

Overview of FDA Regulation of Human Cellular and Tissue-Based Products

MARTHA A. WELLS, M.P.H. *

I. INTRODUCTION

Over the years the Food and Drug Administration (FDA) has regulated most cellular and tissue-based products on a case-by-case basis. Technological advancements have resulted in the development of new products and increasing numbers of transplantations. Many of these products are used in novel ways that warrant clinical evaluation, while some of the uses would be considered medical practice. As described later in this article, FDA's major concerns relating to oversight of some of these products pertain to protection of recipients from transmission of communicable disease, safety during processing and storage, efficacy, the need for reliable recordkeeping, and both product and recipient identification.

Human tissues for transplantation have been regulated by FDA since 1993 under an interim rule,¹ which provides minimal oversight based on issues of infectious disease transmission and requirements for donor testing and screening. Other human tissues, such as dura mater, heart valves, corneal lenticules, and skin that is grown *in-vitro* on a synthetic matrix, have been regulated as medical devices.

Policies and regulations for cellular products also have developed as needed. FDA has regulated blood and blood products under the Public Health Service (PHS) Act² and the Federal Food, Drug, and Cosmetic Act (FDCA)³ for decades. A policy was published in October 1993 concerning somatic cell and gene therapy.⁴ This policy included autologous, allogeneic, and xenogeneic cells that act systemically, and excluded minimally-manipulated bone marrow cells. A new cell product class called manipulated autologous structural (MAS) cells was the subject of two public meetings that resulted in a published guidance document in May 1996.⁵ In September 1996, FDA further refined its policy concerning xenotransplantation of cells and tissues in a draft PHS guideline on infectious disease issues.⁶ In 1995 and 1996, FDA sponsored workshops and developed draft documents addressing the regulation of peripheral blood and placental/umbilical cord blood stem cells.⁷ All of these regulations and

* Ms. Wells is a regulatory scientist, Human Tissue Program, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration. This article is an updated version of speeches presented at FDLI's seminar "Understanding FDA Tissue and Cellular Product Regulation," Washington, D.C. (May 7, 1997) and FDLI's Biologics Update '97, Washington, D.C. (July 24-25, 1997).

¹ Human Tissue for Transplantation; Interim Rule, 58 Fed. Reg. 65,514 (Dec. 14, 1993) (codified at 21 C.F.R. pt. 1270 (1996)).

² Ch. 288, 37 Stat. 309 (1912) (codified at 42 U.S.C. §§ 201 et seq. (1994)).

³ Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301 et seq. (1994)).

⁴ Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice, 58 Fed. Reg. 53,248 (Oct. 14, 1993).

⁵ Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex-Vivo and Intended for Structural Repair or Reconstruction; Availability, 61 Fed. Reg. 26,523 (May 28, 1996).

⁶ Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation; Notice, 61 Fed. Reg. 49,920 (Sept. 23, 1996).

⁷ Draft Document Concerning the Regulation of Placental/Umbilical Cord Blood Stem Cell Products Intended for Transplantation or Further Manufacture into Injectable Products; Availability, 61 Fed. Reg. 7087 (Feb. 26, 1996).

policies address controls to adequately protect the public health and to ensure both product safety and patient benefit. This approach to regulation of emerging therapies, however, has resulted in gaps in regulation, occasional inconsistency in oversight, and in some cases confusion in regulation or policy implementation. Even with intercenter memoranda of understanding among FDA's Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and Center for Drug Evaluation and Research (CDER), and with the implementation in 1991 of designating procedures for determining regulatory authority for combination products based on their primary mode of action,⁸ the application of regulation has not always been uniform.

II. SCOPE OF TISSUE AND CELL INDUSTRY AS CURRENTLY KNOWN

Although FDA has not yet required registration of tissue establishments, fairly accurate information has been gathered from other sources. Many establishments have been identified by professional associations such as the American Association of Tissue Banks (AATB), the Eye Bank Association of America (EBAA), and the American Society for Reproductive Medicine (ASRM). Other establishments have been identified through FDA inspectional record reviews, as well as from complaints from competing establishments. In 1992 AATB surveyed fifty-eight known tissue banks; forty-two banks responded, identified 5202 donors, and indicated that 303,000 grafts had been distributed.⁹ A survey sponsored by FDA in 1994 and conducted by Dr. Jeffrey Prottas identified fifty-two out of sixty-seven bone banks that reported 6650 donors and 140,000 grafts distributed.¹⁰ This survey did not record the 200,000 units of bone powder provided for dental use. EBAA annually reports statistics on the activities of their associated banks. In 1996, 108 eye banks reported that there were 92,162 donations and 46,300 corneal transplants; approximately 35,000 donations were used for research or training, and 10,716 were rejected due to the quality of the tissue or because donor testing and screening criteria were not satisfied.¹¹

FDA currently does not regulate reproductive tissue banks, and will need to propose a regulation requiring establishment registration to confirm actual numbers. In a 1994 AATB survey reported by Dr. John Critzer of Indianapolis, ninety-one out of 135 known banks reported procurement of anonymous sperm; thirty-five out of ninety-one banks reported 90,000 semen units distributed, and an average number of twenty-nine qualified donors.¹² A report¹³ published in 1990 by ASRM/Society of Assisted Reproductive Technology (SART), provides an estimate for the actual usage of reproductive tissue with 180 fertility clinics reporting 25,744 stimulation cycles for 19,095 women, with 5159 pregnancies and 3941 live deliveries.

Unlike the data available from surveys for tissue products, cellular therapy is a

⁸ Assignment of Agency Component for Review of Premarket Applications; Final Rule and Notice, 56 Fed. Reg. 58,754 (Nov. 21, 1991) (codified at 21 C.F.R. pt. 3).

⁹ D.M. Strong, T. Eastlund, & J.C. Mowe, *Tissue Banking Activity in United States: 1992 Survey of AATB-Inspected Tissue Banks*, 3(1) AATB TISSUE & CELL REP. 15-18 (1996).

¹⁰ Jeffrey Prottas, A Study of the Tissue Procurement and Distribution Systems of the United States — October 1995, Address Before the Blood Prod. Advisory Comm., FDA (Dec. 14, 1995).

¹¹ EYE BANK ASS'N OF AM., EYE BANKING STATISTICAL REPORT (1996).

¹² John Critsen, Ph.D., Address at the FDA Workshop on Tissues for Transplantation and Reproductive Tissue: Scientific and Regulatory Issues and Perspectives (June 20-21, 1995).

¹³ Medical Research Int'l & Society of Assisted Reproductive Tech., *In Vitro Fertilization-Embryo Transfer (IVF-ET) in the United States: 1990 Results from the IVF-ET Registry*, 57 FERTILITY & STERILITY 15 (1992).

rapidly developing field in which there is no central source of information on the number of establishments and the number of procedures accomplished. Many somatic and gene therapies are considered medical practice, and some are becoming commercialized. Similarly, the effectiveness of hematopoietic stem cells derived from peripheral blood and umbilical cord blood is only recently being evaluated as a medical therapy and only preliminary data is available concerning the extent of the use of these cells and their efficacy.

III. KNOWN COMMUNICABLE DISEASE TRANSMISSIONS

The number of known transmissions of communicable disease is low for transplanted human tissues and cells, and most of these transmissions occurred before mandatory donor testing and screening was in effect. One of the more well-known incidents of transmission of infectious disease by tissue was reported in 1991 when a donor tested negative for Human Immunodeficiency Virus (HIV) at procurement in 1985 but was positive when retested in 1991 with more sensitive tests. It later was confirmed that seven of the forty-one tested recipients of organs and minimally processed (fresh-frozen) tissues had contracted HIV.¹⁴ Another well-known incident was reported initially in 1987¹⁵ and identified transmission of Creutzfeldt-Jakob disease (CJD) from a dura mater transplant. To date approximately sixty-three cases of CJD transmission have been reported from dura mater transplants.¹⁶

The most comprehensive report on disease transmission through cell, tissue, and organ transplantation was published by Dr. Ted Eastlund.¹⁷ He observed a number of reports of bacterial and fungal transmissions from all the tissue allografts he surveyed. Focusing on other reported transmissions, he noted that bone has transmitted hepatitis C virus (HCV), tuberculosis, and HIV; corneas have transmitted rabies, CJD, hepatitis-B virus (HBV), cytomegalovirus (CMV), and herpes simplex virus (HSV-1); tendon has transmitted HIV and HCV; and dura mater has transmitted CJD. HIV and CMV transmission from skin has been reported but not confirmed. Other articles have documented transmission of HIV, HBV, *Neisseria gonorrhoea*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, HSV-2, and *Chlamydia trachomatis* from semen.

Dr. Eastlund also reported bacterial transmission as well as transmission of HBV, HCV, Epstein Barr virus, CMV, and malaria through marrow transplantation.¹⁸ As previously noted about the scope of the industry, cellular therapy is a more recently evolving field, and there is no professional organization that routinely surveys these establishments or assesses the incidence of disease transmission as there is with tissue products.

¹⁴ R.J. Simmonds, S.P. Holmberg, R.L. Hurwitz et al., *Transmission of Human Immunodeficiency Virus Type 1 from a Seronegative Organ and Tissue Donor*, 326 N. ENG. J. MED. 726-32 (1992).

¹⁵ Centers for Disease Control, *Rapidly Progressive Dementia in a Patient Who Received a Cadaveric Dura Matter Graft*, 36 MORTALITY & MORBIDITY WKLY. REV. 49-50, 55 (1987).

¹⁶ Recent communication from the Centers for Disease Control to be reported in the *Mortality and Morbidity Weekly Review* with 1996 data on 43 cases from Japan.

¹⁷ Ted Eastlund, *Infectious Disease Transmission Through Cell, Tissue, and Organ Transplantation: Reducing the Risk Through Donor Selection*, 4 CELL TRANSPLANTATION 455 (1995).

¹⁸ *Id.* at 457, 463.

IV. OVERSIGHT OF HUMAN TISSUE FOR TRANSPLANTATION

A. *The Interim Rule*

The interim rule for human tissue intended for transplantation was published in the *Federal Register* on December 14, 1993.¹⁹ It was effective immediately to address a perceived threat of contaminated tissue being imported into the United States from donors who were inadequately screened and tested. It provided a minimal level of safety for infectious disease control under the authority of section 361 of the PHS Act. This rule covered establishments or persons involved in recovery, processing, storage, or distribution of banked human tissue²⁰ such as musculo-skeletal bone and tendon, skin, and ocular tissue such as cornea and sclera. The rule focused on donor testing for HIV-1 and 2, HBV, and HCV. Donor screening for medical history, behavioral risk factors, and clinical evidence of disease also was required. Written procedures for all significant steps of infectious disease testing and the medical history determination had to be established, and documented release from quarantine when donor testing and screening was complete was required. Under the interim rule, relevant records were required to be retained for ten years and were to be available for inspection. The rule also authorized FDA to perform unannounced inspections of establishments, the frequency of which was left to the agency's discretion, as well as to retain, recall, and destroy violative tissue.

B. *Final Rule/Guidance for Screening and Testing Donors*

The final rule for regulation of tissue for transplantation²¹ was published in the *Federal Register* on July 29, 1997, and is considered a modification or clarification of the interim rule with no major regulatory changes. The preamble to the rule addresses the seventy-three comments to the docket of the interim rule. These were submitted from tissue and eye banks, hospitals, physicians, processors, individuals, Lions Clubs, and other federal and state government agencies. Many of the changes or clarifications found in the final rule are based on these comments and/or on discussions held during three subsequent workshops sponsored by FDA. Because many of the comments requested FDA to be more specific and to define the terms used, fifteen new definitions were added and others revised. Examples of some of the terms for which new definitions are included in the rule are "plasma dilution," "physical assessment," "donor medical history interview," and "summary of records."

The rule clarifies the requirement that infectious disease tests for HIV-1 and 2, and for hepatitis B and C, be FDA-approved screening tests when available. Any repeat reactive test would result in rejection of the donor. When tests are approved for cadaveric specimens, they must be used. The rule also noted that a mother's specimen would be acceptable for a neonate donor.

¹⁹ 58 Fed. Reg. at 65,514.

²⁰ The interim rule defined "banked human tissue" as any tissue derived from a human body that is intended for administration to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease; is recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics; is not currently regulated as a human drug, biological product, or medical device; excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ; and excludes semen or other reproductive tissues, human milk, and bone marrow. *Id.* at 65,520.

²¹ Human Tissue Intended for Transplantation; Final Rule, 62 Fed. Reg. 40,429 (July 29, 1997).

The rule specifies that there be written procedures developed and followed for infectious disease testing; obtaining, reviewing, and assessing relevant medical records; designating and identifying quarantined tissue; and prevention of infectious disease contamination or cross-contamination during processing. It also allows for use of standard written procedures prepared by another organization such as AATB or EBAA. In other words, the rule specifies that written procedures need to be in place but does not specify what the contents of those procedures should be.

The final rule reiterates the recordkeeping requirements specified in the interim rule, such as maintaining records concurrent with the performance of each significant step of donor screening/testing and documenting the destruction or other disposition of human tissue. Some of the new recordkeeping requirements include the specification of who is required to retain certain records generated in determining donor suitability and what information is needed on a summary of records accompanying the released tissue, and a requirement for keeping records that document receipt of the tissue. The final rule clarifies the record retention requirement such that records shall be retained for no less than ten years beyond the dates of transplantation (if known), distribution, disposition, or expiration of the tissue, whichever is latest. This rule will become effective on January 26, 1998, and will be applicable to all human tissue procured on or after this date.²²

Also on July 29, 1997, the *Federal Register* included a notice of availability of a guidance document²³ that provides technical recommendations to assist establishments in complying with the final rule for the donor screening and testing requirements. This guidance was revised after the draft was published in 1995 and discussed at an FDA workshop held in June 1995. The guidance provides specific recommendations for determining plasma dilution and for applying a testing algorithm. It also recommends what behavioral and high-risk information, and what clinical and physical evidence should be documented to evaluate donors effectively.

V. PROPOSED APPROACH TO THE REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

Recently FDA re-assessed the many different regulations and policies that were developed on a case-by-case basis over the years for the regulation of tissue and cellular products. FDA recognized that the regulatory strategy in place was perceived as potentially inconsistent, with over regulation for some products and under or no regulation for others. The agency also perceived a need to address regulation of the many diverse and novel products resulting from developing technology. This need was tempered by other concerns, such as the need to extend regulation without accompanying increases in agency resources and without levying unnecessary regulatory burdens on the industry.

To achieve these goals, FDA published in February 1997 its sixth Reinventing Government report, entitled *Reinventing the Regulation of Human Tissue*,²⁴ as part of Vice President Al Gore's National Performance Review for streamlining government

²² *Id.* at 40,429.

²³ Guidance for Industry; Screening and Testing of Donors of Human Tissue Intended for Transplantation; Notice, 62 Fed. Reg. 40,536 (July 29, 1997).

²⁴ FOOD AND DRUG ADMIN., DEPARTMENT OF HEALTH AND HUMAN SERVS., NATIONAL PERFORMANCE REVIEW: REINVENTING THE REGULATION OF HUMAN TISSUE (1997).

regulation. Published at the same time was a more detailed analysis of FDA's revised regulatory plan, entitled *A Proposed Approach to the Regulation of Cellular and Tissue-Based Products*.²⁵ These documents laid out a plan for a rational, comprehensive, and flexible regulatory framework for products derived from human cells and tissues. The plan calls for a tiered approach to regulation that is proportionate to the degree of risk the product poses to the public health. To accomplish this, the approach invokes the authority to regulate under the PHS Act and/or the FDCA, depending on specific characteristics of the product. It addresses regulation of a range of diverse products derived from human tissue or cells such as musculo-skeletal and ocular tissue, heart valves, dura mater, demineralized bone, reproductive tissue, cellular therapies, stem cells, and combination products consisting of cells or tissue and other regulated products. Because comprehensive regulation already exists under other authorities, or the risk issues are different, the proposed approach does not include regulation of vascularized organs, minimally manipulated bone marrow, xenografts, cellular transfusable blood products, and secreted or extracted products.

The three stated goals for this approach are 1) to prevent the potential for transmission of communicable disease, 2) to prevent improper handling/processing that might contaminate or damage tissue/cells, and 3) to ensure clinical safety and effectiveness for certain cells and tissues with increased potential risk. Five areas of product concern were identified that needed to be addressed for all of these products, and the degree of regulation is based on the varying levels of risk determined. These areas of concern are direct transmission of communicable disease; control of processing; clinical safety and effectiveness; promotion and labeling; and a baseline knowledge of industry. All products will be required to adhere to certain requirements for donor testing and screening for risk of communicable disease transmission. Donor screening and testing procedures would be recommended, rather than required, for autologous cells and tissues and for reproductive tissues from sexually intimate partners because these raise lesser communicable disease concerns than do allogeneic use. All establishments will be required to register with FDA and list their products. Concerning requirements for processing controls, clinical evaluation, and promotion and labeling, the degree of regulation will vary based on specified product characteristics and associated levels of potential risk. The level of risk will be defined by the extent of processing, whether the product functions systemically, whether it is combined with a nontissue component, or if it is used for other than its homologous function. Those products identified as having a higher potential risk will require premarket assessment including clinical study. Lower-risk products will adhere to regulations that will be proposed and promulgated under section 361 of the PHS Act for control of infectious disease transmission and related processing controls and limits for promotional claims and labeling.

VI. MAJOR COMMENTS AND CONCERNS WITH THE PROPOSED APPROACH

FDA held an open public meeting on March 17, 1997,²⁶ at which twenty organizations or individuals expressed their opinions on the proposed approach. The major

²⁵ FOOD AND DRUG ADMIN., PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS (FDA Dkt. No. 97N-0068) (1997). See also *A Proposed Approach to the Regulation of Cellular and Tissue-Based Products*, 62 Fed. Reg. 9721 (Mar. 4, 1997).

²⁶ Comments from FDA Open Public Meeting, Rockville, MD (Mar. 17, 1997) (transcript and comments available from Dockets Management Branch, FDA). See also *supra* note 25.

concerns expressed at that meeting, and in thirty-eight comments to the public docket, can be broken into several areas of concern. Regarding the communicable disease transmission proposals, which *recommended* donor testing and screening for autologous cells and tissue and for certain reproductive tissue, and *required* same for all allogeneic products, meeting participants expressed concern that all products should have the same requirement if they are stored, due to the possibility of cross-contamination and improper release. Other participants noted and took issue with the fact that the testing requirements for hematopoietic stem cells differ from other blood products.

A major concern focused on the definitions of the factors that will be used to assess whether a product requires the higher standard of regulations. For example, meeting participants wondered about the practical construction of terms such as “minimal manipulation during processing,” “homologous function,” and “nontissue component.” Clarification of what the agency considers to be good tissue practices was requested, as well as the processes by which these requirements will be developed and how the regulation ultimately would be enforced. All commentators were in favor of required registration and listing. As to the topics of promotion and labeling, meeting participants’ major concern centered on what promotion would be allowed for tissue and cells that would not require premarket evaluation and how those claims would be assessed for these products.

In the agency’s proposed approach, formation of a tissue reference group was suggested and described therein as a CDRH/CBER group whose purpose would be to ensure consistent policy.²⁷ Many comments at the public meeting asked for additional explanation as to what the group’s responsibilities are, how it will function, and how its decisions would relate to product jurisdiction questions currently addressed in FDA’s Office of the Chief Mediator and Ombudsman. Many questioned how FDA will take on an increased compliance and enforcement burden of regulating additional establishments without supplemental inspectional resources. FDA was asked to clarify if exemptions to compliance would be allowed, whether third-party inspections would be permitted, and whether compliance with industry standards would be deemed the equivalent of meeting FDA’s regulations. Additional substantive comments disagreed with the proposed approach’s premise that demineralized bone should be regulated as a Class I exempt medical device rather than as a tissue, because of the extent of processing manipulation. The history of safe use for demineralized bone was cited and concern was expressed over the definition of “minimal manipulation.” Another major area of concern addressed the proposed regulation of hematopoietic stem cells; the comments varied from one extreme (that all of these products, even those that are not manipulated and are for autologous use, should be required to have premarket assessment) to the other (that no regulation is needed for what is considered medical practice). The proposed approach offered a compromise under which regulation will be phased in without an up-front requirement for an investigational new drug submission so that clinical experience with these new products can progress and industry would have an opportunity to establish product standards.

VII. CONCLUSION

FDA has re-assessed its approach to the regulation of tissue and cellular prod-

²⁷ FOOD AND DRUG ADMIN., *supra* note 25, at 15, 17.

ucts. This plan generally has been well received. This re-assessment, as defined in the agency's proposed approach,²⁸ addresses FDA's concern that application of drug or device regulations to achieve uniform regulation of the entire range of current products might inhibit the development of valuable new products and create unnecessary regulation. Implementation of the proposed approach will allow the level of regulation to be based on potential or actual risk to the public health, and will allow FDA to serve the public better by allowing the agency to concentrate its efforts on the most significant health issues.

FDA's current thinking concerning implementation of the proposals for regulating cells and tissues includes the development of proposed rules regarding registration and listing, communicable disease controls, good tissue practices, promotion and labeling, and enforcement and compliance. These proposed rules will consider comments received in public discussions. In the meantime, the agency will function according to current regulation or policy. As discussed at the March 1997 public meeting, FDA also plans to publish a *Federal Register* notice requesting that establishments develop and submit to FDA proposed standards based on clinical and laboratory data that could be used to define licensing requirements for peripheral and cord blood stem cell products. Further input to the dockets for these proposed rules and future public meetings will aid in fine tuning these proposals before implementation.

²⁸ See generally 62 Fed. Reg. at 9721.