rewards are not, in fact, disguised forms of payment for donated cells, tissues or organs. Incentives in the form of "rewards" with monetary value that can be transferred to third parties are not different from monetary payments.

While the worst abuses involve living organ donors, dangers also arise when payments for cells, tissues and organs are made to next of kin of deceased persons, to vendors or brokers, or to institutions (such as mortuaries) having charge of dead bodies. Financial returns to such parties should be forbidden.

This Principle permits compensation for the costs of making donations (including medical expenses and lost earnings for live donors), lest they operate as a disincentive to donation. The need to cover legitimate costs of procurement and of ensuring the safety, quality and efficacy of human cell and tissue products and organs for transplantation is also accepted as long as the human body and its parts as such are not a source of financial gain.

Incentives that encompass essential items which donors would otherwise be unable to afford, such as medical care or health insurance coverage, raise concerns. Access to the highest attainable standard of health is a fundamental right, not something to be purchased in exchange for body parts. However, free periodic medical assessments related to the donation and insurance for death or complications that arise from the donation may legitimately be provided to living donors.

Health authorities should promote donation motivated by the need of the recipient and the benefit for the community. Any measures to encourage donation should respect the dignity of the donor and foster societal recognition of the altruistic nature of cell, tissue and organ donation. In any event, all practices to encourage the procurement of cells, tissues and organs for transplantation should be defined explicitly by health authorities in a transparent fashion.

National legal frameworks should address each country's particular circumstances because the risks to donors and recipients vary. Each jurisdiction will determine the details and method of the prohibitions it will use, including sanctions which may encompass joint action with other countries in the region. The ban on paying for cells, tissues and organs should apply to all individuals, including transplant recipients who attempt to circumvent domestic regulations by travelling to locales where prohibitions on commercialization are not enforced.

Guiding Principle 6

Promotion of altruistic donation of human cells, tissues or organs by means of advertisement or public appeal may be undertaken in accordance with domestic regulation.

Advertising the need for or availability of cells, tissues or organs, with a view to offering or seeking payment to individuals for their cells, tissues or organs, or, to the next of kin, where the individual is deceased, should be prohibited. Brokering that involves payment to such individuals or to third parties should also be prohibited.

Commentary on Guiding Principle 6

This Principle does not affect general advertisements or public appeals to encourage altruistic donation of human cells, tissues or organs, provided that they do not subvert legally established systems of organ allocation. Instead, it aims to prohibit commercial solicitations, which include offering to pay individuals, the next of kin of deceased persons, or other parties in possession (such as undertakers), for cells, tissues or organs; it targets brokers and other intermediaries as well as direct purchasers.

Guiding Principle 7

Physicians and other health professionals should not engage in transplantation procedures, and health insurers and other payers should not cover such procedures, if the cells, tissues or organs concerned have been obtained through exploitation or coercion

of, or payment to, the donor or the next of kin of a deceased donor.

Commentary on Guiding Principle 7

Health care professionals should only proceed with the removal, intermediate management or implantation of cells, tissues or organs when donations are unpaid and truly voluntary. (In the case of live donors, a psychosocial evaluation of the donor is usually indicated, as described in Guiding Principle 3). Failing to ensure that the person consenting to the donation has not been paid, coerced or exploited breaches professional obligations and should be sanctioned by the relevant professional organizations and government licensing or regulatory authorities.

Physicians and health care facilities should also not refer patients to transplant facilities in their own or other countries that make use of cells, tissues or organs obtained through payments to donors, their families or other vendors or brokers; nor may they seek or accept payment for doing so. Post-transplant care may be provided to patients who have undergone transplantation at such facilities, but physicians who decline to provide such care should not face professional sanctions for such refusals, provided that they refer such patients elsewhere.

Health insurers and other payers should reinforce adherence to high ethical standards by refusing to pay for transplants that violate the Guiding Principles.

Guiding Principle 8

All health care facilities and professionals involved in cell, tissue or organ procurement and transplantation procedures should be prohibited from receiving any payment that exceeds the justifiable fee for the services rendered.

Commentary on Guiding Principle 8

This provision reinforces Guiding Principles 5 and 7 by forbidding profiteering in cell, tissue and organ recovery and implantation. Health authorities should monitor the fees charged for transplantation services to ensure that they are not disguised charges for the cells, tissues or organs themselves. All persons and facilities involved should be accountable for all payments for transplantation services. A medical or other health care practitioner uncertain whether a fee is justifiable should seek the opinion of an appropriate licensing or disciplinary authority before proposing or levying the fee. Fees charged for similar services may be used as a reference.

Guiding Principle 9

The allocation of organs, cells and tissues should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, and transparent.

Commentary on Guiding Principle 9

Where donation rates do not meet clinical demand, allocation criteria should be defined at national or subregional level by a committee that includes experts in the relevant medical specialties, bioethics and public health. Such multidisciplinarity is important to ensure that allocation takes into account not only medical factors but also community values and general ethical rules. The criteria for distributing cells, tissues and organs should accord with human rights and, in particular, should not be based on a recipient's gender, race, religion, or economic condition.

This principle implies that the cost of transplantation and follow-up, including immunosuppressive treatment where applicable, should be affordable to all patients concerned – that is, no recipient should be excluded solely for financial reasons.

The concept of transparency is not exclusive to the allocation process but is central to all aspects of transplantation (as is discussed in the commentary on Guiding Principle 11, below).

Guiding Principle 10

High-quality, safe and efficacious procedures are essential for donors and recipients alike. The long-term outcomes of cell, tissue and organ donation and transplantation should be assessed for the living donor as well as the recipient in order to document benefit and harm.

The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported, both nationally and for exported human products.

Commentary on Guiding Principle 10

Optimizing the outcome of cell, tissue and organ transplantation entails a rules-based process that encompasses clinical interventions and ex vivo procedures from donor selection through long-term follow-up. Under the oversight of national health authorities, transplant programmes should monitor both donors and recipients to ensure that they receive appropriate care, including information regarding the transplantation team responsible for their care.

Evaluation of information regarding the long-term risks and benefits is essential to the consent process and for adequately balancing the interests of donors as well as recipients. The benefits to both must outweigh the risks associated with the donation and transplantation. Donors should not be permitted to donate in clinically hopeless situations.

Donation and transplant programmes are encouraged to participate in national and/or international transplant registries. All deviations from accepted processes that could elevate the risk to recipients or donors, as well as any untoward consequences of donation or transplantation, should be reported to and analysed by responsible health authorities.

Transplantation of human material which does not involve maintenance treatment may not require active, long-term follow-up, though traceability should be ensured for the anticipated lifetime of the donor and the recipient. Internationally agreed means of coding to identify tissues and cells used in transplantation are essential for full traceability.

Guiding Principle 11

The organization and execution of donation and transplantation activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients are always protected.

Commentary on Guiding Principle 11

Transparency can be summarized as maintaining public access to regularly updated comprehensive data on processes, in particular allocation, transplant activities and outcomes for both recipients and living donors, as well as data on organization, budgets and funding. Such transparency is not inconsistent with shielding from public access information that could identify individual donors or recipients while still respecting the necessity of traceability recognized in Principle 10. The objective of the system should be not only to maximize the availability of data for scholarly study and governmental oversight but also to identify risks – and facilitate their correction – in order to minimize harm to donors or recipients.

Acknowledgments Document WHA63/2010/REC/1, Annex 8. The World Health Organization has granted the Publisher permission for the reproduction of this article; previously published in Transplantation 90(3): 229-233, 2010.

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: ADVERSE REACTIONS

DEFINITION

Version 1

"Adverse Reaction" means an event where there is potential for the unanticipated transmission of communicable disease or malignancy.

Version 2

"Adverse Reaction" means an unintended recipient response, including communicable disease, that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity and is consequent to or for which there is a reasonable possibility of being related to procurement activities.

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: ADVERSE REACTIONS

POLICIES/PROCEDURES

Each OPO, Tissue Bank, or Eye Bank engaged in the distribution of organs, eyes, or tissues within Florida shall establish and maintain written policies and procedures for adverse reactions. Such policies and procedures must include:

_____

_____

_____

_____

_____

_____

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: ADVERSE REACTIONS

Each OPO, Eye Bank or Tissue Bank engaged in distribution within or to Florida shall ensure that physicians and hospital personnel involved in the transplantation of organs, tissues, or eyes are provided a copy of and educated to the policies and procedures regarding the reporting of adverse reactions to the distributing OPO, Eye Bank or Tissue Bank.

In accordance with subsection 59A-1.005(14), F.A.C. each distributing OPO, Eye Bank or Tissue Bank shall, upon notification of an adverse reaction:

- Immediately suspend distribution of organs, tissue or eyes coming from that donor;

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: ADVERSE REACTIONS

- Notify the medical examiner if the adverse reaction involved donation from a medical examiner's case;
- Initiate an investigation to determine whether or not the adverse reaction has a reasonable possibility of being related to procurement activities;
- Coordinate investigation with necessary procurement organizations involved in the recovery, processing, and storage of involved organ, eye, or tissue, if other than the distributing OPO, Eye Bank or Tissue Bank; and
- Submit to the Agency for Health Care Administration, Division of Health Quality Assurance, within fifteen calendar days, Part I of the AHCA's Organ and Tissue Adverse Reaction Reporting Form, AHCA Form 3140-

2003-OCT 95. This entire form is incorporated herein by reference and available from the Agency for Health Care Administration, Laboratory Unit, 2727 Mahan Drive, Mailstop 32, Tallahassee, Florida 32308.

Where it is determined that the adverse reaction has a reasonable possibility of being related to procurement activities, each distributing OPO, Eye Bank, or Tissue Bank shall institute recall procedures in accordance with subsection 59A-1.005(14), F.A.C., and, when necessary, look back procedures in accordance subsection 59A-1.005(15) F.A.C.

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: ADVERSE REACTIONS

Once a final determination of the cause of an adverse reaction is made, the distributing OPO, Eye Bank, or Tissue Bank shall submit within 15 calendar days of the determination, Part II of AHCA's Organ and Tissue Adverse Reaction Reporting Form, AHCA Form 3140-2003-OCT 95, to Agency for Health Care Administration, Laboratory Unit, 2727 Mahan Drive, Mailstop 32, Tallahassee, Florida 32308.

Agency for Health Care Administration
Laboratory Unit
2727 Mahan Drive, Mail Stop 32
Tallahassee, FL 32308
Phone #: (850) 414-0359 Fax #: (850) 410-1511

Adverse Reaction Report Form *

*Adverse reactions are to be reported to AHCA immediately. Part I of the form is to be submitted to AHCA within 2 days of the event. Part II is to be submitted when the final determination of cause has been determined. When the adverse reaction is due to donor organs or tissues, recall procedures shall be instituted in accordance with Ch. 59A-1.005(15), F.A.C., and look back procedures in accordance with Ch. 59A-1.005(16), F.A.C.

Part I

Report ID #:_____

I. Procurement Agency Information

Processing Agency Name: _____

AHCA Certification/License #: _____ Telephone #: _____

Street Address: _____

_____

Procurement agency:

Mailing Address, if different: _____

II. Notification

Date Processing Agency Notified: _____

Notifying Official: _____

Notifying Institution: _____

Institution Street Address: _____

Telephone #: _____

III. Nature of Adverse Reaction:

☐ Bacterial Infection (Specify Type): _____

☐ Transmission of Viral Disease (Specify Type): _____

☐ Other (Describe): _____

IV. Organ/Tissue/Identification and Recovery

Type of Organ/Tissue: _____ Organ/Tissue ID #: _____

Procurement Date: _____ Procurement Time: _____

Preservation Method: _____ Lot #: _____

Transportation Method: _____ Depart Time: _____ Arrive Time: _____

Preservation Days: _____ Surgery Interval Days: _____

Donor ID #: _____ Donor Age: _____ Donor Sex: _____

Donor Cause of Death: _____

Were Screening Criteria Met? ☐ yes ☐ no

Other organs/Tissues Recovered: _____

V. Recipient Information

Patient Name: _____

Social Security #: _____ Medical Record #: _____

VI. Transplanting Surgeon Information

Name of Surgeon: _____

Address: _____

Telephone #: _____ Transplantation Date: _____

VI. Transplanting Surgeon Information (continued):

Description of Adverse Reaction: _____

Other Significant Information: _____

VII. Quality Management Action Plan

A. Notification (Include dates of all persons and agencies notified.)

Medical Dir: _____

AHCA _____

FDA _____

Accrediting Body (Specify which one): _____

Others: _____

B. Initial Findings (List all actions taken and the results):

_____

C. Future Actions (List plan of future investigation, if necessary.):

_____

VIII. Person Filing Report

Name (Print): _____ Signature: _____

Title: _____ Date: _____

Agency for Health Care Administration
Hospital and Outpatient Services Unit
2727 Mahan Drive, Mail Stop 31
Tallahassee, FL 32308
Phone #: (850) 487-2717 Fax #: (850) 922-4351

Adverse Reaction Report Form *

*Adverse reactions are to be reported to AHCA immediately. Part I of the form is to be submitted to AHCA within 2 days of the event. Part II is to be submitted when the final determination of cause has been determined. When the adverse reaction is due to donor organs or tissues, recall procedures shall be instituted in accordance with Ch. 59A-1.005(15), F.A.C., and look back procedures in accordance with Ch. 59A-1.005(16), F.A.C.

Part II

Date: _____ Report ID #: _____

I. Determination of Cause:
Cause:

☐ Probably due to donor organ or tissue

☐ Probably not due to donor organ or tissue

Basis for determination of cause:

_____

II. Action Plan Completion:

Describe all actions completed in accordance with the action plan submitted in Part I:

_____

III. Person Filing Report:

Name (print): _____ Signature: _____

Date: _____

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD

JUNE 8, 2012 MEETING

MATERIALS FOR AGENDA ITEM IV., b.: MEDICAL DIRECTOR QUALIFICATIONS

MEDICAL DIRECTOR REQUIREMENTS

FLORIDA REGULATIONS

59A-1.005(1)(a)3, Florida Administrative Code states:
"3. Medical Director. Each OPO, tissue bank, and eye bank shall employ or have under contract a physician medical director, licensed to practice medicine and surgery in the state in which the agency is incorporated. In the case of Florida-based agencies, the physician must be licensed to practice medicine and surgery in Florida. The medical director shall provide direction and supervision to coordinators and all other staff who assist in the procurement of organs, tissues or eyes for transplantation. With the exception of organ procurement surgery, this may be by indirect physician supervision. The medical director or his designee shall be available at all times, in person or by telephone, to provide medical direction, consultation, and advice in cases of tissue donation and retrieval. Responsibility for technical performance must rest with the licensed physician medical director."

FEDERAL AND ACCREDITATION REQUIREMENTS

I. ORGAN PROCUREMENT ORGANIZATIONS (OPO)

- **United States Code (USC)**

  42 USC 273(b)(1)(G) states:
  "(b) Qualified Organizations
  (1) A qualified organ procurement organization for which grants may be made under subsection (a) of this section is an organization which, as determined by the Secretary, will carry out the functions described in paragraph (2) and - …
  (G) has a director and such other staff, including the organ donation coordinators and organ procurement specialists necessary to effectively obtain organs from donors in its service area, and…"

- **Code of Federal Regulations (CFR)**

  42 CFR Parts 413, 441, 486, 498 do not address medical director requirements or qualifications.

- **Organ Procurement and Transplantation Network (OPTN) Policies**

  Current OPTN Policies do not address medical director requirements or qualifications.

- **Association of Organ Procurement Organizations (AOPO)**

  AOPO accreditation standards were not available for review.

II. Eye Banks and Tissue Banks

- **United States Code (USC)**

  42 USC 216, 243, 263a, 264, and 271 do not address medical director requirements or qualifications.

- **Code of Federal Regulations (CFR)**

  21 CFR Part 1270 does not address medical director requirements or qualifications.

  21 CFR Part 1271.170 states:
  "(a) *General.* You must have personnel sufficient to ensure compliance with the requirements of this part.
  (b) *Competent performance of functions.* You must have personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions. Personnel must perform only those activities for which they are qualified and authorized.
  (c) *Training.* You must train all personnel, and retrain as necessary, to perform their assigned responsibilities adequately."

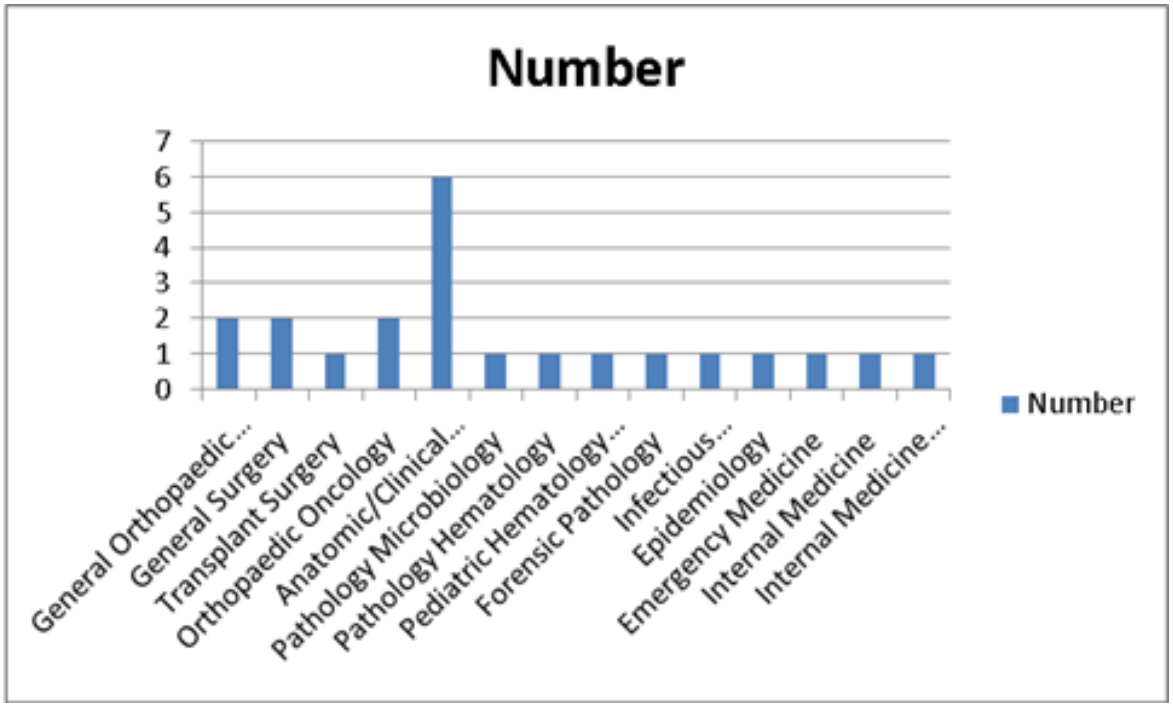
- **Eye Bank Association of America (EBAA)**

  Review of the EBAA Medical Standards (November 2010 Edition) indicate that:
  1. A Medical Director and a back-up Medical Director are required;
  2. Both must be ophthalmologists and
     - Have completed a corneal fellowship, or
     - Have demonstrated expertise within specified fields;
  3. Participation in designated, on-going education is required at regular intervals.

- **American Association of Tissue Bank (AATB)**

  Review of the AATB Standards for Tissue Banking (12th Edition) indicate that:
  1. A Medical Director is required;
  2. He/she must maintain a valid license from any state (or equivalent for international members); and
  3. He/she should have training/experience in certain areas (if not satisfied an alternative is provided)

UNITED STATES TISSUE BANK
MEDICAL DIRECTOR SPECIALTY COMPOSITION



RAW DATA

*Some Medical Directors represent more than one tissue bank.

Specialty	Number	Specialty	Number
General Orthopaedic Surgery	2	Forensic Pathology	1
General Surgery	2	Infectious Disease/Microbiology	1
Transplant Surgery	1	Epidemiology	1
Orthopaedic Oncology	2	Emergency Medicine	1
Anatomic/Clinical Pathology	6	Internal Medicine	1
Pathology Microbiology	1	Internal Medicine Urology	1
Pathology Hematology	1		
Pediatric Hematology Oncology	1		

Note: List compiled from the American Association of Tissue Banks (AATB) and submitted to the Organ and Tissue Procurement and Transplantation Advisory Board by Dr. H. Thomas Temple.

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: MEDICAL DIRECTOR QUALIFICATIONS

The following questions are intended to facilitate discussion on this topic.

1. Should the Advisory Board's language for recommended revisions to Florida's Medical Director regulations include…

a.) Specific licensure requirements for the Medical Director of:

1. An OPO?
2. An Eye Bank?
3. A Tissue Bank?

b.) Requirements for specific:

1. Board Certifications?
2. Education/Training?
3. Experience?

2. Should the Advisory Board's language for recommended revisions to Florida's Medical Director regulations be tailored to facility type? (OPO vs. Eye Bank vs. Tissue Bank)

3. Should the Advisory Board's language for recommended revisions to Florida's Medical Director regulations be dependent upon the procurement activities performed? (Recovery/Retrieval vs. Processing vs. Storage vs. Distribution)

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD'S

RECOMMENDED LANGUAGE DEVELOPMENT
SUBJECT: MEDICAL DIRECTOR QUALIFICATIONS

4. Should the Advisory Board's language for recommended revisions to Florida's Medical Director regulations contemplate the physical location of the facility? (Florida based vs. out-of-state vs. international)

ORGAN AND TISSUE PROCUREMENT AND TRANSPLANTATION ADVISORY BOARD

JUNE 8, 2012 MEETING

MATERIALS FOR AGENDA ITEM V., a.: PLASMA DILUTION CRITERIA

2.0 MINIMUM PROCUREMENT STANDARDS FOR AN ORGAN PROCUREMENT ORGANIZATION (OPO)

In order to maximize the gift of donation and optimize recipient outcomes and safety, the Organ Procurement Organization (OPO) must comply with the following policies for minimum procurement standards.

2.1 HOST OPO. The OPO responding to an organ donor call from a hospital is the "Host OPO" for that particular donor. The Host OPO is responsible for identifying, evaluating and maintaining the donor, obtaining consent for the removal of organs, complying with OPTN policy throughout the donation process, and organ allocation.

Additionally, the Host OPO is responsible for ensuring that donor tissue typing information is entered into UNet^{SM} and that the approved OPTN automated organ allocation computer algorithm is executed for each donor organ.

The Host OPO shall make reasonable attempts to obtain a medical/behavioral history from individual(s) familiar with the donor.

The Host OPO is responsible for organ procurement quality including appropriate preservation, and packaging of the organs, and assurance that adequate tissue typing material is procured, divided, and packaged.

The Host OPO is responsible for written documentation of donor evaluation, donor maintenance, consent for donation, death pronouncement, and organ procurement quality accompanies the organ as described in Policy 5.0 (Standardized Packaging and Transporting of Organs and Tissue Typing Materials).

2.2 EVALUATION OF POTENTIAL DONORS. The Host OPO is responsible for performing the following activities and communicating this information to the importing OPO or transplant center for every donor:

2.2.1 Verifying that death has been pronounced according to applicable laws.

2.2.2 The Host OPO must perform the following evaluations and provide this information to the OPO or transplant center. The Host OPO must document in the donor record circumstances when such information is not available.

The Host OPO must determine whether there are conditions which may influence donor acceptance by:

2.2.2.1 Obtaining the donor's medical/behavioral history.

The Host OPO will attempt to obtain a history on each potential donor to screen for medical conditions that may affect the donated organ function and for the presence of transmissible diseases and/or malignancies, treated and untreated, or any other known condition that may be transmitted by the donor organ that may reasonably impact the candidate or recipient.

This history should also be used to identify whether the potential donor has factors associated with increased risk for disease transmission, including blood borne pathogens HIV, Hepatitis B, and Hepatitis C. If the donor meets the criteria set forth in the current US

Public Health Service (PHS) guidance[1], the Host OPO must communicate this

[1] The "Exclusionary Criteria" in Rogers MF, Simonds RJ, Lawton KE, et al. Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissues and Organs. CDC MMWR Recommendations and Reports. 1994; May 20/43 (RR-8):1-17. http://www.cdc.gov/mmwr/preview/mmwrhtml/00031670.htm

information regarding donor history to all transplant programs receiving organs from the donor.

Potential donors who have received Human Pituitary Derived Growth Hormone (HPDGH) from human tissue (not recombinant) carry potential risk of prion disease. The Host OPO will attempt to obtain information regarding whether a potential donor has history of risk of prion disease (prior exposure or receipt of non recombinant HPDGH). If so, the Host OPO must communicate this information to all transplant programs receiving organs from the donor.

2.2.2.2 Reviewing the donor's medical record.

2.2.2.3 Performing a physical examination of the donor including obtaining the potential donor's vital signs.

2.2.3 SCREENING POTENTIAL ORGAN DONORS.

2.2.3.1 All blood samples obtained and used for screening tests required by OPTN policy must be assessed for hemodilution (defined as a sample with plasma dilution sufficient to affect the results of communicable disease testing) utilizing an FDA-approved hemodilution calculation. Any specimen without evidence of hemodilution will be referred to as a qualified specimen, and should be used for donor screening tests if available.

If a qualified (non-hemodiluted) specimen is not available for testing, a hemodiluted specimen should be used for testing purposes. In such cases, the donor will be considered as having increased risk for disease transmission per US PHS guidelines. As hemodilution can result in false negative serology testing, any screening results from such a specimen must be communicated to the accepting Transplant Program(s) and additional information including:

- which tests were completed using hemodiluted specimens; and
- The hemodilution calculation used for this donor's specimen (if requested).

A complete history of all transfusions received by the donor since admission must be documented in the donor medical record.

2.2.3.2 All potential donors are to be tested by use of a serological screening test licensed by the U.S. Food and Drug Administration (FDA) for Human Immune Deficiency Virus (Anti-HIV-1 and Anti-HIV-2).

NOTE: The amendments to Policy 2.2.3.2 shall be effective August 27, 2011. (Approved at the June 29-29, 2011 Board of Directors Meeting).

If the sample is qualified, the screening test for HIV is negative, and blood for subsequent transfusions has been tested and found to be negative for HIV, re-testing the potential donor for HIV is not necessary.

2.2.3.3 NOTA and the Final Rule require standards for preventing the acquisition of organs from individuals known to be infected with human immunodeficiency virus/acquired immune deficiency virus. As a result, OPTN Members shall not knowingly participate in the procurement or transplantation of organs from donors who are known to be infected with HIV OPTN members may only recover organs if the laboratory data and medical- social history indicates that the donor is not HIV infected.

If multiple tests related to HIV are performed, the results of all tests must be communicated directly to all institutions receiving organs from the donor. Exceptions for cases in which the testing cannot be completed prior to transplant are provided in paragraph 2.2.3.4 below.

2.2.3.4 Exceptions to the guidelines set forth above may be made in cases involving non-renal organs, when, in the medical judgment of the staff of the Host OPO and recipient institution, an extreme medical emergency warrants the transplantation of an organ which has not been tested for HIV.

The Host OPO must provide all available information regarding donor medical and social history to the transplant program and treat this as a donor with increased risk for disease transmission based upon USPHS Guidelines due to the inability to obtain donor testing.

The transplant program must obtain and document informed consent from the recipient or next of kin, the legal next of kin, designated health care representative or appropriate surrogate before use in such cases (See Policy 4.2).

2.2.3.5 Informing Personnel. Health care personnel caring for potential donors or donors who test positive for HIV should be so informed only when necessary for medical decision making purposes.

2.2.4 **DONOR EVALUATION**. Donor evaluation must be performed or coordinated by the Host OPO. All donor laboratory testing must be performed in an appropriately accredited laboratory utilizing FDA licensed, approved, or cleared serological screening tests. In the event that a required screening test is not commercially available prior to transplant, then a FDA-licensed, approved or cleared diagnostic test is permissible, and the Host OPO must document in the donor record which assay was utilized to assess the potential donor and must also provide this information to the transplant program(s).

Exceptions: Diagnostic testing is NOT acceptable for Anti-HIV.
FDA-approved diagnostic testing IS acceptable for VDRL/RPR.

2.2.4.1 For all potential deceased donors:

- ABO typing (and confirmation as outlined in Policy 3.2.4) with sub-typing for ABO-A donors;
- FDA licensed Anti-HIV I, II (diagnostic testing not acceptable);
- CBC;
- Electrolytes;
- Hepatitis screen serological testing; including HBsAg, HBcAb, and Anti-HCV;
- VDRL or RPR (FDA-approved diagnostic tests are acceptable);
- Anti-CMV;
- EBV serological testing;
- Blood and urine cultures;
- Urinalysis within 24 hours prior to cross clamp;
- Arterial blood gases;
- Chest x-ray; and
- Serum Glucose.

If a Host OPO completes additional testing in addition to what is required in policy for a potential donor, the results of these tests must be communicated immediately to all recipient institutions.

Additional Organ Specific information is required as follows:

2.2.4.2 For potential renal donors:

- Creatinine; and
- B.U.N.

2.2.4.3 For potential liver donors:

- AST;
- ALT;
- Alkaline phosphatase;
- Direct and total bilirubin
- INR (PT if INR not available); and
- PTT.

2.2.4.4 For potential heart donors:

- 12 Lead ECG; and
- Cardiology consult and/or echocardiogram.

2.2.4.5 For potential pancreas donors:

- Serum amylase.

2.2.4.6 For potential lung donors:

- Sputum gram stain.

2.2.5 Follow-up on Donor Testing. The Host OPO is responsible for timely follow-up and reporting of any new or changed donor test results to the transplant program(s).

The Host OPO must establish a procedure that defines its process for obtaining post-recovery donor testing results.

The Host OPO must establish and implement a process to report all positive screening or diagnostic tests received to the transplant center's Patient Safety Contact (as defined in Policy 4.4) within 24 hours of receipt by the OPO. The OPO must report updates such as identification of organism and sensitivity to the transplant program(s) as the OPO receives the information.

If during this follow-up a new disease or malignancy is discovered in the donor that may potentially be transmitted to organ recipients, the Host OPO must report the event to the OPTN Patient Safety System, as outlined in Policy 4.5.

2.2.6 Reporting Disease. The Host OPO is responsible for collecting historical (i.e. medical-social history), testing and laboratory assessments to identify malignant and infectious conditions that may adversely affect a potential organ recipient and sharing this information with the transplant program(s).

The Host OPO must communicate to the transplant program(s) any known or suspected infectious or neoplastic conditions that may be transmitted by the donor organ(s).

2.3 DONOR MAINTENANCE. The Host OPO must make reasonable efforts to maintain the deceased donor, document these efforts, and communicate this information to the OPO or Transplant Center as follows:

2.3.1 Blood pressure is adequate to maintain perfusion of vital organs;

2.3.2 Vital signs are monitored;

2.3.3 I.V. therapy or drugs are administered as required (i.e. vasopressors, vasodilators; etc.);

2.3.4 Antibiotic therapy is administered as required; and

2.3.5 Intake and output.

2.4 OBTAINING CONSENT. The Host OPO must provide evidence of consent for donation according to applicable legal authority.

2.5 ORGAN PROCUREMENT QUALITY. Minimum standards of quality shall include documentation of the following:

2.5.1 All items in section 2.2.

2.5.2 Use of standard surgical techniques in a sterile operating environment.

2.5.3 Maintenance of flush solutions and preservation media at appropriate temperatures and recording of flush solutions and additives with their respective lot numbers; organ anatomy, organ flush characteristics, flush solution amount and type, and organ abnormalities or surgical damage if any. The Host OPO is responsible for ensuring that the donor medications are given at appropriate times and that medication administration, including flush solutions and additives, is recorded during the retrieval process.

2.5.4 Each OPO, and their respective histocompatibility laboratory(s), will define and document the minimum tissue typing material required to generate match runs for local or regional placement of all organs. In view of the frequent need for regional shipment of pancreas and kidney allografts, however, sufficient specimens for several crossmatches are required. Minimal typing material to be obtained for EACH kidney and pancreas will include the following:

- One 7 to 10ml. clot (red top) tube for ABO verification, plus
- 2 ACD (yellow top) tubes
- 3 to 5 lymph nodes
- One 2 X 4 cm. wedge of spleen in culture medium, if available

For all other organs, the OPO will provide lymph nodes if requested and available.

2.5.5 Proper packaging of organs for transport (see Policy 5.0).

2.5.6 Complete information must be maintained by the Host OPO for seven years per the Final Rule on any and all organs recovered.

2.5.7 The Host OPO must maintain a serum sample for each donor from which organs were transplanted for a period of at least 10 years after the date of recovery. This serum must be available for use for retrospective testing if needed. The Host OPO must document the type of specimen that has been archived in the donor chart. The specimen should be a qualified (not hemodiluted) specimen if possible.

2.5.8 The Host OPO is responsible for determining that non-local procurement teams have transportation to and from the local airport.

2.6 INITIATING ORGAN PROCUREMENT AND PLACEMENT. In order to maximize the number of transplantable donor organs, tissue typing and crossmatching of an organ donor shall commence as soon as possible, ideally pre-procurement.

2.7 REMOVAL OF NON-RENAL ORGANS. When a non-renal organ is offered for transplantation, the recipient center procurement team must be given the option of removing the non-renal organ unless extenuating circumstances dictate otherwise. This policy also applies to non-renal organs from controlled donation after cardiac death (DCD) donors.

2.7.1 Multiple Abdominal Organ Procurement. It is expected that all authorized organs should be procured from a donor if each organ is transplantable and/or recipients are identified for each organ. The OPO will document the specific reason for non-recovery of an authorized organ. Cooperation between all organ recovery teams is required.

2.8 In order to recover organs from a DCD donor, an OPO must follow an established protocol that contains the standards of the DCD Model Elements as adopted in the OPTN Bylaws, Appendix B, Attachment III.

2. 9 **MULTI-CULTURAL AND DIVERSITY ISSUES.** Each OPO must develop and implement a plan to address a diverse population related to organ donation.

Guidance for Industry

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
August 2007

Contains Nonbinding Recommendations

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue- Based Products (HCT/Ps)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility determinations, with complying with the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C) (Ref. 1). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor-eligibility, including donor screening and testing, for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

This guidance applies to cells and tissues procured on or after the effective date of the regulations contained in 21 CFR part 1271, subpart C (effective date May 25, 2005). This guidance replaces the guidance of the same title, dated February 27, 2007. This guidance does not replace the guidance concerning 21 CFR part 1270, entitled "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," (Ref. 2), which remains applicable to tissues recovered before May 25, 2005 and subject to 21 CFR part 1270.

We recognize that some HCT/Ps (e.g., hematopoietic stem cells), as well as Whole Blood and blood components, can be collected by venipuncture from living donors. We encourage you to contact the Center for Biologics Evaluation and Research (CBER) should you have any questions as to the applicable regulatory framework for collection and further processing of such products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. What is the purpose of this guidance?

This guidance will assist establishments (HCT/P establishments) in complying with the requirements under 21 CFR part 1271, subpart C, for donor-eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases. These requirements apply to all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90.

This guidance finalizes the draft guidance, "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated May 2004," (Ref. 3). This guidance also finalizes the draft guidance, "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated June 2002 (Ref. 4).

B. What is the scope of this guidance?

This guidance is intended for: (1) Establishments responsible for performing any part of donor eligibility screening or testing, or for making donor-eligibility determinations; and (2) establishments that determine that an HCT/P meets release criteria and make the HCT/P available for distribution.

Establishment, as defined under § 1271.3(b), means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps. This includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of HCT/Ps, and includes facilities that engage in contract manufacturing. An establishment may engage another establishment under a contract, agreement, or other arrangement for screening and testing donors and for determining whether donors are eligible. Such allocations of responsibilities must comply with § 1271.150(c)[1].

III. THE DONOR-ELIGIBILITY DETERMINATION (§ 1271.50)

A. What is a donor-eligibility determination?

A donor-eligibility determination is a conclusion that a donor is either eligible or ineligible to donate cells or tissues to be used in an HCT/P, based on the results of donor screening (§ 1271.75) and testing (§§ 1271.80 and 1271.85). Except in certain situations

[1] See Food and Drug Administration, Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements, dated September 2006. http://www.fda.gov/cber/guidelines.htm.

specified under §§ 1271.60(d), 1271.65(b), and 1271.90, an HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible (§ 1271.45(c)).

Under § 1271.50(b), a donor is eligible only if:

- Screening shows that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases, and is free from communicable disease risks associated with xenotransplantation; and
- Test results for relevant communicable disease agents are negative or nonreactive, except as provided in § 1271.80(d)(1) for non-treponemal screening tests for syphilis.

B. Who makes the donor-eligibility determination?

In accordance with § 1271.50(a), a "responsible person" must determine and document the eligibility of a cell or tissue donor. A responsible person is one who is authorized to perform designated functions for which he or she is trained and qualified (§ 1271.3(t)). A responsible person should have appropriate medical training and adequate knowledge of relevant Federal regulations and guidances.

C. What are "relevant communicable disease agents or diseases (RCDADs)"?

There are two groups of relevant communicable disease agents and diseases. The first group consists of those communicable diseases and disease agents specifically listed in § 1271.3(r)(1). The second group consists of communicable diseases and disease agents described under § 1271.3(r)(2), that are not specifically listed in § 1271.3(r)(1). These two groups are as follows:

1. Relevant communicable disease and disease agents specifically listed in § 1271.3(r)(1).

   a. The following communicable diseases and disease agents are relevant for all types of HCT/Ps (§ 1271.3(r)(1)(i)):

   - Human immunodeficiency virus (HIV), types 1 and 2;
   - Hepatitis B virus (HBV);
   - Hepatitis C virus (HCV);
   - Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD)[2]; and
   - *Treponema pallidum* (syphilis).

[2] Variant Creutzfeldt-Jakob disease (vCJD) is not specifically listed in § 1271.3(r)(1)(i), but is an example of human transmissible spongiform encephalopathy.

b. The following cell-associated communicable disease or disease agents are relevant for viable, leukocyte-rich cells and tissues, including reproductive cells or tissues if they are considered to be viable leukocyte rich (see section VI.B.2. of this document) (§ 1271.3(r)(1)(ii)):

- Human T-lymphotropic virus (HTLV), types I and II.

c. The following communicable disease agents or diseases of the genitourinary tract are relevant for reproductive cells or tissues (§ 1271.3(r)(1)(iii)):

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea.*

2. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 1271.3(r)(1), is relevant if it is one:

a. For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with the HCT/P, such as medical personnel, because the disease agent or disease:

i. is potentially transmissible by an HCT/P; and
ii. either (1) has sufficient incidence and/or prevalence to affect the potential donor population (§ 1271.3(r)(2)(i)(B)(*1*)), or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (§ 1271.3(r)(2)(i)(B)(*2*));

b. That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (§ 1271.3(r)(2)(ii)); and

c. For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available (§ 1271.3(r)(2)(iii)).

In summary, FDA considers: (1) Risk of transmission, (2) severity of effect, and (3) availability of appropriate screening measures or tests, in accordance with § 1271.3(r)(2), as factors in determining whether a communicable disease or disease agent, not listed under § 1271.3(r)(1), is relevant. The importance of these factors in determining relevance may be based on the clinical significance of the disease agent or disease. For example, *Ureaplasma urealyticum*, although highly prevalent and transmissible, is not considered a relevant communicable disease agent because its pathogenicity to

reproductive cell and tissue recipients has low clinical significance. However, we require screening for TSEs and screening or testing for HIV-2, although less prevalent, because they pose extremely significant health risks.

D. What communicable disease agents or diseases, not listed in § 1271.3(r)(1), have been determined to be relevant?

We have determined the following communicable disease agents and diseases, not specifically listed under § 1271.3(r)(1), to be relevant under § 1271.3(r)(2). This determination was based on the risk of transmission, severity of effect, and availability of appropriate screening measures or tests as described in section III.C. of this document. A brief discussion of these factors is provided under each relevant disease and agent listed. Additional background information is provided in the appendix, as indicated.

West Nile Virus (WNV)

Risk of Transmission: There is a risk of transmission of WNV by HCT/Ps. This is supported by observations of WNV transmission via organ transplantation, and via blood and blood product transfusion. Although it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5). (See Appendix 6).

Severity of Effect: WNV could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for WNV, such as the medical history interview and clinical evidence (see Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral). (Screening measures for WNV are discussed in sections IV.E. and IV.F. of this document.)
A donor screening test for WNV, using NAT technology, has been licensed for use in living and cadaveric HCT/P donors. IND studies are also ongoing for the development of other NAT screening tests for WNV (see section VI.A. and Appendix 6).

Sepsis

Risk of Transmission: There is a risk of transmission by HCT/Ps of any agent that could cause sepsis. The agents that cause sepsis include various bacterial, fungal, and viral agents. These agents have sufficient incidence and/or prevalence to

affect the potential HCT/P donor population and are potentially transmissible. For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock (see Appendix 6).

Severity of Effect: Sepsis could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Mortality from sepsis is substantial, as sepsis is now among the top ten leading causes of death in the United States (see Appendix 6).

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for detection of sepsis, such as the medical history interview, and clinical and physical evidence. (Screening measures for sepsis are discussed in sections IV.E., IV.F. and IV.G. of this document.)

Vaccinia

Risk of Transmission: There is a risk of transmission of vaccinia (the virus used in smallpox vaccine) by HCT/Ps. Vaccinia has sufficient incidence and/or prevalence to affect the potential donor population, especially in light of current small pox vaccination programs. Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, two different investigators reported that vaccinia virus could sometimes be isolated from a patient's blood 3 to10 days after vaccination (Ref. 8). These studies did not use the less virulent New York City Board of Health (NYCBOH) strain of vaccinia virus that comprises currently available vaccines in the United States. Other investigators using the NYCBOH strain of vaccinia virus were only able to detect virus in the blood of patients with disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination (see Appendix 6).

Severity of Effect: Vaccinia virus could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Historically, for every million people vaccinated in the past, up to 52 people have had a life-threatening reaction to smallpox vaccine and up to two people per million vaccinated have died (Refs. 10 and 11).

The potential consequences of vaccinia infection include severe complications (see Appendix 4). These consequences are more likely to occur in HCT/P recipients who are immunocompromised or who have burns or other serious skin conditions. Vaccinia virus infection rarely causes severe complications such as encephalitis and severe generalized vaccinia in otherwise healthy people. Also, the route of infection could influence the severity of the disease, so that it is possible that vaccinia infection transmitted via HCT/Ps could result in different or more severe infections than when acquired percutaneously (Ref. 12).

Availability of Appropriate Screening and/or Testing Measures: There are appropriate screening measures, such as the medical history interview, and clinical and physical evidence (see Ref. 12 for further information regarding the background and rationale for vaccinia deferral). (Screening measures for vaccinia are discussed in sections IV.E., IV.F. and IV.G. of this document.)

E. How will FDA handle other emerging infectious diseases in regard to HCT/P donor eligibility?

We intend to notify you through a guidance, if we determine that an infectious disease meets the definition of a relevant communicable disease under § 1271.3(r)(2). The guidance would include our comments or recommendations for donor screening and testing. We also intend to notify you through a guidance, if we conclude that a disease identified as "relevant" under § 1271.3(r)(2), no longer meets the criteria as a "relevant" disease for purposes of the donor eligibility regulations. In suitable situations, we will hold public meetings or consult with advisory committees to help us identify communicable disease agents or diseases for which donor screening and testing must be performed under §§ 1271.75, 1271.80, and 1271.85.

F. What procedures must I establish and maintain?

You must establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility, and complying with all other requirements of part 1271, subpart C (§ 1271.47(a)). A responsible person must review and approve all procedures before their implementation (§ 1271.47(b)). These procedures must be readily available to personnel in the area where the procedures are performed, or if this is not practical, in a nearby area (§ 1247(c)).

Under § 1271.47(d), at the time a departure occurs, you must record and justify that departure from a procedure relevant to preventing risks of communicable disease transmission. Before distributing an HCT/P manufactured under a departure from a procedure, a responsible person must determine that the departure did not increase the risk of communicable disease transmission.

We consider a departure to be an intended change from an established procedure, including a standard operating procedure (SOP), which occurs before the HCT/P is distributed, and is consistent with applicable regulations and standards. For example, a

departure might include the use of a different manufacturer's reagents because the usual manufacturer's reagents were not available at the recovery site. In this example, although the use of the different manufacturer's reagent might represent a change from the established procedures, the change might be consistent with applicable regulations, standards, or established specifications. A departure is different from an HCT/P deviation, which under § 1271.3(dd) is defined as an event that is inconsistent with applicable regulations, standards, or established specifications, or is unexpected or unforeseeable.

You are authorized under §1271.47(e) to use appropriate standard procedures developed by another organization, provided that you have verified that the procedures are consistent with and at least as stringent as the requirements in part 1271. For example, you may use a current donor medical history questionnaire developed by a professional organization, provided that you have reviewed the questionnaire and determined that it meets the requirements for donor screening.

G. What records must accompany the HCT/P after the donor-eligibility determination has been completed?

Under § 1271.55(a) you must provide the following records with each HCT/P, after the donor-eligibility determination has been completed:

- A distinct identification code (such as an alphanumeric code) affixed to the HCT/P container, that relates the HCT/P to the donor and to all records pertaining to the HCT/P and, except in the case of autologous donations, directed reproductive donations, or donations made by first-degree or second-degree blood relatives, does not include an individual's name, social security number, or medical record number;
- A statement whether, based on the results of screening and testing, the donor is determined to be eligible or ineligible; and
- A summary of the records used to make the donor-eligibility determination.

Under 1271.55(b), the summary of records in § 1271.55(a)(3) must include:

- A statement that the communicable disease testing was performed by a laboratory or laboratories: (1) certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or (2) meeting equivalent requirements, as determined by the Centers for Medicare and Medicaid Services (CMS);
- A listing and interpretation of the results of all tests performed for relevant communicable disease agents or diseases, and, if applicable, for CMV (§ 1271.85(b)(2))[3];

[3] If a repeat anonymous semen donor has multiple tests for CMV and during this time he seroconverts (he initially tests CMV negative and subsequently tests CMV positive), then in the summary of records you should indicate the CMV positive result, or you may provide information about all CMV test results.

- The name and address of the establishment that made the donor-eligibility determination; and
- A statement noting the reason for the determination of ineligibility in the case of an HCT/P from a donor who is ineligible based on screening and released under § 1271.65(b).

The records referenced in § 1271.55 must accompany an HCT/P when it is placed into distribution (as defined in § 1271.3(bb)), including distribution that occurs within the same facility (e.g., peripheral blood stem/progenitor cells are collected within a facility's cell processing laboratory and are then sent to a patient's floor in that same facility). Once the consignee receives the accompanying records with the HCT/P, it is not necessary that those records physically accompany the HCT/P into the operating room or at the bedside (except for any information that is affixed to the HCT/P container). You should make accompanying records available for review by any medical personnel needing access to those records in order to provide patient care. Electronic access to accompanying records within a facility would satisfy the regulatory requirements under § 1271.55(a), as long as they are in compliance with § 1271.55(c) – deletion of personal information.

Records that must accompany an HCT/P shipped under quarantine are discussed in section III.J. of this document.

H. What records must I retain, and for how long?

Under § 1271.55(d)(1), you must retain records of results and interpretation of all testing for relevant communicable disease agents and screening for communicable diseases, the name and address of the testing laboratory, and the donor eligibility determination, including the name of the responsible person who made the donor eligibility determination, and the date of the determination.

Under § 1271.55(d)(2), all records must be accurate, indelible, and legible.

Under § 1271.55(d)(4), you must retain records pertaining to a particular HCT/P for at least 10 years after the date of its administration. This includes records created by laboratories performing donor eligibility testing (§§ 1271.55(d)). If the date of administration is not known, then you must retain records at least 10 years after the date of distribution, disposition, or expiration, whichever is latest (§ 1271.55(d)(4)). Testing laboratories that are not aware of the date of administration, distribution, disposition or expiration, should retain records for at least 10 years after the record was created (i.e., after the testing was performed).

I. What do I do with the HCT/Ps before the donor-eligibility determination has been completed?

Before the completion of the donor-eligibility determination, you must keep an HCT/P in quarantine and clearly identify it as in quarantine (§ 1271.60(a) and (b)). The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution (§ 1271.60(b)).

Quarantine means the storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation (§ 1271.3(q)). An example of automated designation is the use of a validated computer system to maintain information on bar-code-labeled HCT/Ps held in a freezer. When you release the HCT/P, the computer system is activated to assure identification and retrieval of the specific HCT/P for the intended recipient.

J. May I ship an HCT/P that is in quarantine?

Yes, you may ship an HCT/P before completion of the donor-eligibility determination (§ 1271.60(c)). However, in accordance with § 1271.60(c), the HCT/P must be kept in quarantine and must be accompanied by records that:

- Identify the donor (e.g., by a distinct identification code affixed to the HCT/P container);
- State that the donor-eligibility determination is not complete; and
- State that the HCT/P must not be implanted, transplanted, infused, or transferred until the donor-eligibility determination is complete, except in cases of urgent medical need under § 1271.60(d), and described in section VIII.C. of this document.

K. How do I store HCT/Ps from a donor who has been determined to be ineligible?

Under § 1271.65(a), if a donor is determined to be ineligible you must store or identify the HCT/Ps from the ineligible donor in a physically separate area clearly identified for such use, or follow other procedures that are adequate to prevent improper release, until the HCT/Ps are destroyed or distributed for use in certain limited circumstances identified in § 1271.65 (b) and (c), and described in section VIII.D. of this document. Examples of ways in which you may comply with this requirement, include employing separate refrigerators or freezers, using separate shelves in a single refrigerator or freezer, and using an automated designation system.

In accordance with § 1271.47(a), you must describe in your standard operating procedures (SOPs) the method you choose to store or identify the HCT/Ps from the ineligible donor.

IV. DONOR SCREENING (§ 1271.75)

A. For what diseases or conditions must I screen cell and tissue donors?

Under § 1271.75(a), you must screen a cell and tissue donor by reviewing relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases; and communicable disease risks associated with xenotransplantation, unless an exception identified in § 1271.90(a) applies. For donors of viable, leukocyte-rich cells or tissue, you must also screen for HTLV (§ 1275.75(b)). You must also screen donors of reproductive cells and tissue for the additional diseases identified as relevant to those HCT/Ps in § 1271.75(c). (See section III.C. of this document for discussion of relevant communicable disease agents and diseases.)

B. How do I screen a donor who is one month of age or younger?

Under § 1271.75, you must screen all donors, including infant donors one month of age or less, except as provided under § 1271.90. Since a donor who is one month of age or younger cannot participate in the donor medical history interview, you must interview another individual able to provide the information sought in the interview (§ 1271.3(n)(2)).

You should also screen the birth mother when an infant is one month of age or less. Donor screening of the birth mother should involve a donor medical history interview and review of available medical records; the physical examination or physical assessment of the birth mother is recommended when practical.

C. What sources of information do I review?

When you screen a potential cell or tissue donor, you must review "relevant medical records" for risk factors for, and clinical evidence of, the relevant communicable diseases listed in § 1271.75(a)(1). Risk factors are described in section IV.E., clinical evidence in section IV.F., and physical evidence in section IV.G.

Relevant medical records, as defined under § 1271.3(s), means a collection of documents that includes: (1) a current donor medical history interview; (2) a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and (3) other available records listed in § 1271.3(s)(1) through (4). We describe these three elements as follows:

1. The donor medical history interview (§ 1271.3(n)) is a documented dialogue concerning the donor's medical history and relevant social behavior:

a. With a living donor; or

b. If the donor is not living or is unable to participate in the interview, then with one or more individuals who can provide the information sought. These individuals might be:

- The donor's next of kin;
- The nearest available relative;
- A member of the donor's household;
- An individual with an affinity relationship with the donor (e.g., caretaker, friend, partner); or
- The donor's primary treating physician.

In accordance with § 1271.47, you must establish and maintain standard operating procedures to assure that receipt and review of relevant medical records are properly conducted. In addition, for medical records created for the purpose of assisting in determining donor eligibility, such as records of the donor medical history interview and the report of a physical assessment of a cadaveric donor, you must establish and maintain SOPs to assure that such records are current, complete, and reliable.

The medical history interview may take place in person or by telephone.

Since a donor medical history interview is a documented dialog (§ 1271.3(n)), if a donor medical history questionnaire is self-administered, the interviewer should review and verify the answers with the individual who has filled out the questionnaire form.

2. The purpose of the physical assessment of a cadaveric donor or the physical examination of a living donor is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease. For a cadaveric donor, the physical assessment means a limited autopsy, or a recent antemortem or postmortem physical examination (§ 1271.3(o)). For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health care professionals (see section IV.G. of this document for discussion about physical evidence). Because this is a step in determining donor eligibility, you must establish and maintain standard operating procedures (SOPs) for the conduct of the physical assessment or physical examination (§ 1271.47).

3. If they are available, the following other records also meet the definition of relevant medical records (§ 1271.3(s)).

- Laboratory test results (other than the results of testing required for the donor-eligibility determination);

- Medical records;
- Coroner and autopsy reports; and
- Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease). Examples of these records include: medical examiner reports, police records, and information from other tissue or medical establishments, if applicable.

You should make inquiries into these records and other information when the circumstances indicate that follow-up information might be relevant for screening a potential cell or tissue donor. For example, when reviewing the relevant medical records, including the medical/social history interview, the tissue bank might find information to suggest that the donor might have been incarcerated, pursued by the police, or been under police investigation, or that the cause of death resulted in a police report (e.g., fatal gunshot wound). If that is the case, the tissue bank should make inquiries to obtain all relevant information regarding the eligibility of the donor, which is available from and disclosable by the police department.

We define "available" to mean that a record or information exists, or is pending, and can be obtained through due diligence, within a reasonable amount of time. A "reasonable" amount of time is a period of time that would allow for the collection of important information without compromising the utility of the tissue. Examples of these terms are as follows:

Example 1: A living donor brings his medical records with him to the screening site. These records are available, and you would review them.

Example 2: A cadaveric donor dies as a result of an event that leads to the creation of a police report. If the police report was disclosable to you within a reasonable period of time, you would review it.

Example 3: You know that an autopsy report will be prepared on a cadaveric donor, but the report will not be complete for several weeks. If waiting several weeks to review the autopsy report would compromise the utility of the tissue, perhaps because your HCT/P (e.g., cornea) needs to be released within a limited timeframe, then the report could not be obtained in a reasonable time period. Under these circumstances, it might not be necessary to wait to review the final report of autopsy results before distribution of the HCT/P. If this is the case, you should use the available information when considering the donor's eligibility, including the presumed cause of death and other relevant preliminary autopsy findings and all other information obtained about the donor. Also, you should review the final autopsy report when it becomes available. If any new information in the final report indicates that the donor is ineligible, you should consider notifying the consignees of the distributed HCT/Ps and submit to FDA an HCT/P deviation report within 45 days, if applicable.

D. When may I perform an abbreviated donor screening procedure?

Section 1271.75(e) states, "If you have performed a complete donor screening procedure on a living donor within the previous 6 months, you may use an abbreviated donor screening procedure on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior."

If you perform an abbreviated screening:

- You do not need to conduct a new physical examination or a new review of relevant medical records.
- You should remind the donor about behaviors that could put him/her at risk of a relevant communicable disease. If any new behavioral risk has been identified in the interval since the last donation, you should also address that new behavioral risk.
- We do not require that this information be presented in any specific way. Possible methods include the use of a pamphlet or a wall chart, or other effective means of communication.
- You should then ask the donor if there have been any changes in donor history or risk factors since the previous donation.

If you wish to perform an abbreviated donor screening procedure, you must have conducted a complete donor screening procedure on the living donor (including donor history questionnaire, physical examination, and review of any new medical records, if applicable) within 6 months prior to the abbreviated procedure (§ 1271.75(e)).

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.

1. Men who have had sex with another man in the preceding 5 years (Refs. 17 through 46) (risk factor for HIV and Hepatitis B).

2. Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections (Refs. 18, 21, 22, 25, 27, 29, 33, 34, 36, 38, 42, and 45 through 59) (risk factor HIV, Hepatitis B and Hepatitis C).

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.

4. Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years (Refs. 18, 21, 22, 24, 25, 27, 29, 33, 34, 38, 40, 44, 45, 46, 61, 62, and 63) (risk factor for HIV, Hepatitis B and Hepatitis C).

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).

6. Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 18 and 64).

7. Children born to mothers with or at risk for HIV infection:

- If 18 months of age or younger, or
- If breast-fed within the preceding 12 months.

Note: We do not recommend deferral of a donor who is a child born to a mother with or at risk for HIV infection if the child is over 18 months of age and has not been breast-fed within the preceding 12 months, provided that the child's HIV antibody tests, physical examination, and medical records do not indicate evidence of HIV infection (Ref. 18).

8. Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months (Refs. 29, 67, and 68) (risk factor for HIV, Hepatitis B and Hepatitis C).

9. Persons who have lived with (resided in the same dwelling) another person who has hepatitis B or clinically active (symptomatic) hepatitis C infection in the preceding 12 months (Ref. 69).

10. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used (Ref. 69).

11. Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday (Refs. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as being caused by hepatitis A virus, Epstein-Barr Virus (EBV), or cytomegalovirus (CMV).

12. Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death. For example, if a statement such as "rule-out sepsis" is noted in the medical records, and subsequent notations indicate a diagnosis other than sepsis, a potential donor might still be eligible.

13. Persons who have had smallpox vaccination (vaccinia virus) in the preceding 8 weeks (Ref. 12) should be evaluated as follows:

a. For persons who had no vaccinia complications (see Appendix 4 for definition of vaccinia complication):

- You should defer the donor until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date, and until the physical examination or physical assessment includes a confirmation that there is no scab at the vaccination site.
- In cases where a scab was removed before separating spontaneously, you should defer the donor for two months after vaccination.

Note: We do not recommend deferral of a cadaveric donor who was vaccinated at least 21 days ago and who has no visible scab, if you are unable to obtain a history of how the scab separated.

b. For persons who have experienced vaccinia complications (see Appendix 4), you should defer the donor until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had vaccinia complications but who currently has no visible signs of vaccinia complications, if you are unable to obtain a history of the exact date of resolution of the vaccinia complications.

14. Persons who acquired a clinically recognizable vaccinia virus infection by contact with someone who received the smallpox vaccine (i.e., touching the vaccination area or the scab, including the covering bandages, or touching clothing, towels, or bedding that might have come into contact with an unbandaged vaccination area or scab) (Ref. 12).

- For living donors who developed skin lesions as a result of contact with someone who received the smallpox vaccine, you should question the donor regarding the loss of the scab, and you should examine the skin. For cadaveric donors, you should examine the skin.
- If no scab is present, we do not recommend deferral of:
    - a cadaveric donor;
    - a living donor if the scab spontaneously separated; or
    - after three months from the date of vaccination of the vaccine recipient, a living donor whose scab was otherwise removed.
- If a scab is present, you should consider:
    - a cadaveric donor to be ineligible; or
    - a living donor to be deferred until the scab spontaneously separates.

You should defer persons who developed other complications of vaccinia infection acquired through contact with a vaccine recipient until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had complications of vaccinia acquired through contact with a vaccine recipient, but has no visible signs of vaccine complications, if the date of resolution of the vaccinia complications is unknown.

We do not recommend deferral of contacts who never developed skin lesions or other complications of vaccinia infection.

15. Persons who have had a medical diagnosis or suspicion of WNV infection (based on symptoms and/or laboratory results, or confirmed WNV viremia) you should defer for 120 days following diagnosis or onset of illness, whichever is later (Refs. 5, 6, and 7).

16. Persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days (Refs. 5 and 7).

17. Persons who have been treated for or had syphilis within the preceding 12 months. We do not recommend deferral of donors if evidence is presented that the treatment occurred more than 12 months ago and was successful.

18. Reproductive HCT/P donors who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection in the preceding 12 months. We do not recommend deferral of persons who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection if evidence is presented that the treatment occurred more than 12 months ago and was successful.

Example: A potential donor has a medical record indicating that she was treated for Chlamydia 14 months ago. No follow-up testing was performed at the time of treatment. The medical record serves as evidence that she received treatment more than 12 months ago. Since the medical record does not include information that a follow-up test was performed after treatment and was negative, there is no evidence that the treatment was successful. However, a current negative test for Chlamydia (as part of the current donor testing) may serve as evidence that the treatment that occurred more than 12 months ago was successful.

19. Persons who have been diagnosed with vCJD or any other form of CJD (Refs. 3 and 75).

Note: Numbers 19 to 26 in this section are designed to screen for TSEs, including CJD and vCJD. If the living donor or the individual knowledgeable about the donor's medical and travel history is not familiar with the term "Creutzfeldt-Jakob Disease" or "variant Creutzfeldt-Jakob Disease," you may try to describe those in layman's terms. If the person being interviewed is still not familiar with those terms, you may consider the lack of familiarity with those terms as a negative response to questions using those terms.

20. Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or other neurological disease of unknown etiology (Refs. 3 and 75). Potential donors who have a diagnosis of delirium (e.g., delirium caused by toxic/metabolic diseases or recent head trauma) would not necessarily be considered to have a diagnosis of dementia and should be evaluated by the Medical Director. (HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident or brain tumor and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director).

21. Persons who are at increased risk for CJD (Refs. 3 and 75). Donors are considered to have an increased risk for CJD if they have received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD (see criterion 22 of this section).

22. Persons who have a history of CJD in a blood relative (Refs. 3 and 75) unless:

- The diagnosis of CJD was subsequently found to be an incorrect diagnosis;
- The CJD was iatrogenic; or
- Laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

23. Persons who spent three months or more cumulatively in the United Kingdom (U.K.) (see Appendix 5) from the beginning of 1980 through the end of 1996 (Refs. 3 and 75).

24. Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996 (Refs. 3 and 75).

25. Persons who spent 5 years or more cumulatively in Europe (see Appendix 5) from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996) (Refs. 3 and 75).

26. Persons who received any transfusion of blood or blood components in the U.K. or France between 1980 and the present (Refs. 3 and 75).

27. Persons or their sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

28. Persons who have received a blood transfusion or any medical treatment that involved blood in the countries listed in criterion 27, after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

Note: Establishments utilizing an HIV-1/2 antibody donor screening test that has been licensed by FDA and is specifically labeled in the Intended Use Section of the package insert as sensitive for detection of HIV group O antibodies may delete items 27 and 28 from their screening procedures. If such establishments continue to ask items 27 and 28, the donor eligibility may be based on the results of the donor screening test regardless of the answers to items 27 and 28. Establishments that do not utilize an HIV antibody donor screening test that has been licensed by FDA for detection of HIV group O antibodies should continue to ask these items.

29. Persons who are xenotransplantation product recipients or intimate contacts of a xenotransplantation product recipient (Ref. 77).

a. For the purpose of this document, we define the following terms:

i. Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (1) live cells, tissues, or organs from a nonhuman animal source; or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

ii. Xenotransplantation products include live cells, tissues, or organs used in xenotransplantation. Biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.

iii. Xenotransplantation product recipient means a person who undergoes xenotransplantation.

iv. Intimate contact of a xenotransplantation product recipient means a person who has engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with a xenotransplantation product recipient. Examples of intimate contacts include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. We do not consider sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, to be intimate contact.

b. To determine whether a potential HCT/P donor is a xenotransplantation product recipient, or is the intimate contact of a person who has received a xenotransplantation product, you should determine whether the potential donor, his/her sexual partner, or any member of his/her household has ever had a transplant or other medical procedure that involved being exposed to live cells, tissues, or organs from an animal. If the potential donor or his/her sexual partner is the recipient of a xenotransplantation product, you should defer the donor. If the potential donor is a member of the xenotransplantation product recipient's household, you should determine whether the potential donor has been exposed to blood, saliva, or other body fluids from the xenotransplantation product recipient. If the potential donor has been exposed to any of these fluids, you should defer the donor.

Note: There are circumstances in which it might not be necessary to defer a potential HCT/P donor who is an intimate contact of a recipient of certain xenotransplantation products. For example, an advisory

committee recommended and we concur that intimate contacts of persons who have received the product Epicel™ do not need to be deferred from blood donation, because the risk of zoonotic transmission from this product is minimal as the non-human animal cells used in the manufacture of this product originate from a well-characterized cell line. For this same reason, intimate contacts of Epicel™ recipients need not be deferred from tissue donation (Ref. 78) (Note: You should defer Epicel™ recipients from tissue donation).

F. What clinical evidence do I look for when screening a donor?

You must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (§ 1271.75). For cadaveric donors, you should:

- Determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, or,
- If an autopsy was performed, whether any special precautions were taken that would suggest there was special concern over the risk of transmission of a communicable disease from the donor.

You should look for the following examples of clinical evidence of relevant communicable disease. 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 examples of clinical evidence of relevant communicable disease.

1. HIV infection:

    - A prior positive or reactive screening test for HIV;
    - Unexplained weight loss;
    - Unexplained night sweats;
    - Blue or purple spots on or under the skin or mucous membranes typical of Kaposi's sarcoma;
    - Disseminated lymphadenopathy (swollen lymph nodes) for longer than one month;
    - Unexplained temperature of $> 100.5^{o}F$ ($38.06^{o}C$) for more than 10 days;
    - Unexplained persistent cough or shortness of breath;
    - Opportunistic infections;
    - Unexplained persistent diarrhea; and/or
    - Unexplained persistent white spots or unusual blemishes in the mouth (Ref. 79).

2. Hepatitis infection:

- A prior positive or reactive screening test for hepatitis B virus or hepatitis C virus;
- Unexplained jaundice;
- Unexplained hepatomegaly; and/or
- Past diagnosis of clinical, symptomatic viral hepatitis after the 11th birthday (Ref. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as caused by hepatitis A virus, EBV, or CMV.

Note: Records of the following laboratory data might assist you in making the donor-eligibility determination in the face of an inconclusive history of hepatitis infection: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or prothrombin time (Ref. 71). If these tests are abnormal, but a cause other than viral hepatitis was established, we do not recommend that you defer the donor.

3. Syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* infection (Screening and donor deferral for *Chlamydia trachomatis* and *Neisseria gonorrhea* required only for reproductive donors):

- Persons who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* in the preceding 12 months (Ref. 79). We do not recommend deferral of donors who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* more than 12 months ago, if evidence is presented that treatment occurred more than 12 months ago and was successful (Ref. 80).

4. Vaccinia infection (see IV. E., 13. and 14. for specific deferral criteria for recent smallpox vaccination or acquired vaccinia infection by contact with someone who received the smallpox vaccine):

- Recent smallpox vaccination;
- Eczema vaccinatum;
- Vesicular rash indicative of generalized vaccinia in a person who has had recent smallpox immunization or who is a contact of someone with recent smallpox immunization, as specified in IV. E. 14.;
- Progressive necrosis in an area of vaccination consistent with vaccinia necrosum;
- Postvaccinial encephalitis; and/or
- Vaccinial keratitis (Ref. 12).

5. WNV infection (Refs. 5, 6, and 7). Because signs and symptoms of WNV can be nonspecific, you should consider the following clinical evidence in light of other information obtained about the donor in making a donor eligibility determination.

- Mild symptoms might include fever, headache, body aches, or eye pain;
  - mild symptoms might also occasionally be accompanied by a skin rash on the trunk of the body; or
  - swollen lymph glands.
- Severe illness;
  - 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 or paralysis.

6. Sepsis (includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) or septic shock):

In reference to deceased donors, if any of these conditions is specifically diagnosed in the medical records during a hospital stay immediately preceding death, you should determine the donor to be ineligible (see section IV.E. criterion 12 of this document). If a living donor appears healthy, the donor usually does not need to be evaluated for sepsis.

Sepsis may be described by the following clinical evidence (Ref. 84). You should consider these signs in light of other information obtained about the donor in making a donor eligibility determination.

- Clinical evidence of infection; and
- Two or more of the following systemic responses to infection if unexplained:
  - Temperature of >100.4º F (38º C);
  - Heart rate >90 beats/min;
  - Respiratory rate >20 breaths/min or PaCO2 <32; or
  - WBC >12,000 cells/mm^3, < 4,000 cells/mm^3, or >10% immature (band) forms.
- More severe signs of sepsis include unexplained hypoxemia, elevated lactate, oliguria, altered mentation, and hypotension.
- Positive (pre-mortem) blood cultures might be associated with the above signs.

7. HTLV infection (Screening and donor deferral for HTLV required only for viable, leukocyte-rich HCT/P donors):

- A prior positive or reactive screening test for HTLV;
- Unexplained paraparesis; and/or
- Adult T-cell leukemia (Refs. 85 and 86).

G. What physical evidence do I look for?

Relevant medical records (§ 1271.3(s)) include the report of the physical assessment of a cadaveric donor (§ 1271.3(o)) or the physical examination of a living donor. For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health professionals. You should review the records of the physical assessment or physical examination for any of the following signs that may indicate high-risk behavior for or infection with a relevant communicable disease. Some of the following are not physical evidence of HIV, hepatitis, syphilis, or vaccinia but rather are indications of high-risk behavior associated with these diseases and would 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 examples of physical evidence of relevant communicable disease or high-risk behavior associated with these diseases (see Refs. 12 and 87).

1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, chancroid (you should consider these signs in light of other information obtained about the donor in making a donor eligibility determination) (seen in HIV, Hepatitis B virus, *Chlamydia trachomatis*, and *Neisseria gornorrheae*).

2. Physical evidence for risk of, or evidence of syphilis.

3. For a male donor, physical evidence of anal intercourse including perianal condyloma (seen in HIV and Hepatitis B).

4. Physical evidence of nonmedical percutaneous drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (seen in HIV, Hepatitis B and Hepatitis C).

5. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 12 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used (seen in HIV, Hepatitis B and Hepatitis C).

6. Disseminated lymphadenopathy (seen in HIV).

7. Unexplained oral thrush (seen in HIV).

8. Blue or purple spots consistent with Kaposi's sarcoma (seen in HIV).

9. Unexplained jaundice, hepatomegaly, or icterus (seen in Hepatitis B and Hepatitis C).

Note: Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed.

10. Physical evidence of sepsis, such as unexplained generalized rash or fever.

11. Large scab consistent with recent history of smallpox immunization.

12. Eczema vaccinatum (seen in vaccinia).

13. Generalized vesicular rash (generalized vaccinia).

14. Severely necrotic lesion consistent with vaccinia necrosum.

15. Corneal scarring consistent with vaccinial keratitis.

V. DONOR TESTING: GENERAL (§ 1271.80)

A. What requirements apply to laboratories performing donor testing for relevant communicable disease agents or diseases?

1. Under § 1271.1, you must be registered with FDA.

2. Under § 1271.80(c):

   - You must use appropriate FDA licensed, approved or cleared donor screening tests, if such tests are available, in accordance with the manufacturer's instructions.
   - You must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available.
   - You must be certified to perform such testing on human specimens either under the Clinical Laboratory Improvement Amendments (CLIA) or you must meet equivalent requirements as determined by the Centers for Medicare and Medicaid Services. Examples of the latter include laboratories that have been accredited by accrediting organizations approved by CMS. Certain states are exempt under CLIA because CMS

has found their state programs to be in compliance with CLIA standards.[4] Information about the CLIA program is available at the website: http://www.cms.hhs.gov/clia/.

3. Under §§ 1271.55(d), you must maintain documentation of results and interpretation of all testing for at least 10 years.

B. What type of test must I use?

You must test using an appropriate FDA-licensed, approved, or cleared donor screening test (if applicable to your HCT/P and available) in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of the relevant communicable disease agent or disease (§ 1271.80(c)).

- You should choose a test that is adequate, appropriate and available for detecting the relevant communicable disease agent or disease. We list tests that we currently consider to meet the requirements in § 1271.80(c) in section VI. of this document.
- In some instances, you may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. For example, to test for HIV-1, it is appropriate to use a test that detects viral nucleic acid (e.g., a nucleic acid test) and a test that detects antibody to HIV-1 (e.g., an enzyme immunoassay). If HIV-1 infection is present, each test may be reactive at different times during the course of the disease.
- If you are testing a specimen of cadaveric blood (i.e., taken from a donor whose heartbeat has ceased), you must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test, when such a test is applicable and available (§ 1271.80(c)). You can find a list of donor screening tests that have been licensed for use with cadaveric specimens on CBER's website: http://www.fda.gov/cber/tissue/prod.htm. We intend to update the website periodically as additional tests are licensed, cleared or approved for this use and become available.

C. How do I perform the test and interpret test results?

You must perform the test according to the manufacturer's instructions in the test kit's package insert (§ 1271.80(c)). The manufacturer's instructions also provide information about interpretation of test results.

---

[4] CMS has approved the following accrediting organizations: AABB, the American Osteopathic Association, the American Society for Histocompatibility and Immunogenics, the College of American Pathologists, COLA, and the Joint Commission on Accreditation of Healthcare Organizations. CMS has determined two states to be exempt: New York and Washington. Since these lists are subject to change, we recommend that you consult CMS for the most current information. http://www.cms.hhs.gov/clia/.

Some HCT/P establishments routinely rely solely on the test results obtained by an organ procurement organization (OPO), while other establishments routinely perform their own donor testing with the awareness that OPOs are performing donor testing on the same donors. The use of an appropriate screening test, performed in accordance with the manufacturer's instructions for use, would satisfy the requirements of §§ 1271.80 and 1271.85. However, because of testing practices related to organ donor screening as described by the Centers for Disease Control and Prevention (CDC), some OPOs may run an enzyme immunoassay donor screening test initially in triplicate (Ref. 18). The manufacturer's instructions for use of HCT/P donor screening tests currently do not provide instructions for initial triplicate testing, interpretation of test results of such testing, or for retesting after an initially reactive test when the tests are initially run in triplicate. Therefore, if initial tests are run in triplicate and one or more reactive results are obtained, manufacturers do not provide instructions on determining whether the sample is actually (repeatedly) reactive. Accordingly, if you engage an OPO to perform testing for you or if you routinely perform your own tests but are aware that an OPO is also performing tests on that donor, and that OPO performs initial testing in triplicate, then under §§ 1271.50 and 1271.150 you must obtain and review the results of all three tests performed by that OPO. If any of those initial tests is reactive or positive, then the donor would not be eligible to donate.

D. If a donor is one month of age or younger, from whom must I collect a specimen?

If a donor is one month of age or younger, you must collect and test a specimen from the birth mother instead of the donor (§ 1271.80(a)). The specimen for testing from the birth mother must be collected within seven days of donation by the infant (§ 1271.80(b)), unless the donation consists of peripheral blood stem/progenitor cells or bone marrow according to 1271.80(b)(1). If a specimen from the birth mother of a donor one month of age or younger is unavailable, the donor is ineligible. Specimens collected for any infant donor more than one month of age, including adopted infants, should be collected from the donor rather than the birth mother.

E. When do I collect a specimen for testing?

You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or within seven days before or after the recovery of cells and tissue (§ 1271.80(b)), with some exceptions as described in this section. As you are permitted under § 1271.80(b) to collect the donor specimen up to seven days before recovery of cells or tissues, you may use a premortem specimen to test a cadaveric donor, as long as the specimen is collected within that timeframe.

In the case of donation of hematopoietic stem/progenitor cells (HPCs) obtained from peripheral blood or bone marrow (if not excepted under § 1271.3(d)(4)), we realize that the recipient may begin myeloablative chemotherapy more than 7 days before the transplant. Therefore, the identified allogeneic donor might need to be qualified before

this time, including screening and testing of the donor for relevant communicable diseases. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (§ 1271.80(b)(1)).

In the case of donation of oocytes that do not undergo a period of cryopreservation prior to implantation, an oocyte donor might need to be qualified before the 7 days prior to donation due to the time necessary for receiving hormonal stimulation. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (§ 1271.80(b)(1)).

Although there is no requirement that specifies when to test the collected specimen, you should perform testing as soon as possible after collection and in accordance with the time limits stated in the manufacturer's instructions for use of the test kit.

F. May I test a specimen from a donor who has undergone transfusion or infusion?

Transfusion or infusion might dilute plasma, making test results unreliable (Refs. 18 and 88). You may test a specimen taken before the transfusion or infusion and up to seven days before recovery of cells or tissue, or if an adequate pre-transfusion/infusion specimen is not available, you may use an appropriate algorithm to determine whether plasma dilution is or is not sufficient to affect test results. In the absence of an appropriate specimen to test under either of these options, you must determine the donor to be ineligible (§ 1271.80(d)(2)).

For adult donors who have suffered blood loss sufficient to require fluid replacement, certain volumes of transfusions and/or infusions (described in section V.F.1. of this document) should be suspected of affecting test results. Blood loss might occur internally or externally. For donors 12 years of age or younger, you should suspect that any transfusion or infusion might affect test results regardless of blood loss. There might be other clinical situations involving transfusion or infusion that should also be suspected of affecting test results. Autologous blood removed pre-operatively or peri-operatively and reinfused during the same surgical procedure would not need to be included in plasma dilution calculations.

1. Adult Donor (§ 1271.80(d)(2)(ii)(A))

   In accordance with § 1271.80(d)(2)(ii)(A), you must suspect plasma dilution sufficient to affect the results of communicable disease agent testing where blood loss is known or suspected in a donor over 12 years of age in any of the following situations:

   a. The donor received a transfusion or infusion of more than 2000 milliliters of blood (e.g., whole blood or red blood cells) or colloids either: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen for testing is collected post-mortem, whichever occurred earlier.

b. The donor received more than 2000 milliliters of crystalloids within either: (i) the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if the specimen for testing is collected post-mortem, whichever occurred earlier.

c. The donor received more than 2000 milliliters of any combination of whole blood, red blood cells, colloids, and/or crystalloids within the applicable time frames set out in paragraphs (a) and (b) in this section.

2. Pediatric Donor (§ 1271.80(d)(2)(ii)(B))

In accordance with § 1271.80(d)(2)(ii)(B), you must suspect plasma dilution sufficient to affect the results of communicable disease agent testing, regardless of the presence or absence of blood loss, in a donor 12 years of age or under, in any of the following situations.

a. Any transfusion of blood or colloids: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.

b. Any crystalloids: (i) within the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.

3. Other Clinical Situations

We cannot provide guidance that anticipates every possible clinical situation where plasma dilution might affect test results. As the establishment that collects donor specimens for testing, you might be aware of additional circumstances in which plasma dilution might affect test results. Your SOPs should identify any additional circumstances where you believe plasma dilution might have occurred, and you should use a pre-transfusion/infusion specimen or apply an algorithm in those instances.

Examples: In the following situations, the donor has received a transfusion or infusion, but circumstances are not otherwise consistent with the examples set out in sections V.F.1. and 2. of this document. Nevertheless, you should consider test results on specimens collected at the time of donation to be potentially unreliable, triggering the need to test a pre-transfusion or pre-infusion sample, or to apply the algorithm, in the following circumstances:

- A donor who has previously had blood loss, stabilizes, then expires, but has received fluids in the 48 hours before specimen collection;
- A donor who is obese;
- A donor who in the absence of bleeding may have received large amounts of infusions which the medical director or designee believes may affect test results;
- A donor who weighs less than 45 kilograms or more than 100 kilograms.

  For situations falling outside those described in your SOPs, but where plasma dilution is still suspected, your SOPs should indicate how the situation would be handled (for example, by consulting the medical director).

4. Pre-Transfusion/Infusion Specimen

As part of establishing procedures for all steps in testing in accordance with § 1271.47(a), establishments making donor eligibility determinations must have SOPs that define those elements necessary to determine whether a pre-transfusion/infusion blood specimen is adequate for infectious disease testing (e.g., the amount of hemolysis, storage conditions, and age of the specimen). Testing laboratories must perform tests in accordance with the manufacturer's instructions (§ 1271.80(c)), including any instructions concerning factors that might affect specimen stability.

5. Algorithms

An appropriate algorithm must evaluate the fluid volumes administered in the 48 hours before collecting the specimen from the donor and show that plasma dilution sufficient to affect test results has not occurred (§ 1271.80(d)(2)(i)(B)). A plasma dilution of greater than 50% (1:2 dilution) could make test results unreliable. Therefore, you should use a method that compares the actual fluid volumes administered with both the donor's plasma and blood volumes to assess whether a greater than 50% dilution has occurred.

If the algorithm shows that greater than a 50% dilution has occurred, then you should not use the post-transfusion/infusion specimen for testing. You should not use further procedures that attempt to qualify the ineligible specimen.

When calculating blood and plasma volumes for donors in the 45 to 100 kilogram range, where there is blood loss with replacement, you should calculate and assess both blood volume and plasma volume as follows:

- Determine the blood volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.015, or alternatively by multiplying the body weight in kilograms by 70 mL/kg.

- Determine the plasma volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.025, or alternatively by multiplying the body weight in kilograms by 40 mL/kg.

  (See Appendices 1, 2, and 3)

G. What are some useful definitions related to hemodilution?

1. *Blood component* means a product containing a part of human blood separated by physical or mechanical means (§ 1271.3(i)).

2. *Colloid* means: (1) a protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or (2) blood components such as plasma and platelets (§ 1271.3(j)).

3. *Crystalloid* means an isotonic salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer's lactate solution, 5 percent dextrose in water (§ 1271.3(k)), or total parenteral nutrition (TPN) (Ref. 89).

4. *Plasma dilution* means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids (§ 1271.3(p)).

VI. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

You must test all donors of HCT/Ps, unless subject to an exemption in § 1271.90(a), for the diseases listed in section VI.A.1. through 5., as required in § 1271.85(a). You must use an FDA-licensed, approved, or cleared screening test, as described in section V. (§ 1271.80(c)). Current FDA-licensed donor screening tests for HIV, Hepatitis B, Hepatitis C, and HTLV are listed at the website: www.fda.gov/cber/products/testkits.htm. You may also check this website: http://www.fda.gov/cber/tissue/prod.htm for links to HCT/P-related, FDA-licensed, approved or cleared donor screening tests. The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable disease. Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. HIV, type 1 (FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2 (Refs. 79 and 90); and FDA-licensed screening NAT test for HIV-1, or combination NAT); (establishments

not utilizing an FDA-licensed screening test that tests for group O antibodies must evaluate donors for risk associated with HIV group O infection as described in section IV.E.27. and 28. (Refs. 66 and 76))

2. HIV, type 2 (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2) (Refs. 79 and 90);

3. HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) (Ref. 72) and for total antibody to Hepatitis B core antigen (anti-HBc)(IgG and IgM) (Refs. 91 through 98);

4. HCV (FDA-licensed screening test for anti-HCV[5]; and FDA-licensed screening NAT test for HCV, or combination NAT) (Refs. 2, 69, 90, 91, and 99); and

5. *Treponema pallidum* (FDA-cleared screening test for syphilis or FDA-cleared diagnostic serologic test for syphilis[6]) (Refs. 80 and 100).

As an exception for syphilis test results under § 1271.80(d)(1), you may determine to be eligible a donor whose specimen tests positive or reactive on a non-treponemal screening test for syphilis and negative or nonreactive on a specific treponemal confirmatory test (e.g., fluorescent treponemal antibody with absorption test (FTA-ABS), so long as all other required testing and screening are negative or nonreactive. A donor whose specimen tests positive or reactive on either a specific treponemal confirmatory test for syphilis or on a treponemal screening test is not eligible. If a cadaveric specimen is too hemolyzed to interpret the Rapid Plasma Reagin (RPR) test result, you should use another test, such as the FTA-ABS test result.

Discussion of Syphilis Assays

a. Nontreponemal assays, such as the Venereal Disease Research Laboratory (VDRL) test, the RPR test, and the Automated Reagin Test (ART), detect nonspecific antibodies (Reagin) to an antigen called cardiolipin present in host tissues as well as in treponemes. These assays are useful in monitoring the progression of disease and response to therapy. However, positive or reactive tests might be due to diseases other than syphilis (i.e., biological false positives). Samples that give positive or reactive results using nontreponemal assays may be retested using a treponemal-based assay as a confirmatory assay, such as the FTA-ABS. Nontreponemal test results usually become nonreactive within a year or two after successful treatment of syphilis.

---

[5] On July 22, 2004, FDA approved the Abbott Laboratories Supplement to their Biological License Application for Hepatitis C Virus Encoded Antigen to modify the intended use of the Abbott HCV EIA 2.0 to include the testing of cadaveric specimens. This specifically labeled test kit is now available for commercial use.

[6] For purposes of this guidance, we consider FDA-cleared diagnostic serological tests to be adequate for use in donor screening for syphilis.

b. Treponemal assays incorporate specific treponemal antigens into the testing system and detect specific antibodies to these antigens. With a few exceptions, unlike nontreponemal assays, results of tests for treponemal antigens remain positive or reactive for specific antibodies throughout an individual's life, even after successful treatment for syphilis. Treponemal assays include the FTA-ABS, the *Treponema pallidum* immobilization test (TPI) and the *T. pallidum* hemagglutination assay (TPHA). Since both types of assays detect antibodies, they might not identify some very early syphilis infections before antibodies to either cardiolipin or specific treponemal antigens have appeared (Ref. 100).

c. Serological tests for syphilis may be either non-treponemal or treponemal-based assays. Because of the potential for false-positive results in non-treponemal assays, § 1271.80(d)(1) provides that a specific treponemal confirmatory test, such as FTA-ABS, may be used to determine the syphilis status of an HCT/P donor when a positive result on a non-treponemal assay is obtained. If the confirmatory test is positive or reactive, the donor is ineligible.

6. p24 Antigen Tests: We are aware that HIV-1 p24 antigen tests are not readily available because they are not currently being manufactured. Therefore, you are not required to use the HIV-1 p24 antigen test for HCT/P donors. There are currently more sensitive tests available (Refs. 90 and 101).

Discussion About Additional Testing

You or someone else might perform additional testing not listed in section VI.A. If you perform donor testing for relevant communicable diseases using tests in addition to those listed in section VI.A.1. through 5., VI.B., and VI.C., as applicable, or if you are aware that other establishments are performing such tests and the test results are available, such test results must be included in the donor's relevant medical record (see § 1271.3). Because these test results are part of the medical record, you must consider any results from those tests when you make a donor eligibility determination (§ 1271.75(a)). By "available" we mean that the test result exists or is obtainable within a reasonable amount of time. A "reasonable" amount of time is a period of time that would not compromise the utility of the tissue.

Example: An eye bank is aware that a tissue bank performs an investigational NAT assay on a shared donor. The eye bank is not informed of the test results until after the corneas need to be released in order to maintain their utility. The eye bank does not have to wait for the investigational NAT results before releasing the corneas. The eye bank should inform the consignee that the investigational NAT results are pending, and subsequently report the result.

Confirmatory tests: You should consider performing confirmatory tests when a positive or reactive screening test result is received for such purposes as donor counseling or investigating discordant test results. However, if you perform a confirmatory test, negative or nonreactive results on a confirmatory test would not override a positive or reactive screening test (except for syphilis tests as previously described in this section).

> Example: A potential donor's specimen tests reactive for antibody to HCV. However, a confirmatory test (e.g., radioimmunoblot assay) is negative. The donor would be considered ineligible despite the negative confirmatory test.

Hepatitis B surface antibody (anti-HBs) test: If you obtain a positive or reactive anti-HBs test and other markers for Hepatitis B infection are negative or non-reactive, the donor may be eligible.

> Example: Your contract laboratory routinely performs three different tests for HBV: Hepatitis B surface antigen (HBsAg) test, Hepatitis B core antibody (anti-HBc) test, and anti-HBs test. You have a potential donor who is negative or nonreactive for HBsAg and anti-HBc, but positive or reactive for anti-HBs. The presence of anti-HBs alone would not disqualify the donor, because it usually is an indication of vaccination against Hepatitis B. However, in this situation, if the anti-HBc were also positive or reactive, the donor is ineligible. Data suggests that such results can be associated with infectivity (Refs. 92 through 98).

B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use?

1. You must test donors of viable, leukocyte-rich cells or tissue for the following diseases, in addition to those listed in section VI.A. of this document (§ 1271.85(b)). You must use an FDA-licensed, cleared, or approved donor screening test where such a test is available (§ 1271.80(c)). A list of currently licensed donor screening tests for HCT/Ps can be found at the website: http://www.fda.gov/cber/tissue/prod.htm.

The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable diseases:

a. Human T-lymphotropic virus, types I and II (FDA-licensed screening test for anti-HTLV I/II) (Refs. 85 and 86).

b. Cytomegalovirus (FDA-cleared screening test for anti-CMV) (total IgG and IgM).

Special note on CMV: CMV is not a relevant communicable disease agent or disease. However, establishments are required to test donors of viable, leukocyte-rich cells or tissues for CMV. A donor who tests positive or reactive for CMV (total antibody) is not necessarily ineligible to donate HCT/Ps. You must

establish and maintain an SOP regarding donors whose specimens test positive or reactive for CMV (§ 1271.85(b)(2)). This latter requirement only applies to establishments that make available for distribution HCT/Ps for which CMV testing is required.

Establishments should include procedures in their SOPs for communicating test results of donors who are positive or reactive for CMV antibody (total). The SOP should at least specify how the CMV test results should be communicated to the physician responsible for accepting the HCT/P. For example, the SOP should require that this information appear in materials accompanying the HCT/P, so that physicians may rely on this information to make informed decisions about the use of an HCT/P in a particular recipient's situation. An establishment's SOPs may also clarify that repeated testing of donors who are positive or reactive for CMV antibody (total) is unnecessary once it is established that a particular donor is positive or reactive, so long as this information is contained in the summary of records.

2. Examples of viable, leukocyte-rich cells or tissue include, but are not limited to:

- Hematopoietic stem/progenitor cells
- Semen

You should consider cells and tissues to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing might remove leukocytes.

3. Examples of cells or tissue that are not considered viable, leukocyte-rich cells or tissues include, but are not limited to:

- Corneas
- Sclera
- Skin
- Heart valves
- Dura mater
- Bone
- Tendons
- Ligaments
- Cartilage
- Oocytes

Under § 1271.45(b), in the case of embryos or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor. Therefore, although an embryo might not be considered leukocyte-rich, when an embryo is transferred to an individual who is not a sexually intimate partner, the semen donor should be tested for HTLV types I and II and for CMV.

C. How do I assess a donor of dura mater for TSE?

You must perform an adequate assessment for donors of dura mater to detect evidence of TSE (§ 1271.85(e)). After the dura mater has been removed, you should have a qualified pathologist perform an examination of the donor's brain. Following fresh examination, the brain should be fixed and sliced, gross examination of the entire brain should be conducted (including multiple cross sections), and multiple specimens of tissue should be obtained (from different parts of the brain) for histological examination. Exclude potential donors when any possible evidence of TSE-related changes is observed on histological examination. There are currently no FDA-licensed, approved, or cleared donor screening tests for prions.

VII. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, AND 1271.85)

A. Do I need to screen and test all donors of reproductive cells and tissue?

Except as provided in § 1271.90, you must screen and test all directed reproductive donors (as defined in § 1271.3(l)) and anonymous donors of reproductive cells and tissues (§§ 1271.75, 1271.80, and 1271.85) (Refs. 102 through 138).

B. What additional screening must I do for donors of reproductive cells and tissue?

In addition to the screening required for all cell and tissue donors and, if applicable, the screening requirements for viable, leukocyte-rich cell and tissue donors, you must review the relevant medical records of donors of reproductive HCT/Ps (who are not sexually intimate partners) for risk factors for and clinical evidence of infection due to relevant sexually transmitted and genitourinary diseases that can be transmitted with the recovery of the reproductive cells or tissue (§ 1271.75(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea*.

Specific donor screening recommendations are described in section IV. of this document.

C. What additional testing must I perform on donors of reproductive cells and tissue?

In addition to the testing required for all cell and tissue donors, and, if applicable, the testing required for donors of viable, leukocyte-rich cells and tissues, you must test donors of reproductive HCT/Ps (who are not sexually intimate partners) for evidence of infection due to relevant genitourinary disease agents (§ 1271.85(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhea*.

Special note on *Chlamydia trachomatis* and *Neisseria gonorrhea* testing: Although there are diagnostic tests available, there are currently no FDA-licensed, approved, or cleared tests for donor screening. In the absence of such screening tests, you must use an FDA-licensed, approved, or cleared diagnostic test labeled for the detection of these organisms in an asymptomatic, low-prevalence population (§ 1271.80(c)). FDA recommends *Chlamydia trachomatis* and *Neisseria gonorrhea* test kits utilizing NAT technology to adequately and appropriately reduce the risk of infectious disease transmission (Refs. 81, 139 through 148). You can find a listing of FDA-licensed or approved test kits for *Chlamydia trachomatis* and *Neisseria gonorrhea* at the following website: http://www.fda.gov/cber/tissue/prod.htm.

Exception from testing requirement:

If the reproductive cells or tissue are recovered by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* are not required (§ 1271.85(c)). However, if these tests are performed and one or both results are reactive, the donor must be determined ineligible, regardless of the recovery method used (§ 1271.80(d)(1)).

D. What follow-up testing is required for anonymous semen donors?

At least 6 months after the donation, you must collect a new specimen from the anonymous semen donor and repeat testing required under § 1271.85(a) through (c) (§ 1271.85(d)). You must quarantine the donated semen until the retesting is complete and the donor is determined to be eligible (§ 1271.60(a)). See IV. D. for a discussion of screening of repeat donors.

Note: If a repeat anonymous semen donor discontinues donations, you should wait at least 6 months from the final donation and re-test the donor for all RCDADs in order to qualify the final donation, except that you may use the results of tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* obtained at the final donation, or any time later than that, as the test of record to qualify that final donation.

Example: A donor tests negative or nonreactive for HBsAg and Hepatitis B core antibody. He is retested 6 months later, and is still negative or nonreactive for HBsAg, but is positive or reactive for Hepatitis B core antibody. The donor is ineligible. The semen in quarantine should not be transferred to an anonymous recipient.

E. Is follow-up testing required for directed donors of semen?

No, we do not require follow-up testing when semen is donated for directed use. Specimens collected for use in donor eligibility testing must be collected within 7 days of each collection (§ 1271.80(b)). You may alternately elect to perform quarantine of semen and retesting of the directed donor as described for anonymous semen donors in section VII.D. of this document (§ 1271.85(d)), rather than performing donor testing within 7 days of each collection.

F. Is a donor eligibility determination required for gestational carriers or surrogate carriers?

No. Gestational or surrogate carriers are not considered to be donors according to the FDA definition of a donor (§ 1271.3(m)). Gestational or surrogate carriers are considered to be HCT/P recipients.

G. Is a donor eligibility determination required for donors of reproductive cells and tissues that are transferred to gestational or surrogate carriers?

Section 1271.45(b) states that in the case of an embryo or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor. In complying with screening and testing requirements when embryos are involved, you should consider the relationship between the gestational carrier and the oocyte and semen donors separately in order to determine which donor eligibility requirements apply.

The following examples assume that when the embryos were formed, they were intended for transfer to a gestational carrier.

Example: A gestational carrier known to a couple will carry an embryo formed from the woman's oocyte and a mixture of semen from the man and an anonymous donor. The embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so both members of the couple are considered directed donors (§ 1271.3(l)).
- A donor eligibility determination must be made for both members of that couple (§ 1271.45(b)), but the use of reproductive cells or tissue from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65 (b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).
- The other semen donor is not known to the gestational carrier, so that donor is considered an anonymous donor and must have a donor eligibility determination (§ 1271.3(l)). If the semen donor is ineligible, the semen may not be used (§ 1271.45(b)).
- Quarantine of the anonymous donor's semen and retesting of the anonymous semen donor is required (§§ 1271.60(a) and 1271.85(d)).

Example: A gestational carrier known to a couple will carry an embryo formed from an oocyte donated by a donor who is known to the couple, but not to the gestational carrier, and semen from a member of that couple. The embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so the semen donor in this situation would be a directed donor (§ 1271.3(l)).
- A donor eligibility determination must be made for the directed semen donor each time he donates semen, but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).
- The oocyte donor is known to the couple but not known to the gestational carrier, so the donor is considered an anonymous donor (§ 1271.3(l)).
- The oocyte donor must have a donor eligibility determination (§ 1271.45(b)). If the oocyte donor is ineligible, the oocytes may not be used (§ 1271.45(c)).

Example: A surrogate carrier is known to a couple. The surrogate's oocyte(s) and semen from a member of that couple will be used to form embryo(s) that will be carried for the couple by the surrogate.

- No donor eligibility determination is required for the surrogate.
- The couple is known to the surrogate, so the semen donor would be a directed donor (§ 1271.3(l)).
- A donor eligibility determination is required for the semen donor each time he donates semen (§ 1271.45(b)), but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).

VIII. EXCEPTIONS FROM THE REQUIREMENTS FOR DETERMINING DONOR ELIGIBILITY AND SPECIAL CIRCUMSTANCES (§§ 1271.90, 1271.60(d), 1271.65(b), AND 1271.65(c))

This section describes: (1) situations when you are not required to perform a donor-eligibility determination; (2) situations in which the donor-eligibility determination is incomplete; and (3) situations in which the use of cells or tissue from a donor who has been determined to be ineligible is not prohibited. These situations require special labels. We define the term "label" when used in this guidance and in §§ 1271.60(d), 1271.65(b), and 1271.90(b), to mean either (1) a printed label affixed to the HCT/P container, or (2) a printed label affixed as a tie-tag to the HCT/P container. However, if it is not physically possible to comply with (1) or (2), either because the container is too small to affix all of these labels to the container, or because the

container is frozen, and therefore affixing the labels or attaching a tie-tag is not feasible, then the "Warning" statements in sections VIII.B.3., 5., and 6. of this document may accompany the HCT/P.

A. When is a donor eligibility determination not required? (§ 1271.90)

There are five situations in which you are not required to make a determination of donor eligibility or to perform donor screening and testing (§ 1271.90(a) and § 1271.15(a)). You must apply special label requirements if you do not screen and test (§ 1271.90(b)).

Donor eligibility determinations are not required (§ 1271.90(a) (1) through (4)) for:

1. Cells and tissue for autologous use (§ 1271.90(a)(1));

2. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use (§ 1271.90(a)(2);

3. Cryopreserved cells or tissue for reproductive use, other than embryos, exempt at the time of donation as described in 1 and 2, above, that are subsequently intended for directed donation, provided that

   a. additional donations of suitable cells and tissues are unavailable due to the infertility or health condition of a donor of the cryopreserved reproductive cells or tissue; and

   b. appropriate measures (see note after section VIII.A.4. of this document) are taken to screen and test the donor(s) before transfer to the recipient (§ 1271.90(a)(3)).

This exception addresses the situation where the donor was not screened and tested at the time of cryopreservation of the reproductive cells or tissue, and where the donor cannot make additional donations (e.g., the woman is post-menopausal or has had her ovaries or uterus removed, or because the man has undergone chemotherapy which renders him infertile). The donor wishes to make a directed donation of the cryopreserved semen or oocytes to someone the donor knows. Under these circumstances, you should screen and test the donor at least six months after recovery of the cryopreserved HCT/Ps and before the donation is made. In such cases, as in other cases involving directed donations of reproductive tissue, we would not prohibit the use of an HCT/P from an ineligible directed donor (section VIII.D.2. of this document).

4. A cryopreserved embryo, originally excepted under § 1271.90(a)(2) at the time of cryopreservation, that is subsequently intended for directed or anonymous donation. When possible, you should take appropriate measures (see note after section VIII.A.4. of this document) to screen and test the semen and oocyte donors before transfer of the embryo to the recipient (§ 1271.90(a)(4)).

This exception addresses the situation where sexually intimate partners were not screened and tested at the time of cyropreservation of their embryos, and later wish to make a directed or anonymous donation of their cryopreserved embryo(s). Under these circumstances, you should cryopreserve the embryos for at least 6 months and when the decision is made to donate the embryo(s) to an individual or a gestational carrier, you should screen and test the semen and oocyte donors when possible. In such cases, as in other cases involving directed donations of reproductive tissue (section VIII.D.2. of this document), the use of embryos from an ineligible directed donor is not prohibited. In addition, although FDA requires appropriate screening and testing when possible, if appropriate screening and testing are not possible (e.g., because one of the donors is unavailable), you may still transfer the embryo into a recipient. Labeling requirements apply, regardless of whether the semen and oocyte donors were screened and tested (those labeling requirements are described in section VIII.B. of this document).

Because one of the gamete donors would already have been found eligible, FDA also intends to apply this policy to a sexually intimate couple's cryopreserved embryos where one of the gametes is from a qualified (i.e., eligible) third party gamete donor, and the other gamete is from the sexually intimate partner of the intended recipient. In this circumstance, you should also screen and test the sexually intimate partner gamete donor when possible, and labeling requirements would apply.

Note: By "appropriate measures", we mean that you screen and test the donor(s) for those communicable disease agents for which a donor of such reproductive cells or tissue would ordinarily be tested at the time of donation, and a donor eligibility determination be made, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea*. The reason is that testing for *Chlamydia trachomatis* or *Neisseria gonorrhea* at the time of donation of the reproductive cells or tissue would not provide information about the status of the donor(s) for these agents at the time of the earlier cryopreservation.

To meet the donor testing requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., if the donor(s) cannot be tested due to death or inability to locate the donor, you should use the most recent available specimen from the donor(s) to perform the appropriate testing.

To meet the donor screening requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., if the donor(s) cannot be interviewed in person due to death or inability to locate the donor(s), then the donor medical history interview may be performed with another individual as described in § 1271.3(n), and section IV.C. of this document.

5. In accordance with § 1271.15(a), you are not required to make a determination of donor eligibility or to perform donor screening and testing if you are an establishment that uses HCT/Ps solely for nonclinical scientific or educational purposes (see section VIII.E. for those labeling requirements). The § 1271.90 labeling requirements do not apply.

B. What special labeling is required for HCT/Ps that are excepted under the provision of § 1271.90(a) from the donor eligibility determination (§ 1271.90(b)(1)through (6))?

Note: More than one of the following label requirements may apply to a particular HCT/P.

1. For HCT/Ps excepted under § 1271.90(a)(1), if the HCT/Ps are stored for autologous use, then under § 1271.90(b)(1) you must label the HCT/Ps "FOR AUTOLOGOUS USE ONLY."

2. For HCT/Ps excepted under § 1271.90(a)(1 through 4), if you do not test and screen a donor, then under § 1271.90(b)(2) you must label the HCT/Ps from that donor "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" unless you have performed all otherwise applicable screening and testing under §§ 1271.75, 1271.80, and 1271.85. For instance, if you perform some but not all of the testing and screening that would otherwise be required in these sections, or if you do not use a registered, CLIA-certified laboratory, or FDA licensed, cleared, or approved donor screening tests, this label would apply. This label would not apply to reproductive cells and tissue labeled in accordance with § 1271.90(b)(6).

Example 1: You must label an HCT/P from an autologous donor who has not been screened and tested under the exception in § 1271.90(a)(1), "FOR AUTOLOGOUS USE ONLY" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

Example 2: A man wishes to donate his stored semen to his sexually intimate partner. You test the man for HIV-1 and HIV-2 before he donates the semen to his sexually intimate partner, but under the § 1271.90 (a)(2) exception you are not required to test for any of the other relevant communicable diseases for which anonymous or directed sperm donors would be required to be tested. If you do not perform all of the additional testing, you must label the stored semen "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

3. For HCT/Ps excepted under § 1271.90(a)(2 through 4), (excluding HCT/Ps for autologous use), you must under § 1271.90(b)(3) label the HCT/P with "WARNING: Advise recipient of communicable disease risks" when either the donor eligibility determination has not been completed or if screening or testing indicates the presence of relevant communicable disease agents and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases.

4. For HCT/Ps excepted under § 1271.90(a), if donor screening or testing indicates the presence of relevant communicable disease agents or diseases and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases, then under 1271.90(b)(4) you must label the HCT/P with the Biohazard legend shown in § 1271.3(h).

5. If HCT/Ps are recovered under § 1271.90(a) from donors who have positive or reactive test results for any relevant communicable disease agent or disease, then under § 1271.90(b)(5) you must label the HCT/P with "WARNING: Reactive test results for (name of disease agent or disease)."

6. If reproductive tissue will be donated to a directed recipient under § 1271.90(a)(3) or a directed or anonymous recipient under § 1271.90(a)(4), and the screening and testing is performed before transfer to the recipient rather than at the time of recovery, then under § 1271.90(b)(6) you must label the HCT/P, "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently." Before transfer, if you have not performed all otherwise applicable screening and testing under §§ 1271.75, 1271.80, and 1271.85, then § 1271.90(b)(2) would apply.

Example: HCT/Ps from a sexually intimate couple are used to form embryos. The partners were not required to be screened and tested (§ 1271.90(a)(2)). Some embryos are transferred to the female partner and other embryos are cryopreserved. It is determined that the female partner cannot carry a fetus to term. The couple then decides to transfer the cryopreserved embryos to a gestational carrier who is known to the couple.

- No donor eligibility determination is required for the gestational carrier.
- The couple agrees to be screened and tested now, in accordance with §§ 1271.75, 1271.80, and 1271.85, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea* (See note in section VIII. A. of this document). They are both determined to be eligible.
- Under § 1271.90(b)(6), you must prominently label the HCT/P with the statement: "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently."
- The cryopreserved embryos are transferred to the gestational carrier.

- Note that if it was not possible to take appropriate measures to screen and test the donors (e.g., because one donor resides outside the United States and is unavailable) the embryos could nevertheless be transferred to the gestational carrier. In that case, the labeling would contain the statements: "Not evaluated for infectious substances" (§ 1271.90(b)(2)) and "Warning: Advise recipient of communicable disease risk" (§ 1271.90(b)(3)).

The records required under section § 1271.55 (see section III.G. of this document), including the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, based on the results of the screening and testing, and the summary of records are NOT required for HCT/Ps excepted under § 1271.90(a). The reason is that § 1271.55 applies only after a donor eligibility determination is complete, and this does not occur in the situations in § 1271.90. However, you should include this information, if known.

C. Can cells or tissue from a donor be used before the donor eligibility determination under § 1271.50 (a) is completed?

Yes. The use of cells or tissues from a donor before the donor eligibility determination is completed, is not prohibited under § 1271.60(d) if there is a documented urgent medical need. However, you must comply with the following requirements under § 1271.60(d)(2) through (4).

1. If an HCT/P is made available based on a physician's request for urgent medical need before completing the donor-eligibility determination, you must document the urgent medical need and label the HCT/P prominently: "NOT EVALUATED FOR INFECTIOUS SUBSTANCES," and "WARNING: Advise patient of communicable disease risk."

2. The HCT/P must be accompanied by a statement of: (a) the results of any required donor screening that has been completed; (b) the results of any required testing that has been completed; and (c) a list of any required screening and testing that has not yet been completed.

3. The manufacturer of the HCT/P must document that the physician using the HCT/P was notified that the testing and screening were not complete.

4. You must complete the donor-eligibility determination during or after the emergency use of the HCT/P, and inform the physician of the results of the determination.

D. Can cells or tissue from an ineligible donor ever be used for implantation, transplantation, infusion, or transfer? (§ 1271.65(b))

Yes. Under § 1271.65(b), an HCT/P from an ineligible donor, based on required testing and/or screening results, is not prohibited from use for implantation, transplantation, or transfer in the following three circumstances.

1. The HCT/P is for allogeneic use in a first-degree or second-degree blood relative. (Parents, children, and siblings are considered first-degree relatives. Aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren are second-degree relatives. Relations by adoption or marriage are not included);

2. The HCT/P consists of reproductive cells or tissue from a directed reproductive donor. (A directed reproductive donor means a donor of reproductive cells or tissue, including semen, oocytes, and embryos, to which the donor contributed the spermatozoa or oocyte, to a specific recipient, and who knows and is known by the recipient before donation. The term does not include a sexually intimate partner (§ 1271.3(l)); or

3. There is an urgent medical need for the HCT/P based upon a physician's request documented by the establishment. (An urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P (§ 1271.3(u)).

An HCT/P made available under these provisions from an otherwise ineligible donor must be labeled prominently with the Biohazard legend (§ 1271.3(h)) and with the statement "WARNING: Advise patient of communicable disease risk," and, in the case of reactive or positive test results, "WARNING: Reactive test results for (name of disease agent or disease)" (§ 1271.65(b)(2)). The records required under § 1271.55 must accompany the HCT/Ps used under § 1271.65(b). The records required under § 1271.55 (section III.G. of this document) include the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, and the summary of records. If the donor was determined to be ineligible based on screening, the summary of records must contain a statement noting the reason or reasons for the determination of ineligibility (§ 1271.55(b)(4)).

Moreover, if you are the manufacturer of an HCT/P used in the previously described circumstances, you must document that you notified the physician using the HCT/P of the results of screening and testing (§ 1271.65(b)(3)).

Note: If testing and screening are not required under the regulations, such as when a donor donates reproductive tissue to a sexually intimate partner, then the reproductive tissue may be donated in accordance with that exception, even if you know that the donor is otherwise ineligible.

E. Are there any other uses for HCT/Ps from donors determined to be ineligible?

Yes. The use of HCT/Ps from a donor determined to be ineligible, is not prohibited for nonclinical uses, so long as they bear the Biohazard legend and are labeled "For Nonclinical Use Only" (§ 1271.65(c)).

IX. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than 6 months after the original issuance date of this guidance (February 27, 2007).

X. REFERENCES

1. Food and Drug Administration, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, Final Rule; 69 FR 29786. http://www.fda.gov/cber/rules/suitdonor.htm.
2. Food and Drug Administration, Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation, dated July 1997. http://www.fda.gov/cber/guidelines.htm.
3. Food and Drug Administration, Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps), dated May 2004. http://www.fda.gov/cber/gdlns/tissdonor.htm.
4. Food and Drug Administration, Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), dated June 2002. http://www.fda.gov/cber/guidelines.htm.
5. Food and Drug Administration, Draft Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection dated April 2005. http://www.fda.gov/cber/guidelines.htm.
6. Food and Drug Administration, Guidance for Industry: Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection, dated June 2005. http://www.fda.gov/cber/guidelines.htm.
7. Food and Drug Aministration's Current Thinking on Donor Deferral for Potential or Documented Infection With West Nile Virus. Blood Products Advisory Committee (BPAC) Meeting, Holiday Inn Gaithersburg, October 22 2004. http://www.fda.gov/ohrms/dockets/ac/cber04.html#BloodProducts.
8. Fenner, I., et al., Smallpox and its eradication: World Health Organization, 1988.
9. Blattner, R.J., et al., Antibody Response to Cutaneous Inoculation with Vaccinia Virus: Viremia and Viruria in Vaccinated Children. J Pediatr 1964; 64:839-52.

10. Kempe C.H., Studies Smallpox and Complications of Smallpox Vaccination. Pediatrics 1960; 26:176-89.
11. Centers for Disease Control and Prevention. Smallpox Vaccine (Vaccine Information Sheet) - Version II. 2003. http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/smallpox-vis.pdf.
12. Food and Drug Administration. Guidance for Industry: Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients, dated December 2002. http://www.fda.gov/cber/guidelines.htm.
13. Centers for Disease Control and Prevention. In the Absence of SARS-CoV Transmission Worldwide: Guidance for Surveillance, Clinical and Laboratory Evaluation, and Reporting (Version 2). January 21 2004. http://www.cdc.gov/ncidod/sars/pdf/absenceofsars.pdf.
14. Centers for Disease Control and Prevention. Revised U.S. Surveillance Case Definition for Severe Acute Respiratory Syndrome (SARS) and Update on SARS Cases --- United States and Worldwide, December 2003. Morbidity and Mortality Weekly Report 2003; 52(49):1202-1206. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5249a2.htm.
15. Centers for Disease Control and Prevention. Update: Severe Acute Respiratory Syndrome --- Worldwide and United States, 2003. Morbidity and Mortality Weekly Report 2003; 52(28):664-665. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5228a4.htm.
16. Peiris, J.S., et al., The Severe Acute Respiratory Syndrome. N Engl J Med 2003; 349:2431-41.
17. Human Cells, Tissues and Cellular and Tissue-Based Products: Risk Factors for Semen Donation, Blood Products Advisory Committee (BPAC) Meeting, Hilton Silver Spring Hotel, 14 December 2001. http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3817t2.doc.
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.
19. Buchbinder, S.P., et al., Feasibility of Human Immunodeficiency Virus Vaccine Trials in Homosexual Men in The United States: Risk Behavior, Seroincidence, And Willingness to Participate. J Infect Dis 1996; 174:954-61.
20. Busch, M.P., et al., Estimation of HIV Incidence in U.S. Blood Donors Using A Novel Detuned Anti-Hiv Eia Test Strategy, 5th Conf Retrovir Oppor Infect 1998; abstract no. 531.
21. Centers for Disease Control and Prevention. Guidelines for National Human Immunodeficiency Virus Case Surveillance, Including Monitoring for Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. MMWR Recomm Rep 1999; 48(RR13):1-31.
22. Coleman, P.J., et al., Incidence of Hepatitis B Virus Infection in the United States, 1976-1994: Estimates from the National Health and Nutrition Examination Surveys. J Infect Dis 1998; 178:954-9.
23. Cowan, D.N., et al., The Incidence of HIV Infection Among Men in the United States Army Reserve Components, 1985-1991. AIDS 1994; 8:505-11.

24. Davis, S.F., et al., Trends in HIV Prevalence Among Childbearing Women in the United States, 1989-1994. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:158-64.
25. Glynn, S.A., et al., Demographic Characteristics, Unreported Risk Behaviors, and The Prevalence and Incidence Of Viral Infections: A Comparison of Apheresis and Whole-Blood Donors. The Retrovirus Epidemiology Donor Study. Transfusion 1998; 38:350-8.
26. Hawkins, R.E., et al., Risk of Viral Hepatitis Among Military Personnel Assigned to US Navy Ships. J Infect Dis 1992; 165:716-9.
27. Holmberg, S.D., The Estimated Prevalence and Incidence Of HIV In 96 Large Us Metropolitan Areas. Am J Public Health 1996; 86:642-54.
28. Hyams, K.C., et al. Geographic risk Factors for Viral Hepatitis and Cytomegalovirus Infection Among United States Armed Forces Blood Donors. Transfusion 1992; 32:644-7.
29. Karon, J.M., et al., Prevalence of HIV Infection in the United States, 1984 to 1992. Jama 1996; 276:126-31.
30. Katz, M.H., et al., Continuing High Prevalence of HIV and Risk Behaviors Among Young Men Who Have Sex With Men: The Young Men's Survey in the San Francisco Bay Area in 1992 to 1993 and in 1994 to 1995. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:178-81.
31. Koblin, B.A., Taylor, P.E., Avrett, S., Stevens, C.E., The Feasibility of Hiv-1 Vaccine Efficacy Trials Among Gay/Bisexual Men In New York City: Project Achieve. AIDS Community Health Initiative Enroute to the Vaccine Effort. AIDS 1996; 10:1555-61.
32. McFarland, W., et al., Detection of Early HIV Infection and Estimation of Incidence Using A Sensitive/Less-Sensitive Enzyme Immunoassay Testing Strategy at Anonymous Counseling and Testing Sites in San Francisco. J Acquir Immune Defic Syndr 1999; 22:484-9.
33. McFarland, W., et al., Estimation of Human Immunodeficiency Virus (HIV) Seroincidence Among Repeat Anonymous Testers in San Francisco. Am J Epidemiol 1997; 146:662-4.
34. McQuillan, G.M., et al., H.S. Prevalence of Hepatitis B Virus Infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. Am J Public Health 1999; 89:14-8.
35. Parrish, E.M., et al., HIV Infection in Disadvantaged Out-Of-School Youth: Prevalence for U.S. Job Corps Entrants, 1990 through 1996. Clinical Laboratory Science 1995; 8:350-353.
36. Peterman, T.A., et al., Decreasing Prevalence Hides a High HIV Incidence: Miami. AIDS 1995; 9:965-70.
37. Renzullo, P.O., et al., Human Immunodeficiency Virus Type-1 Seroconversion Trends Among Young Adults Serving in the United States Army, 1985-1993. United States Military Medical Consortium for Applied Retroviral Research. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 10:177-85.
38. Seage, G.H., et al., Feasibility of Conducting HIV-1 Vaccine Trials in the United States: Recruitment, Retention and HIV-1 Seroincidence From the HIV Network for Prevention Trials (HIVNET) Vaccine Preparedness Study (VPS). 12th World AIDS Conference, 1998.

39. Tabet, S.R., et al., Incidence of HIV and Sexually Transmitted Diseases (STD) in a Cohort of HIV-negative Men Who Have Sex With Men (MSM). AIDS 1998; 12:2041-8.
40. Thomas, D.L., et al., Hepatitis C, Hepatitis B, and Human Immunodeficiency Virus Infections Among Non-Intravenous Drug-Using Patients Attending Clinics for Sexually Transmitted Diseases. J Infect Dis 1994; 169:990-5.
41. Torian, L., et al., High HIV Seroincidence in Nonwhite Bisexual Men Making Repeat Visits to A New York City Sexually Transmitted Disease Clinic, 1994-1995: Results of A Blinded Longitudinal Survey., 4th Conference on Retroviruses and Opportunistic Infections 1997, 1997.
42. Valdiserri, R.O., et al., Trends in HIV Seropositivity in Publicly Funded HIV Counseling and Testing Programs: Implications for Prevention Policy. Am J Prev Med 1998; 14:31-42.
43. Valleroy, L.A., et al., HIV Infection in Disadvantaged Out-Of-School Youth: Prevalence for U.S. Job Corps Entrants, 1990 through 1996. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:67-73.
44. Weinstock, H., et al., HIV Seroincidence and Risk Factors Among Patients Repeatedly Tested For HIV Attending Sexually Transmitted Disease Clinics in the United States, 1991 to 1996. STD Clinic HIV Seroincidence Study Group. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:506-12.
45. Centers for Disease Control and Prevention. HIV and AIDS - United States, 1981-2000. Morbidity and Mortality Weekly Report 2001; 50:430-4. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5021a2.htm.
46. Centers for Disease Control and Prevention. HIV Prevalence Trends in Selected Populations in the United States: Results from National Serosurveillance, 1993-1997. 2001. http://www.cdc.gov/hiv/pubs/hivprevalence/toc.htm.
47. Alter, M.J., et al., The Prevalence of Hepatitis C Virus Infection in the United States, 1988 through 1994. N Engl J Med 1999; 341:556-62.
48. Armstrong, G.L., et al., The Past Incidence of Hepatitis C Virus Infection: Implications for the Future Burden of Chronic Liver Disease in the United States. Hepatology 2000; 31:777-82.
49. Centers for Disease Control and Prevention. Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-related Chronic Disease. MMWR Recomm Rep 1998; 47:1-39.
50. Des Jarlais, D.C., et al., HIV Incidence Among Injection Drug Users in New York City, 1992-1997: Evidence for a Declining Epidemic. Am J Public Health 2000; 90:352-9.
51. Edlin, B.R., et al., High HIV Incidence Among Young Urban Street-Recruited Crack Cocaine Smokers, XI International Conference on AIDS, 1996.
52. Garfein, R.S., et al., Prevalence and Incidence of Hepatitis C Virus Infection Among Young Adult Injection Drug Users. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 18 Suppl 1:S11-9.
53. Garfein, R.S., et al., Viral Infections in Short-Term Injection Drug Users: The Prevalence of The Hepatitis C, Hepatitis B, Human Immunodeficiency, and Human T-lymphotropic Viruses. Am J Public Health 1996; 86:655-61.
54. Hagan, H., et al., Syringe Exchange and Risk af Infection With Hepatitis B and C Viruses. Am J Epidemiol 1999; 149:203-13.

55. Kerndt, P.R., et al., HIV Incidence Among Injection Drug Users Enrolled in a Los Angeles Methadone Program. Jama 1995; 273:1831-2.
56. Meyers, K., et al., Will Preventive HIV Vaccine Efficacy Trials Be Possible With Female Injection Drug Users? J Acquir Immune Defic Syndr Hum Retrovirol 1995; 10:577-85.
57. Nelson, K.E., Temporal trends, demographic and behavioral risk factors for HIV incidence among injection drug users in Baltimore. Am J Epidemiol 1999; 149:S10.
58. Nelson, K.E., et al., Temporal Trends in the Incidence of Human Immunodeficiency Virus Infection and Risk Behavior Among Injection Drug Users in Baltimore, Maryland, 1988-1998. Am J Epidemiol 2002; 156:641-53.
59. Villano, S.A., et al., Incidence and Risk Factors for Hepatitis C Among Injection Drug Users in Baltimore, Maryland. J Clin Microbiol 1997; 35:3274-7.
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.
61. Onorato, I.M., et al., Prevalence, Incidence, and Risks for HIV-1 Infection in Female Sex Workers in Miami, Florida. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 9:395-400.
62. Rosenblum, L., et al., Sexual Practices in The Transmission Of Hepatitis B Virus and Prevalence of Hepatitis Delta Virus Infection in Female Prostitutes in the United States. Jama 1992; 267:2477-81.
63. Williams, C.M., Sexual Practices Associated With Hepatitis C Virus Infection Among Non Injecting-Drug-Using Female Prostitutes in the United States, 6th International Symposium on Hepatitis C & Related Viruses: Molecular Virology and Pathogenesis, 1999.
64. Public Health Service. PHS Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C. Morbidity and Mortality Weekly Report 1991; 40:1-17. http://www.cdc.gov/mmwr/preview/mmwrhtml/00043883.htm.
65. NIH Consensus Statement. Management of Hepatitis C: 2002. 2002; 19:24. http://www.consensus.nih.gov/cons/116/116cdc_intro.htm.
66. Food and Drug Administration, Draft Guidance for Industry: Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Human Donors of Blood and Blood Componentsdated May 2004. http://www.fda.gov/cber/guidelines.htm.
67. Food and Drug Administration Memorandum to All Blood Establishments for "Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma" June 8, 1995. http://www.fda.gov/cber/bldmem/060895.txt.
68. Ruiz, J.D., et al., Prevalence and Correlates of Hepatitis C Virus Infection Among Inmates Entering The California Correctional System. West J Med 1999; 170:156-60.
69. Food and Drug Administration Revised Recommendations Memorandum to All Blood Establishments for "Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)" April 23, 1992. http://www.fda.gov/cber/memo.htm.

70. Food and Drug Administration Memorandum to All Blood Establishments for "Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven Years to Serve as Donors of Whole Blood and Plasma: Alternative Procedures, 21 CFR 640.120" April 23, 1992. http://www.fda.gov/cber/bldmem/042392ex.txt.
71. Food and Drug Administration Recommendations to All Blood Establishments for "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis" December 22, 1993. http://www.fda.gov/cber/bldmem/122293.txt.
72. Centers for Disease Control and Prevention. Clinical Guidance on the Identification and Evaluation of Possible SARS-CoV Disease Among Persons Presenting with Community-Acquired Illness (Version 2). January 8, 2004. http://www.fda.gov/cber/memo.htm.
73. Food and Drug Administration, Guidance for Industry: Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS dated April 2003. http://www.fda.gov/cber/gdlns/sarsbldgd1.htm.
74. Food and Drug Administration, Guidance for Industry: Revised Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS dated September 2003. http://www.fda.gov/cber/guidelines.htm. http://www.fda.gov/cber/blood/bldguid.htm
75. Food and Drug Administration, Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products dated January 2002. http://www.fda.gov/cber/guidelines.htm.
76. Food and Drug Administration Recommendations to all Blood Establishments for "Interim Recommendations for Deferral of Donors at Increased Risk for HIV-1 Group O Infection", December 11, 1996. http://www.fda.gov/cber/bldmem/mem121196a.txt.
77. Food and Drug Administration, Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts, dated February 2002. http://www.fda.gov/cber/gdlns/zoobldxeno.htm.
78. Report of the Food and Drug Administration Subcommittee on Xenotransplantation: meeting of January 13, 2000, Center for Biologics Evaluation and Research. Xenotransplantation 2000; 7:75-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10961289.
79. Food and Drug Administration Revised Recommendations to all Blood Establishments for "The Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products", April 23, 1992. http://www.fda.gov/cber/memo.htm.
80. Food and Drug Administration Recommendations to all Blood Establishments for "Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing", December 12, 1991. http://www.fda.gov/cber/memo.htm.
81. Centers for Disease Control and Prevention. Outbreak of Severe Acute Respiratory Syndrome ---Worldwide, 2003. Morbidity and Mortality Weekly Report 2003; 52(11):226-228. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5211a5.htm.

82. Centers for Disease Control and Prevention. Updated Interim Surveillance Case Definition for Severe Acute Respiratory Syndrome (SARS)---April 29, 2003. 2003; 52(17):391-393. http://www.cdc.gov/ncidod/sars/casedefinition.htm.
83. Centers for Disease Control and Prevention. Severe Acute Respiratory Syndrome; "Current SARS Situation". http://www.cdc.gov/ncidod/sars/situation.htm.
84. Mandell: Principles and Practice of Infectious Diseases, 5th ed.: Churchill Livingstone, Inc., 2000:806-808; 1991-2000.
85. Food and Drug Administration Recommendations to all Blood Establishments for "HTLV-I Antibody Testing", November 29, 1988. http://www.fda.gov/cber/bldmem/112988.txt.
86. Food and Drug Administration, Guidance for Industry: Donor Screening for Antibodies to HTLV-II, dated August 1997. http://www.fda.gov/cber/guidelines.htm.
87. Centers for Disease Control and Prevention. Smallpox Home Page. Last modified date: April 4, 2005. http://www.bt.cdc.gov/agent/smallpox/index.asp.
88. Chopek, M.M., Protein and Biochemical Changes During Plasma Exchange. Therapeutic Hemapheresis: A Technical Workshop Presented by the Committee on Technical Workshops, American Association of Blood Banks 1980; 1980:13-52.
89. Dudrick, S.J., Professor of Surgery, Yale University, 2005: Personal Communication.
90. Food and Drug Administration, Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV dated October 2004. http://www.fda.gov/cber/guidelines.htm.
91. Food and Drug Administration Recommendations to all Blood Establishments Concerning "Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc)", September 10, 1991. http://www.fda.gov/cber/bldmem/091091.txt.
92. Hsia, C.C., et al., Molecular and Serological Aspects of HBsAg-negative Hepatitis B Virus Infections in North America. J Med Virol 2003; 70:20-6.
93. Minuk, G.Y., et al., Occult Hepatitis B Virus Infection in a North American Community-Based Population. J Hepatol 2005; 42:480-5.
94. Nakamoto, N., et al., Genomic Mutations With Amino Acid Substitutions of Circulating Hepatitis B Virus Found in Non-B, Non-C Patients With Hepatocellular Carcinoma. Intern Med 2003; 42:322-30.
95. Takaguchi, K., et al., Detection of Hepatitis B Virus DNA in the Liver and Serum of Patients With Hepatitis B Surface Antigen and Hepatitis C Virus Antibody Negative Chronic Liver Disease. Hepatol Res 2002; 22:139-144.
96. Torbenson, M., et al., High Prevalence of Occult Hepatitis B in Baltimore Injection Drug Users. Hepatology 2004; 39:51-7.
97. Weber, B., et al., Hepatitis B Virus Markers in Anti-HBc Only Positive Individuals. J Med Virol 2001; 64:312-9.
98. Fagan, E.A., et al., Persistence of Free HBV DNA in Body Secretions and Liver Despite Loss of Serum HBV DNA After Interferon-Induced Seroconversion. J Med Virol 1986; 20:183-8.
99. Zou, S., et al., Probability of Viremia with HBV, HCV, HIV, and HTLV Among Tissue Donors in the United States. N Engl J Med 2004; 351:751-9.

100. Food and Drug Administration, Draft Guidance for Industry: Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis, dated June 2003. http://www.fda.gov/cber/guidelines.htm.
101. Food and Drug Administration Recommendations to all Blood Establishments for "Donor Screening with a Licensed Test for HIV-1 Antigen", August 8, 1995. http://www.fda.gov/cber/bldmem/hiv-ag.txt.
102. Ali, B.A., et al., Detection and Expression of Hepatitis B Virus X Gene in One And Two-Cell Embryos From Golden Hamster Oocytes in Vitro Fertilized with Human Spermatozoa Carrying HBV DNA. Mol Reprod Dev 2005; 70:30-6.
103. Bertrand, E., et al., Presence of HIV-1 in Follicular Fluids, Flushes And Cumulus Oophorus Cells Of HIV-1-Seropositive Women During Assisted-Reproduction Technology. AIDS 2004; 18:823-5.
104. Bourlet, T., et al., Multicenter Quality Control for the Detection of Hepatitis C Virus RNA In Seminal Plasma Specimens. J Clin Microbiol 2003; 41:789-93.
105. Bujan, L., et al., Intermittent Human Immunodeficiency Type 1 Virus (HIV-1) Shedding in Semen and Efficiency of Sperm Processing Despite High Seminal HIV-1 RNA levels. Fertil Steril 2002; 78:1321-3.
106. Bujan, L., et al., Factors of Intermittent HIV-1 Excretion in Semen and Efficiency of Sperm Processing in Obtaining Spermatozoa Without HIV-1 Genomes. AIDS 2004; 18:757-66.
107. Bujan, L., et al., Insemination With Isolated and Virologically Tested Spermatozoa is a Safe Way For Human Immunodeficiency Type 1 Virus-Serodiscordant Couples With an Infected Male Partner to Have a Child. Fertil Steril 2004; 82:857-62.
108. Cassuto, N.G., et al., A Modified RT-PCR Technique to Screen for Viral RNA in the Semen of Hepatitis C Virus-Positive Men. Hum Reprod 2002; 17:3153-6.
109. Davison, F., et al., Detection of Hepatitis B Virus DNA in Spermatozoa, Urine, Saliva and Leucocytes, of Chronic HBsAg Carriers. A Lack of Relationship with Serum Markers of Replication. J Hepatol 1987; 4:37-44.
110. Dejucq, N., Jegou, B. Viruses in the Mammalian Male Genital Tract and Their Effects on the Reproductive System. Microbiol Mol Biol Rev 2001; 65:208-31.
111. Devaux, A., et al., Hepatitis C Virus Detection in Follicular Fluid and Culture Media From HCV+ Women, And Viral Risk During IVF Procedures. Hum Reprod 2003; 18:2342-9.
112. Englert, Y., et al., Medically Assisted Reproduction in the Presence of Chronic Viral Diseases. Hum Reprod Update 2004; 10:149-62.
113. Garrido, N., et al., Report of the Results of a 2 year Programme of Sperm Wash and ICSI Treatment for Human Immunodeficiency Virus and Hepatitis C Virus Serodiscordant Couples. Hum Reprod 2004; 19:2581-6.
114. Gilling-Smith, C.. HIV Prevention. Assisted Reproduction in HIV-Discordant Couples. AIDS Read 2000; 10:581-7.
115. Hadchouel, M., et al., Presence of HBV DNA in Spermatozoa: A Possible Vertical Transmission of HBV via the Germ Line. J Med Virol 1985; 16:61-6.
116. Hanabusa, H., et al., An Evaluation of Semen Processing Methods for Eliminating HIV-1. Aids 2000; 14:1611-6.

117. Huang, J.M., et al., Effects of Hepatitis B Virus Infection on Human Sperm Chromosomes. World J Gastroenterol 2003; 9:736-40.
118. Huang, J.M., et al., Studies on the Integration of Hepatitis B Virus DNA Sequence in Human Sperm Chromosomes. Asian J Androl 2002; 4:209-12.
119. Leruez-Ville, M., et al., Assisted Reproduction in HIV-1-Serodifferent Couples: The Need for Viral Validation of Processed Semen. AIDS 2002; 16:2267-73.
120. Lesourd, F., et al., Transmissions of Hepatitis C Virus During the Ancillary Procedures for Assisted Conception. Hum Reprod 2000; 15:1083-5.
121. Letur-Konirsch, H., et al., Safety of Cryopreservation Straws for Human Gametes Or Embryos: A Study with Human Immunodeficiency Virus-1 Under Cryopreservation Conditions. Hum Reprod 2003; 18:140-4.
122. Levy, R., et al., Pregnancy After Safe IVF With Hepatitis C Virus RNA-Positive Sperm. Hum Reprod 2002; 17:2650-3.
123. Levy, R., et al., Transmission Risk of Hepatitis C Virus in Assisted Reproductive Techniques. Hum Reprod 2000; 15:810-6.
124. Maertens, A., et al., Validation of Safety Procedures for the Cryopreservation of Semen Contaminated With Hepatitis C Virus in Assisted Reproductive Technology. Hum Reprod 2004; 19:1554-7.
125. Manno, M., et al., Preliminary Evidence on The Safety of ICSI with Testicular Spermatozoa in Hcv-Infected Male: A Case Report. Hum Reprod 2003; 18:1666-8.
126. Marina, S., et al., Human Immunodeficiency Virus Type 1--Serodiscordant Couples Can Bear Healthy Children After Undergoing Intrauterine Insemination. Fertil Steril 1998; 70:35-9.
127. Meseguer, M., et al., Comparison of Polymerase Chain Reaction-Dependent Methods for Determining The Presence of Human Immunodeficiency Virus and Hepatitis C Virus in Washed Sperm. Fertil Steril 2002; 78:1199-202.
128. Nicopoullos, J.D., et al., The Effect of Human Immunodeficiency Virus on Sperm Parameters and the Outcome of Intrauterine Insemination Following Sperm Washing. Hum Reprod 2004; 19:2289-97.
129. Papaxanthos-Roche, A., et al., PCR-Detected Hepatitis C Virus RNA Associated with Human Zona-Intact Oocytes Collected From Infected Women for ART. Hum Reprod 2004; 19:1170-5.
130. Pasquier, C., et al., Intermittent Detection of Hepatitis C Virus (HCV) in Semen From Men With Human Immunodeficiency Virus Type 1 (HIV-1) and HCV. J Med Virol 2003; 69:344-9.
131. Passos, E.P., et al., Hepatitis C Virus Infection and Assisted Reproduction. Hum Reprod 2002; 17:2085-8.
132. Payne, M.A., Lamb, E.J., Use of Frozen Semen to Avoid Human Immunodeficiency Virus Type 1 Transmission by Donor Insemination: A Cost-Effectiveness Analysis. Fertil Steril 2004; 81:80-92.
133. Politch, J.A., et al., Separation of Human Immunodeficiency Virus Type 1 From Motile Sperm By The Double Tube Gradient Method Versus Other Methods. Fertil Steril 2004; 81:440-7.
134. Semprini, A.E., et al., Insemination of HIV-Negative Women with Processed Semen of HIV-Positive Partners. Lancet 1992; 340:1317-9.

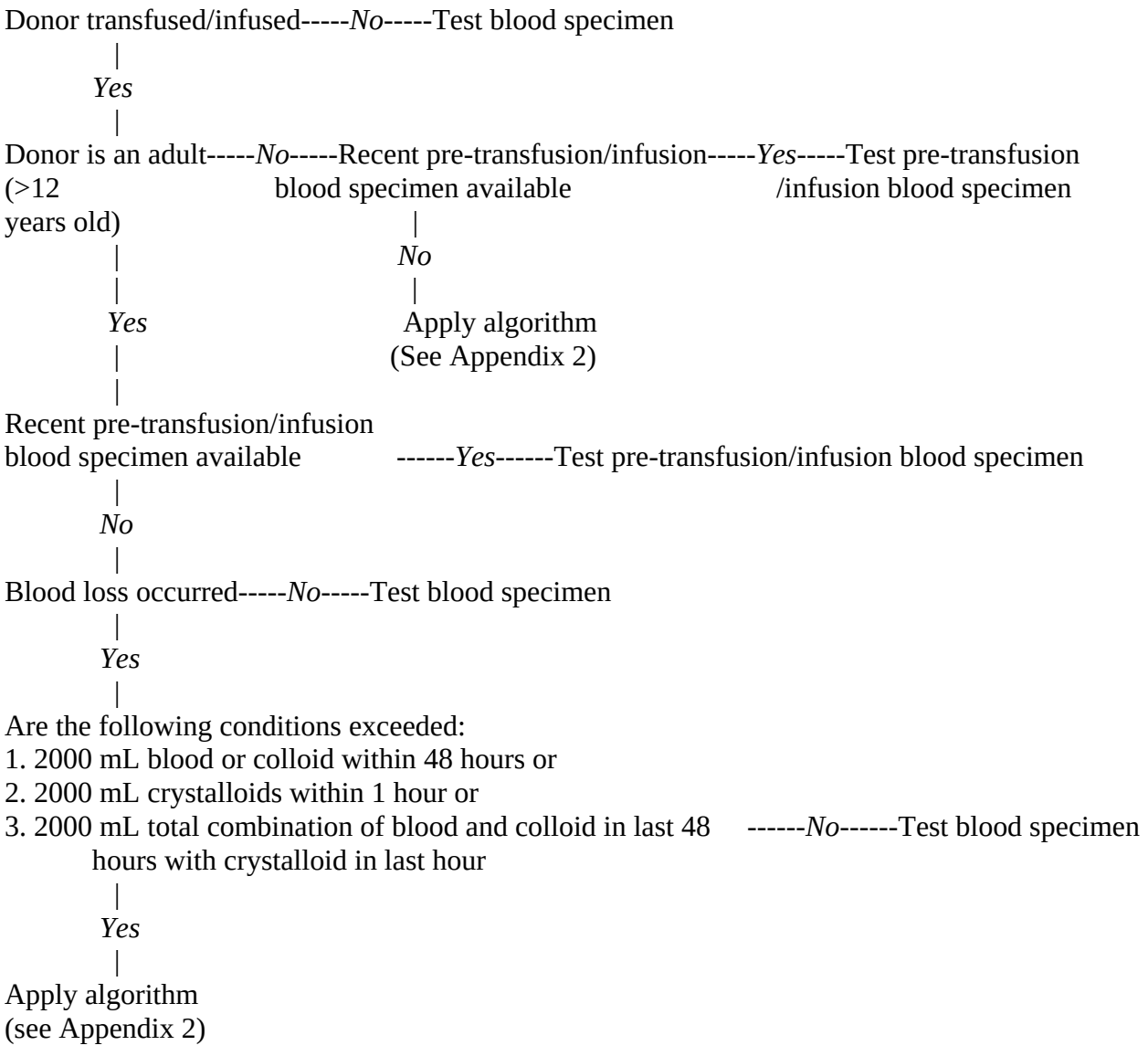
135. Steyaert, S.R., et al., Infections in IVF: Review and Guidelines. Hum Reprod Update 2000; 6:432-41.
136. Tedder, R.S., et al., Hepatitis B Transmission from Contaminated Cryopreservation Tank. Lancet 1995; 346:137-40.
137. Wang, S., et al., Identification of Hepatitis B Virus Vertical Transmission from Father to Fetus by Direct Sequencing. Southeast Asian J Trop Med Public Health 2003; 34:106-13.
138. Zhang, H., et al., Human Immunodeficiency Virus Type 1 in the Semen of Men Receiving Highly Active Antiretroviral Therapy. N Engl J Med 1998; 339:1803-9.
139. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR Recomm Rep 2002; 51(RR06):1-80. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5106a1.htm.
140. Chacko, M.R., et al., Chlamydia and Gonorrhea Screening in Asymptomatic Young Women. J Pediatr Adolesc Gynecol 2004; 17:169-78.
141. Dowell, S.F., et al., Standardizing Chlamydia Pneumoniae Assays: Recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). Clin Infect Dis 2001; 33:492-503.
142. Ford, C.A., et al., Testing for Chlamydial and Gonorrheal Infections Outside of Clinic Settings: A Summary Of The Literature. Sex Transm Dis 2004; 31:38-51.
143. Fredlund, H., et al., Molecular Genetic Methods for Diagnosis and Characterisation of Chlamydia Trachomatis and Neisseria Gonorrhoeae: Impact On Epidemiological Surveillance And Interventions. Apmis 2004; 112:771-84.
144. Rager, K.M., Biro, F.M., Techniques of Testing For Sexually Transmitted Diseases. Curr Womens Health Rep 2001; 1:111-5.
145. Schneede, P., et al., Sexually Transmitted Diseases (STDs)--A Synoptic Overview for Urologists. Eur Urol 2003; 44:1-7.
146. Wiesenfeld, H.C., et al., Self-Collection of Vaginal Swabs for the Detection of Chlamydia, Gonorrhea, and Trichomoniasis: Opportunity to Encourage Sexually Transmitted Disease Testing Among Adolescents. Sex Transm Dis 2001; 28:321-5.
147. Centers for Disease Control and Prevention. Screening Tests to Detect Chlamydia Trachomatis and Neisseria Gonorrhoeae Infections--2002. MMWR Recomm Rep 2002; 51(RR15):1-38; quiz CE1-4. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12418541.
148. Holland-Hall, C.M., et al., Self-Collected Vaginal Swabs for the Detection of Multiple Sexually Transmitted Infections in Adolescent Girls. J Pediatr Adolesc Gynecol 2002; 15:307-13.
149. Centers for Disease Control and Prevention. Possible West Nile Virus Transmission to an Infant Through Breast-Feeding --- Michigan, 2002. Morbidity and Mortality Weekly Report 2002; 51:877-888. http://www.cdc.gov/mmwr//preview/mmwrhtml/mm5139a1.htm.
150. Pealer, L.N., et al., Transmission of West Nile Virus Through Blood Transfusion in the United States in 2002. N Engl J Med 2003; 349:1236-45.
151. Centers for Disease Control and Prevention. Intrauterine West Nile Virus Infection --- New York, 2002. Morbidity and Mortality Weekly Report 2002; 51:1136-1136.

152. Centers for Disease Control and Prevention. Erratum: Vol. 52, No. 38. Morbidity and Mortality Weekly Report 2003; 52:942. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5239a8.htm.
153. Centers for Disease Control and Prevention. Update: Detection of West Nile Virus in Blood Donations --- United States, 2003. Morbidity and Mortality Weekly Report 2003; 52:916-919. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5238a6.htm
154. Centers for Disease Control and Prevention. West Nile Virus Home. Access date: 20 April 2005. Last Update Date: 11 January 2005.
155. Centers for Disease Control and Prevention. West Nile Virus Activity --- United States, November 3--8, 2004. Morbidity and Mortality Weekly Report 2004; 53:1050-1051. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5344a7.htm
156. Centers for Disease Control and Prevention. West Nile Virus Activity --- United States, November 9--16, 2004. Morbidity and Mortality Weekly Report 2004; 53:1071-1072. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5345a4.htm.
157. Martin, G.S., et al., The Epidemiology of Sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348:1546-54. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12700374.
158. Centers for Disease Control and Prevention. Septic Arthritis Following Anterior Cruciate Ligament Reconstruction Using Tendon Allografts---Florida And Louisiana, 2000. Morbidity and Mortality Weekly Report 2001; 50:1080-1083. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5048a3.htm.
159. Centers for Disease Control and Prevention. Unexplained Deaths Following Knee Surgery---Minnesota, November 2001. Morbidity and Mortality Weekly Report 2001; 50:1035-1036. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5046a3.htm.
160. Centers for Disease Control and Prevention. Update: Allograft-Associated Bacterial Infections --- United States, 2002. Morbidity and Mortality Weekly Report 2002; 51:207. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5110a2.htm.
161. Centers for Disease Control and Prevention. Update: Unexplained deaths following knee surgery---Minnesota, 2001. Morbidity and Mortality Weekly Report 2001; 50:1080. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5048a2.htm
162. Eastlund, T., Infectious Disease Transmission Through Cell, Tissue, And Organ Transplantation: Reducing the Risk Through Donor Selection. Cell Transplant 1995; 4:455-77.
163. Brecher, M.E., Hay, S.N., Bacterial Contamination Of Blood Components. Clin Microbiol Rev 2005; 18:195-204.
164. Centers for Disease Control and Prevention. Fatal Bacterial Infections Associated with Platelet Transfusions --- United States, 2004. Morbidity and Mortality Weekly Report 2005; 54:168-170. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5407a2.htm.
165. Angus, D.C., et al., Epidemiology of Severe Sepsis in the United States: Analysis of Incidence, Outcome, and Associated Costs of Care. Crit Care Med 2001; 29:1303-10.
166. Annane, D., et al., Septic Shock. Lancet 2005; 365:63-78.
167. McBean, M., Rajamani, S. Increasing Rates of Hospitalization Due to Septicemia in the US Elderly Population, 1986-1997. J Infect Dis 2001; 183:596-603.

168. Sessler, C.N., Shepherd, W., New Concepts in Sepsis. Curr Opin Crit Care 2002; 8:465-72.
169. Angus, D.C., Wax, R.S., Epidemiology of Sepsis: An Update. Crit Care Med 2001; 29:S109-16.
170. Cono, J., et al., Smallpox Vaccination and Adverse Reactions. Guidance for clinicians. MMWR Recomm Rep 2003; 52:1-28.
171. Lupatkin, H., et al., Smallpox in the 21st century. Anesthesiol Clin North America 2004; 22:541-61, viii.
172. Sepkowitz, K.A., How Contagious Is Vaccinia? N Engl J Med 2003; 348:439-46.
173. Centers for Disease Control and Prevention. Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. Morbidity and Mortality Weekly Report 2001; 50(RR10):1-25. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm.
174. Koplan, J.P., Marton, K.I., Smallpox vaccination revisited. Some Observations on the Biology of Vaccinia. Am J Trop Med Hyg 1975; 24:656-63.
175. Department of Defense Health Care Provider's Briefing, January 16, 2004.
176. Lorich, M.F., et al., Conjugal Transfer Vaccinia. J Am Acad Dermatol 2004; 51:460-2.
177. Deputy Secretary of Defense. Memorandum for Secretaries of the Military Departments: Expansion of Force Health Protection Anthrax and Smallpox Immunization Programs for DOD Personnel. June 28, 2004.
178. The Assistant Secretary of Defense. Memorandum for Secretaries of the Military Departments: Clarification of Service Responsibilities in Vaccinating Department of Defense (DoD) Personnel and Dependents Assigned to Department of State (DoS) Missions or Residing in High-Threat Areas, March 13, 2003.
179. The Assistant Secretary of Defense. Memorandum for Secretaries of the Military Departments: Resumption of Anthrax Vaccinations for Personnel Previously Deferred, July 28, 2004.
180. Under Secretary of Defense. Memorandum for Secretaries of the Military Departments: Expansion of Force Health Protection Anthrax and Smallpox Immunization Programs for Emergency-Essential and Equivalent Department of Defense Civilian Employees, September 22, 2004.
181. The Assistant Secretary of Defense. Memorandum for Assistant Secretaries of the Army, Navy, and Air Force: Status Report of Anthrax and Smallpox Vaccinations, February 11, 2004.
182. Department of Defense. Mil Vax - Smallpox Vaccination Program. Access date: April 19, 2004. Last update date: April 18, 2005.

APPENDIX 1

EXAMPLE OF A FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR INFECTIOUS DISEASE TESTING



ACCOMPANYING QUESTIONS FOR FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR INFECTIOUS DISEASE TESTING

Question #1 – Has the donor had a transfusion or infusion?

- If the answer to question # 1 is no, then test the blood specimen
- If the answer to question #1 is yes, then ask question #2

Question #2 – Is the donor an adult?

- If the answer to question #2 is no, then ask question #2a
- If the answer to question #2 is yes, then ask question #3

Question #2a – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is twelve years of age or younger?

- If the answer to question # 2a is no, then apply the algorithm (see appendix 2)
- If the answer to question #2a is yes, then test the pre-transfusion/infusion blood specimen that is available

Question #3 – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is more than twelve years of age?

- If the answer to Question #3 is yes, then test the pre-transfusion/infusion blood specimen
- If the answer to Question #3 is no, then ask Question #4

Question #4 – Has blood loss occurred?

- If the answer to Question #4 is no, then test the blood specimen
- If the answer to question number 4 is yes, then ask Question #5

Question #5 – Are any of the following conditions exceeded?

- 2000 mL of blood or colloid given to the donor within the past 48 hours;
- 2000 mL of crystalloids within the last hour; or
- 2000 mL total of any combination of blood and colloid within past 48 hours, and crystalloid within the past hour
- If the answer to Question #5 is no, then test the blood specimen
- If the answer to Question #6 is yes, then apply algorithm (see Appendix 2)

APPENDIX 2

EXAMPLE OF AN ALGORITHM

DONOR ID # _____

Date and Time of Specimen Collection _____
Donor's weight in kg _____

A = Total volume of blood transfused in the 48 hours before death or sample collection, whichever comes first

B = Total volume of colloid infused in the 48 hours before death or sample collection, whichever comes first

C = Total volume of crystalloid infused in the 1 hour before death or sample collection, whichever comes first

BV = donor's blood volume

Calculated blood volume = donor's weight (kg) / 0.015 OR
donor's weight (kg) x 70 mL/kg

PV = donor's plasma volume

Calculated plasma volume = donor's weight (kg) / 0.025 OR
donor's weight (kg) x 40 mL/kg

Calculate <u>both</u>:

1. Is B + C > PV?
2. Is A + B + C > BV?

[Enter a zero if a category (A, B, or C) was not transfused/infused.]

<u>Determination of Sample Acceptability for Infectious Disease Tests</u>:

If the answers to <u>both</u> 1 and 2 are NO, the post-transfusion/infusion sample is acceptable.

If the answer to <u>either</u> 1 <u>or</u> 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

APPENDIX 3

Example of a Plasma Dilution Worksheet (Using Appendix 2 Algorithm)

Donor ID # _____

Date and Time of Sampling……. _____ am/pm

Donor Weight in kg …… _____ kg

Blood Volume (BV) = donor's weight (kg) _____ ÷ 0.015 ……

OR (BV) = donor's weight (kg) _____ X 70 mL/kg……. _____ mL

Plasma Volume (PV) = donor's weight (kg) _____ ÷ 0.025 ……

OR (PV) = donor's weight (kg) _____ X 40 mL/kg……. _____ mL

A. Total Volume of Blood Transfused/48 hours (before death or sample collection, whichever comes first)

Volume of: RBCs transfused/48 hours _____

\+ whole blood transfused/48 hours _____ A = _____ mL

B. Total Volume of Colloid Infused/48 hours (before death or sample collection, whichever comes first)

Volume of: dextran _____ mL

\+ plasma _____ mL

\+ platelets _____ mL

\+ albumin _____ mL

\+ hetastarch _____mL

\+ Other _____ mL _____

_____mL _____

B = _____ mL

C. Total Volume of Crystalloid Infused/1 hour (before death or sample collection, whichever comes first)

Volume of: saline _____ mL

\+ Dextrose in water _____ mL

\+ Ringer's lactate _____ mL

\+ Other _____ mL _____

_____ mL _____ C = _____ mL

Determination of Sample Acceptability for Infectious Disease Tests:

[Calculate both 1. and 2. Enter a zero if a category (A, B, or C) was not transfused/infused]

1. Is B + C > PV? Y N

2. IS A + B + C > BV? Y N

* If the answers to <u>both</u> 1 and 2 are NO, the post-transfusion/infusion sample is acceptable

* If the answer to either 1 or 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

APPENDIX 4

MODERATE AND SEVERE COMPLICATIONS OF SMALLPOX VACCINATION AND INADVERTENT VACCINIA VIRUS INFECTION

Complications of smallpox vaccine or of inadvertent vaccinia virus infection, for the purpose of this guidance, are defined as the following, and are consistent with CDC definitions of moderate to severe adverse reactions to the smallpox vaccine, or to inadvertent vaccinia virus infection in contacts of vaccine recipients (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm).

Eczema vaccinatum
Generalized vaccinia
Progressive vaccinia
Postvaccinial encephalitis
Vaccinial keratitis

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in someone with eczema (atopic dermatitis) or a history thereof, or with other chronic or exfoliative skin conditions.

Generalized vaccinia is characterized by a vesicular rash of varying extent that can occur among persons without underlying illnesses. The rash is generally self-limited and requires minor or no therapy except in rare cases, when the vaccine recipient is systemically ill.

Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic vaccinia lesions. It has occurred almost exclusively among persons with cellular immunodeficiency.

Postvaccinial encephalitis is a rare but serious complication of vaccinia virus infection.

Vaccinial keratitis is an infection of the cornea, which can cause corneal scarring and visual impairment. This condition is usually caused by accidental self-inoculation of the eye from the vaccine site, or from self-inoculation after contact with another vaccine recipient, and is not believed to be due to hematogenous spread or associated with a secondary viremia.

APPENDIX 5

LIST OF BSE-AFFECTED COUNTRIES APPLICABLE TO DONOR DEFERRAL

European Countries to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

[1]For purposes of this guidance, the United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

APPENDIX 6

West Nile Virus (WNV)

WNV was first identified in the United States in 1999, in an epizootic outbreak among birds and horses and an epidemic of meningitis and encephalitis in humans in the New York City area. Throughout 2000 - 2001, avian mortality surveillance documented geographic spread to about half of the United States. In 2001, 66 human cases of WNV encephalitis or meningitis occurred in 10 states. In 2002, a major epizootic outbreak of WNV was detected in many parts of the United States combined with the largest human WNV meningoencephalitis outbreak ever documented, and the largest outbreak of meningoencephalitis from any cause in North America. In 2002, the number of human cases far surpassed those reported in 2001 with 4,161 cases of WNV illness and 277 deaths reported as of March 12, 2003. Ninety-nine percent of the human cases occurred between July 1 and October 31, 2002. Human cases were reported in 736 counties in 39 states and the District of Columbia. The 2002 WNV epidemic involved the first documented cases of WNV transmission through organ transplantation, blood transfusion, and possibly breastfeeding (Refs. 149 and 150). In addition, intrauterine infection was reported (Ref. 151). Surveillance reports published weekly in Morbidity and Mortality Weekly Report (MMWR) indicated that WNV was active in the United States in 2003 and had spread to additional areas of the country as compared to 2002. Blood establishments began using WNV nucleic acid amplification tests (NAT) under investigational drug exemptions (IND) beginning late June 2003. It is estimated that, through 2004, at least 1017 presumptively viremic donations were removed from the blood supply as a result of blood establishments' voluntary participation in WNV NAT screening studies (Ref. 5). In 2003, a total of 9,862 cases of human illness, including 2,775 neuroinvasive disease cases and 264 fatalities were reported to CDC (Refs. 5, 152, 153, and 154). In the 2004 WNV epidemic, CDC reported WNV activity in 47 continental states, with 2,470 reported human cases and 88 fatalities (Refs. 5, 154, 155, and 156).

WNV has the potential to be spread via HCT/Ps, as evidenced by its transmission via organ transplantation, and via blood and blood product transfusion. Though it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5).

Our current recommendation is only for donor screening. Some HCT/P donors are being tested under the IND previously mentioned, though testing with an investigational product is not a requirement. In WNV infection, 80% of persons are asymptomatic, 20% have mild symptoms, and only about 1/150 persons experience severe illness. Because symptoms occur in only approximately 20% of persons infected with WNV, donor exclusions based on donor health screening will have limited effectiveness. Laboratory screening tests to detect donor infections with WNV will be needed if the epidemic persists. We may recommend routine use of appropriate licensed donor screening test(s) to detect acute infections with WNV using NAT

technology once such tests are available. (See Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral.)

Sepsis

For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock. The causative agent in sepsis has been changing over the years. Fungal pathogens have become an increasingly important cause of sepsis. Gram-negative organisms were the most common organisms leading to sepsis between 1979 and 1987, but, by 2000, gram-positive organisms caused 52.1% of cases and gram-negative organisms were responsible for about 37.6% (Ref. 157). Various bacterial, fungal, and viral agents have been shown to be transmissible via HCT/Ps (Refs. 158 through 162) and bacterial infection potentially resulting in sepsis with associated morbidity and mortality is a widely recognized risk from transfused blood and blood products (Refs. 163 and 164).

A recent study in the New England Journal of Medicine (NEJM) reviewed the epidemiology of sepsis in the United States from 1979 through 2000 by looking at discharge data contained in the National Hospital Discharge Survey (Ref. 157). This study showed that the incidence of sepsis has been increasing over that time period and estimated the incidence as of 2000 to be 240.4 cases/100,000 population. The NEJM study also cited references stating that sepsis is now among the top ten leading causes of death in the United States. Another widely cited sepsis study by Angus, et al. reviewed all the 1995 discharge data from a sample of hospitals in 7 states that collectively served approximately 25% of the population of the United States (Ref. 165). The Angus study estimated the incidence of sepsis over that year to be about 3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges. The Angus study estimated that in 1995, about 9.3% of all deaths in the United States were a direct or indirect result of sepsis – similar to the number of deaths caused by myocardial infarction over the course of that year. The mortality rate of sepsis in these studies was estimated to be about 17.9% and 28.6%, respectively. These studies (Refs. 157 and 165), as well as others (Refs. 166, 167, and 168), agree that the risk of sepsis is increased with age (after one year old), male sex, comorbid illness, and in non-whites. The incidence and prevalence of sepsis is widely believed to be increasing (Refs. 157, 165, 166, 167, and 169). While the mortality rate of sepsis has been decreasing slightly with advances in medical care, the overall number of deaths due to sepsis has been increasing (Ref. 157).

Vaccinia

Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, FDA believes that vaccinia virus is potentially transmissible via HCT/Ps. Two different investigators, in 1930 and 1953, reported that vaccinia virus could sometimes be isolated from a patient's blood 3-10 days after vaccination (Ref. 8). These studies did not use the less virulent NYCBOH strain of vaccinia virus that comprises currently available vaccines in the U.S. Using the NYCBOH strain of vaccinia virus, other investigators were only able to detect virus in the blood of patients with

disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination.

A frequent complication of smallpox vaccination is autoinoculation or inadvertent inoculation of a contact (Refs. 170, 171, and 172). Vaccinia virus is readily recovered from the vaccination site until the vaccination scab spontaneously separates from the skin. The scabs themselves contain infectious virus. Thus, although viremia is unlikely once an immune response is initiated, recipients of the vaccine could still inadvertently infect contacts that touch the vaccination site or dressing (Ref. 173). Vaccinia virus can be recovered from the skin at the vaccination site for a mean duration of 7.8 days, with a range of 0 to 18 days (Ref. 174). After an individual is vaccinated with the vaccinia virus, vaccinia can be accidentally spread to other parts of the body and to others since the virus is capable of contact transmission (Refs. 11, 172, and 175). Nosocomial spread of vaccinia has also been reported (Ref. 172). Recent literature describes the conjugal transfer of vaccinia from 2 different active-duty military personnel to their respective partners after smallpox vaccination (Ref. 176).

Smallpox vaccination was routinely performed in the U.S. until 1971. In recent years, smallpox vaccination has been recommended only for laboratory personnel working with certain orthopox viruses, including vaccinia and smallpox. On June 20, 2002, the Advisory Committee for Immunization Practices (ACIP) of the CDC recommended that smallpox vaccine also be given to persons pre-designated to conduct investigation and follow-up of initial smallpox cases and to personnel in facilities that are pre-designated to serve as referral centers to provide care for initial smallpox cases. On December 13, 2002, President Bush announced his decision to begin a smallpox vaccination campaign targeted to those military and civilian personnel who have an occupational risk of contracting smallpox. There is a policy in place to vaccinate Department of Defense (DoD) personnel who are deployed to areas designated as high-threat by the Secretary of Defense. In addition, DoD offers voluntary smallpox vaccination for military members and their families, civilian employees and their family members, and contract personnel serving at Department of State missions in Near East Asia, Israel, Turkey, North Africa, Lebanon, Syria, Jordan, Egypt, and Korea (Refs. 177 through 180). Implementation and review of these policies appear to be ongoing (Ref. 181). According to the DoD Smallpox Vaccination Program website (updated 4/14/05) (Ref. 182), more than 760,000 people have been vaccinated with smallpox vaccine since December 2002 through its vaccination program. Since the smallpox vaccination program affects a large number of people throughout the country, we believe the incidence of vaccinia in the donor population is sufficient to warrant its addition to the list of relevant communicable diseases.

Guidance for Industry

Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit comments on this guidance at any time to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact Melissa Greenwald, M.D., at 301-827-2002.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2004

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry

Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides to you, medical device manufacturers of communicable disease tests, information about performing studies to support modifying the indication for use to include testing of cadaveric blood specimens to screen donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps). This guidance makes recommendations about:

- Sensitivity and specificity studies
- Reproducibility studies
- Number of test kit lots to include in studies
- Plasma dilution issues
- Information about specimen collection times to be included

This document contains information which has been provided in Center for Biologic Evaluation and Research's (CBER's) letters to manufacturers of communicable disease tests. We, FDA, continue to encourage manufacturers of communicable disease tests to evaluate these tests for cadaveric HCT/P donor use and seek such labeling.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Recognizing the need for appropriately evaluated and labeled test kits, we issued letters in 1995 to manufacturers of donor screening tests introducing the subject of expanding the indication for use of blood donor screening tests to include testing of cadaveric blood specimens and suggesting a minimum protocol. In the Federal Register of July 29, 1997 (62 FR 40429), we issued a final rule, "Human Tissue Intended for Transplantation," (the tissue final rule) which requires "certain infectious disease testing, donor screening, and recordkeeping to help prevent the transmission of the human immunodeficiency virus (HIV), and hepatitis viruses through human tissue used in transplantation" (62 FR 40429 at 40429) (Ref. 1). Additionally, the tissue final rule requires that "FDA licensed screening tests labeled for cadaveric specimens must be used when available" (21 Code of Federal Regulations 1270.21(d)). Also, in the Federal Register of July 29, 1997 (62 FR 40536), we announced the availability of a "Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation," dated July 1997, which further discussed the use of donor screening tests (Ref. 2).

We approved two biologic license supplements with the modified indication for use to include testing of cadaveric blood specimens. On December 28, 1999, FDA approved the Genetic Systems Corporation's Supplement to its Product License Application for Antibody to Hepatitis B Surface Antigen (Mouse Monoclonal) Enzyme-Linked Immunosorbent Assay to modify the intended use of the Genetic Systems HBsAg EIA 2.0 and the Genetic Systems HBsAg Confirmatory Assay 2.0 to include the testing of cadaveric serum samples. On February 9, 2000, FDA approved the Genetic Systems Corporation's Supplement to their Product License Application for Human Immunodeficiency Virus Types 1 and 2 (Synthetic Peptide) to modify the intended use of the Genetic Systems HIV-1/HIV-2 Peptide EIA to include the testing of cadaveric serum samples. These approved tests detect antibodies to Hepatitis B Surface Antigen and antibodies to Human Immunodeficiency Virus (HIV)-1 and HIV-2, respectively, in a cadaveric donor's serum.

In June 2000, we issued a "Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens" (the June 2000 guidance), which informed establishments of the availability of these two licensed donor screening tests labeled for use with cadaveric blood specimens (Ref. 3). In the Federal Register of May 25, 2004 (69 FR 29786), we issued a final rule "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (Ref. 4) which requires that donors of cells and tissue be tested for evidence of infection due to relevant communicable disease agents or diseases. Those relevant communicable disease agents include HIV, types 1 and 2; hepatitis B virus; and hepatitis C virus, and, for certain donors, Human T-Lymphotrophic Virus, types I and II. Manufacturers of tests used to screen blood donors for communicable diseases have requested information on studies to support modifying the indication for use to include testing of cadaveric blood specimens from donors of HCT/Ps.

III. DISCUSSION

We recommend you address the following areas when preparing a protocol to modify the indication for use to include testing of cadaveric blood specimens.

A. What data about specificity and sensitivity are recommended when matched pairs of pre- and post-mortem serum/plasma specimens are available?

1. Specificity

   We recommend that you test at least 50 paired specimens (1 pre- and 1 post-mortem specimen from the same donor).

   a. Clinical Specificity

      Clinical specificity is a measure of how often the test is negative in non-diseased donors.

      We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on frequency of false positive results.

   b. Analytical Specificity

      Analytical specificity measures a test's ability to exclusively identify a target substance rather than different substances.

      We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on signal strength.

2. Sensitivity

   We recommend that you test at least 50 paired reactive specimens (1 pre- and 1 post-mortem specimen from the same donor).

   a. Clinical Sensitivity

      Clinical sensitivity is a measure of how often the test is positive in diseased donors.

      We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on frequency of false negative results.

b. Analytical Sensitivity

Analytical sensitivity measures a test's ability to detect a low concentration of a given substance.

We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on signal strength and endpoint dilutions of positive specimens.

B. What data about specificity and sensitivity are recommended when matched pairs of pre- and post-mortem serum/plasma specimens are not available?

1. Specificity

We recommend that you concurrently test at least 50 cadaveric (post-mortem) specimens from 50 different cadaveric donors and an equal number of random living donor specimens (unmatched pre-mortem specimen) with the same test kit lots.

a. Clinical Specificity

We recommend that you determine if a statistically significant difference exists between the cadaveric specimens and the random living donor specimens based on the frequency of false positive results, i.e., the number of pre-mortem nonreactives/post mortem reactives.

b. Analytical Specificity

We recommend that you determine if a statistically significant difference exists between the cadaveric specimens and the random living donor specimens based on signal strength.

2. Analytical Sensitivity

We recommend that you concurrently test at least 50 nonreactive cadaveric specimens from 50 different cadaveric donors with an equal number of random living donor specimens with the same kit lots, with both types of specimens spiked with the infectious disease marker at a potency near the assay's cutoff. You should use a minimum of 5 individual positive sources for the spiking experiment.

We recommend that you determine if a statistically significant difference exists between the spiked living donor specimens and the spiked cadaveric specimens based on signal strength.

C. What is an example of a recommended reproducibility study?

We recommend that you conduct a reproducibility study to determine if a statistically significant difference exists between the coefficients of variations of cadaveric specimens compared to those of living donors. One possible experimental design might include comparing at least 20 random cadaveric specimens with at least 20 random living donor specimens (confirmed true positives may be excluded) spiked to be reactive near the cutoff. Test each specimen individually, in 6 separate runs on 6 separate days using each of 3 different kit lots (18 data points per specimen). We also recommend that the specimens to be tested on 6 separate days be stored at 4° Centigrade to avoid repeated freezing and thawing.

D. How many test kit lots are recommended to be included in the studies?

We recommend that you include at least three test kit lots in all studies.

E. What plasma dilution issues are recommended for consideration?

Prior to including a cadaveric blood specimen in these studies, we recommend that you determine whether the specimen has been appropriately evaluated for plasma dilution. You can obtain information about plasma dilution from FDA's "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," dated July 1997 (the July 1997 guidance). This document can be found on the Internet at www.fda.gov/cber/tissue/docs.htm. As stated in the July 1997 guidance, plasma dilution is due to the transfusion or infusion of fluids into the donor prior to specimen collection, and can result in false negative test results. In an adult donor, if blood loss is known or suspected to have occurred and there was transfusion/infusion of more than 2000 mL of blood or colloids within 48 hours, or more than 2000 mL of crystalloids within 1 hour, or any combination thereof, prior to the collection of the blood specimen, plasma dilution may have occurred. In this case, we recommend that you use a specimen taken from the donor prior to transfusion or infusion, or an algorithm designed to evaluate volumes administered in the 48 hours prior to specimen collection, to ensure that plasma dilution sufficient to affect test results has not occurred. An example of an algorithm can be found in the July 1997 guidance.

F. What information about specimen collection times does FDA recommend I note?

1. We recommend that you note the time between death and specimen collection. In order to accurately document test kit performance, we recommend that the time at which cadaveric specimens are taken incorporate the full range of time points typically encountered during tissue recovery, e.g., 0-24 hours.

2. We recommend that you include hemolyzed specimens in the study, since a large percentage of cadaveric specimens are hemolyzed due to biological processes that occur immediately post-mortem. You should quantify the degree of hemolysis, if possible, of the cadaveric specimens.

3. We recommend that you note information about storage and handling conditions of both living donor specimens and cadaveric specimens.

G. Where do I submit my data?

We intend to review any applications for cadaveric blood specimens jointly in the Offices of Cellular, Tissue and Gene Therapies and Blood Research and Review.

1. If you seek an indication for use of cadaveric blood specimens and blood donor specimens, you may submit an Investigational New Drug Application (IND), or a Biologics License Application (BLA), as appropriate, with data for both intended uses, to:

   Center for Biologics Evaluation and Research
   Attn: Office of Blood Research and Review
   HFM-99, Suite 200N
   1401 Rockville Pike
   Rockville, MD 20852-1448

2. If an IND or BLA has already been submitted for blood donor screening, and you seek to modify the indication for use to include testing of cadaveric blood specimens, you may submit an amendment to the IND, or a supplement to the BLA with cadaveric blood specimen data, as appropriate, to the same address as above.

3. If you seek to modify the indication for use to include testing of cadaveric blood specimens only, you may submit an IND or BLA with cadaveric blood specimen data, to:

Center for Biologics Evaluation and Research
Attn: Office of Cellular, Tissue and Gene Therapies
HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If you have questions about this guidance, please contact Melissa Greenwald in the Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

IV. REFERENCES

1. Human Tissue Intended for Transplantation; Final Rule, July 29, 1997 (62 FR 40429), (http://www.fda.gov/cber/genadmin/frtissue.txt or http://www.fda.gov/cber/tissue/docs.htm).

2. Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation; Notice of Availability, July 29, 1997 (62 FR 40536), (http://www.fda.gov/cber/gdlns/tissue2.txt or http://www.fda.gov/cber/tissue/docs.htm).

3. Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens, June 2000, (http://www.fda.gov/cber/gdlns/cadbld.htm or http://www.fda.gov/cber/tissue/docs.htm).

4. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule, May 25, 2004 (69 FR 29786), (http://www.fda.gov/cber/tissue/docs.htm).