CHAPTER 8

LEGAL AND REGULATORY ISSUES

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INTRODUCTION

Emerging biomedical products utilizing living tissues present a new order of magnitude of complexity in their interactions with human patients. As such, they challenge established processes for protecting patients and the public health from deleterious adventitious agents, while testing the capacity of those processes to ensure timely access to beneficial therapies. At the same time, using human tissues for purposes of medical product development—or, less benignly, for cloning or optimization of selected functional capabilities—present potentially very troubling legal and ethical issues.

The U.S. Food and Drug Administration (FDA) has been moving toward a comprehensive scheme for the regulation of engineered tissue products over the past eight years, especially since early 1997. FDA’s classification and pre-market reviews of first generation engineered tissue products have demonstrated that it is actively engaged in developing rational product approval pathways for engineered tissue products. However, such pathways are available and must function within the limits of a well-established statutory scheme for regulatory classification of medical products, into which engineered tissues do not necessarily fit easily.

This emerging U.S. approach can be contrasted with the present uncertain regulatory status of such products within the European Union and Japan. Inconsistency between regions or a lack of transparency in the application of a national (or, in the case of the EU, pan-national) regulatory authority over engineered tissue products is likely to increase the complexity of introducing new medical technologies incorporating human tissues without materially advancing public health or safety.

While critical to the general advance of medical research, access to human tissues for research or product development is highly sensitive to public
disclosure of practices where tissues are taken or used without consent or under circumstances suggesting a commercial market in body parts. The absence of comprehensive federal or state legislation governing “research” tissues deprives the biomedical community of clear, consistent guidelines to follow in acquiring and using tissues, while simultaneously representing a legislative vacuum that may be filled with substantial adverse unintended consequences if done suddenly in response to some public outcry. Absent effective coordination, the initiatives of individual federal agencies to establish policies for research involving human tissues or subjects may impose conflicting requirements or expectations.

FDA REGULATION

Broad authority to control the distribution and sale of medical products in the United States has been granted to the FDA under the federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act). The FD&C Act contains numerous provisions regarding the development and distribution of medical products, many of which have been introduced or substantially rewritten through a series of amendatory statutes. For example, the 1976 Medical Devices Amendments and 1990 Safe Medical Devices Act significantly expanded and clarified the FDA's authority to regulate medical products classified as devices. Recently, the 1997 FDA Modernization Act (FDAMA) has introduced a number of substantive revisions to a wide range of FDA product approval and enforcement practices; the implications of FDAMA, especially for products derived from emerging biomedical technologies, has yet to be fully realized. The PHS Act contains just two sections of particular importance to FDA regulation of medical products, especially those derived through tissue engineering: §351 prohibits the distribution of unlicensed "biological products" and establishes criteria and procedures the FDA shall observe in issuing such licenses; and §361 empowers the FDA to prevent the spread of communicable diseases.

Exercising its authority under these statutes, the FDA has adopted a complex set of regulations that control virtually every aspect of the development and marketing of a medical product according to the potential risk of harm the product may pose to patients or the public health. Thus, the FDA regulates the introduction, manufacture, advertising, labeling, packaging, marketing and distribution of, and record-keeping for, such products. The FDA (also referred to here as the Agency) exercises its regulatory authority over medical products through three divisions, or Centers, each generally responsible for exercising the FDA’s regulatory authority over a particular class of medical products, as indicated by their names:

- Center for Drug Evaluation and Research (CDER)
- Center for Devices and Radiological Health (CDRH)
- Center for Biologics Evaluation and Research (CBER)

As a rule, the FDA requires a sponsor of a new medical product to submit a formal application for approval to market the product after the completion of
preclinical studies and phased clinical trials that demonstrate to the Agency’s satisfaction that the product is safe and effective. The form and review of that request to initiate human trials and the subsequent marketing application vary according to the classification of the product with reference to categories established in the statutes granting regulatory authority to the FDA. In fact, the FDA’s classification of a new medical product carries implications beyond identifying the Center responsible for regulatory review or the particular approval pathways the product may subsequently follow.

Classification of Medical Products

Under current federal law, every medical product is classifiable as a drug, device, biological product (a “biologic”), or “combination product” (that is, a combination device/drug, device/biologic, etc.). The classification of the product determines the particular processes of review and approval the FDA may employ in determining the safety and efficacy of the product for human use.

Under the FD&C Act (at §201(g)(1)), a “drug” is broadly defined as:

... [an article] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease ... [or] ... intended to affect the structure or any function of the body.

The FD&C Act (at §201(h)) defines a “device” largely by what it is not (that is, neither a drug nor a biologic):

... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar related article ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease ... or intended to affect the structure or any function of the body ... and which does not achieve any of its primary intended purposes through chemical action within or on the body ... and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

[Emphasis added.]

Finally, the PHS Act (at §351(a)) defines a “biologic” as:

... any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment or cure of diseases or injuries.

Not surprisingly, the advance of medical technology has produced products not readily classifiable as drugs, devices, or biologics as those terms have been defined by federal statute. To provide for the expanding varieties of products expressing features of more than one of those classifications, the FDA has been authorized to recognize “combination products.” A combination product is classified, assigned to a particular Center, and regulated as a drug, device, or biologic according to its “primary mode of action,” as determined by the FDA. Disputes over the classification of a combination product between a sponsor and the FDA or between Centers are submitted to the FDA’s Ombudsman for
resolution. In fact, the FDA’s current approach to the regulation of engineered tissue products began with the Ombudsman’s consideration of the classification of the Carticel™ autologous cartilage repair service developed by Genzyme Tissue Repair in 1995.

Implications of Product Classifications

While some medical products simply are what they are (that is, an artificial hip joint is obviously a device and aspirin is clearly a drug), the idea of the combination product suggests that relevant features or intended uses of a new product may exist primarily in the eye of the beholder. At least, the FDA’s classification of the product may be influenced by what the sponsor does or does not claim for it and how it has been designed to achieve a particular therapeutic benefit.

Why should the classification of a new medical product for purposes of FDA regulatory review really matter? With few exceptions, all products subject to such review for marketing approval must be safe and effective, regardless of classification. There may be some subtle variation in the measurement of those qualities among the FDA Centers, or approval pathways may seem more efficient or predictable for, say, devices compared to biologics. The real significance of classification lies in the benefits or encumbrances that attach to the product either before or after the actual process of marketing review.

With respect to engineered tissue products, the consequences inuring to the device and biologic classifications deserve particular attention. First, and most importantly, a medical product cannot be a device if its therapeutic or diagnostic benefit is obtained through metabolization, a limitation in the statutory definition of a device that might appear to exclude any product incorporating and depending on the function of any living human tissues. Nevertheless, allogeneic skin products such as Organogenesis’s Appligraf have been classified and granted market approval as devices. As engineered tissue products become less “structural” and more “functional” in nature, a “device” classification may become more difficult to square with the current statutory definition, although a product sponsor’s desire to obtain this classification for its product may be undiminished.

Depending upon the manner of marketing approval, a tissue product classified as a device may be insulated from product liability litigation, while no such protection by reason of FDA review is available for tissue products classified as biologics. More immediately, only products classified as drugs or biologics are subject to the Prescription Drug User Fee Act. Under this act, sponsors of biologics are assessed fees in excess of $250,000 in conjunction with the filing and review of an application for marketing approval; sponsors of devices do not pay such fees. On the other hand, certain biologics may qualify for a special product designation that may waive the user fee payment and provide other benefits not otherwise available for devices.

In most cases, the classification of an engineered tissue product is effectively predetermined by the nature of the product itself and the manner in which it is intended to convey a therapeutic benefit. Nevertheless, consideration should be given to the greater implications of product classification early in the
development process and certainly before discussing applicable methods of regulatory review with the FDA.

**Special Product Designations**

The FD&C Act recognizes that demand for all new medical products is not equally large or robust, such that the cost of obtaining marketing approval for a given product may be prohibitive in view of the relatively small size of the population it will benefit. To reduce the likelihood that a financial cost-benefit analysis applied to rarer diseases will leave them untreated, the FDA is authorized to grant special considerations and exceptions to reduce the economic burden upon developers of products under such conditions. Thus, the FDA may be petitioned to grant a “humanitarian device exemption” for certain devices (FD&C Act, §520(m)) or to recognize certain drugs or biologics as “orphan drugs” (FD&C Act, §525, et. seq.). However, the significance or value of these designations—especially for sponsors of tissue products—varies considerably according to the classification of the product in question.

**Humanitarian use devices** are those intended to treat a disease or condition that affects fewer than 4,000 people in the United States. The FDA is authorized to exempt a sponsor from the obligation to demonstrate the effectiveness of such a device to obtain marketing approval; however, the sponsor is precluded from selling the product for more than the cost to develop and produce it.

**Orphan drugs** are those intended to treat a disease or condition affecting fewer than 200,000 persons in the United States, or for which there is little likelihood that the cost of developing and distributing it in the United States will be recovered from sales of the drug in the United States. The orphan drug designation was established through an amendment of the FD&C Act by the 1982 Orphan Drug Act (ODA) prior to the creation of the humanitarian device exemption. In contrast to the humanitarian use devise designation, the orphan drug designation could be important to sponsors of certain engineered tissue products classifiable as biologics, illustrating the larger implications of the classification process. An orphan drug is defined to include biologics specifically licensed under §351 of the PHS Act, a distinction which may be relevant under the FDA’s proposed plan for regulating engineered tissue products (see below). The FDA is empowered, under certain conditions, to grant marketing exclusivity for an orphan drug in the United States for a period of seven years from the date the drug is approved for clinical use; this exclusivity is stronger than and far less expensive to maintain than that provided by a patent. Additional benefits of the orphan drug designation include: certain tax credits for clinical research expenses; cash grant support for clinical trials; and waiver of the expensive prescription drug filing fee. A petition for orphan drug designation must be filed before any application for marketing approval.

**Human Cellular and Tissue-Based Products**

Human tissues used for medical purposes that have been regulated by the FDA as products have been classified as devices (including dura mater, human lenticules, and allograft heart valves) or as biologics (including blood, blood components, and blood products) (see Figure 8.1). Consequently, engineered
human “tissue products” can be expected to be regulated by the FDA under these classifications as well (with at least the possibility of classification as a drug), although the criteria and process for such classification and subsequent marketing review will be substantially influenced by new regulations that the FDA is developing for cellular and tissue-based products.

In October 1993 the FDA announced that it considered its existing statutory authority mandated its regulation of autologous or allogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in their biological characteristics _ex vivo_, and intended to be administered to humans for the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries (58 Federal Register 53248; October 14, 1993). The FDA also announced that the same statutory authority would extend to gene therapy products containing genetic material administered to modify or manipulate the expression of genetic material in order to alter the biological properties of living cells. The announcement explained that the FDA expected such somatic cell and gene therapy products would be classifiable as biologics subject to then-existing product and establishment licensure requirements (since consolidated under the current biologics license), but it noted that drug and device classifications could also be applicable.

A few months later, the FDA announced proposed rulemaking with regard to the acquisition and distribution of human tissue intended for transplantation (58 Federal Register 65514; Dec. 14, 1993). In contrast with its approach to somatic and gene therapies, the FDA did not claim transplanted tissues would be regulated as medical products. Instead, persons involved in the transfer of these tissues would be subject to donor screening, record-keeping, and processing standards pursuant to the FDA's authority under §361 of the PHS Act to prevent the spread of communicable diseases.

Much of the regulatory framework for engineered tissues is now being promulgated by the FDA through formal, binding, rule-making procedures. Previously, the FDA had issued a number of documents which, while not binding upon the Agency, did provide the public with a formal expression of its
evolving thinking regarding the future regulation of human cellular or tissue-based products (see Table 8.1). Of these documents, by far the most important has been the *Proposed Approach to Regulation of Cellular and Tissue-Based Products* ("Proposed Approach") that the FDA issued on February 28, 1997.

Building upon the concepts and strategies set out in the Agency's 1993 pronouncements regarding somatic cell therapies and transplanted tissues, its Proposed Approach outlines a plan of regulatory oversight, which may include a pre-market approval requirement, for such tissue products based upon a matrix ranking the products, classified by certain characteristics, within identified areas of regulatory concern. These tissue products would be classified according to the relationship between the donor and the recipient of the biological material used to produce the tissue product; the degree of *ex vivo* manipulation of the cells comprising the tissue product; and whether the tissue product is intended for a homologous use, for metabolic or structural purposes, or is to be combined with a device, drug, or another biologic (see Figure 8.2).

The Proposed Approach also announced the establishment of an inter-Center Tissue Reference Group to act as an ombudsman to resolve product classification disputes and assure Agency-wide consistency in the application of relevant regulatory authority over harvested or engineered tissues used as medical therapies.

Since issuing the Proposed Approach almost five years ago, the FDA has been working to formalize its regulation of human tissue and cell therapies through a rulemaking process to amend the U.S. Code of Federal Regulations ("CFR") (see Table 8.1).
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<td>FDA Notice of Public Hearing: Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Implantation for Structural Repair or Reconstruction (60 FR 36808; July 18, 1995).</td>
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<td>6.</td>
<td>FDA Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Structural Repair or Reconstruction.</td>
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<td>7.</td>
<td>FDA Proposed Approach to Regulation of Cellular and Tissue-Based Products (February 28, 1997).</td>
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<td>8.</td>
<td>FDA Notification of proposed regulatory approach regarding cellular and tissue-based products (62 FR 9721; March 4, 1997).</td>
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<td>11.</td>
<td>FDA Guidance to Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation (July 29, 1997).</td>
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<td>15.</td>
<td>FDA Proposed Rule: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (66 FR 1508; January 8, 2004).</td>
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* With the exception of Document #1, each document listed here can be obtained through the FDA website (www.fda.gov/cber). While provisions of the FD&C and PHS Acts and the Final Rules, codified as part of the Code of Federal Regulations (CFR), promulgated thereunder by the FDA, have the force of law and are binding on the agency, FDA guidance documents are not. Nevertheless, Guidances are clearly helpful in anticipating the Agency's response to particular marketing approval and other regulatory issues.
Marketing Review and Approval Pathways

As discussed above, the particular program(s) of regulatory review applicable to a medical product are predetermined according to its FDA classification. Thus, the FD&C Act requires a sponsor to submit a device Pre-Market Application (PMA) or Product Development Protocol (PDP) to market a device, or a new drug application (NDA) to market a drug. The PHS Act provides that marketing approval for a biologic shall be obtained through the submission of a Biologics License Application (BLA). Certain drugs or biologics may qualify for special designation as orphan drugs under the Orphan Drug Act.

In addition, the FDA requires that sponsors of regulated products must first obtain preliminary approval for the clinical trials on humans that will support a subsequent application for full marketing approval. Clinical trials in support of a PMA application or as part of a PDP for a device may be conducted only after the FDA has issued an investigational device exemption (IDE); clinical trials in support of an application for marketing approval of a drug or biologic cannot be initiated until the FDA has approved an investigational new drug (IND) application.

Devices

The FDA has divided devices into three classes to identify the level of regulatory control applicable to them. The highest category, Class III, includes those devices for which pre-market approval is or will be required to determine the safety and effectiveness of the device (21 CFR, §860.3(c); 21 U.S.C., §360c(a)(1)(C)). Absent a written statement of reasons to the contrary, the FDA classifies any “implant” or “life-supporting or life-sustaining device” as Class III (21 CFR, §860.93; 21 U.S.C., §360c(c)(2)(C)).

There are two primary pathways by which the FDA permits a medical device to be marketed: pre-market clearance by means of a 510(k) notification, or pre-market approval by means of a PMA or PDP submission.

A sponsor may seek clearance for a device by filing a 510(k) pre-market notification with the FDA, which demonstrates that the device is “substantially equivalent” to a device that has been legally marketed or was marketed before May 28, 1976. The sponsor may not place the device into commercial distribution in the United States until the FDA issues a substantial equivalence determination notice. This notice may be issued within 90 days of submission but usually takes longer. The FDA, however, may determine that the proposed device is not substantially equivalent, or require further information such as additional test data or clinical data, or require a sponsor to modify its product labeling, before it will make a finding of substantial equivalence.

If a sponsor cannot establish to the FDA’s satisfaction that a new device is substantially equivalent to a legally marketed device, it will have to seek approval to market the device through the PMA or PDP process. This process involves preclinical studies and clinical trials to demonstrate that the device is safe and effective.

FDA regulations (21 CFR, §860.7(d)) provide that, based on “valid scientific evidence,” a device shall be found to be “safe:”
... when it can be determined ... that the probable benefits to health from use of the device for its intended uses and conditions of use ... outweigh any probable risks,[4]

and that a device shall be found to be “effective:”

... when it can be determined ... that in a significant portion of the target population, the use of the device for its intended uses and conditions of use ... will provide clinically significant results.

Testing in humans to obtain clinical data demonstrating these qualities in support of a PMA or pursuant to a PDP must be conducted pursuant to an investigational device exemption. The IDE is the functional equivalent of the IND that governs clinical trials of drugs and biologics. As with other medical products, clinical testing is typically conducted in multiple phases, with the earliest phases primarily intended to demonstrate safety and later phases addressing both safety and efficacy considerations. The sponsor of the device must also demonstrate compliance with applicable current good manufacturing practices (cGMPs, now also known as Quality System Regulations) before the FDA may approve the product for marketing by granting the PMA or accepting the completion of the PDP.

**The Product Development Protocol.** The 1976 Medical Device Amendments (MDA) to the FD&C Act included a section which provided the sponsor of a Class III device with two product approval pathways, the PMA or the PDP. The legislative history of the MDA reveals an expectation within Congress that most Class III devices would be approved by the FDA in response to a PMA. Nevertheless, in providing the PDP alternative, faster development of innovative devices could be achieved, and certain sponsors, especially small device sponsors, would benefit from an approval process that merged the investigation of the device and the development of the information necessary for its approval into one regulatory mechanism. The conventional device approval model—the linear process of clinical investigation followed by premarket approval application—provides for little to no interaction between the sponsor and the FDA once an IDE has been granted. Anticipating that many medical devices are subject to frequent modification during development and that small device sponsors, in particular, may lack the financial resources to repeat or rework clinical trials to bolster perceived deficiencies in a PMA, the drafters of the 1976 MDA added the PDP process.

The PDP process replaces the linear PMA model with an early, collaborative interaction between product sponsor and FDA to produce a focused clinical development plan that both parties anticipate will satisfy the statutory requirements for proof of safety and effectiveness within an established timeframe. In addition, the PDP process allows for modification of the development plan in consultation with FDA reviewers (or in accordance with established guidance) to assure that the development plan as revised, or the device or modified device, will obtain prompt approval upon submission of a notice of completion of the PDP at the conclusion of the clinical trial(s) contemplated under the PDP plan.
8. Legal and Regulatory Issues

The PDP process is not an alternative to the PMA process in the sense that the statutory requirements for proof of safety and effectiveness are relaxed; rather, it incorporates the clinical development and regulatory review elements of the IDE-PMA process within a framework that can efficiently manage deviations from the original plan made necessary by experience. In addition, a PDP may demonstrate to prospective investors of an emerging biomedical company that a clear, predictable plan and timetable exists for achieving marketing approval for products upon which the company's future revenues and profitability may depend.

Biologics

Until recently, permission to market a biologic required two applications: one to obtain a product license application (PLA) for the biologic itself and another for approval of the facility where the biologic would be prepared, that is, an establishment license application. The 1997 FDA Modernization Act amended the PHS Act by eliminating the separate product and establishment license applications in favor of a single biologics license application (BLA), which, like the PMA or PDP for devices, includes an evaluation of compliance with appropriate quality controls and current cGMP as part of the assessment of the safety and efficacy of the product in question.

§351 of the PHS Act directs the FDA to approve a BLA on the basis of a determination that the biologic in question is “safe, pure, and potent.” Those terms are defined in FDA regulations promulgated to give effect to that statutory authority:

… safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time[;]

… purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product … [and] includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances[;]

… potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Testing in humans to obtain clinical data demonstrating these qualities in support of a BLA must be conducted pursuant to an investigational new drug application. The IND is the functional equivalent of the IDE that governs clinical trials of devices. As with other medical products, clinical testing is typically conducted in multiple phases, with the earliest phases primarily
intended to demonstrate safety, and later phases intended to address both safety and efficacy considerations.

The emphasis given to process by the earlier requirement of a separate approval of the manufacturing facility illuminates the dual nature of the regulatory authority created under the PHS Act and ultimately exercised by the FDA. Besides assuring that only safe, pure, and potent biologics are marketed in the United States, the FDA is also charged with a general duty to prevent the introduction, transmission, or spread of communicable disease (PHS Act, §361(a)). While the BLA is an amalgam of product and process quality criteria, a particular emphasis upon the authority to eliminate sources of dangerous infection reappears in the context of the FDA’s proposed regulatory triage for engineered tissues.

**Human Cellular and Tissue-Based Products**

In introducing the February 1997 “Proposed Approach,” the FDA identified five areas of regulatory concern raised by the development of new medical products derived from the manipulation of human biological materials: communication of infectious disease; processing and handling; clinical safety and efficacy; indicated uses and promotional claims; and monitoring and education.

The FDA has proposed that autologous tissue that is banked, processed, or stored should be tested for disease, and it will require companies to keep appropriate records to assure that patient tissues are not mismatched or commingled. The Agency proposes that allogeneic tissue be tested for disease, that donors be screened, and that appropriate records be kept, although the extent of the required testing or screening will not be as great for nonviable tissue. Periodic submissions to the Agency showing compliance with the testing or record-keeping requirements will not be necessary; the FDA assumes that a company’s observation of these requirements will be assured through the accreditation they can be expected to maintain with professional tissue banking or processing societies.

The extent of the FDA’s proposed regulatory intervention in the areas of processing and handling and clinical safety and efficacy vary according to the characteristics of the particular tissue product in question. To the extent that a tissue product undergoes more than minimal manipulation in processing, is intended for a nonhomologous use, is combined with nontissue components, or is intended to achieve a metabolic outcome, the Agency will require a greater demonstration of safety and efficacy through appropriate clinical trials.

“Manipulation,” in the Agency’s Proposed Approach, is a measure of the extent to which the biological characteristics of a tissue have been changed *ex vivo*. The FDA has stated it presently considers cell selection or separation, or the cutting, grinding, or freezing of tissue, to constitute minimal manipulation. Cell expansion and encapsulation are examples of more than minimal manipulation.

To the extent that the tissue product only undergoes minimal manipulation, is intended for a homologous application to achieve a structural outcome (or reproductive or metabolic outcome, as between family members related by
blood), and does not combine with non-tissue components, the FDA will expect “good tissue practices” to be observed but will not impose any reporting duties or, consistent with its authority under §361 of the PHS Act, any product licensing or pre-market approval requirements. Any other tissue product requires submission of appropriate chemistry, manufacturing, and controls information and BLA approval for any tissue product that does not incorporate nontissue components. Tissue products that are combinations of tissue and devices or tissue and drugs may be regulated according to established pre-market approval (PMA or PDP) or new drug application (NDA) schemes.

The FDA has announced its intention to initiate formal rule-making to establish binding regulations regarding cellular and tissue-based products. To that end, it has recently proposed regulations to compel the registration of sponsors and other persons engaged in production and distribution of such products.

OTHER CONSIDERATIONS RELEVANT TO ENGINEERED TISSUES

FDA Regulation and Product Liability

Protection from product liability lawsuits, in the form of an immunity from such litigation, may come from satisfying the federal regulations that govern the design and manufacture of, as well as the warnings to be provided with, medical products.

By virtue of the Supremacy Clause of the U.S. Constitution (Article VI, cl. 2), the federal government is permitted to regulate certain affairs free of state interference. State civil litigation is a form of regulation, so it is a form of interference. If Congress elects to exclusively regulate certain conduct, then litigation under state law regarding the same conduct is prohibited, as it may produce inconsistent or conflicting standards regulating that conduct.

The public policy arguments in favor of federal preemption with respect to the regulation of medical products are readily discernible. While both state and federal regulation have the enhancement of public health and safety as their goals, establishment of nationwide labeling and design criteria for medical products promotes uniformity and regularity in the interpretation of applicable regulations and ensures that enforcement of these regulations is conducted in the public interest, rather than through isolated lawsuits that may produce inconsistent results. In addition, the natural preeminence of a federal administration administering such regulations simplifies and improves communication between the regulators and the medical product sponsors. Federal preemption, then, is not a shield for bad medical products; rather, it protects a process of reasoned, scientific inquiry.

Ownership of Human Tissues

Significant advances in medical research over the past several years have contributed substantially to the commercial utility of human biological materials. Consequently, the source of such materials used in the creation of engineered tissue products may become important for reasons beyond—and certainly removed from—the possible transfer of adventitious agents or the
management of immunological responses. Simply put, the use of allogeneic materials raises issues of ownership, donation, and consent not to be found with respect to autologous tissues.

The common law of the United States recognizes a severely restricted property interest in human bodies or organs. In a broad sense, a “property interest” in something may be thought of as a “bundle of rights” to possess, to use, to profit from, to dispose of, and to deal in that thing. Courts have granted next of kin nothing more than a “quasi-property” right—or right of sepulcher—in a decedent’s body for the purposes of burial or other lawful disposition. In place of an exegesis of the religious or cultural prohibitions against recognizing a property interest in a dead body, it is clear that the limited right that has been fashioned by the courts has been intended to offer nothing more than that some interested person may ensure the remains are disposed of with dignity.

The limited biological resources to support organ transplantation have certainly created the conditions for a market for human body parts. In response, Congress and state legislatures have enacted statutes prohibiting the sale of any human organ. The National Organ Transplant Act (42 U.S.C., §§273 et seq.) was passed to regulate the availability of organs for transplantation through voluntary donation exclusively by explicitly prohibiting organ purchases. The same prohibition has been passed into law by the 15 states, to date, that have adopted the Uniform Anatomical Gift Act (1987). Other state statutes have imposed criminal penalties for the purchase of organs or tissue from either living or cadaveric providers.

These federal and state statutes effectively banning purchases of human organs were enacted in the mid-1980s in immediate response to the prospect of a widespread trade in these body parts to supply the growing demand for transplant material. The vision of a vendor peddling livers and kidneys—or worse, a patient harvesting one of his own organs for money—clearly hovered over the debate leading to the passage of this legislation. But that vision imagined people self-dismantling for cash; it did not really allow for a trade in renewable body parts, especially cells.

Whether the law would also abhor the sale of naturally regenerating cells was answered in the affirmative by the 1990 decision of the California Supreme Court in Moore v. Regents of University of California (51 Cal.3d 120, 271 Cal.Rptr. 146, 793 P.2d 479, 1990). The plaintiff, John Moore, claimed he held a property interest in the T-lymphocytes that had been harvested by his physician when his spleen and other bodily substances had been removed in the course of treating his hairy-cell leukemia. The T-lymphocytes were subsequently used to develop a cell line capable of producing a potentially lucrative strain of lymphokines. The development of the cell line and the financial rewards to be reaped from it were not disclosed to Mr. Moore when he consented to the surgical procedures necessary to treat his disease. Mr. Moore sued his physician and others for, among other things, conversion of his tissues, including his spleen, blood and the cell line derived from his cells. The California Supreme Court rejected Mr. Moore’s conversion action; it refused to concede to him a property interest in his excised cells.
In the years following the *Moore* decision, few courts in the United States have had occasion to give further consideration to the nature of donors’ ownership interests in their tissues. However, in order to provide for the privacy of genetic information, legislation proposed in some state assemblies has suggested donors may have an economic interest in such information and, by inference, in the tissues from which it would be derived.

**REGULATION OF PHARMACEUTICAL/MEDICAL HUMAN TISSUE PRODUCTS IN EUROPE**

Regulation of medical products incorporating viable human tissue products among or within the member states of the European Union is marked by inconsistency but is presently the subject of substantial discussion and debate. As part of the overall coordination of national laws and governmental activities within the EU, the regulation of the marketing of certain medical products by national authorities is being consolidated within designated EU agencies, especially the European Medicines Evaluation Agency (EMEA).

Within the scope of what medical products are considered pharmaceutical and regulated, there are two broad subcategories, medicinal products and medical devices, as shown in Figure 8.3.

The EMEA was established in 1993 by the European Economic Community (EEC, now EU) Council Regulation No. 2309/93 to implement procedures to give effect to a single market for “medicinal products” among the member states. In conjunction with three directives adopted concurrently (Council Directives 93/39EEC, 93/40EEC and 93/41EEC), the regulation authorized EMEA to manage a “centralized procedure” for an EEC authorization to market medicinal products for either human or veterinary use. The directives also established a “mutual recognition procedure” for marketing authorization of medicinal products based upon the principle of mutual recognition of authorizations granted by national regulatory bodies. These procedures came into effect on January 1, 1995, with a three-year transition period until December 31, 1997. As of January 1, 1998, the independent authorization procedures of the member states are strictly limited to the initial phase of mutual recognition (i.e., granting marketing authorization by the “reference Member State”) and to medicinal products that are not marketed in more than one member state. Consequently, sponsors seeking marketing authorization for

![Fig. 8.3. European classifications of regulated medical products.](image-url)
medicinal products throughout the EU are obliged to seek such approval through the centralized procedure administered by EMEA.

The concept of a “medicinal product” in EEC legislation substantially predated the organization of EMEA. Council Directive 65/65EEC of January 26, 1965, defined the term medicinal product to include

any substance or combination of substances presented for treating or preventing disease in human beings or animals.

[and]

any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals ….

A “substance” is further defined to include “[a]ny matter irrespective of origin which may be human … animal … vegetable … [or] chemical” (Directive 65/65/EEC, Article 1). However, the directive also makes clear that its regulation of medicinal products (and, through amendments to the directive recognizing the authority of EMEA, the “centralized procedure”) does not apply to products “intended for research and development trials” (Directive 65/65/EEC, Article 2).

Sponsors of medical products derived through tissue engineering have reported substantial inconsistency among the regulatory bodies of EU member states regarding the classification of such products for purposes of determining the applicability of national or EU marketing authorization requirements (see Table 8.2). A determination that engineered tissue products are “medicinal products” subject to the centralized procedure for authorization administered by EMEA will substantially clarify and rationalize the process by which such products may be marketed throughout the European Community.

Table 8.2
Classification of Human Tissue Products by EU Member States

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Regulatory Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>Viable allogeneic skin replacement</td>
<td>Austria; Denmark; Germany; Spain; Sweden; UK</td>
</tr>
<tr>
<td>Nonviable allogeneic skin replacement</td>
<td>Austria; Germany</td>
</tr>
<tr>
<td>Autologous implant</td>
<td>Austria; Germany; Sweden</td>
</tr>
</tbody>
</table>

Source: Allison Dale, Smith & Nephew
The EMEA has in place a Biotechnology Working Party that has considered, among other things, safety issues in the delivery of human somatic cell therapies and a definition of a “cell therapy medicinal product” (CPMP/BWP/41450/98 draft). This definition would consider engineered human tissues to be “medicinal products” within the meaning of Directive 65/65/EEC, provided the engineered tissue was the product of both the following:

a. … an industrial manufacturing process carried out in dedicated facilities. The process encompasses expansion or more than minimal manipulation designed to alter the biological or physiological characteristics of the resulting cells, and

b. further to such manipulation, the resulting cell product is definable in terms of qualitative and quantitative composition including biological activity.

(Points to Consider on Human Somatic Cell Therapy, CPMP/BWP/41450/98, draft, page 3/9.)

The Biotechnology Sector of EMEA is likely to have primary responsibility for considering the authorization of engineered tissue products in the event they are classifiable as “medicinal products.”

Human tissue and cellular products may not be presently definable as “medicinal products” subject to regulation, to the extent they are the result of modest manipulation of autologous tissues in the course of treating a fairly small patient population. Under these circumstances, the regulation of such cellular products is more likely to remain with the competent authorities of the Member States (with substantial variability in the classification and resulting regulation of such products, as outlined in Table 8.2). Nevertheless, an EMEA decision to accept an engineered tissue product as a “medicinal product” could occur in response to a petition from a sponsor of such a product. To be successful, such a petition should probably stress the “industrial” nature of the fabrication process and the extent of manipulation of the human biological material to produce the engineered tissue product. Assuming an engineered tissue product could be established to be a “medicinal product,” there does not appear to be any EU rule that could limit the ability of EMEA to grant market authorization according to the type or source of tissue from which the product had been derived.

EMEA is aligned with Enterprise DG (formerly DG III; the department of the European Commission primarily responsible for establishing and implementing rules promoting the Single Market for products). A unit of Enterprise DG oversees application of EU directives regulating marketing authorization of medical devices. Providing for engineered tissue products could require some reconsideration of the specific areas of responsibility of the units or agencies involved in regulating medical products.

REGULATION OF PHARMACEUTICAL/MEDICAL HUMAN TISSUE PRODUCTS IN JAPAN

It appeared at the time of the WTEC panel’s visit to Japan that the Government of Japan was only beginning to focus on codifying regulation of
engineered human tissue products within its scheme of regulating other medical products. The WTEC panel was unable within the scope of this study to provide an analysis of Japan’s medical product approval process as potentially applied to engineered human tissue products. However, presented here is an outline of Japan’s process and agencies responsible for regulation of medical products generally.

The Pharmaceutical and Medical Safety Bureau (PMSB) has primary responsibility within the Japanese Ministry of Health, Labour and Welfare for administering the requirements established for the safety and efficacy of medical products under Japan’s Pharmaceutical Affairs Law. This legislation was substantially amended in 1996 (with the reforms made effective in April 1997) to provide for the present medical product review and approval system.

Applications for approval of new drugs and medical devices are referred by PMSB to the Central Pharmaceutical Affairs Council (CPAC) to obtain its recommendation. The CPAC, in turn, is advised by the Pharmaceutical and Medical Devices Evaluation Center (PMDEC), an expert body organized in July 1997 to evaluate the quality, efficacy, and safety of medical products administered to humans. Specific authority within PMSB to approve recommendations received from CPAC regarding the discrete aspects of the clinical testing, licensing, and use of new medical products is distributed among relevant divisions, such as the Evaluation and Licensing Division (pre-marketing and supplemental application approvals) and the Safety Division (adverse reaction measures). A regulatable medical product in Japan is classified as either a medical device or a pharmaceutical (Figure 8.4).

Advice concerning the design and conduct of clinical trials, as well as the adequacy of applications for approval of pharmaceuticals, is provided to PMDEC and to the product sponsor by the Drug Organization, a quasi-governmental agency established in 1979 as a fund to support patients experiencing adverse drug reactions. It is not clear whether the Drug Organization serves a similar function with respect to medical devices, or if there exists an equivalent medical device organization. However, applications for approval of “copy-cat” devices are referred to the Japan Association for the Advancement of Medical Equipment for a determination of the equivalence of the new device to devices already approved for clinical use. For a more detailed

Regulated Medical Product

Medical Device  Pharmaceutical

Fig. 8.4. Japanese classification of regulated medical products.
description of Japan’s general medical product approval process, see, for example, Hirayama 1998 and Yamada 1997.

CONCLUSION

No part of the process of bringing new biomedical products from the laboratory to the patient occurs in isolation from or independent of all of the other aspects of organizing and maintaining that technology development effort, including intellectual property protection and financing, just to mention two. While pre-market approval is the most obvious form of external control over the introduction of new medical products in any country, it is not the only one. Healthcare reimbursement regulations and private insurer practices are critical components of establishing market acceptance. The approach to regulatory oversight itself requires careful analysis of product classification (including special designation) options. The novelty, variety, and potential complexity of forms of tissue engineering compel strategic analysis of external controls over the commercial development of human cellular and tissue-based products.

Regulatory issues present a major challenge to the worldwide development of the tissue engineering industry. The FDA approach to the regulation of products incorporating human tissues is comprehensive but not fully implemented. In the absence of an EU regulatory program, those European governments that have addressed the status of engineered tissue products have employed an array of classification schemes that further complicate international application of tissue engineering technologies. Like a number of European states, Japan has yet to articulate its own regulatory policies.

The implications of governmental authority over access to human tissues for research purposes are equally clouded by multiple responses to the legal, ethical, and cultural issues presented, with the recent debate over the use of embryonic stem cells highlighting these different approaches. Tissue engineering can proceed along two paths: the management of the natural process of proliferation and differentiation from the embryonic stage to produce only the specific tissues required; or the manipulation of differentiated somatic cells or partially differentiated stem cells to build functioning tissues. With the introduction of the additional ethical, cultural, and legal issues that attend upon the nontherapeutic experimentation on embryonic tissues, what might otherwise be simply a scientific debate has become an intensely political one.

Taken as a whole, this WTEC study’s examination of legal and regulatory issues revealed the following:

- In comparison with the rapid progress being made to establish the therapeutic potential of human cellular and tissue-based strategies, the legal transfer and subsequent status of human tissues for research and product development is not well articulated, even within the United States. The result is that commercial development of engineered tissue therapies may be determined as much by tissue access and regulatory approval pathway as by clinical outcome.

- The pace and direction of the development and clinical introduction of engineered tissue products can be affected by many federal agencies.
A general disengagement of the biomedical community from the policy-making processes of these agencies can deprive them of an important perspective on proposed actions.

As the U.S. FDA evolves its strategy for managing engineered tissue products, it should emphasize cross-Center consistency in product classification and product approval paradigms that respond to the particular attributes and challenges of products incorporating living human tissues. The FDA’s effort to develop a rational approach to the regulation of engineered tissue products is well begun; it should be continued and expanded globally through international harmonization programs.

REFERENCES


U.S. Food and Drug Administration Notice of Public Hearing: Products comprised of living autologous cells manipulated ex vivo and intended for implantation for structural repair or reconstruction (60 Federal Register 36808; July 18, 1995).


