

The International Harmonization of Human Tissue Regulation: Regulatory Control Over Human Tissue Use and Tissue Banking in Select Countries and the Current State of International Harmonization Efforts

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I. INTRODUCTION

Human tissues play a critical role in modern medicine, particularly in this era of biotechnology.¹ Beyond immediate therapeutic uses, e.g., transplantation, tissues (unlike organs) may be stored for an indefinite time period in traceable and often coded form and later used for biomedical research purposes,² teaching, quality control in healthcare, and the manufacture and production of therapeutic and diagnostic aids.³ Both living donors and cadavers serve as sources of human tissue.

However, whether procured from a living or deceased donor, subjected to sophisticated tissue engineering⁴ or used in transplantation in its unprocessed, basic form, human tissue is no longer limited by national borders. Keeping pace with the globalization of the marketplace, the increasingly international scope of human tissue use presents new challenges in cross-border disease control.⁵ In response, the regulatory authorities of several industrialized countries, along with consumer and industry leaders

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¹ For the purposes of this paper, "human tissues" are defined as constituent parts of the human body including, but not limited to, bones, skin, heart valves, tendons, corneas, arteries, veins, dura mater, and cells intended for grafting. While fetal tissue generally falls within the scope of this definition, this paper does not address the myriad of ethical considerations associated with the use of human fetal tissue. Whole organs, blood, and blood products (including fetal cord blood) are deemed beyond the parameters of this definition. *See, e.g.,* Robin Elizabeth Margolis, *Should Human Tissue Transplants be Regulated?*, HEALTHSPAN, Dec. 1992, at 17.

² This paper does not examine the ethical and legal aspects of human tissue stored in biological banks for medical research purposes, including DNA examination. Some ethics questions generated in this area do bear mentioning, including: 1) to what extent should biomedical storage be allowed, and what use of such material is permissible; 2) must the donor give consent for such preservation and use, and to what degree must the donor be informed of any use (i.e., must donor consent be secured for every different use of his/her tissue, even years after donation); 3) may old biomaterials which were retrieved without donor consent (i.e., residual tissues from surgery) be used for research purposes; 4) who is the owner of the biomaterial—the person who donated the tissue, the research institution, the individual researcher, society as a whole; 5) as a corollary, should human tissue, an intrinsic part of the human body, even be considered as property; and 6) to what degree must confidentiality be maintained. In essence, the protection of a donor's autonomy, privacy, and human dignity must be balanced against the fundamental societal interests of freedom of research and efficiency of medical care. Where DNA analysis of a donor's tissue may reveal his genetic profile and future health and by extension relevant medical information on his biological family, yet another ethical consideration is what obligation, if any, researchers bear to inform the donor of any genetic concerns (i.e., diseases or disease markers) discovered. *See* Linda Nielsen, *Legal and Ethical Aspects of Further Use of Human Tissue*, 20 EUR. J. HEALTH L. 109, 109-110, 112 (1995).

³ *Introduction: Human Tissues; Health Care and the Rights of Patients*, 2 EUR. J. HEALTH L. 101, 101-02 (1995).

⁴ In tissue engineering, human cells or tissues may be combined with biodegradable synthetic polymers to create a "neo-tissue."

⁵ Linda Horton, *Mutual Recognition Agreements and Harmonization*, 29 SETON HALL. L. REV. 692, 693 (1998).

in the pharmaceutical, medical device, and healthcare fields, have turned their attention to the development of a globally-accepted set of standards governing human tissue use and tissue banking.

This paper examines the ethical considerations associated with human tissue use, the regulation of human tissue at the national level (focusing on the United States and three European Union (EU) member states), the regulation of human tissue at the regional EU level, and the current multi-country effort toward international harmonization of human tissue use and tissue banking. The paper concludes by highlighting a number of factors that should be considered in this endeavor.

II. ETHICAL ASPECTS OF THE USE OF HUMAN TISSUE

While benefits of human tissue in clinical medicine and medical research are well recognized, so too are the bioethical considerations presented. In this age of biotechnology, human tissue can be engineered to create biopolymeric body parts, an accomplishment regarded favorably by many. But human tissue also can be analyzed to provide genetic information not only about the donor (which may be of use to the donor), but about his family, race, culture, and sex (which may cross accepted borders of privacy, with profound implications).⁶

Society cannot (and perhaps should not) disregard the human origin of human tissue substances and the consequent ethical considerations. Developmental psychologists highlight that in order for an individual to be psychologically healthy, he must experience both self-agency (the ability to control what happens to one's body) and self-coherence (the ability to maintain the body as an integrated, nonfragmented whole).⁷ An individual's human body serves as a means to establish identity and convey value to others.⁸ That individual may indicate his personal value system by placing limits on the use of his body parts; for instance, he may be willing to donate body tissue for therapeutic use in transplantation, but object to use of the donated tissue in the commercialized setting of a biotechnology firm.⁹

Body tissue possesses social significance beyond the individual. In some developing countries, hair, blood, and placenta play an important role in social rituals, defining community identification and reinforcing the governing rules and values of acceptable behavior.¹⁰ Even within western societies, the way a person displays and manipulates his body suggests how he identifies with the community.¹¹ And within these same western societies, where one might expect the mores to be more homogeneous, different ideological beliefs and legal traditions have resulted in varying legislative attitudes toward human tissue use. For instance, Great Britain emphasizes the principle of individual freedom and consequently permits human embryo research and artificial reproductive technology, whereas in Germany and France, the principle of human dignity (combined with the influence of Christianity in France) has resulted in the severe restriction or complete prohibition of human embryo research.¹²

Religious and humanistic beliefs may significantly impact an individual's attitude toward human tissue donation and use. Both Jewish and Christian traditions

⁶ Lori Andrews & Dorothy Nelkin, *Whose Body is it Anyway? Disputes Over Body Tissue in a Biotechnology Age*, 351 LANCET 53, 53-57 (Jan. 3, 1998).

⁷ *Id.*

⁸ *Id.*

⁹ *Id.*

¹⁰ *Id.*

¹¹ *Id.*

¹² Jason T. Corsover, *The Logical Next Step? An International Perspective on the Issues of Human Cloning and Genetic Technology*, 4 ILSA J. INT'L & COMP. L. 697, 715 (Spring 1998).

affirm that human beings were created in the image of God and, therefore, regard the human body as profoundly linked and identified with the spirit.¹³ The concept of human dignity, both in life and death, is emphasized.¹⁴ In Judaism, these beliefs are reflected in prohibitions against mutilation and delayed internment of and derived benefits from a corpse, although the immediate saving of a human life overcomes most of these constraints.¹⁵ Thus, nonexperimental cadaveric organ, and even cornea, transplantation may be permitted in light of its high probability of immediate life-saving (or significant life-enhancing) benefit.¹⁶ Roman Catholicism and Protestantism propound the themes of voluntarism and altruism, generally viewing the donation of cadaveric organs and tissues as praiseworthy, although not necessarily obligatory.¹⁷ The requirement of a direct and immediate benefit by such donation imposed under Judaism is not as highly emphasized.¹⁸ Islam, in contrast, has traditionally objected to cadaveric organ and tissue transplantation as conflicting with the belief of bodily resurrection.¹⁹ As in Judaism, the Islamic religion provides for rapid burial and the avoidance of a corpse's mutilation and cremation.²⁰ More recently, however, the majority of Islamic religious authorities are accepting organ and tissue donation in the interest of saving human life and necessity, with the requirement that the decedent or a relative first grant permission.²¹

Whether human tissue is donated by a living donor or retrieved from a cadaver, the reason for donation is usually altruistic in nature—a genuine desire to help another or to make something positive come out of the death of a relative.²² Also in both instances, it is generally required that tissue donation be voluntary and uncompensated.²³ In the United States, tissue donation requires explicit consent from the donor, or in the case of a deceased person, from the donor's family or a signed donor card.²⁴ In some European countries, i.e., France and Belgium, an alternative system of "presumed consent" operates, under which the permission for tissue donation by a donor or his family is presumed to be given if these individuals do not expressly object to the donation.²⁵

Certain ethical and legal considerations regarding tissue donation depend upon whether the tissue donor is living or dead. In the case of tissue harvested from cadavers, there may be an issue as to who has which rights, and which rights they have, over cadaveric body parts.²⁶ Does the decedent's family, the promised recipients of those

¹³ James F. Childress, *Organ and Tissue Procurement: Ethical and Legal Issues Regarding Cadavers: Religious and Humanistic Beliefs, Attitudes, and Practices*, 4 *ENCYCLOPEDIA OF BIOETHICS* 1854, 1863 (Warren Thomas Reich ed., 2d ed. 1995).

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ *Id.*

²¹ *Id.*

²² Childress, *supra* note 13, at 1854. Those opposed to donating tissue often cite a mistrust of the medical establishment and the donation process, including the fear that a commitment to donation will compromise the care or prolong the suffering of a relative. *Id.*

²³ *Id.* at 1856. There is great ethical concern about the "donation" of tissues and organs by persons in dire economic need, particularly in developing countries, who receive some financial compensation for their donation. Peter A. Ubel & Mary B. Mahowald, *Ethical and Legal Issues Regarding Living Donors*, 4 *ENCYCLOPEDIA OF BIOETHICS* 1865, 1869 (Warren Thomas Reich ed., 2d ed. 1995).

²⁴ Childress, *supra* note 13, at 1856.

²⁵ *Id.*

²⁶ *Id.* at 1857.

parts, or the community at large possess such rights?²⁷ More recently, consideration has been given to the potential strengthening of the donation system through the offer of financial or other tangible incentives as a “reward” for organ/tissue donation. This begs the question of whether the act of donation can still be preserved while allowing for society to express its gratitude to the deceased donor’s family by, for instance, covering a certain amount of the funeral expenses.²⁸

Procurement of tissues from living donors involves at least four relevant considerations: 1) the risks and benefits to the donor; 2) the risks and benefits to the recipient; 3) the actual potential for voluntary, informed consent; and 4) donor privacy and confidentiality.²⁹ Risks and benefits to the donor include whether the body can replace the donated material (e.g., as with bone marrow); the invasiveness, discomfort, and risks associated with the tissue retrieval process; and the donor’s increased self-esteem as a result of his altruistic act.³⁰ Risks and benefits to the tissue recipient are primarily contingent upon the prospects for success and the potential for alternative therapy, such as cadaver donation.³¹ The issue of voluntary consent by a living donor may be complex, and may involve such considerations as undue influence, family pressure upon a member to donate, the potentially limited time in which to make an “informed” choice, and the donor’s actual physical and mental capacity to offer voluntary, informed consent—or lack thereof in the case of minors and incompetent or institutionalized adults.³² Finally, the factor of donor privacy and confidentiality relates to the concern that both donor and recipient retain their anonymity (as in the case of tissue transplant between unrelated principals) and medical confidentiality.³³

In light of the numerous controversial ethical considerations in human tissue banking and use, a number of advisory commissions, comprised of experts in medicine, law, and ethics, have been established both at the national and regional levels to develop guidelines.³⁴ As will be discussed later, however, progress has been limited.

III. REGULATION OF HUMAN TISSUE IN THE UNITED STATES

In the United States, the Food and Drug Administration (FDA) is the federal agency responsible for the regulation of human cellular and tissue-based products. Within a regulatory context in the United States, human tissue is generally defined as:

any tissue derived from a human body, which; 1) [i]s intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease; 2) [i]s recovered, processed, stored or distributed by methods that do not change tissue function or characteristics; 3) [i]s not currently regulated as a human drug, biological product, or medical device; (4) [e]xcludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ, and; (5) [e]xcludes semen or other reproductive tissue, human milk, and bone marrow.³⁵

²⁷ *Id.*

²⁸ *Id.* at 1862.

²⁹ Ubel & Mahowald, *supra* note 23.

³⁰ *Id.* at 1866.

³¹ *Id.*

³² *Id.* at 1866-68.

³³ *Id.* at 1867-68.

³⁴ See, e.g., *The Commission Sets Up a European Group on Ethics in Science and New Technologies*, Ethical Legal and Social Aspects of the Life Sciences and Technologies, Press Release No. IP/97/1196 (Dec. 31, 1997) (last visited Aug. 1999) <www.europa.eu.int/comm/dg12/life/elsa/pr311297.html>.

³⁵ Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429, 40,444 (1997) (codified at 21 C.F.R. pt. 1270 (1999)).

FDA derives its regulatory authority over these products from section 361 of the Public Health Service Act³⁶ (PHSA), which authorizes the Secretary of the Department of Health and Human Services (DHHS), of which FDA is a component agency, to create and enforce such regulations as deemed necessary to prevent the introduction, transmission or spread of communicable diseases from state to state or from foreign countries into the United States.³⁷ Section 361 of the PHSA further authorizes the inspection and destruction of products determined to be so infected or contaminated as to present risk of dangerous infection to humans.³⁸

The United States may now be regarded as the country with the most comprehensive regulatory approach toward human tissue intended for transplantation. Prior to the 1990s, however, FDA had confined its oversight of these products to a case-by-case basis, as necessary, with certain human tissue products classified as medical devices and, therefore, separately regulated under the Federal Food, Drug, and Cosmetic Act (FDCA).³⁹ The “medical devices,” such as dura mater,⁴⁰ corneal lenticules,⁴¹ and allograft cultured skin and heart valves, had been required to meet both safety and efficacy criteria for premarket approval, as provided for in the FDCA, rather than simply to satisfy the safety standards mandated by the PHSA. This classification system proved to be particularly controversial for human heart valve allografts, with both tissue banks and surgeons spearheading the argument that subjecting human tissues (versus a man-made product) to a multi-year, expensive data collection and approval process made little sense.⁴² Classification of human heart valves as investigational devices further jeopardized reimbursement of processing fees and transplant costs, as Medicare and other third-party payers generally did not provide coverage or reimbursement for investigational devices.⁴³ Of particular concern was the potential for primarily nonprofit tissue banks to be forced into becoming proprietary commercialized enterprises selling tissues for profit in order to offset charges incurred due to the FDA regulation.⁴⁴

While human tissue use was subject to minimal federal oversight, human tissue banks were essentially unregulated by the federal government until the recent FDA-proposed rule requiring establishment registration and listing for manufacturers of

³⁶ 42 U.S.C. § 264 (1994).

³⁷ 21 C.F.R. pts. 16, 1270; 62 Fed. Reg. at 40,430-31.

³⁸ 62 Fed. Reg. at 40,431. Section 361 of the PHSA is enforced in part under the authority of the Act's section 368 (42 U.S.C. § 271), which provides penalties for those individuals violating section 361 provisions. *Id.*

³⁹ Martha A. Wells, *Overview of FDA Regulation of Human Cellular and Tissue-Based Products*, 52 FOOD & DRUG L.J. 401 (1997); Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301 et seq. (1994)).

⁴⁰ Dura mater is the outer meningeal tissue covering the brain. Marc O. Williams, *The Regulation of Human Tissue in the United States: A Regulatory and Legislative Analysis*, 52 FOOD & DRUG L.J. 409, 415 (1997). It is extracted from cadavers and used to patch the brain sacs of live human beings. *FDA Investigating Firm Making Device Implicated in CJD Case*, INSIDE WASH.'S FDA WK., Dec. 11, 1998, at 12.

⁴¹ Corneal lenticules, a human tissue product derived from the human cornea, is applied to the cornea to correct vision problems. Williams, *supra* note 40, at 415.

⁴² Margolis, *supra* note 1.

⁴³ D. Michael Strong, *Tissue Banks: Drafting New Rules for Grafting*, BUS. & SOC'Y REV., Sept. 22, 1991, at 42. FDA defended this classification as necessary in light of the agency's findings that there was little tissue bank consistency in new processing techniques affecting human heart valves and that not all heart valves were subjected to state-of-the-art donor screening and testing. Margolis, *supra* note 1, at 18.

⁴⁴ *Id.* This potential commercialization of human tissue banks was perceived as likely to negatively impact tissue bank donations, as altruistic donors and their families would be disinclined to donate tissues under such circumstances. *Id.*

human cellular and tissue-based products.⁴⁵ The only standardization and regulation of some tissue banks came in the form of oversight by such scientific and professional societies as the American Association of Tissue Banks (AATB). The AATB, a private, voluntary association, was formed in 1976 with six primary objectives in mind: 1) the encouragement of voluntary donation of tissue cells and organs; 2) the promotion of scientific and technical expertise in the areas of tissue cell and organ retrieval, processing, storage, and transportation; 3) the promotion of research and education in these areas; 4) the provision of a sufficient tissue cell and organ supply for clinical and research purposes; 5) the establishment of codes and standards for tissue banks, and 6) the inspection and accreditation of tissue banks.⁴⁶ Utilizing the latest, scientifically-approved standards, AATB developed an inspection and accreditation program for human tissue banks that was designed to ensure complete documentation on the safety and quality of human tissues at a particular, participating tissue bank.⁴⁷ While the accreditation process of the AATB is highly regarded by professionals in the field, tissue bank membership in the AATB (with the accompanying, requisite oversight) is voluntary, and in the early 1990s, only forty of an estimated 400 or more tissue banks nationwide had been inspected and accredited by the AATB.⁴⁸ Moreover, the AATB, along with other private organizations in this area, had (and has) no ability to compel compliance by participating tissue banks, aside from the penalty of expulsion from the association as a result of noncompliance with the voluntary standards.⁴⁹

A. *The Winds of Change in the United States*

On December 14, 1993, in response to concern about the immediate threat of contaminated tissue from inadequately screened and tested donors being imported into the United States, FDA issued a sweeping interim rule applicable to human tissue intended for transplantation.⁵⁰ The rule was issued under the authority of the PHS Act.⁵¹

The interim rule was applicable to all "banked human tissue and to establishments or persons engaged in the recovery, processing, storage, or distribution of banked human tissue."⁵² An exception to this regulation was made for organs and those human tissue products already regulated by FDA as drugs, biologics, or medical devices.⁵³ With a focus on required donor testing for hepatitis B, hepatitis C, and the AIDS virus, the rule mandated that donors also be screened for medical history, be-

⁴⁵ Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26,744 (to be codified at 21 C.F.R. pts. 207, 807, 1271). In the late 1980s and early 1990s, several alarming instances of transmission of serious illness (including AIDS and tuberculosis) from tissue donors prompted federal government efforts to pass comprehensive legislation regulating human tissue banks. Lynn Wagner, *Tough Rules Urged for Tissue Banks*, MOD. HEALTHCARE, Oct. 12, 1992, at 17. The proposed legislation (i.e., Senator Paul Simon's (D-IL) suggested "Human Tissue Transplantation Act of 1992"), however, never achieved the necessary accord for passage into law. See, e.g., Margolis, *supra* note 1, at 18. Concerns over the safety of human tissues used in transplants have remained. In a December 1997 report to Congress on the matter, the General Accounting Office (GAO) evaluated FDA oversight of different transplanted human tissue. The GAO concluded that, despite the passage of a 1997 FDA rule regulating human tissue intended for transplantation (effective January 1998), a number of safety issues remained unaddressed or inadequately addressed by existing regulations. *FDA Must Improve Human Tissue Oversight*, GAO Says, ANDREWS HEALTH L. LITIG. REP. 15 (Jan. 1998).

⁴⁶ *The Regulation of Human Tissue and Organs*, 46 FOOD DRUG COSM. L.J. (special issue) 1, 47 (1991).

⁴⁷ *Id.* at 50.

⁴⁸ Lynn Wagner, *Tough Rules Urged for Tissue Banks*, MOD. HEALTHCARE, Oct. 12, 1992, at 17.

⁴⁹ *The Regulation of Human Tissue and Organs*, *supra* note 46, at 56.

⁵⁰ Human Tissue Intended for Transplantation; Interim Rule, 58 Fed. Reg. 65,514 (1993) (codified at 21 C.F.R. pt. 1270).

⁵¹ *Id.*; 42 U.S.C. § 264.

⁵² 21 C.F.R. § 1270.1(a).

⁵³ *Id.* § 1270.3(b).

havioral risk factors, and clinical evidence of disease.⁵⁴ Comprehensive records detailing the results and interpretations of tests, information on the donor's identity and medical history, and the destruction of violative banked human tissue were required.⁵⁵ FDA was authorized to conduct unannounced inspections of all tissue establishments within the rule's scope, and to retain, recall, and destroy unsuitable tissue.⁵⁶

On July 29, 1997, FDA issued the final rule for the regulation of human tissue intended for transplantation, effective as of January 28, 1998, which clarifies and/or modifies a number of the provisions of the interim rule.⁵⁷ Among the highlights, the regulations to be applied to human tissue obtained from foreign sources or processed in foreign countries are clarified.⁵⁸ Tissues intended for transplantation within the United States under those circumstances must be held in quarantine until cleared by FDA.⁵⁹ Suitable tissue further must be "accompanied by a summary of records, indicating that all infectious disease testing and screening . . . has been completed, reviewed by the person responsible, and found to be negative."⁶⁰ For tissue that has *not* been determined to be suitable for transplantation prior to import, accompanying records must so note this, as well as indicate and ensure the identity of the donor.⁶¹ The final rule requires the development of, and adherence to, written procedures for infectious disease testing; the retrieval, review, and assessment of medical records; the designation and identification of quarantined tissue; and infectious disease contamination prevention during processing.⁶² Actual procedures, however, are not specified by FDA.

In conjunction with the issuance of the final rule, FDA indicated its preparation of a document entitled "Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation."⁶³ The Guidance is described as essentially advisory and not binding on either FDA or the public, although it reflects the agency's mindset on the matter.⁶⁴

B. FDA-Reinvention of the Regulation of Human Tissue

In February 1997, FDA issued a proposed approach to the regulation of human cellular and tissue-based products to clarify and harmonize the then existing "highly fragmented" cell and tissue regulations.⁶⁵ The PHSA and/or the FDCA (depending upon the specific characteristics of the human tissue product subject to regulation) were cited as providing the legal authority for FDA action.⁶⁶ Human tissue products

⁵⁴ Wells, *supra* note 39, at 404.

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ 62 Fed. Reg. at 40,429.

⁵⁸ *Id.* at 40,439-40.

⁵⁹ *Id.* at 40,439.

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² Wells, *supra* note 39, at 405.

⁶³ 62 Fed. Reg. at 40,430.

⁶⁴ *FDA Issues Final Rule on Human Tissue Intended for Transplantation; New Regulations Effective Jan. 26, 1998*, 7 TRANSPLANT NEWS, Aug. 11, 1997, available in 1997 WL 8941086.

⁶⁵ *A Proposed Approach to the Regulation of Cellular and Tissue-Based Products*, FDA, Feb. 28, 1997, at 3. At the same time, FDA also published a less detailed analysis of the proposed regulations entitled, *Reinventing the Regulation of Human Tissue, as a Component of Vice President Al Gore's National Performance Review for Streamlining Government Regulation*, FDA, DHHS, NATIONAL PERFORMANCE & REV.: REINVENTING THE REG. OF HUMAN TISSUE (1997) [hereinafter *Reinventing the Regulation of Human Tissue*].

⁶⁶ Wells, *supra* note 39, at 406. The Medical Device Amendments to the FDCA, enacted on May 28, 1976, establish the basic framework governing the regulation of medical devices. Further legislation relevant to medical device regulation includes the Safe Medical Devices Act of 1990, the Medical Device Amendments of 1992, and sections of the FDA Export Reform and Enhancement Act of 1996 and the Food and Drug Administration Modernization Act of 1997. *FDA Center for Devices and Radiological Health (CDRH)* (last visited Aug. 1, 1999) <www.fda.gov/cdrh/devadvice/371.html#global>.

targeted for regulation under the tiered proposal include musculo-skeletal and ocular tissue, dura mater, demineralized bone, cellular therapies, stem cells, reproductive tissue, combination products containing cells/tissue, and other regulated products.⁶⁷ Specifically excluded from the proposed approach are vascular organs, xenografts, cellular transferable blood products, minimally manipulated bone marrow, and secreted or extracted products, all of which either are already comprehensively regulated under other authorities, or present different issues of risk.⁶⁸ Under the new framework, the level of government regulation of applicable human cellular and tissue-based products will be proportionate to the degree of risk that each product poses to the public health.⁶⁹

The proposed approach was developed with three general goals in mind: 1) to prevent the transmission of infectious diseases through inadvertent use of contaminated tissues; 2) to prevent improper processing or handling which might contaminate or damage tissues; and 3) to ensure the clinical safety and effectiveness of certain cells and tissues.⁷⁰ In designing the tiered framework, the agency sought to respond to five public health and regulatory questions associated with the use of cellular and tissue-based products. Those questions were: 1) How can the transmission of communicable disease be prevented? 2) What processing controls are necessary to prevent contamination and maintain the integrity of cells and tissues? 3) How can clinical safety and effectiveness be ensured? 4) What type of labeling should be mandated and what kind of promotion is permissible to ensure that the product be used properly? and 5) How can FDA acquire a baseline knowledge of, and promote effective communication with, the cell and tissue industry?⁷¹

The resulting approach is intended to gear the degree of FDA regulation of a human tissue product to the level of risk to the public health the product is deemed to pose, with certain procedures as mandatory regardless of risk. Thus, registration and provision of product lists will be mandated for all tissue processing facilities. Likewise, certain requirements for donor testing and screening for risk of communicable disease transmission will be imposed on all products.⁷² For autologous cells and tissues and for reproductive tissues from sexually intimate partners, donor screening and testing measures will be recommended, rather than required, in light of the reduced concern for communicable diseases than with allogeneic use.⁷³ The requirements imposed for clinical evaluation, processing controls, and product promotion and labeling will vary according to specified product characteristics and associated potential risk levels.⁷⁴ A human cell/tissue product's risk level will be defined by the degree of processing to which it is subjected, whether the product acts systemically, is combined with a nontissue component, or is used for its homologous function or for some other purpose.⁷⁵ Under this scheme, some tissue products that are minimally manipulated will be subject to very limited regulation for control of infectious disease transmission (as promulgated under section 361 of the PHSA), while other exten-

⁶⁷ Wells, *supra* note 39, at 406.

⁶⁸ *Id.*

⁶⁹ *Reinventing the Regulation of Human Tissue*, DHHS, February 28, 1997 (last visited Aug. 1, 1999) <www.medscape.com/govmt/DHHS/1997/mar/RegulationOfHumanTissue.html> (Medscape site is free to use but requires user to register for password).

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² *Id.*

⁷³ Wells, *supra* note 39, at 406.

⁷⁴ All product labeling and promotion must be accurate, clear, balanced, and non-misleading. *Reinventing the Regulation of Human Tissue*, *supra* note 65.

⁷⁵ Wells, *supra* note 39, at 406.

sively processed and novel products will need FDA premarket approval under the FDCA, which includes a clinical study requirement.⁷⁶

C. FDA-Proposed Tissue Bank Registration

On May 14, 1998, FDA took the “first step” toward its implementation of “a comprehensive new system for human cellular and tissue-based products” by proposing a rule directed at all tissue processing facilities.⁷⁷ The proposed rule would require manufacturers of human cellular and tissue-based products, not now regulated as biologics, drugs, or medical devices, to register their establishment and provide a periodically-updated list of their products to the agency.⁷⁸ FDA stated that it would amend the registration and listing regulations currently applicable to such human substance products now-regulated as biological drugs (a drug and biologic combination) in order to allow for one comprehensive database.⁷⁹

In its *Federal Register* notice, FDA reiterated that the new system seeks to achieve several goals, with the primary objective being “the improved protection of the public health without the imposition of unnecessary restrictions on research, development, or the availability of new products.”⁸⁰ It is the agency’s position that the registration and product listing of these establishments will allow FDA to characterize the human tissue.⁸¹ This characterization, in turn, will enable FDA to identify public health concerns and directly communicate appropriate warnings, guidances, and other information to particular industry segments.⁸² As with earlier regulations in this area, FDA cited section 361 of the PHSA as the legal authority for this proposed rule.⁸³

The specifics of the proposed rule are as follows. All FDA-identified⁸⁴ foreign and domestic operators and owners of establishments that manufacture human cellular and tissue-based products must register and list their products if the product is minimally manipulated, as defined in the proposed rule; is not labeled or advocated for any use other than a homologous use, again as defined in the proposed rule; is not combined with or modified by the addition of any nontissue or noncellular element that is a drug or a device; and does not have a systemic effect, except in the case where the product meets the first three criteria and is used for autologous, family-related allogeneic or reproductive purposes.⁸⁵

Certain human substances are excluded from coverage under the rule, as they already are under the purview of other rules, regulations, or standards, and/or they often involve different manufacturing, safety, and effectiveness concerns.⁸⁶ These products include vascularized human organs for transplantation; whole blood or blood components or blood derivative products; minimally manipulated bone marrow; extracted or secreted human products, such as collagen, milk, and cell factors; ancillary

⁷⁶ Nancy Chew, *Agony and Ecstasy in Biopharmaceutical Regulation*, *BIOPHARM* 20, Sept. 1, 1997, available in 1997 WL 9637433.

⁷⁷ 63 Fed. Reg. 26,744 (1998).

⁷⁸ *Id.* at 26,746.

⁷⁹ *Id.*

⁸⁰ *Id.* at 26,745. See also 21 C.F.R. §§ 1271.21, 1271.22, 1271.25, 1271.26.

⁸¹ *Supporting Statement for Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products*, OMB No. 0910-0372.

⁸² *Id.*

⁸³ 63 Fed. Reg. at 26,747.

⁸⁴ Registration and listing requirements are not contingent on the human tissue product entering into interstate commerce. *Id.* at 26,754.

⁸⁵ *Id.* at 26,754 (to be codified at 21 C.F.R. § 1271.10).

⁸⁶ *Id.* at 26,745-46.

products used in cell or tissue propagation; and animal cells, tissues, or organs.⁸⁷ These tissue/cell-based products would remain regulated as biologics or devices and require premarket approval, as well as infectious disease testing/screening, good tissue practice compliance, and good manufacturing practice (GMP) compliance.⁸⁸ In its determination of whether a product should be regulated as a tissue, a device, or biologic, "FDA has tentatively decided to focus on whether a cellular or tissue-based product is promoted or labeled by its manufacturer for a nonhomologous use, rather than on the intent of the practitioner who uses the product."⁸⁹

The *Federal Register* notice on this proposed regulation requested that comments on the rule be submitted by interested parties to FDA for consideration by August 12, 1998.⁹⁰ The comment period, however, was not closed until February 1999.⁹¹ In light of this extended input period, it does not appear that a final rule on the matter will be issued in the very near future.

D. FDA's Future Plans for the Reinvention of the Regulation of Human Tissue

Further rules regulating human tissue use are planned by FDA in the foreseeable future. Two proposed rules, currently under consideration at the agency, will address the screening and testing of human tissue donors and the continued development of good tissue practices. The proposed regulation on the determination of suitability of donors of cellular and tissue-based products is currently in the late stages of review at FDA, and is expected to be published in the *Federal Register* for comment within the next two months.⁹² The proposed rule on current good tissue practice (including FDA inspections and enforcement) for manufacturers of cellular and tissue-based products is in an earlier stage of development, and is anticipated to be presented for review in approximately six months.⁹³

IV. REGULATION OF HUMAN TISSUE IN THREE MEMBER STATES OF THE EUROPEAN UNION

A. Belgium

Human tissue use and human tissue banks in Belgium are subject to one of the most developed regulatory systems on the matter in the European Union. The comprehensive legislation is based on two principal texts: the *Crown Order of 13 June 1986* and the *Crown Order in Council of 15 April 1988*.⁹⁴

⁸⁷ *Id.* at 26,745.

⁸⁸ *All Tissue/Cell Product Firms Must Register With CBER Under Proposed Rule*, F-D-C REP. ("The Pink Sheet"), May 25, 1998, available in 1998 WL 8441307.

⁸⁹ *Id.*

⁹⁰ 63 Fed. Reg. at 26,753.

⁹¹ Telephone Interviews with Steve Falter, Director of Regulations, Policy Staff, Center for Biologics Evaluation & Research (CBER), FDA, Rockville, MD (Aug. 2, 1999) and Jennie Butler, Administrative Proceedings Officer of FDA, Rockville, MD (July 1999).

⁹² Falter, *supra* note 91.

⁹³ *Id.*

⁹⁴ *Adoption of an Opinion on Human Tissue Banking: Legislations and Ethical Guidelines with Regard to Human Tissue Banking in the Member States of the EU*, European Group on Ethics in Science and New Technologies to the European Commission (July 21, 1998) [hereinafter *Opinion on Human Tissue Banking*].

The *Crown Order of 13 June 1986* regulates the retrieval and grafting of organs and tissues, with its scope limited to therapeutic uses.⁹⁵ Effective since February 1987, the *Crown Order* provides that every Belgian citizen or foreigner (who has lived in Belgium for more than six months) above the age of eighteen is a potential donor of organs and/or tissues, unless express proof of that individual's opposition is available ("assumed or presumed consent").⁹⁶ If the tissue/organ removed seriously affects the donor's health, or is nonregenerable, it may be donated only if the recipient's life is in danger, and similar donation from a cadaver "could not produce an equally satisfactory result."⁹⁷ In the case of minors (under age eighteen), donation is forbidden despite the donor's consent (or guardian's consent if the donor is under age fifteen), *unless* the donation would not normally seriously affect the donor or if the substances removed are regenerative, *and* the removal is intended for transplantation into the donor's sister or brother.⁹⁸ The consent or opposition of any potential donor may be expressed through the National Register at the Belgian Ministry of Public Health.⁹⁹ Close relatives may offer guidance on donation by a family member, if that family member-donor is unable to communicate directly his own wishes (i.e., due to unconsciousness or state of coma).¹⁰⁰

Belgium places a premium on the free, informed consent of a donor. Living donors may withdraw their consent at any time.¹⁰¹ In contrast, Belgian law permits tissue retrieval from any deceased Belgian who resided in the country, *unless* there is expressed opposition against such retrieval (i.e., by the deceased in the National Register).¹⁰²

In addition to free, informed consent, the *Crown Order of 13 June 1986* reiterates two widely-accepted precepts of organ or tissue donation: 1) there may be no profit associated with this donation, therefore, the sale of body or body parts is forbidden,¹⁰³ and 2) confidentiality of donation must be maintained— anonymity applies to both donor and recipient.¹⁰⁴

The *Crown Order in Council of 15 April 1988* regarding human tissue banking addresses the care and storage of human tissue from the time of donation until transplantation in the recipient.¹⁰⁵ Its goal is to promote tissue quality and safety at non-profit human tissue banks through tissue bank accreditation and activity supervision.¹⁰⁶ Under the *Royal Order*, a human tissue bank (HTB) is defined as "a technical unit in

⁹⁵ *Id.* It would appear that the dominant legislation governing organ and tissue removal for diagnostic and research purposes is Resolution (78) 29 on the harmonization of member state legislation relating to removal, grafting, and transplantation of human substances, which was adopted by the Committee of Ministers of the Council of Europe on May 11, 1978. Herman Nys, *Therapeutic Use of Human Organs and Tissues Under Belgian Law*, 12 MED. L. 131, 132 (1993). As this paper is limited to discussion of the therapeutic use of human tissue, that legislation is not now addressed.

⁹⁶ *Law of 13 June 1986 on the Removal and Transplantation of Organs (Article 6)*, Moniteur Belge, 14 February 1987, No. 32, at 2192-2132, reprinted in 38 INT'L. DIG. HEALTH LEGIS. 523, 524 (1987).

⁹⁷ *Id.* art. 7.

⁹⁸ *Id.*

⁹⁹ B. Van Haelewiejck et al., *How to Improve the Public Image of Organ Donation*, ORGAN AND TISSUE TRANSPLANT IN THE EUROPEAN UNION: MANAGEMENT OF DIFFICULTIES AND HEALTH RISKS LINKED TO DONORS 180, 181-82 (Yvon Englert ed., 1995).

¹⁰⁰ Nys, *supra* note 95, at 134-35.

¹⁰¹ *Opinion on Human Tissue Banking*, *supra* note 94.

¹⁰² *Id.* Brain death must be established by three doctors who are independent of the organ retrieval or transplantation team. Van Haelewiejck, *supra* note 99, at 182.

¹⁰³ *Id.* In order to guard against profit from organ/tissue donation, the Belgian Minister of Health sets the prices for delivery of homografts, with publication of the prices in the Belgian official Gazette. *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Opinion on Human Tissue Banking*, *supra* note 94.

¹⁰⁶ *Id.* As noted earlier, the Belgian Minister of Health fixes prices for each allograft in order to guarantee the nonprofit operation of human tissue banks in Belgium.

a hospital, with the assignment to guarantee the quality of the tissues from the moment the tissues are retrieved to the moment they are used as an allograft, more particularly during the preparation, storage, distribution, transportation, and the delivery."¹⁰⁷ Establishment of an HTB requires prior approval by the Minister of Health (in conjunction with certain other specified criteria), with authorization for the HTB granted for a limited duration and HTB activities subject to strict monitoring.¹⁰⁸ Accordingly, the *Royal Order* requires clinical, biological, microbiological, and immunological donor and donor tissue testing.¹⁰⁹ It also mandates the keeping of detailed records tracking the origin, processing, and handling of human tissue, thereby ensuring traceability of the tissue implant.¹¹⁰

Belgium may be one of the few countries within the European Union that restricts the import of tissues from abroad.¹¹¹ Limited importation from a foreign tissue bank is permitted in response to an HTB physician's express request, but only if 1) the tissue is unavailable in Belgium, 2) the tissue is of the same type as tissues stored at the Belgium HTB, 3) the foreign tissue bank applies identical or equivalent regulatory criteria, and 4) the country of tissue origin provides a certificate of guaranty.¹¹²

B. France

Since 1994, France has enacted comprehensive legislation regulating human tissue use and banking. The legislation responds in part to such early 1990s incidents as the removal of a dead child's eyes for transplant without his parents' knowledge or express consent, a widespread scandal over contaminated blood used in transfusions, and the use of tissue not properly screened for HIV and other transmissible diseases.¹¹³

Human tissue is regulated in France primarily by *Law 94-654*, which addresses donation and use of elements and products of the human body.¹¹⁴ The 1994 law emphasizes the principles of donor consent, donor/recipient confidentiality, tissue safety and noncommercialization of the donation process.¹¹⁵ Explicit consent must be obtained from living donors, while donation from deceased persons operates under the presumed consent system with opting-out through registration in a computerized national register.¹¹⁶ Donors of every tissue must be identified. Before any tissue is used,

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ L.F. Markenstein, *An Analysis of the State of the Debate on Further Use of Human Tissue in Various European Countries*, 2 EUR. J. OF HEALTH L. 125, 130 (1995).

¹¹⁰ C. Delloye, *Specific Difficulties in Widespread Tissue Banking*, ORGAN AND TISSUE TRANSPLANT IN THE EUROPEAN UNION: MANAGEMENT OF DIFFICULTIES AND HEALTH RISKS LINKED TO DONORS 145 (Yvon Englert ed., 1995).

¹¹¹ L. Muylle, *Origin and Circulation of Tissues for Grafting*, ORGAN AND TISSUE TRANSPLANT IN THE EUROPEAN UNION: MANAGEMENT OF DIFFICULTIES AND HEALTH RISKS LINKED TO DONORS 134 (Yvon Englert ed., 1995).

¹¹² *Id.*

¹¹³ Tara Patel, *France's Troubled Transplant Trade*, NEW SCIENTIST, July 3, 1993, at 12-13. A 1992 French decree mandated that all tissue donors be tested for transmissible diseases. However, a 1993 report on tissue banks by France's Inspector General of Social Affairs revealed that when some orthopedic units requested that patients who donated bone undergo blood tests for HIV screening three months later (and were refused by some), the tissues were nonetheless reused. *Id.*

¹¹⁴ *Opinion on Human Tissue Banking*, *supra* note 94.

¹¹⁵ *Id.*

¹¹⁶ *Id.* On July 31, 1998, Circular DGS/DH/EFG No. 98-489 was issued, putting into service the national computerized register of refusals with regard to tissue/organ removal from deceased persons. The Circular mandates consultation of the register by health establishments prior to any removal. *Circular DGH/DH/EFG No. 98-489 of 31 July 1998 On the Putting Into Service of the National Computerized Register of Refusals With Regard to the Removal of Organs, Tissues, and/or Cells from Deceased Persons, and on the Consultation of This Register by Health Establishments Prior to Any Removal*, *Bulletin Officiel*, 5 Sept. 1998, No. 98/34, Vol. I, Text No. 22206, pp. 127-131, *reprinted in* INT'L DIG. HEALTH LEGIS. 635 (1998).

it must be stored for a period sufficient to allow for a follow-up HIV test on the donor.¹¹⁷ Public health authorities or nonprofit organizations serve as tissue banks, unless the activity at issue is highly technical (or involves private sector research and development), thereby warranting special permission for intervention by a commercial company.¹¹⁸ Authorization for public or nonprofit human tissue banks is given according to tissue type for a five-year renewable period.¹¹⁹

Decree No. 94-416 of 24 May 1994 provides additional detail on the required testing of donors and tissues for the following conditions in order to prevent infectious disease transmission: AIDS virus, hepatitis B and C, syphilis, toxoplasmosis, and infections by the cytomegalovirus and Epstein-Barr virus.¹²⁰ In conjunction with *Law 94-654* and *Decree No. 94-416*, the French Transplantation Establishment (*De l'Établissement Français des Greffes*) was set up to coordinate tissue/organ removal and transplantation activities, formulate rules of good practice for these processes, and promote donation.¹²¹

Subsequent legislation has augmented and clarified the basic framework provided by the 1994 regulations. For instance, donations from living persons may only be secured for therapeutic use and must comply with specific ethical, hygienic, and safety guidelines.¹²² For deceased donors, tissue/organ retrieval may be used only for therapeutic and scientific purposes. As noted, presumed consent applies, with opposition to be recorded in the national register.¹²³ More recent legislation provides that if a deceased person has failed to so register, the willingness of the deceased person to donate organs/tissues should be sought through his family.¹²⁴ In any event, complete records which include relevant information essential for the follow-up and traceability of elements and products of the human body used in transplantation must be kept.¹²⁵ The *Decree of 1 April 1997* addresses good practice rules on tissue procurement.¹²⁶ *Decree No. 97-928 of October 9, 1997* specifies health safety rules (i.e., screening/testing requirements) applicable to the removal of human tissue/organs for therapeutic purposes.¹²⁷ Finally, the *Order of 29 December 1998* approves the rules of good practice with regard to human tissue/organ storage, processing, and transportation associated with transplantation.¹²⁸

¹¹⁷ Tara Patel, *French Law Clamps Down on Tissue Traders*, NEW SCIENTIST, July 2, 1994, at 6.

¹¹⁸ Law No. 193 of July 24, 1996, J.O., Aug. 20, 1996, pp. 12543-44; 47 INT'L DIG. HEALTH LEGIS. 464 (1996) (on the nature of the examinations to be carried out for the detection of biological markers of infection by the human immunodeficiency virus (HIV-1 and HIV-2) and by the hepatitis-C virus prior to any therapeutic use in human beings of elements and products of the human body for the purposes of transplantation, with the exception of gametes and blood and blood products). The July 24, 1996 Order was made pursuant to Decree No. 92-174 of Feb. 25, 1992 on the prevention of the transmission of certain infectious diseases. *Id.*

¹¹⁹ Tissue bank monitoring is "foreseen" by Law No. 95-116 of Feb. 4, 1995, with infringements penalized. *Opinion on Human Tissue Banking*, *supra* note 94.

¹²⁰ *Decree No. 94-416 of May 24, 1994*, J.O., May 28, 1994, pp. 7654-7655; 45 INT'L DIG. HEALTH LEGIS. 316 (1994) (amending Decree No. 92-174 of Feb. 25, 1992, on the prevention of the transmission of certain infectious diseases).

¹²¹ *Opinion on Human Tissue Banking*, *supra* note 94.

¹²² *Id.*

¹²³ *Id.*

¹²⁴ *Id.*

¹²⁵ *Draft Report of Presentations and Discussion, Regulation: The Present and the Future; Answer to Expectations*, ETABLISSEMENT FRANCAIS DES GREFFES MEETING ON TISSUE AND CELL ALLOGRAFTS REGULATION IN EUROPE (International Association of Prosthesis Manufacturers) (June 8, 1998) [hereinafter *Present and Future*].

¹²⁶ *Opinion on Human Tissue Banking*, *supra* note 94.

¹²⁷ *Decree No. 97-928 of Oct. 9, 1997*, J.O., Oct. 12, 1997, pp. 14865-14866; 49 INT'L DIG. HEALTH LEGIS. 312, 312-14 (1998) (on the health safety rules applicable to all removals of elements or all collection of products of the human body and their use for therapeutic purposes, with the exception of gametes, blood and blood components and their derivatives, and reagents, made for the implementation of Articles L. 665-10 and 665-15 of the Public Health Code and amending that Code (Second Part: Decrees made after consulting the *Conseil d'Etat*)).

¹²⁸ *Law No. 302 of Dec. 29, 1998*, J.O., Dec. 30, 1998, pp. 19824-19843; 50 INT'L DIG. HEALTH LEGIS. 32 (1999) (approving the rules of good practice with regard to the storage, processing, and transportation of tissues of human origin used for therapeutic purposes).

Two other pieces of French legislation highlight France's emphasis on tissue and organ safety and merit consideration. On October 16, 1996, an order was issued prohibiting the manufacture, import, export, supply, distribution, and use of dura maters of human origin and products containing them.¹²⁹ (Use of retrous bone derivatives also has been prohibited.)¹³⁰ And on April 16, 1996, *Decree No. 96-327* regulating the import and export of human organs, tissues, and cells was issued.¹³¹ It mandates that all previously discussed safety and ethics provisions apply to these human substances.¹³² It also requires that all approved tissue bank establishments and bodies secure appropriate authorization for export and/or import, which may be granted for a limited time period by the Minister responsible for Health.¹³³

In recent years, France has proved to be particularly cognizant of, and reactive to, the health risks posed by human substances, as well as by medical devices and pharmaceuticals (regardless of human tissue content). As will be discussed shortly, French regulatory authorities repeatedly have lobbied for more stringent control over these products by the EU, with resulting French legislation occasionally more restrictive than regulations imposed by the EU (and therefore potentially violative of EU provisions for the free flow of trade).¹³⁴

C. United Kingdom

In the United Kingdom, two Acts constitute the principal legislation on human tissue: the Human Tissue Act 1961 and the Organ Transplants Act 1989.¹³⁵ The Human Tissue Act 1961 addresses the conditions under which body parts may be taken from a deceased person for the purposes of therapy (i.e., transplantation), education, or research.¹³⁶ The Act provides for a "contracting-in system," whereby the donor has previously indicated in writing or orally (in the presence of two witnesses) his interest in donating his organs/tissues upon his death and for what purpose.¹³⁷ Alternatively, if no such request for donation exists, "the person lawfully in possession of the body of a deceased person" may authorize organ/tissue donation for transplantation *only* after making "reasonable enquiries" to confirm that neither the deceased nor his surviving relatives object.¹³⁸ Critics of the 1961 Act note that it fails to define the moment at which death occurs, and also is ambiguous with regard to the terms "surviving relative" and "reasonable enquiries."¹³⁹ In 1998, the United Kingdom revised the *Code of*

¹²⁹ *Law No. 248 of Oct. 16, 1996*, J.O., Oct. 23, 1996, p. 15496; 48 INT'L DIG. OF HEALTH LEGIS. 12 (1997) (prohibiting the manufacture, import, export, distribution, supply, and use, and ordering the withdrawal, of dura maters of human origin and products containing them). Use of dura mater has been associated with the contraction of Creutzfeldt-Jakob disease, a rare and fatal human neurodegenerative condition.

¹³⁰ *Present and Future*, *supra* note 125.

¹³¹ *Decree No. 96-327 of Apr. 16, 1996*, J.O., Apr. 18, 1996, pp. 5954-5957; 47 INT'L DIG. HEALTH LEGIS. 331 (1996) (on the import and export of organs, tissues, and cells of the human body, with the exception of gametes, and amending the Public Health Code (Second Part: Decrees made after consulting the *Conseil d'Etat*)).

¹³² *Id.* at 332-34.

¹³³ *Id.* at 332-35.

¹³⁴ *France Calls for European Medical Device Agency*, CLINICA: WORLD MED. DEVICE & DIAGNOSTIC NEWS, May 19, 1997, at 1. *Extra French Device Controls Against EU Directives*, EUR. DRUG & DEVICE REP., July 7, 1997, at 7.

¹³⁵ *Opinion on Human Tissue Banking*, *supra* note 94.

¹³⁶ *Id.*

¹³⁷ *Id.* In contrast, Belgium and Spain regulate human tissue donation under a presumed consent-with-opt-out theory, as previously discussed. *British Organ Donor Society* (last visited July 26, 1999) <www.argonet.co.uk/body/index.html>.

¹³⁸ Siobhan Deehan, *The Gift of Life*, 144 NEW L.J. 1143 (1994).

¹³⁹ *Id.*

Practice associated with the Human Tissue Act 1961 to provide guidelines for identification and management of tissue.¹⁴⁰

The Organs Transplants Act 1989 governs the use of tissue and organs from living donors, with the express purpose of protecting both the individual donor's autonomy and vulnerability, as well as deterring abuse of the donation process.¹⁴¹ Accordingly, the following actions are prohibited: 1) commercial transactions involving human tissues and/or organs, 2) publication or distribution of any advertisement soliciting persons to offer or supply organs for payment, and 3) organ/tissue removal from living persons unrelated to the recipient without prior approval from the Unrelated Live Transplant Regulatory Authority.¹⁴² In light of the Act's emphasis on altruism (versus commercialism), consent of the living donor must be given freely and without coercion.¹⁴³ This consent encompasses agreement on donation, use, and screening for infection.¹⁴⁴

In 1995, the United Kingdom's Nuffield Council on Bioethics presented a report on the legal and moral issues related to the medical and scientific use of human tissue in the United Kingdom.¹⁴⁵ The report was designed to provide guidance to lawmakers formulating human tissue policy. Four requirements were presented as the foundation for legitimate tissue use: 1) injury avoidance and limitation for the donor, 2) a direct or indirect therapeutic intention, 3) the donor's consent (or the equivalent in the case of incompetents), and 4) the absence of commercial motivation.¹⁴⁶

While the United Kingdom has implemented legislation addressing (at least to some degree) human tissue use, human tissue banks in the United Kingdom remain essentially unregulated. The British Association of Tissue Banks, a professional organization similar to the American Association of Tissue Banks, has issued guidelines that participating tissue banks may choose to follow.¹⁴⁷ The United Kingdom regulatory authorities have recommended that tissue banks maintain records for a minimum of eleven years post-transplantation that include donor medical history and screening/testing results (while still ensuring for donor anonymity), as well as details on subsequent tissue processing, storage, and issue to the transplant surgeon.¹⁴⁸ It appears, however, that the United Kingdom recommendations are merely guidelines, not mandates, and that at present no legislation delineating standards and requiring tissue bank registration and inspection exists.

V. REGIONAL REGULATION OF HUMAN TISSUE: THE EUROPEAN UNION

A. Background

The European Union, established in 1952 via the *Treaty of Rome*, currently consists of fifteen member states.¹⁴⁹ These member countries yield a part of their sover-

¹⁴⁰ In 1986, the United Kingdom's Department of Health issued a guideline document on the microbiological safety of human tissues and organs. *Present and Future*, *supra* note 125. It is unclear whether this guideline document applies to cadaveric donors, living donors, or both. However, living tissue donors are required to undergo repeat testing for HIV antibodies and other markers mandatorily tested in blood donors, 180 days or more after donation. D. Fehly & R.M. Warwick, *Safe Tissue Grafts*, 314 BRIT. MED. J. 1141 (1997).

¹⁴¹ Deehan, *supra* note 138.

¹⁴² *Id.*

¹⁴³ *Id.*

¹⁴⁴ In 1996, the United Kingdom issued a guideline on serological testing of donors. A social and medical risk questionnaire for the assessment of lifestyle risks also has been issued. *Present and Future*, *supra* note 125.

¹⁴⁵ Andrew Grubb, *The Nuffield Council Report on Human Tissue*, 3 MED. L. REV. 235 (1995).

¹⁴⁶ *Id.* at 236.

¹⁴⁷ *Present and the Future*, *supra* note 125.

¹⁴⁸ *Opinion on Human Tissue Banking*, *supra* note 94.

¹⁴⁹ Current member states of the European Union include Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Professor Linda Horton, Int'l Food, Drug, and Medical Device Law, Georgetown University Law Center 1028-1029 (Summer 1999) (class materials on file with author).

eighty over goods, persons, services, and capital to EU “supranational” lawmaking bodies in an effort to promote balanced and sustainable European economic and social progress “in an ever closer union among the peoples of Europe, in which decisions are taken as closely as possible to the citizen.”¹⁵⁰ Several bodies within the European Union bear responsibility for the drafting and enactment of regulations, laws, and directives based on the *Treaty of Rome* and other subsequent EU treaties.¹⁵¹ Directives so issued require EU member states to “transpose” or incorporate the substance of the directives into their national laws via legislation or binding administrative rules.¹⁵²

EU directives regulating food, drugs, and medical devices in an effort toward harmonization of member state standards have taken two directions — the “old approach,” applied to many foods and drugs, and the “new approach,” which encompasses medical devices.¹⁵³ Under the “old approach” directives (regulating food and pharmaceutical products), an effort was made to define virtually all of the characteristics of a particular product, which hampered progress in light of very diverse member state requirements.¹⁵⁴ In contrast, the new approach, adopted by the EU Council on May 7, 1985, limits EU directives to essential requirements, with voluntary standards supplementing those requirements in particular areas, such as medical devices.¹⁵⁵

¹⁵⁰ The ABC of the European Union—Citizenship (last visited July 1999) <www.europa.eu.int/abc-en.htm>.

¹⁵¹ The European Commission maintains exclusive power to draft EU legislation, while the European Council acts as the principal lawmaking body of the EU (with the political interests of member state countries represented accordingly), and the European Parliament serves as a “significant voice for the ideological blocs of Europe.” Horton, *supra* note 149, at 1028. On October 2, 1997, the Treaty of Amsterdam was signed by European Union member states. This treaty amends previous EU treaties, and includes provisions on consumer protection, health, increased transparency, and the European Parliament’s enhanced role in Community decisions. The new Article 129 provides in part:

4. The Council, acting in accordance with the procedure referred to in Article 189b and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting:

(a) measures setting high standards of quality and safety of origin and substances of human organ, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;

(b) by way of derogation from Article 43, measures in the veterinary and phytosanitary fields which have as their direct objective the protection of public health;

(c) incentive measures designed to protect and improve human health, excluding any harmonization of the laws and regulations of the Member States.

The Council, acting by a qualified majority on a proposal from the Commission, may also adopt recommendations for the purposes set out in this Article.

Treaty Of Amsterdam, Oct. 2, 1997, art. 129.

¹⁵² Horton, *supra* note 149.

¹⁵³ *Id.* at 1030-31.

¹⁵⁴ *Id.* at 1031.

¹⁵⁵ *Id.* In the European Union, a medical device has been defined as:

any instrument, apparatus, appliance material or other article, whether use[d] alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, or alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Information About the EC Medical Device Directives, Medical Devices Agency, Bulletin No. 8 (June 1998) (electronic copy on file with author) [hereinafter Bulletin No. 8].

As in the United States, the European Union has a risk-based medical device classification system, consisting of four categories. Unlike the medical device regulations administered by FDA in the United States, which include review for safety and effectiveness, the EU medical device regulatory system reviews only for safety and performance as the manufacturer intended. Moreover, it is the EU member state manufacturer, not the EU regulatory body, who determines the appropriate class for a new device, based on classification rules in the directives (although that classification may be subject to change if the final regulatory authority disagrees with it). *Medical Device Regulation: Too Early to Assess European System’s Value as Model for FDA*, U. S. General Accounting Office (GAO/HEHS-96-65), Report to the Chairman, Committee on Labor and Human Resources 2, 6, 10 (Mar. 1996).

Each member state must ensure that the requirements of EU directives are appropriately implemented within that country.¹⁵⁶

A country's "competent authority," such as the Secretary of the State of Health of the Medical Devices Agency in the United Kingdom, is the body designated to ensure that manufacturers comply with the device regulations.¹⁵⁷ The competent authority thus performs a preclinical assessment of devices intended for clinical investigation, and evaluates manufacturers' adverse incident reports.¹⁵⁸ The competent authority also designates at least one notified body, which is an independent certification organization directly responsible for testing or evaluating products (i.e., making conformity assessments) and designing/certifying quality systems.¹⁵⁹ The notified body may be a private sector testing house, a standards body, or a government agency, but in any event, must be confirmed to be competent under one or more directives.¹⁶⁰ Each member state provides the EU with a list of that country's notified bodies.¹⁶¹

While new approach directives specify essential requirements for the protection of health, safety, and the environment, these requirements actually serve as the foundation for EU regional standards bodies (i.e., CEN and CENELEC)¹⁶² which develop Europe-wide standards, with due consideration given to international standards.¹⁶³ Thus, the new approach system standards are voluntary to the degree that manufacturers may refer to other standards in compliance certification of a directive.¹⁶⁴

Once an acceptable assessment by the proper authorities is completed, a certificate (or CE mark), which is valid for a specific period of time, appears on a medical device or its packaging.¹⁶⁵ This certificate of approval indicates fulfillment of the essential requirements for acceptability for marketing in not only the approving member state, but throughout the EU.¹⁶⁶ Accordingly, no EU country may reject the results of a notified body conformity assessment made in another EU country, unless the rejecting country provides extremely compelling reasons to the contrary, brought under a provision referred to as the safeguard clause.¹⁶⁷ As a corollary, in principle, no EU country may retain national legislation that deviates from an EU directive unless that country can prove that such retention is essential for the health and safety of its citizens or protection of the environment, as stipulated in Article 36 of the *Treaty of Rome*.¹⁶⁸

¹⁵⁶ Bulletin No. 8, *supra* note 155.

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

¹⁵⁹ *Id.*

¹⁶⁰ Horton, *supra* note 149, at 1032.

¹⁶¹ *Id.*

¹⁶² CEN is the European Committee for Standardization, whose mission is to "promote voluntary technical harmonization in Europe in conjunction with worldwide bodies and its partners in Europe." *About CEN and European Standardization* (last visited Aug. 1999) <www.cenorm.be/AboutCEN/AboutCEN.htm>. One of CEN's partners is CENELEC, the European Committee for Electrotechnical Standardization. *General Information* (last visited Aug. 1999) <www.cenelec.be/generalinfo/hp_general_info.htm>.

¹⁶³ Horton, *supra* note 149, at 1033.

¹⁶⁴ *Id.*

¹⁶⁵ *Id.* Bulletin No. 8, *supra* note 155.

¹⁶⁶ Horton, *supra* note 149, at 1034. Member states further bear responsibility for post-market surveillance of approved products, as well as for enforcement actions for removal of dangerous products from the market. Additionally, member states are charged with taking actions to strip a notified body of its conformity assessment role under an EU directive if it has not followed requirements of eligibility. *Id.* at 1031-32.

¹⁶⁷ *Id.* at 1033.

¹⁶⁸ *Id.* at 1034. Article 36 of the Treaty of Rome states that:

The provisions of Articles 30 to 34 [prohibiting quantitative restrictions on products exported between Member States] shall not preclude prohibitions or restrictions on imports, exports or goods in transit justified on grounds of public morality, public policy or public security; the protection of health and life of humans, animals or plants . . . Such prohibitions or restrictions shall not, however, constitute a means of arbitrary discrimination or a disguised restriction on trade between Member States.

Treaty of Rome, art. 36, <www.hrc.org/docs/Rome57/Part3Title01.html>; Treaty of Rome, Mar. 25, 1957, art. 129, <www.hri.org/docs/Rome57/Part3Title10.html>.

In 1997, the government of France evoked this rationale of insufficient protection of the public health of its citizens as the basis for objection to the "new approach" adopted in the EU to regulate medical devices.¹⁶⁹ France claimed that the new approach had resulted in citizen deaths from faulty CE-marked devices that were certified by third-party notified bodies.¹⁷⁰ The country called for a new system for approving medical devices in the EU, with registration and premarket approval for all devices controlled by a centralized European agency, such as the European Medicines Evaluation Agency (EMA), which bears responsibility for approval of EU pharmaceuticals.¹⁷¹ Thus, central registration would replace the current system of EU device directives.¹⁷² France's heightened concern for public safety stemmed from a nationwide blood contamination scandal due to inadequate regulations, which had rocked the country several years earlier.¹⁷³ While France's 1997 efforts to overhaul the EU medical device approval system were largely unsuccessful, elements of its proposal are now being considered in the formulation of human tissue regulations, as will be discussed shortly.¹⁷⁴

B. *Regulation of Human Tissue as Medical Devices in the European Union*

In recent decades, profound advances in biotechnology (including human organ and tissue transplantation) have challenged governments to keep pace in their assessment of the safety and efficacy of resulting products. Government efforts have focused on the delicate balancing of the sometimes competing interests of health safety and the promotion of new drug, device, and therapy development. This balancing is a particularly formidable goal for a regional establishment such as the EU, where member states' differing legal systems, approaches to health regulation, and longstanding bioethical beliefs have stymied the development and implementation of a unified approach to human tissue regulation.

To date, there is no comprehensive regulation of human tissue products under either medical device or pharmaceutical law within the EU, although EU focus appears to be on medical device integration (as consequently will be this section). Tissue products remain regulated under the varying national laws of each member state (if at all), which creates difficulties in European trade and negatively impacts the range of human tissue medical devices available.¹⁷⁵ In contrast, harmonized controls on hu-

The revised Article 129a, § 5, of the Treaty of Amsterdam provides likewise:

Measures adopted pursuant to paragraph 4 [EU measures designed to support, supplement and monitor the health safety and consumer protection policies of Member States] shall not prevent any Member State from maintaining or introducing more stringent protective measures. Such measures must be compatible with this Treaty. The Commission shall be notified of them.

Treaty Of Amsterdam, Oct. 2, 1997, art. 129.

¹⁶⁹ *France Wants Registration to Replace EU Device Directives*, EUR. DRUG & DEV. REP., June 9, 1997, at 7.

¹⁷⁰ *Id.*

¹⁷¹ *Id.* Approval of pharmaceuticals within the European Union is achieved through complex systems which vary according to the type of drug (innovative medicines, biotechnology-based or conventional medicines) presented for evaluation. Basically, two processes govern market entry of a pharmaceutical product in the European Union: 1) the London-based EMA, which spearheads the centralized procedure for innovative and biotechnology-based pharmaceuticals; and 2) the Mutual Recognition Process, a decentralized procedure that is applied to conventional medicines and involves drug approval by one EU member state (the reference country) with mutual recognition of the reference country's approval requested of the other fourteen EU member states. Thus, the decentralized Mutual Recognition Process operates similarly to the EU process for premarket medical device approval. Horton, *supra* note 149, at handout (*European Medicine and Evaluation Agency*).

¹⁷² *France Wants Registration to Replace EU Device Directives*, *supra* note 169.

¹⁷³ *Id.*

¹⁷⁴ *Id.*

¹⁷⁵ Sara Lewis, *Europe: Tissue Devices*, 341 LANCET 684 (1993).

man tissue medical devices within a single system would ensure that such devices, regardless of where manufactured in the EU, met common standards of performance and safety. Further, manufacturers would have to comply with only one set of rules—rather than fifteen different sets.¹⁷⁶

The European Community has long recognized the need to draft and implement EU-wide legislation regulating human tissue products and has made several unsuccessful overtures in that direction, via medical device directives.¹⁷⁷ As early as December 1992, the European Commission proposed drafting a supplementary directive encompassing devices either made from or that used human or viable animal tissue.¹⁷⁸ However, efforts to this end were stopped by France, which had its blood transfusion service tarnished by a highly publicized contamination scandal that same year.¹⁷⁹ France advocated that the stricter EC pharmaceutical legislation be extended to cover tissue products such as arterial replacements produced from human umbilical cord.¹⁸⁰ The EC pharmaceutical legislation was argued as offering better protection from potential contamination problems.¹⁸¹ Opponents maintained, however, that manufacturers making both tissue products and other devices would be subject to two sets of legal requirements and the corresponding additional costs.¹⁸² No progress was made on this issue, although the EU was able to gain approval for and implement two nonhuman tissue-related medical device directives in the early-to-mid-1990s—the Active Implantable Medical Devices Directive and the Medical Devices Directive.¹⁸³

In April 1995, a third medical device directive on *in vitro* diagnostic medical devices, the *IVD Directive*, was proposed for consideration by the EU Ministers.¹⁸⁴ This directive encompassed reagents, instruments, and equipment for examining tissue substances or tissues from the human body for medical purposes.¹⁸⁵ Significantly, Article 19 of the proposal called for the scope of the directive to extend coverage to medical devices utilizing substances derived from human cells or tissues.¹⁸⁶ Staunch opposition to Article 19 was immediately encountered. France, Portugal, and Italy cited the need for stiffer regulatory requirements for medical devices containing human tissue.¹⁸⁷ The United Kingdom, in concert with France, highlighted the need to recognize the human origin of human tissue products, even when they have been processed.¹⁸⁸ Ultimately, after much discussion, Article 19 was removed from the *IVD*

¹⁷⁶ Bulletin No. 8, *supra* note 155.

¹⁷⁷ Interestingly, until very recently, the EU apparently had not attempted to subject human tissue regulation to the centralized, pharmaceutical regulatory system, which is positively regarded by several member states (i.e., France) as more rigorous and therefore more likely to ensure the protection of the public health.

¹⁷⁸ Lewis, *supra* note 175.

¹⁷⁹ *Id.*

¹⁸⁰ *Id.*

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ The Active Implantable Medical Devices Directive covers all powered implants or partial implants which are left in the human body (i.e., heart pacemakers), and became effective on January 1, 1995. The Medical Devices Directive, which originally was proposed to cover medical devices incorporating human tissues, encompasses most other medical devices, such as ECG and heart valves, hip prostheses, and first aid bandages. Bulletin No. 8, *supra* note 155. Implementation of the Medical Devices Directive was subject to a transitional period until June 14, 1998, during which time medical device manufacturers could choose to either follow the existing national controls in force as of December 31, 1994, or to follow the regulatory system created by the Directive. *Id.*

¹⁸⁴ *HEALTH: Council Nears Agreement on In Vitro Diagnostic Devices*, EUR. REP., May 24, 1997.

¹⁸⁵ *Id.*

¹⁸⁶ *Id.*

¹⁸⁷ *Removal of Clauses Pertaining to Human Tissue May Revive IVD Directive*, Oct. 29, 1997, (last visited July 1999) <www.deviceink.com/news/97/10/3172.html>.

¹⁸⁸ *EU to Leave Many Human Tissue Devices Unregulated*, EUR. DRUG & DEVICE REP., Nov. 9, 1998.

Directive, which thereafter met with final approval by the European Parliament and European Council on October 27, 1998.¹⁸⁹

The potential regulation of human tissue products on a regional EU level continues to generate significant controversy to this day, with little progress made. On June 8, 1998, a meeting in Paris of member states sponsored by the *Etablissement Francais des Greffes* was held to exchange information on tissue and cell allograft regulation in Europe.¹⁹⁰ Ethical and legal issues surrounding human tissue use were discussed in detail, with participants in accord that comprehensive legislation in the area was urgently needed.¹⁹¹ On April 20, 1999, device officials from EU nations met in a council working group to discuss the possibility of having the EMEA regulate devices incorporating substances derived from human blood, such as albumin-coated products.¹⁹² At that point, debate was limited to the possible regulation of blood-derived devices, with the even more controversial topic of other tissue products removed from the table.¹⁹³ EMEA regulation of blood products has garnered major support from the participating EU nations; in particular, industry views EMEA oversight (as with drugs) as a better option than differing national laws, but not as preferable as regulation under the medical device system.¹⁹⁴ A legal question did arise as to whether such regulation by the EMEA would require a change in the agency's legal statute, thereby precipitating a lengthy legislative process.¹⁹⁵

Since the April meeting, EU governments have focused on the role the EMEA should play in human tissue product regulation. Initially, it was suggested that human tissue devices should be treated like other high-risk class III devices, with notified body certification and the added component of the EMEA also evaluating the product.¹⁹⁶ If the EMEA issued a negative opinion of the product, then the notified body would be unable to certify the device as in compliance with the planned directive on human tissue devices.¹⁹⁷ In the event of a positive opinion by the EMEA, the notified bodies would still be required to certify the product in the usual manner and, significantly, would retain discretion to reject the product as noncompliant.¹⁹⁸ In addition to the revised certification scheme, Portugal and France have proposed that any directive on human tissue devices contain requirements for the tracing of the devices back to the source.¹⁹⁹ Such traceability requirements have been incorporated in the EU blood products directive.²⁰⁰

The EMEA, for its part, is adamant that it be allowed to conduct a full assessment of a particular human tissue device,²⁰¹ rather than simply review a "thin *dossier*" on

¹⁸⁹ *Directive on In Vitro Diagnostic Medical Devices*, SPICERS CENTRE FOR EUROPE, DEC. 7, 1998, available in 1998 WL 857106 (C.E.A.). December 7, 1998, was the date set for mandatory compliance with the IVD Directive by member states.

¹⁹⁰ Medical electronic mail interview with Victoria Ann Dedrick, Secretary and General, International Association of Prosthesis Manufacturers, Europe (Aug. 1999). Ms. Dedrick provided a copy of her "Published Statement Concerning the Status in the European Union."

¹⁹¹ *Id.*

¹⁹² *EMEA Could Regulate Medical Devices Made From Human Substances*, EUR. DRUG & DEVICE REP., Apr. 12, 1999.

¹⁹³ *Id.*

¹⁹⁴ *Id.*

¹⁹⁵ *Id.*

¹⁹⁶ Sara Lewis, *EU Will Not Have Human Tissue Rules Until at Least 2000*, EUR. DRUG & DEVICE REP., June 7, 1999.

¹⁹⁷ *Id.*

¹⁹⁸ *Id.*

¹⁹⁹ *Id.*

²⁰⁰ *Id.*

²⁰¹ A full assessment includes a risk analysis of a particular product, resulting in a scientific opinion. Sara Lewis, *EU Consensus That EMEA to Approve Human Tissue Devices*, EUR. DRUG & DEVICE REP., July 19, 1999.

the product provided by the notified bodies, with all other information kept confidential from both the public and the EMEA.²⁰² It appears, however, that the EMEA may not possess the discretion to refuse to evaluate human tissue products, or, at the very least, human blood products, as the EMEA already has statutory authority to deal with blood and its derivatives and could therefore be mandated to act on human blood devices.²⁰³ In contrast, some EU legal experts argue that the agency's statutes would require modification by EU legislation for the agency to be properly authorized to assess human blood devices, and certainly human tissue devices.²⁰⁴

At this time, the only proposal on the table regarding EU regulation of human "substances" is a proposal on EU regulation of devices made from human blood, which are considered as high-risk class III devices. Under this proposal, the EMEA would be charged with rendering a scientific opinion, including a full risk assessment, on these devices. Final certification of the devices would be issued by notified bodies that could not certify a device that had received a negative EMEA opinion, but could reject a product given a positive opinion by the EMEA.²⁰⁵ Significantly, this approval system might be extended later to cover other human tissue devices, although not in the foreseeable future.²⁰⁶ While the proposal in its limited form apparently has sufficient EU member state majority support for adoption under the EU's weighted voting system, both the European Commission and member state governments prefer to gain unanimous approval for the plan, thereby hastening its progress through the decision-making process.²⁰⁷

C. Regulation of Human Tissue Banks in the European Union

According to European regulatory authorities, "a tissue bank is deemed to exist when viable or nonviable human tissues are procured, processed, preserved, and distributed for clinical use."²⁰⁸ Tissue banks may be hospital-based or community-wide,²⁰⁹ but in either instance remain largely unregulated both at the national (member state) and EU levels, despite recognition of the health risks. There is some oversight of the procurement of human tissue in most European countries, but only a limited few EU member states (including Belgium and, more recently, France) have enacted comprehensive regulations on human tissues.²¹⁰ Likewise, few countries within the EU have a

²⁰² *Id.*

²⁰³ *Id.*; Sara Lewis, *EMEA Might Refuse Limited Human Tissue Device Approval*, EUR. DRUG & DEVICE REP., July 5, 1999.

²⁰⁴ Lewis, *supra* note 201.

²⁰⁵ Sara Lewis, *EU Split Over EMEA Regulating Human Tissue Devices*, EUR. DRUG & DEVICE REP., Aug. 2, 1999, at 6.

²⁰⁶ *Id.* A "human tissues directive" within the EU is not likely to appear in the near future. Electronic mail interviews with Alan Kent, Former (retired) Chief Executive, United Kingdom Medical Devices Agency (Aug. 6, 1999) and Karen Howes, the Directorate General III of the European Commission (Aug. 2, 1999).

²⁰⁷ With majority consensus, an EU proposal must be formally discussed by ministers at an Internal Market Council meeting. In contrast, a unanimously supported proposal allows EU officials to reach accord on the text, which then may be rubberstamped as approved "as an A point" by ministers at a council on any subject—without further discussion. Lewis, *supra* note 205.

²⁰⁸ Muylle, *supra* note 111.

²⁰⁹ *Id.*

²¹⁰ Octavi Quintana, *Human Tissue Banks in Europe*, HUMAN DNA: LAW & POLICY: INTERNATIONAL AND COMPARATIVE PERSPECTIVES. PROCEEDINGS OF THE FIRST INTERNATIONAL CONFERENCE ON DNA SAMPLING AND HUMAN GENETIC RESEARCH: ETHICAL, LEGAL, AND POLICY ASPECTS, HELD IN MONTREAL, CANADA, 6-8 SEP 1996, 423-24 (Bartha Maria Knoppers ed., 1997). It should be noted, however, that certain human tissues have been subject to long-standing regulations. These tissues include blood and its derivatives, tissues related with reproductive functions (such as sperm, ova, and embryos) and corneas. *Id.* at 424. There also is an arguable understanding within the European Community that either the norms governing organs apply to tissues or that no norm is needed. *Id.* at 423.

formal licensing system, including provisions for inspections, for human tissue banks.²¹¹ Thus, while most countries prohibit tissue collection for commercial purposes, very few European countries regulate tissue processing, preservation, or distribution.²¹² Consequently, tissue from any tissue bank around the world may be procured by most EU countries, for use within the importing country or for distribution elsewhere in Europe, with no guarantees for public health (such as proof of medical examination of the donor or medical testing of the tissue) and no indication of tissue origin.²¹³

EU tissue banks are "subject" to voluntary guidelines set forth by such organizations as the European Association of Tissue Banks (EATB). In 1994, that association published draft ethical rules containing provisions about human tissue quality, safety, and noncommercialization.²¹⁴ The association's goal was to "achieve harmonization of the ground rules to which the tissue banks conform."²¹⁵ However, it is important to recognize that EATB guidelines are *voluntary* codes of conduct, and therefore do not mandate compliance by tissue banks within the EU.

It is well recognized by the European Union that both national and, more preferably, EU-wide regulations on the use of human tissue and the functioning of human tissue banks are necessary. In 1993, for instance, the Council of Europe issued a *Draft Recommendation on Human Tissue Banking*, which advocated tissue bank licensing by national health authorities or recognition by the competent authorities.²¹⁶ The Council further recommended that 1) tissue banks be restricted to nonprofit-making institutions, 2) all tissue collected be stored safely according to scientifically-accepted state-of-the-art techniques, and 3) records of all tissues retrieved and issued contain clearly identifiable information as to the tissues' source and destination, with record access restricted to the degree necessary for the protection of the confidentiality of information and individual privacy.²¹⁷ Also in the early 1990s, the Group of Advisors on Ethical Implications of Biotechnology of the European Commission advised that the following human tissue-related activities be standardized within the EU: 1) tissue bank accreditation and registration, 2) collection and implant center accreditation and registration, 3) health authority monitoring, 4) procedural quality control, and 5) donor-tissue-recipient tracing.²¹⁸ And in 1997, the EU Council of Ministers of Health requested that the European Commission place before the Council and the European

²¹¹ A. Rejman, *Legal Aspects of Tissue Banking in the EU—Current and Future*, ORGAN AND TISSUE TRANSPLANT IN THE EUROPEAN UNION: MANAGEMENT OF DIFFICULTIES AND HEALTH RISKS LINKED TO DONORS 153 (Yvon Englert ed., 1995).

²¹² Quintana, *supra* note 210, at 424. As of June 1998, Ms. Octavi Quintana Trias was the Director at the Spanish Ministry for Public Health and the Vice-President of the European Group on Ethics in Science and New Technologies.

²¹³ *Id.* While human tissue bank regulation is a major focus of this paper, it should be noted that this limited regulation is not the only problem in the area of organ and tissue transplants in the EU. Another issue facing EU organ and tissue transplant facilities and health administrations is the lack of a comprehensive, centralized communications network that can provide timely information on organ and tissue availability and need. The Transplant European Computer Network (TECN), a fully integrated communication system in Europe supported by the Commission of the European Communities, has served to coordinate and disseminate information relevant to organ (and to a lesser extent, tissue) transplant, but is a voluntary consortium whose membership as of the mid-1990s included only two tissue banks: Bio Implant Services in Leiden, the Netherlands, and France Tissues in Marseilles, France. P. Romano & J. Hors, *The Transplant European Computer Network Project*, in ORGAN AND TISSUE TRANSPLANT IN THE EUROPEAN UNION: MANAGEMENT OF DIFFICULTIES AND HEALTH RISKS LINKED TO DONORS 1, 117-18 (Yvon Englert ed., 1995).

²¹⁴ European Association of Tissue Banks, *New Rules Proposed for Tissue Banks*, BULL. MED. ETH., May 1994, 10-11.

²¹⁵ *Id.* at 10.

²¹⁶ Rejman, *supra* note 211.

²¹⁷ Nielsen, *supra* note 2, at 113.

²¹⁸ Quintana, *supra* note 210, at 424-25.

Parliament a communication on the safety and quality of tissues and organs of human origin planned for medical use, with the proviso that the following three issues be discussed: 1) member states' current practice regarding tissues and organs, including, but not limited to: traceability, quality assurance, accreditation and inspection, protection of donors and patients and rules for allocation; 2) EU cooperation with international organizations concerned with public health, such as the Council of Europe and the World Health Organization (WHO); and 3) the *Amsterdam Treaty's* provisions on cross-border cooperation involving human tissues and organs intended for medical use within the EU.²¹⁹

Despite the aforementioned efforts to institute safety regulations on human tissue use and tissue banking in the EU,²²⁰ little progress was made in the mid-1990s, and the issue appeared to be placed on the back-burner. In mid-1998, however, in light of the unprecedented clinical use of human tissues and amidst reports of an eye tissue donor who was subsequently discovered to have Creutzfeldt-Jakob disease, an EU scientific advisory body again sounded an alarm for greater regulation of human tissue banks. On July 21, 1998, the European Group on Ethics in Science and New Technologies²²¹ issued a press release on the ethical aspects of human tissue banking, which declared the safety of human tissues as a "major ethical imperative."²²² Inspired by Article 152 (formerly Article 129) on public health of the new *Treaty of Amsterdam*, which mandates high standards of safety and quality in the treatment of substances of human origin,²²³ the Group advocated the creation of a European structure for the protection of health, acting in concert with the European Agency for the Evaluation of Medicinal Products, as well as the strict control of human tissue bank activity.²²⁴

In sum, four principal recommendations were made: 1) licensed banks should be responsible for human tissue collection to ensure tissue safety and that donation is voluntary, free, and anonymous; 2) consent should be absolute; 3) the flow of information should be improved to promote donation; and 4) the operation of tissue banks should be on a noncommercial basis.²²⁵ The Group further proposed the conduct of periodic surveys in member states on practices relating to procurement, storage, distribution, and import (from outside the EU) of human tissues.²²⁶ Increased "transparency" of human tissue bank activity also was advocated as potentially facilitating more equitable access to the tissues.²²⁷ The Group's recommendations were to be presented to the EU Council of Ministers, the European Parliament, and the European Commission, with the Com-

²¹⁹ Henriette D.C. Roscam Abbing, *New Developments in International Health Law*, 5 EUR. J. HEALTH L. 155, 160-61 (1998).

²²⁰ The author's recounting of the preceding movements to facilitate regulation of human tissue and tissue banks is not intended to be comprehensive, but rather representative of EU efforts in that area in the 1990s.

²²¹ The European Group on Ethics in Science and New Technology was organized by the European Commission in December 1997 as replacement of the Group of Advisors for the Ethical Implications of Biotechnology. The new Group was charged with a broader mandate—coverage of ethical implications of biotechnology and "science and new technologies" in the framework of the drafting and implementation of European Community Legislation. *The Commission Sets Up a European Group on Ethics in Science and New Technologies*, Ethical Legal and Social Aspects of the Life Sciences and Technologies, Press Release No. IP/97/1196 (Dec. 31, 1997) (last visited Aug. 1999) <www.europa.eu.int/comm/dg12/life/elsa/pr311297.html>.

²²² *Opinion on Human Tissue Banking*, *supra* note 94.

²²³ *Press Notice of the European Group on Ethics in Science and New Technologies, Human Tissue Banks* (hard copy on file with the author).

²²⁴ *Health: Ethics Group Urges Regulating Human Tissue Banks*, 23 EUR. REP., July 25, 1998, available in 1998 WL 8803077.

²²⁵ BBC Online Network, *Health Controls Wanted on Sale of Human Tissue* (last visited July 26, 1999) <www.news2.thls.bbc.co.uk/hi/english/health/newsid%5F116000/116047.stm>.

²²⁶ *Health: Ethics Group Urges Regulating Human Tissue Banks*, *supra* note 224.

²²⁷ *Id.*

mission then deciding whether to formulate laws thusly.²²⁸ To date, it is unclear as to what actions, if any, the Commission has taken on the recommendations.

VI. INTERNATIONAL HARMONIZATION

A. Background

The globalization of today's marketplace impacts every sector of business, including the healthcare arena. Regulatory authorities and industry have long acknowledged that as national boundaries are crossed on a regular basis, the harmonization of health legislation—resulting in an international consensus on essential safety, efficacy, and quality principles—offers significant benefits to all parties, including the public. These benefits include enhanced public health protection on a global level (where the best elements of national healthcare systems are melded together); increased government efficiency, as governments rely on each other's expertise and experience rather than "reinventing the wheel"; lower healthcare costs to the public; and the increased development and availability of advances in medical technology (including drug and medical device products), with trade thereby augmented.²²⁹

While the benefits of harmonization are recognized by many, the actual term "harmonization" has different meanings to different people and often is used interchangeably with the term "mutual recognition" in the biomedical field. In the European Union, a "mutual recognition agreement" (MRA) between the EU and a third (non-EU) country refers to an accord "based on the mutual acceptance of test reports, certificates, and marks of conformity issued by the conformity assessment bodies of one of the parties of the Agreement in conformity with the legislation of the other party."²³⁰ Within the last few years, several mutual recognition agreements addressing aspects of pharmaceutical and medical device pre- and postmarket approval (e.g., product testing and quality system audits) have been reached between the EU and third countries including Australia, Canada, and the United States.²³¹ The EU's goal

²²⁸ *European Ethics Group Calls for Strict Rules on Use of Human Tissue*, 8 TRANSPLANT NEWS (Aug. 31, 1998), available in 1998 WL 9525584.

²²⁹ Jane E. Henney, M.D., U.S. Food and Drug Administration Commissioner of Food and Drugs, Keynote Address at the Global Harmonization Task Force Meeting in Bethesda, Maryland (June 29, 1999) available in (last visited Aug. 9, 1999) <www.fda.gov/oc/speeches/globalharm.html>.

²³⁰ *Mutual Recognition Agreements* (last visited Aug. 27, 1999) <www.europa.eu.int/comm/dg03/directs/dg3b/b1/indexb1.htm>. If reliance upon another country's conformity assessments is not practical, a mutual recognition agreement also has been interpreted to encompass the exchange of conformity assessment results to assure that the requirements of the receiving country are met. Horton, *supra* note 5, at 716.

²³¹ On June 24, 1998, Europe, Australia, and New Zealand signed a mutual recognition agreement that provides for the assessment (testing, inspection, and certification) of traded products in eight industry sectors (including medical devices and medicinal products, GMP inspection, and batch certification) to be undertaken in the exporting country rather than in the importing country. Australia Therapeutic Goods Administration, *Mutual Recognition Agreement on Conformity Assessment Between the European Community & Australia: Frequently Asked Questions (as at December 1998)*. On May 18, 1998, the United States and the European Community signed an accord on the mutual recognition of pharmaceutical good manufacturing practice inspection reports, certain medical device product evaluation reports, and medical device quality system audit reports. 63 Fed. Reg. 60,122 (to be codified at 21 C.F.R. pt. 26). Under the agreement,

the importing country authority may normally endorse GMP inspection reports for pharmaceuticals provided by the exporting authority determined by the importing authority to have an equivalent regulatory system. Likewise, the importing country authority may normally endorse medical device quality system evaluation reports and certain medical device product evaluation reports provided by conformity assessment bodies determined by the importing country authority to have equivalent assessment procedures.

Id.

has been to facilitate the marketing of EU-produced drugs and medical devices in other countries, through the reduction of drug and device foreign inspection and border batch testing for drugs.²³²

According to an authority on U.S. food and drug law, there are five models of harmonization in which FDA may choose to take part: 1) the agent-in-place model, in which FDA receives the results of a trading partner's work; 2) the enforcement discretion model, in which the products of a country whose domestic regulatory requirements are regarded as reliable by FDA are subjected to lessened scrutiny by the agency; 3) the "deputy sheriff" model, in which an unconditional or conditional commitment is made by FDA to accept another country's verification of compliance with FDA's requirements, subject to U.S. law; 4) the "equivalence" model, in which another country's regulatory requirements are accepted by the United States as equivalent to those of FDA; and 5) the harmonization model, in which regulatory requirement *modification* by both (or all) country parties results in a common approach.²³³ As the United States requires equivalence as a prerequisite to mutual recognition, MRAs in food and drug between the United States and another country are likely to be the category four "equivalence" model.²³⁴

In the last decade, two international task forces have been formed for the express purpose of promoting "true" global harmonization of medical device and pharmaceutical regulation—the Global Harmonization Task Force (GHTF) and the International Conference on Harmonization (ICH). The ICH was established in 1990 as a joint government regulatory/industry project to improve, via harmonization, the efficiency of the development and registration process of new pharmaceutical products in Europe, Japan, and the United States.²³⁵ The goal of the ICH is to ensure that "good quality, safe and effective medicines are developed in the most expeditious and cost effective manner,"²³⁶ with elimination of unnecessary duplication of human clinical

The regulation became effective on December 7, 1998. *Id.* On May 18-19, 1999, the Joint Sectoral Committee, responsible for the implementation of the Pharmaceutical Annex of the U.S.-EC Mutual Recognition Agreement, met in plenary session, discussing such topics as the facilitation of coordination, monitoring, and communication between the participating parties "to ensure consistency and transparency in making equivalence determinations." U.S. Food and Drug Administration, *Joint Summary of the Meeting of the Joint Sectoral Committee of the Pharmaceutical Good Manufacturing Practice Annex of the U.S.-EC Mutual Recognition Agreement* (last visited July 29, 1999) <www.fda.gov/oia/jsmra.htm>. The Committee also discussed the important issue of confidentiality of nonpublic documents, as the U.S. and the EU governments are subject to different requirements for disclosure of information (e.g., the U.S. Freedom of Information Act). *Id.*

²³² Horton, *supra* note 5, at 725.

²³³ *Id.* at 716, n.118 (citing Richard A. Merrill, *FDA and Mutual Recognition Agreements: Five Models of Harmonization*, 53 *FOOD & DRUG L.J.* 133, 135 (1998)).

²³⁴ *Id.* at 722. U.S. regulatory authorities suggest that any agreements reached by the United States and another country under either model 4 or model 5 would require U.S. notice and comment rulemaking. *Id.* at 716. FDA derives its authority to conduct international activities (including entering into both mutual recognition and harmonization agreements) from several sources, including the Food and Drug Administration Modernization Act of 1997 (FDAMA) and sections 301, 307, 351, and 361 of the Public Health Service Act. *Id.* at 712. FDAMA provides a third objective to FDA's statutory mission, "participat[ion] through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements." 21 U.S.C.A. § 393(b)(3) (West Supp. 1998). FDAMA further 1) supplemented an internationally-oriented section of the Federal Food, Drug, and Cosmetic Act pertaining to medical devices, with instruction that FDA "regularly participate in meetings with representatives of other foreign governments to discuss and reach agreements on methods and approaches to harmonize regulatory requirements"; and 2) transferred over FDA's authority to enter into cooperative agreements with other countries on device MRAs and drug and device inspections. Horton, *supra* note 5, at 708-09 (citing 21 U.S.C.A. § 383(b)(3) (West Supp. 1998)).

²³⁵ *A Brief History of ICH*, (last visited July 29, 1999) <www.ifpma.org/ich8.html>. Europe, Japan, and the United States are the geographic areas where the vast majority of new medicines are developed.

²³⁶ *Id.*

trials and minimization of product testing on animals.²³⁷ The best interest of the patient, consumer, and public health is emphasized. The EU provided the major impetus for the creation of the ICH through its 1980s efforts to harmonize regulatory requirements and develop a single market for pharmaceuticals in response to rising healthcare costs, increased research and development costs, and the “public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.”²³⁸

Essentially since its inception, the ICH has focused on four areas of harmonization: 1) efficacy; 2) safety, i.e., preclinical safety testing; 3) quality, i.e., production control or good manufacturing practices; and 4) regulatory communications, i.e., the medical terminology and standards for the electronic transmission of regulatory data and information.²³⁹ ICH harmonization of regulations or technical documents involves a five-step process.²⁴⁰ First, an ICH expert working group develops a draft guidance. Then, comments from citizens, academia, industry, and others are solicited. Next, the draft guidance is revised based on the comments, and is passed on to the ICH steering committee. The committee then approves the guidance and forwards it to the regional regulatory authorities. Finally, the regional regulatory authorities implement the guidance according to their respective national procedures. Within the United States, this involves FDA publication of the guidance in the *Federal Register*.²⁴¹

Thus far, the ICH has succeeded in harmonizing a number of testing procedures and specifications involved in drug production. ICH guidelines adopted by members have been on such topics as test procedures and acceptance criteria for biotechnological/biological products and statistical principles for clinical trials.²⁴² The *ICH Medical Dictionary for Regulatory Activities*, a new dictionary of international medical terminology, was adopted in 1997.²⁴³ In its 1998 Report to the Nation, FDA's Center for Drug Evaluation and Research (CDER) stated that the ICH has launched a second phase of activities that will focus on already-marketed drugs, generic equivalents, and over-the-counter drugs, and will feature increased representation of interested parties.²⁴⁴

In the medical device arena, the GHTF was established in the early 1990s by government and industry officials from North America, Europe, and the Asia-Pacific, with GHTF principal members from the United States, Canada, Australia, Japan, the EC, and the fifteen member states of the EU.²⁴⁵ The mission of the GHTF is

[t]o encourage convergence at the global level in the evolution of regulatory systems for Medical Devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by regulatory means considered to be most suitable. This is achieved by identifying and developing areas of international cooperation in order to facilitate progressive reduction of technical and regulatory differences in systems established to regulate medical devices.²⁴⁶

²³⁷ *Id.*

²³⁸ *Id.*

²³⁹ CDER (*Center for Drug Evaluation and Research*) 1998 Report to the Nation, at 28.

²⁴⁰ *Id.* at 29.

²⁴¹ *Id.*

²⁴² *International Conference on Harmonization Draft Guidelines and Adopted Guidelines* (last visited Aug. 6, 1999) <www.eudra.org/humandocs/humans/ICH.htm>.

²⁴³ CDER 1998 Report to the Nation, *supra* note 239.

²⁴⁴ *Id.* at 29.

²⁴⁵ Horton, *supra* note 5, at 720.

²⁴⁶ *Global Harmonization Taskforce* (last visited Aug. 2, 1999) <www.ghtf.org/general/prevsgl/brussels0399.html> (site no longer active, hard copy of text on file with the author).

Thus, the GHTF aims to achieve its goals “by developing an international consensus to develop equivalent systems with a common basis for how regulatory practices and decisions are carried-out relative to medical devices.”²⁴⁷

At present, four work (or study) groups comprise the GHTF, with a separate focus on product approval-related issues (i.e., regulatory requirements/premarket review), adverse event reporting, good manufacturing practices (quality system requirements and guidance), and audits of quality systems.²⁴⁸ These groups have developed (and continue to develop) harmonized approaches to medical device regulation in each of their areas.²⁴⁹ It is expected that future GHTF efforts will be targeted toward device classification, premarket approval, and essential requirements for devices and standards.²⁵⁰ According to authorities in the industry, global medical device regulation will continue to harmonize “along the lines of a risk class-based system and ISO 9001-based GMP requirements.”²⁵¹

While there is a clear distinction between mutual recognition and true harmonization in the healthcare field, the GHTF nonetheless has been instrumental in the continuing implementation of the 1998 U.S.-EC mutual recognition agreement regarding pharmaceuticals and medical devices. In particular, the four study groups of the GHTF have developed (or are now developing) guidance documents on the harmonization of premarket submissions, adverse event reporting criteria and process, quality systems requirements, and auditing the quality systems of medical device manufacturers.²⁵²

B. *Current State of International Harmonization of Human Tissue Use*

The harmonization of human tissue regulations has experienced more limited progress, despite continued efforts by several countries’ regulatory authorities, as well as by international organizations. In May 1991, the Health Assembly of the WHO²⁵³ endorsed the *Guiding Principles of Human Organ Transplantation*, which recommends to member states specific conditions under which organs and tissues may be removed from living and deceased donors for the purposes of transplantation.²⁵⁴ Mem-

²⁴⁷ *Proposed Memorandum of Understanding Between ISO/TC 210 and the Global Harmonization Task Force [210N135]*, June 1999, (last visited Aug. 19, 1999) <www.ghtf.org/meeting/ghtf-is0-tc210.html> (site no longer active, hard copy of text on file with the author).

²⁴⁸ *Id.*

²⁴⁹ Henney, *supra* note 229.

²⁵⁰ *Id.*

²⁵¹ Matthias Burger, *Designing for a Global Regulatory Environment* (last visited July 2, 1999) <www.raps.org/previous.cfm?artid=318> (must be member to access the information, however, hard copy of text is on file with the author). The International Organization for Standardization (ISO) was established in 1947 with the goal of developing common international standards in many different areas. *ISO 9000 Translated into Plain English* (last visited Aug. 1999) <www.connect.ab.ca/~praxiom/index.htm>. ISO 9000 quality assurance and quality management standards apply to a variety of disciplines, including manufacturing, processing, healthcare, pharmaceuticals, and biotechnology. *Id.* Certification of a quality system under the ISO 9000 guidelines serves as notification that the system has met internationally recognized quality assurance and quality management standards. *Id.*

²⁵² *Transatlantic Cooperation on Medical Devices: FDA and EU Steps Toward Implementing the MRA (United States-European Union Mutual Recognition Agreement)* (last visited Aug. 19, 1999) <www.fda.gov/cdrh/mra/impmra.html>.

²⁵³ WHO, founded in 1948 as a specialized agency of the United Nations, “promotes technical cooperation for health among nations, carries out programs to control and eradicate diseases and strives to improve the quality of human life.” *About WHO: Rapid Overview* (last visited Aug. 27, 1999) <www.who.org/aboutwho/en/rapid.htm>. WHO’s four principal functions are to 1) provide worldwide guidance in the health field, 2) set global standards for health, 3) work with governments to strengthen national health programs, and 4) develop and transfer appropriate health information, technology and standards. *Id.*

²⁵⁴ The May 1991 WHO endorsement appears to be WHO’s most recent action in the arena of international regulation of human tissue intended for transplantation. *Human Organ Transplantation: A Report on Developments Under the Auspices of WHO (1987-1991), I. Guiding Principles on Human Organ Transplantation*, 42 INT’L DIG. OF HEALTH LEGIS. 390 (1991).

ber states have been encouraged to consider these guidelines when formulating their organ transplantation policies. The *Guiding Principles* emphasize the concepts of free informed consent, donation subject to minimum age requirements, the treatment of a potential donor and subsequent determination of his death by a physician who is independent of the organ/tissue removal or implantation medical team, the resort to donation of nonregenerative organs/tissues from living, non-genetically related donors as second choice to cadaveric donation, the noncommercialization of organ/tissue donation, and the equitable distribution of organs/tissues based on a recipient's medical need (versus financial capability).²⁵⁵

With the advent of bio-engineered medical devices, international regulatory authorities turned their focus toward harmonization of tissue-engineered products in the mid-1990s. For instance, in 1996, a biomaterials congress workshop on tissue engineering was held in Toronto by regulatory officials from the United States, Canada, Japan, Australia, and Europe.²⁵⁶ It was proposed that countries' regulatory agencies and relevant industries, consumer groups, healthcare providers, international health and standards associations, and other interested parties collaborate on the global harmonization of standards and guidances addressing preclinical, clinical, manufacturing, and postmarketing surveillance issues associated with tissue-engineered products.²⁵⁷ FDA expressed its strong interest in establishing a consistent international approach to the regulation of tissue-engineered products before national regulatory strategies have become too entrenched, particularly in light of the significant trade implications for United States firms.²⁵⁸

Now, attention has returned to harmonization of more "pure" human tissue products, with the initial question raised as to which harmonization group—the GHTF or the ICH—would be the most appropriate to lead the project. At a June 1999 meeting between officials from the ICH and FDA's Center for Devices and Radiological Health, it was suggested that the ICH would be the more logical choice to oversee tissue harmonization activities, presumably in light of current tissue regulation by FDA's Center for Biologics Evaluation and (quite likely) the EMEA.²⁵⁹ Informed sources expect further meetings on the issue this fall. But for now, the global harmonization of human tissue remains a work in its incipient stage of progress.

VII. CONCLUSION

For over five decades, human tissue transplantation has played a prominent role in the field of medicine. Today, in the face of profound advances in biotechnology and "vanishing" national borders, the potential benefit of human tissue use would seem boundless. Yet, societal restrictions have impeded its widespread use.

With a focus limited to regulation of human tissue used for therapeutic purposes in the United States and select EU member states (as well as the regional EU), this paper presented the ethical and legal considerations relevant to global legislation in this area. One might have expected that western societies would sufficiently share a value system and biomedical technology base such that mutually recognized safety

²⁵⁵ *Id.* at 392-94.

²⁵⁶ INSIDE WASH.'s FDA Wk., June 28, 1996, at 1. Tissue engineering produces biological substitutes generally consisting of living cells or tissues and biomaterials. *Id.* at 2.

²⁵⁷ *Id.*

²⁵⁸ *Id.* at 2.

²⁵⁹ Telephone and electronic mail interviews with Dr. Elaine Esber, FDA's Center for Biologics Evaluation (Aug. 12, 1999) and Michelle Hoyte, Director of International Regulatory Affairs, the American Red Cross (Aug. 1999).

and ethical standards for human tissue use and banking could readily be established. This has not proven to be true. There is further potential for divergent views, as the vantage points of three major “players” outside of the EU in this area (Japan, Australia, and Canada) were not addressed by this paper. These countries possess similarly advanced medical technology and biomedical regulatory systems, but undoubtedly different ideologies (particularly Japan).

Varying belief systems notwithstanding, certain elements are widely recognized as critical in the international harmonization of human tissue use and banking, including: 1) free and informed consent of the donor; 2) noncommercialization of the entire process (i.e., no payment to donors and nonprofit tissue banks);²⁶⁰ 3) confidentiality and anonymity of the donor and the recipient, but for complete, *confidential* records, which ensure the traceability of the tissue from retrieval to implantation; 4) comprehensive screening and medical testing of the donor and his tissue to guard against viruses and other transmissible diseases; and 5) oversight (including periodic inspection) of all tissue banking facilities to ensure appropriate tissue procurement, processing, preservation, storage, quarantine, and distribution, as well as comprehensive record-keeping. Countries also appear to be supportive of a provision instituting a post-implant surveillance process, centralized database for the reporting of adverse events, and product recall procedure. In light of the controversy that human tissue research and development has generated, it is this author’s opinion that initial harmonization efforts would best be restricted to coverage of human tissue used for therapeutic purposes.²⁶¹

Certain other observations may be made, among them that harmonization of standards regulating human tissue use must ensure “adequate” protection of the public health. A country is unlikely to relinquish any autonomy over regulations if international standards are deemed inferior to that country’s national legislation on the matter. Consider France’s repeated protests about the EU’s “new approach” to premarket approval of medical devices, with potentially partial private notified parties bearing responsibility for conformity assessments. France would prefer the more stringent oversight provided by the EMEA in its assessment of pharmaceutical safety. The United States also undoubtedly will seek relatively exacting global standards for regulation of human tissue use and tissue banking, as evidenced by FDA’s recent prolific rulemaking on the issue.²⁶² If a country feels compelled to implement its national regulations over internationally harmonized standards, several significant implications result. One implication is that the country’s trade in the product area may be negatively impacted.²⁶³ While the human tissue “industry” arguably should be a nonprofit venture, it must be remembered that human tissue may serve as a component of a medical device, which would be marketed for profit.²⁶⁴ Another form of repercussion may be realized through the “nonparticipating” country’s reduced access to human tissue.

²⁶⁰ While noncommercialization of the entire process of human tissue donation is the ideal, this author believes it is an unrealistic goal and suggests that limited commercialization, with standardized payments to processing companies, is a more feasible prospect.

²⁶¹ As harmonization of human tissue regulation extends beyond therapeutic purposes, there must be particular attention given to ensure that the potential tissue use comports with a “common level of decency.” Civilized society should not be subject to such macabre human tissue use as lampshades made of human skin, as during the horror of the Holocaust in World War II.

²⁶² In light of these considerations, and the EU’s strong inclination for the EMEA to conduct primary evaluation of human tissue products at some future date, the International Conference on Harmonization appears to be the appropriate body to spearhead harmonization efforts.

²⁶³ See Horton, *supra* note 5, at 724.

²⁶⁴ Human tissue medical devices in a nonprofit environment raises a number of issues, including: 1) how can technology be promoted if research and development companies are not allowed to realize profits on their products, and 2) how should tissue-engineered products be valued, when they reflect a highly processed, transformed product, not the original, unprocessed tissue? Additionally, should there be international patent protection? Who controls the rights to these tissues, and how can these rights be uniformly exercised (i.e., what type of enforcement mechanism should be in place in the case of violations)?

A related issue concerns the imposition of sanctions. Should a country be penalized for sidestepping harmonized standards in favor of its own regulations in its interest to best protect its citizens' public health? And, if so, how will such sanctions (which presumably were agreed upon by participating countries) be enforced? Consider the current beef hormone controversy in which a number of European countries have refused to accept hormone-treated U.S. beef, despite obligating trade agreements and WTO judgments in favor of the United States. In response, the United States has instituted significant tariffs on certain food imports from several offending countries. Eventually, it is the consumer who bears the effects. How could a similar situation in the area of human tissue regulation be avoided?

Another relevant question that harmonization bodies must consider is how to ensure accountability for the sanitary safety of human tissues. Who is responsible for the quality and safety of the tissue to be transplanted? The donor team? The recipient team? The managing structure in charge of human tissue exchange? And what recourse should the patient who contracted AIDS from an improperly screened tissue transplant have? Perhaps harmonized standards should include some type of uniform liability insurance for all those involved with human tissue transplantation. Such a uniform insurance would enforce minimum standards.

Enhanced transparency in human tissue regulation may help to ensure both an increase in accountability and a more fair distribution of tissue based on acknowledged medical need rather than financial capability. In the United States, all regulations issued by FDA on human tissue use and tissue banking have been subject to notice and comment rulemaking, thereby allowing for public awareness and input by interested parties on the matter. U.S. agencies also are subject to the Freedom of Information Act, which permits the public to secure many government documents, unless the particular document falls under a protected exception to the Act. It does not appear that other countries involved in the harmonization process are subject to such provisions, which may present some difficulties.

A final concern that merits serious attention by harmonization bodies is the problem of poverty-stricken individuals selling body parts for profit, particularly in developing countries. This situation violates several principles of organ and tissue donation, including the noncommercialized, perceived altruistic nature of the donation act. It is violative of the dignity of the human body and further fails to comport with the precept of fair distribution of human tissue, as the wealthy may unduly reap the benefit of such "donation." This author suggests that harmonized regulations should ensure the anonymity of the donor and recipient in unrelated transplant cases, in order to decrease the possibility of collusive selling of body parts. The formation of an international blind registry of tissue typing would allow rapid matches for organ/tissue transplants, while still maintaining some control over commercialization.

Human tissue use and tissue banking, even at a national level, are replete with legal and ethical considerations. International harmonization of regulations in this area is likely to present a similar minefield on a larger scale. The profound benefits of such efforts cannot be denied, however, and in fact should be embraced, as we enter the new millennium in the face of advancing medical technology and a globalized marketplace.