DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

DATE: June 12, 2007

FROM: Human Tissue Task Force Chairpersons

TO: Jesse Goodman, MD, MPH, Director,
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SUBJECT: Report of the Human Tissue Task Force

Introduction:

The FDA Human Tissue Task Force (HTTF), is a collaborative effort among those FDA components involved in tissue safety, including the Center for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA), and the Office of the Commissioner (OC), and was established in August 2006 as part of the Agency's efforts to evaluate and, where needed, strengthen its risk-based system for regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps) which went into effect in 2005. The primary goal of the HTTF was to assess challenges that had occurred in implementation of the new system and to identify any additional steps needed to further protect the public health by preventing the transmission of communicable disease while assuring the availability of safe products.

In 1993, FDA began regulating certain human tissues intended for transplantation. The requirements focused on tissue donor screening and testing. In 1997, FDA proposed a new, tiered, risk-based approach to regulation of all HCT/Ps. HCT/Ps that met certain criteria would be regulated solely under section 361 of the PHS Act, and the requirements would focus on preventing the introduction, transmission, or spread of communicable disease to the HCT/P recipient through donor eligibility and current good tissue practice requirements. Clinical data or review of safety and efficacy would not be required prior to marketing. Other HCT/Ps, which were considered higher risk based on criteria described in the regulations, would be regulated as biological products or medical devices, and safety and effectiveness would need to be shown prior to marketing the product. To implement the proposed approach, FDA published three proposed rules for comment. These proposed rules were finalized and became effective on May 25, 2005, and apply to HCT/Ps recovered on or after that date. The first rule required an HCT/P establishment to register with FDA and list all of the HCT/Ps

that it manufactured. Manufacture is defined as all steps in recovery, processing, storage or distribution of the HCT/P and screening and testing of the donor. These steps comprise the "life cycle" of an HCT/P. The second rule required that a determination of donor eligibility be made, based on donor screening and testing for relevant communicable diseases. The third rule required that current good tissue practice (CGTP) be followed during the manufacture of the HCT/P. This rule also required reporting certain adverse reactions and HCT/P deviations to FDA, tracking of all HCT/Ps from the donor to the consignee (but not to the recipient), and labeling. There were provisions for inspection of HCT/P establishments and enforcement of all applicable requirements. The three rules comprise 21 CFR Part 1271.

Of particular concern to the HTTF were recent findings that two tissue recovery establishments were not following basic federal requirements for donor screening and testing, and tissue recovery, creating preventable risks of communicable disease transmission, and necessitating FDA orders that they cease manufacturing. While the current tissue regulatory framework clearly provided the needed regulatory and legal tools to take action in these cases, it was critical to identify any steps with the future potential to better detect and, where possible, prevent such problems, including an evaluation of any areas where FDA regulations or underlying authorities, and the activities of other partners and stakeholders, including the tissue safety system as a whole, may benefit from further strengthening.

The HTTF presents this summary of its findings and recommendations. Based on the concerns raised by FDA's recent investigations of two violative recovery establishments, our effort focused on tissues from non-living donors. Some of our recommendations were immediately implemented in support of tissue safety, while others have been or will be initiated in the near term. Finally, certain additional recommendations may require further study and development work, long-term commitment, and additional actions, or a phased-in approach, where resources may be currently unavailable to fully accomplish and sustain these recommendations. Because the industry is rapidly evolving, a continuing evaluation will be needed going forward. We also recognize (see Outreach section) that other federal partners, states, the medical community, and industry have and will continue to play major roles in enhancing the safety and availability of human tissues that meet important medical needs.

Topic 1: Inspection and Compliance Activities

BACKGROUND: When the new 21 CFR 1271 regulations took effect, in addition to monitoring safety and adverse events, our available resources were initially concentrated on tissue processing, where past infectious disease risks, in particular those of bacterial and fungal contamination, had most commonly arisen or been introduced. However, after the two recent instances involving tissue recovery, which raised new concerns about this stage in manufacture, one focus of the HTTF was to evaluate tissue recovery establishments.

ACTION TAKEN: We acted rapidly to conduct focused inspections (a "blitz") of the domestic inventory of 153 musculoskeletal recovery firms. The inspection assignment,

crafted collaboratively by ORA and CBER as a supplement to the compliance program, was designed to enhance the detection of any violative practices that could potentially result in the use of ineligible donors. The inspections were completed on schedule by the end of 2Q FY07.

RESULTS TO DATE OF BLITZ: While we have identified some deviations from the regulations which require correction, to date we have not seen any major inaccuracies or deficiencies in records that could put tissue recipients at risk for transmission of relevant communicable disease agents or diseases.

RECOMMENDATIONS: There are currently over 2000 registered HCT/P establishments. FY07 resources are expected to permit up to 484 inspections (including those conducted under the blitz). To adequately support tissue safety, the HTTF strongly recommends the following inspectional goals and priorities:

- Biennial inspection coverage of all high-risk tissue establishments,
- Triennial inspection coverage of other registered establishments,
- Prompt reinspection of violative establishments, and
- Prompt compliance/enforcement review, support, and action against violative establishments.

Achieving these goals fully will require a program of robust training and support of personnel engaged in the program as well as additional time, planning, and human and financial resources.

Topic 2: Partnering, Leveraging, Education, and Outreach

BACKGROUND: FDA is not the only entity with an interest in tissue safety. Federal and state partners, industry associations, and the industry itself have important roles and responsibilities in protecting and advancing public health by having a safe supply of tissue available. Recognizing this, the HTTF sought to identify and pursue additional partnering/leveraging opportunities with federal, state, and/or industry stakeholders. We also explored opportunities to enhance tissue safety through education and outreach that would clarify our requirements and improve practices, as well as opportunities to improve our tissue safety program by obtaining and evaluating information from our stakeholders.

ACTION TAKEN: These outreach and education efforts have included the following organizations:

- Federal: Our two major federal partners in the Department of Health and Human Services are the Centers for Disease Control and Prevention (CDC) and the Human Resources Services Administration (HRSA). Communication with the Federal Trade Commission (FTC) is also important because of the oversight they provide to aspects of the death care industry.

    - CDC – FDA and CDC have been in regular communication on tissue safety issues, and have a long history of working together closely in public health investigations of adverse reactions related to tissue and with respect to emerging infectious diseases. CDC has played a major role in working with state public health departments and in working with FDA to provide scientific and public health assessments and advice. To further explore opportunities for enhancing tissue safety and to enhance our ongoing interactions, we have initiated strategic discussions with CDC concerning current activities, tissue regulations, and potential future initiatives.
    - HRSA – Our connection with HRSA is principally in the area of organ donation, where HRSA is the lead federal agency with oversight, and with whom we share information concerning approaches to issues such as donor eligibility and testing, safe tissue processing, and emerging infectious disease threats. We presented information at a recent Advisory Committee on Organ Transplantation (ACOT) meeting. FDA has an ex officio representative on this committee.
    - FTC – We initiated discussion of opportunities to communicate FDA's tissue safety messages through FTC training programs and industry connections.
- States: ORA is continuing to survey several key states to determine the appropriate contacts, authorities, and interest in partnership opportunities. A model partnership agreement to be used with the states is being developed. At this preliminary stage, we see the most likely opportunities for, and benefit from, partnerships with those states that have the most highly developed regulatory programs. Upon identification of appropriate partnership opportunities, ORA will fund or seek funding support for the agreements. The benefits we would expect to receive from an effective partnership agreement include: improvements to our communication network with state regulatory partners, expanded overall inspectional coverage of the industry through sharing of information and leveraging each other's work, and greater knowledge of industry operations and practices through review of information received.
    - In October 2006, we held a 50-state conference call to discuss tissue safety and regulatory oversight of tissue related activities. In advance of the call, we obtained background information from state health agencies regarding their systems of regulation and oversight. Many states have provided information that we are continuing to assess; our preliminary review reveals a varying degree of oversight. At least three states appear to have relatively comprehensive regulatory systems for tissue safety. All states appear to have a registration/licensure program for funeral homes, with varying degrees of inspectional oversight.
    - North Carolina Legislature – At their request, FDA presented an overview of FDA's tissue regulations to support the legislature's consideration of possible legislation to reinforce tissue safety in the state of North Carolina.
- Eye Banking and Tissue Industry: Industry associations present another leveraging opportunity. AATB and EBAA have active accreditation programs.

FDA will continue to communicate and work with these industry associations in activities of mutual interest that support and enhance tissue safety.

  - American Association of Tissue Banks (AATB) is a scientific, not-for-profit, peer group industry supported organization. Its mission is to facilitate the provision of high quality transplantable human tissue in quantities sufficient to meet national needs. AATB has an active accreditation program. AATB has several initiatives to enhance tissue safety.
  - Eye Bank Association of America (EBAA) is a scientific, not-for-profit, peer group industry supported organization of eye banks dedicated to the restoration of sight through the promotion and advancement of eye banking. EBAA represents the ocular tissue industry and has an active accreditation program with nearly all eye banks in the U.S. being accredited.

- Academic/Professional Organizations:
  - The Joint Commission (formerly known as the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO)) has standards for tissue tracking in healthcare organizations. We have contacted this organization to provide information on tissue regulation.
  - American Academy of Orthopedic Surgeons (AAOS) – Orthopedic surgeons are major users of musculoskeletal tissue. We have contacted AAOS to provide information on tissue regulation and have reviewed additional information to be provided by the organization to their members.
  - American Academy of Periodontology (AAP) – Periodontists are also users of musculoskeletal tissue. We have contacted this organization to provide information on tissue regulation.

RECOMMENDATIONS: Partnering, leveraging, education, and outreach activities, could expand, but such expansion would require additional resources. Such activities could enable: improvements to our communication network with state and federal regulatory partners, sharing of information, and greater knowledge of industry operations and clinical practices. Additional resources could also allow enhanced communication with academic and professional organizations.

Topic 3: Adverse Reaction Reporting and Analysis

BACKGROUND: In 2004, CBER formed the Tissue Safety Team (TST) with representation across CBER. The TST was formed to enhance the internal system for receipt, analysis and follow-up of adverse reaction reports received by CBER, to efficiently and effectively respond to emergencies, and to strategically identify policy and outreach needs and opportunities and implement solutions. The HTTF sought to identify ways to further enhance these activities.

ACTION TAKEN: The HTTF reviewed FDA's current procedures for adverse reaction receipt, analysis and follow-up. In addition, FDA enlisted the consultative services of a nongovernmental academic infectious disease specialist with extensive clinical experience to identify opportunities to improve procedures for investigation,

classification, and analysis of adverse reaction reports related to tissue transplants. The input received was utilized to refine the activities of the TST.

RECOMMENDATIONS FEASIBLE WITH CURRENT RESOURCES: The following actions will allow for enhanced surveillance, analysis, response, and systems development:

- Enhancing the investigation, classification, analysis and trending of adverse reaction reports,
- Continuing interactions with outside experts to provide scientific input and assistance for improving our processes in adverse reaction classification, review and analysis,
- Coordinating with CDC regarding the proposed Transplantation Transmission Sentinel Network (TTSN) project to assure that the TTSN complements FDA's existing surveillance system, and
- Sponsoring a workshop on tissue processing, inviting health care providers, scientists and industry to share knowledge and experiences regarding technologies and methods to enhance tissue safety. This recommendation also addresses outreach in Topic 2.

RECOMMENDATIONS THAT MAY BE IMPLEMENTED WITH ADDITIONAL PLANNING AND/OR RESOURCES:

- Expanding MedSun Cell/Tissue Pilot Project. Over 30 hospitals currently contribute to the tissue module of this passive safety surveillance program. Additional facilities continue to express interest. CBER assists CDRH and its contractor in the orientation program for newly participating facilities,
- Assuring successful IT system development and data migration for the replacement of the current adverse reports database with a professionally developed Oracle-based system, and
- Expanding collaborations with CDC and other agencies for the design and implementation of active tissue safety surveillance and other enhanced approaches. Two key potential collaborations with CDC would include the Transplantation Transmission Sentinel Network (TTSN) and the National Healthcare Safety Network (NHSN, formerly the NNIS).

Topic 4: Additional Regulations and Guidance Development

BACKGROUND: As we reviewed the current regulatory system, considered information provided by various stakeholders and reviewed recommendations of the HTTF subgroup, we considered whether any additional regulations, modification to existing regulations, or guidance development was merited for public health protection.

ACTION TAKEN:

- "Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements" was issued on September 8, 2006 for immediate implementation. This document emphasizes that FDA requires establishments that manufacture HCT/Ps to comply with Title 21 Code of Federal Regulations 1271.150(c)(1). In addition, they are responsible for ensuring that any contract establishments that engage in any step in manufacture for them are in compliance with the current good tissue practice (CGTP) requirements of the HCT/P regulations in 21 CFR Part 1271.
- A subgroup of the HTTF was formed to identify opportunities for guidance or regulation development related to manufacturing activities.

RECOMMENDATIONS: Following a review of the HTTF subgroup's work, the HTTF makes the following recommendations:

- *Tracking of tissue from donor to recipient/patient*
  The current regulation, 21 CFR 1271.290, requires tracking to the consignee or final disposition, but not to the patient. We reviewed current tracking requirements in the areas of blood and medical devices to further inform our recommendation. The HTTF recommends the development of a plan to facilitate tissue tracking from donor to recipient and from recipient to donor. This would involve an examination of legal authority and current practices to study whether additional regulation in this area would be effective at protecting and promoting public health.
- *Donor Eligibility Determination*
  The HTTF recommends that guidance be developed for establishments which determine donor eligibility to review original donor records, when possible, when making the determination.
- *Auditing contractors*
  Our guidance document on assuring compliance by contractors, issued September 8, 2006, has been described above. The guidance emphasizes a manufacturer's responsibility for regulatory compliance by their contractors. The HTTF recommends that guidance be developed regarding FDA's current thinking and best practices for auditing of contractors.

Prior to initiation of the HTTF, FDA had begun drafting guidance for industry on Current Good Tissue Practice (CGTP). The CGTP draft guidance will be enhanced by our discussions with and outreach to stakeholders, through the information obtained by the inspection blitz, and from other tissue establishment inspections, and will specifically address practices of concern and opportunities for improvement.

Topic 5: The Science of Tissue Safety

BACKGROUND: A strong scientific program and related expertise are needed to enhance FDA's understanding of tissue processing issues and to facilitate the

development, evaluation and use of modern tools to better ensure tissue safety by prevention, detection and/or inactivation of pathogens that may affect the safety of these products. Development of a scientific base could include core internal tissue testing capacity as well as support for critical path activities and partnerships to evaluate and identify manufacturing practices that reduce infectious disease risks and that facilitate the development and evaluation of innovative methods to enhance pathogen detection and inactivation while preserving tissue quality.

RECOMMENDATION: CBER should initiate a tissue microbiology program through recruitment and support of a scientist with suitable expertise who will devote his/her effort to tissue safety. As this program is developed, it should be part of the CBER managed research program, and planning and implementation would be accomplished with academic and industry input and collaboration to leverage and enhance existing resources. The microbiologic expertise and capacity should also be structured so as to be useful to other program components, for example blood and vaccines. Achieving these goals fully will require additional time, planning, and human and financial resources.

Future Role of the HTTF:

This report concludes the charge to the HTTF, as directed by Dr. Goodman and Ms. Glavin. We appreciate the opportunity to collaborate on this important task. The multidisciplinary approach was very helpful and is a desirable one to carry forward for strategic purposes both as needed and for periodic reassessments. Therefore, we recommend that the group remain available as needed to engage in certain specific issues that remain open or that arise and require review from a cross-agency, multi-disciplinary perspective; and that the group also meet quarterly over the next two years to track implementation and to identify and discuss emerging issues and opportunities. The HTTF will review and evaluate the work products that result from its current recommendations, make further decisions and recommendations as needed, and direct any resulting work into the appropriate, existing CBER/ORA functions.

Respectfully submitted on behalf of the HTTF,

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cc: HTTF Members