CHAPTER 10

Tissue Engineering: Translating Science to Product

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Summary

Advances in engineering and life sciences over the last twenty years have led to therapies for replacing, repairing, restoring, or regenerating human tissue and organ function. While a number of determinants are critical to translating science into products, the procedures of government entities for regulatory oversight is key. This discussion considers strategies in the US, where the responsibility for overseeing commercial development of such therapies within the US federal government is divided among different regulatory bodies. Most, if not all, engineered tissues and regenerative medicine products are regulated by the FDA, a science-based agency in the US Public Health Service (PHS), which has legislative authority for premarket approval, and post-market surveillance and enforcement for a wide range of products in its regulatory preview. Evaluation of products is conducted on a case-by-case basis, and the FDA has adopted a cooperative approach across the appropriate FDA Centers in developing regulatory strategies for engineered tissue and regenerative medicine products. For those products requiring premarket review, the assessments of safety and effectiveness and the manufacturer's claim of intended use constitute the basic elements of the evaluation. Postmarket studies may be necessary when all issues of product safety and effectiveness cannot reasonably be determined during premarket clinical studies.

KEYWORDS: FDA product regulatory process and considerations for tissue-engineered products, Product classification/designation, FDA approved tissue-engineered products, Challenges from science to product, Key steps in commercialization strategy

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INTRODUCTION

Therapeutic approaches for replacement, repair, restoration, or regeneration of diseased or damaged human organs or tissues have evolved over the last several years from human donor organ and tissue transplants and implants of synthetic materials to *in vitro* engineered tissue constructs. Such constructs can be composed of autologous, allogeneic, or xenogeneic cells coupled with synthetic or natural matrix materials, and/or pharmacological agents for either *in vivo* implantation or *ex vivo* use as well as cell therapies using either native, stem, or progenitor autologous or allogeneic cells for *in vivo* delivery. While organ/tissue transplantation and synthetic material implants continue as the standard of care in most cases, donor organ shortages and indications where such approaches may not be feasible have led to a search for alternatives utilizing living tissue, which, in turn, has provided the impetus for engineered tissue solutions.

Engineered tissues can provide either a structural/mechanical or metabolic function.[1,2] Examples, published in the scientific literature, include, among others: artificial skin constructs; musculoskeletal applications, such as autologous cells for cartilage regeneration, engineered ligament and tendon, and bone graft substitutes; approaches for repair and regeneration of the cardiovascular system including the myocardium, valves, and vessels; periodontal tissue repair; engineered cornea and lens; spinal cord repair and nerve regeneration; repair of the urogenital system; and approaches for functional restoration of vital metabolic organs such as the pancreas, liver, and kidney through either biohybrid organ implants or *ex vivo* support systems. The goal is to recapitulate certain features of normal development in order to stimulate cellular differentiation and organization into functional tissue assembly.[3]

The promise of engineered tissue therapies has been realized.[4,5] Skin and musculoskeletal substitutes have been approved for use in the US by the Food and Drug Administration (FDA). Other applications cited above are under either preclinical investigation or regulatory evaluation. Recent advances in stem cell and cytokine biology, materials science, bioreactor technology, engineering, and computer-assisted modeling and design, among others, are contributing to development of second-generation engineered tissue therapies.

In addition to therapeutic applications, *in vitro* engineered tissue constructs are being applied as biosensors in diagnostic systems and as test models for toxicity assessment of pharmacological and other agents. Development of enabling technologies provides promising avenues for establishment of a service industry, e.g., cell banks/repositories, scaffold/matrix

materials and reference material libraries, and customized tissue-specific bioreactors. Engineered tissue constructs can also be utilized as physiologically relevant, controllable *in vitro* models to address basic science issues such as the factors and mechanisms associated with tissue development and function.[6]

Thus, the interdisciplinary field of tissue engineering, which has evolved since the late 1980's, can be envisioned as a process, "among others", by which regenerative medicine products are developed to support the practice of medicine.[7] While there is no generally accepted definition of regenerative medicine, nevertheless, it can be described as the utilization of biomolecules, cells, and materials, individually or in combination, to recapitulate or "restore" the functional architecture of an individual's diseased, "damaged", malformed, or deficient tissue or organ.[8] The National Institutes of Health (NIH) utilizes the following definition to code grants, contracts and research conducted at the NIH in this area (Wang, F., Sipe, J., and Kelley, C., in press). Regenerative medicine/tissue engineering is a rapidly growing multidisciplinary field involving the life, physical and engineering sciences that seeks to develop functional cell, tissue and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or aging. It includes both the regeneration of tissues *in vitro* for subsequent implantation *in vivo* as well as regeneration directly *in vivo*. In addition to having a therapeutic application, tissue engineering can have diagnostic application where the engineered tissue is used as a biosensor. Engineered tissue can also be used for the development of drugs including screening for novel drug candidates, identifying novel genes as drug targets, and testing for drug metabolism, uptake, and toxicity.

Integrity of the science, together with other key determinants, is basic to the successful translation of research in tissue engineering and regenerative medicine into products for the clinic and marketplace (Figure 1). Of these determinants, understanding the strategies developed by government entities for providing appropriate product regulatory oversight is key. Since a primary goal is the establishment of a global industry enabling companies to market products across national boundaries, a harmonized international regulatory approach, such as the International Conference on Harmonization for pharmaceutical products, would be ideal. However, while different national and international groups work toward that goal, and recognizing that the public's perception and subsequent market acceptance can be influenced by local social, political, legal, and ethical concerns, it is important to understand the approaches of

regulatory entities where the research has moved successfully through product development to the marketplace.[10] Although the science is now worldwide and regulatory approaches are being developed in Europe and the Far East, among others, this discussion will be limited to the regulatory strategies and evolving initiatives in the US.

The FDA has recognized that an important segment of the products that it regulates results from applications of novel technology such as tissue engineering, cell therapy, and other regenerative medicine approaches and that ensuing products often pose new and complex issues. Thus, the Agency has worked since the early 1990's on developing appropriate strategies for the regulatory oversight of human cells, tissues, and cellular- and tissue-based products. To date, most, if not all, engineered tissues and regenerative medicine products fall into these categories.

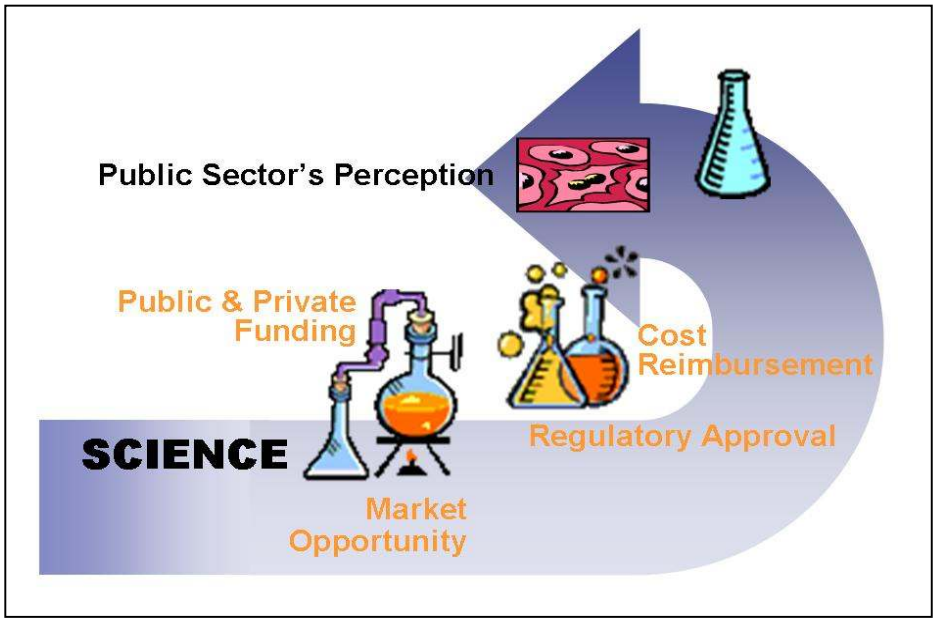

Figure 1. Key Determinants for Translating Science to Products

U.S. FEDERAL GOVERNMENT

LEGISLATIVE AUTHORITY

Laws

Since approaches for organ and tissue replacement, repair, restoration, and regeneration and their source materials span a broad spectrum of potential clinical applications, the responsibility for overseeing their development and commercialization within the US federal government has been

divided among different regulatory agencies, centers, and offices. The Health Resources Services Administration (HRSA) oversees the National Organ Transplant Program and the National Marrow Donor Program. The remaining products are regulated by the FDA.

The FDA is a science-based regulatory agency in the US Public Health Service (PHS). The agency's legislative authority for product oversight, premarket approval, and post market surveillance and enforcement is derived principally from the Federal Food, Drug, and Cosmetic (FD&C) Act and the Public Health Service (PHS) Act. Under these authorities, the FDA evaluates and approves products for the marketplace, inspects manufacturing facilities sometimes before and routinely during commercial distribution, and takes corrective action to remove products from commerce when they are unsafe, misbranded, or adulterated.

FDA Mission and Organization

The FDA's mission is to promote and protect the public health through regulation of a broad range of products by assuring the safety of foods, cosmetics, and radiation-emitting electronic products, as well as assuring the safety and effectiveness of human and veterinary pharmaceuticals, biologicals, and medical devices. The FDA's six centers are staffed with individuals expert in the science and regulations(s) appropriate to a center's mission. The centers with regulatory oversight for human medical products are the: Center for Drug Evaluation and Research (CDER) which regulates drugs; Center for Biologics Evaluation and Research (CBER) which regulates biological products; and the Center for Devices and Radiological Health (CDRH) which regulates medical devices and radiation-emitting electronic products. However, each center can apply any of the statutory authorities to regulate its products. For example, many products reviewed by CBER are regulated under the medical device authority. In addition to the centers, other offices such as the Office of Regulatory Affairs (ORA) and Office of Orphan Products (OOP), provide assistance to the centers on regulatory procedures and facility inspections, when necessary. The Office of Combination Products (OCP) is responsible for the regulatory oversight of combination products. While the office does not perform product reviews for market approval or clearance, it assigns the combination product to the appropriate FDA center, ensures timely and effective premarket review and appropriate post market regulation, and serves as a resource to industry and the FDA centers' review staff.[4,10] The OCP serves a very important function for regulation of engineered tissue and regenerative medicine products,

since many are combination products.

PRODUCT REGULATORY PROCESS

Product Classification

Under federal law, a human medical product is classified as either a drug, biological drug (biologic), device, or combination product, e.g. a combination of a drug, biologic, and/or device. The product's classification determines the premarket regulatory review and approval process for demonstration of safety and effectiveness utilized by FDA, and the FDA center with lead responsibility and jurisdiction for the product. For example, a drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals, and an article (other than food) and other articles intended to affect the structure or any function of the body of humans or other animals [21USC321(g)]. A biologic is defined as a 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 of man [42USC262(a)]. A device is an instrument, apparatus, . . . implant, *in vitro* reagent or other similar or related article which is intended for use in diagnosis of disease or conditions, or in the cure, mitigation, treatment or prevention of disease, in humans or other animals, or intended to affect the structure or any function of the body . . . and which does not achieve any of its principal intended purposes through chemical action within or on the body . . . , and which is not dependent on being metabolized for the achievement of any of its principal intended purposes [21USC201(h)].

On October 1, 2003, FDA transferred certain product oversight responsibilities from CBER to CDER. The consolidation was designed to provide greater opportunities for further development and coordination of scientific and regulatory activities between CBER and CDER, leading to a more efficient, effective, and consistent review program for human drugs and biologics. Under the new structure, the biologic products transferred to CDER will continue to be regulated as licensed biologics, The biologic products now under CDER's review include: monoclonal antibodies for *in vivo* use; cytokines, growth factors, enzymes, immunomodulators, and thrombolytics; proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and other non-invasive immunotherapies.

Combination Products

Advances in biomedical science over the last several years have generated products not readily classifiable as drugs, biologics, or devices as these terms are defined by federal law. As a result, the FDA has been authorized to recognize combination products in order to provide for the expanding varieties of products expressing features of more than one of these classifications. These products constitute a growing category of innovative medical approaches. Examples include a drug with an implantable delivery device, autologous tissues or cells coupled with a scaffold for wound healing or orthopedic use, and drug-eluting cardiovascular stents. While these products contribute to advancing medical care, they also pose a challenge for FDA, since they straddle existing statutory classifications of regulated products, complicating the determination of the appropriate regulatory process.[10]

Congress recognized the existence of combination products when it enacted the Safe Medical Device Act of 1990 and established that the FDA shall classify a combination product according to its primary mode of action [Section 503(g) of the FD&C Act [21USC 353(g)]. From its determination of the product's primary mode of action, the Agency could assign jurisdiction over the product to one of its established centers. For example, if the primary mode of action is that of a drug, the product is assigned to CDER, if that of a device to CDRH, and biologics to CBER. The FDA issued a final rule in 1991 establishing the process, i.e., Request for Designation (RFD), by which a product sponsor could petition the agency to make such an assignment [21CFR3.7] (Figure 2).

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) modified Section 503(g) of the FD&C Act to require the FDA to establish an office with the primary responsibility for providing regulatory oversight of combination products. The Office of Combination Products in the Office of the Commissioner assigns the product to the appropriate FDA center; resolves any disputes over a product's regulation, and is the focal point for both the FDA staff and industry regarding combination products.

There has been much progress since the office was established in making this complex regulatory area more efficient, transparent, and better understood. Because of its role, the office has become the focus and, often, the primary point of entry for sponsors of combination products, as well as single entity-products. The office encourages informal as well as formal

interactions; i.e., through the RFD process, with sponsors regarding product jurisdictional questions.

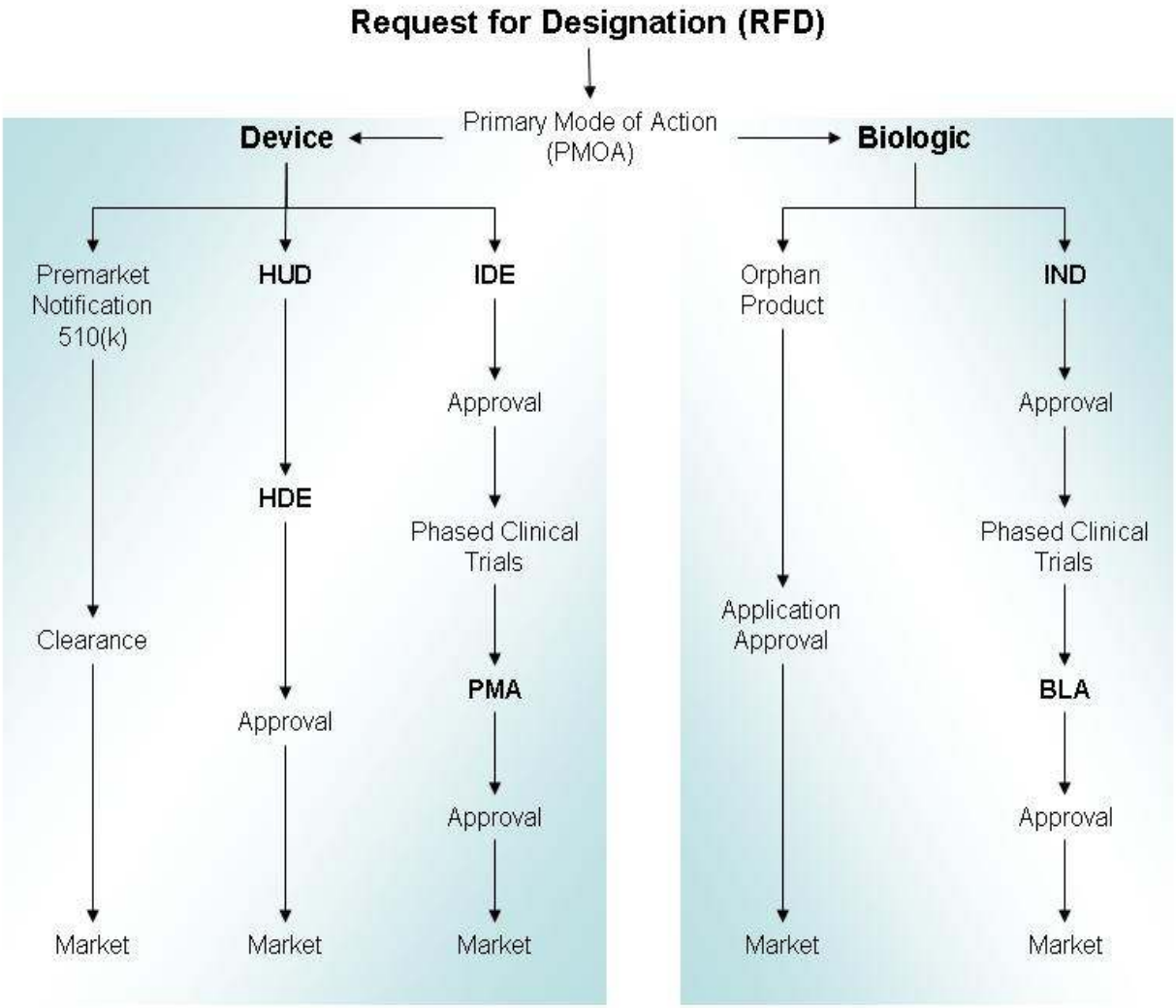

Figure 2. Regulatory Process for Combination Products.

Although the FDA has traditionally required sponsors of a RFD to identify the product's primary mode of action and recommend the lead center for product premarket review and regulation, there has been no statutory definition of what constitutes primary mode of action to guide sponsor in this determination. To address concerns that, without a statutory codified definition, the assignment process has appeared arbitrary at times, the office published a proposed rule to amend the regulations and to define and codify both mode of action and primary mode of action, "Definition of Primary Mode of Action of a Combination Product: Proposed

Rule" (69FR25527, May 7, 2004) (the PMOA Proposed Rule). Almost all comments received from the stakeholder community supported the Proposed Rule. The Final Rule was published on August 25, 2005 (70FR 49848-49862). Mode of action is defined as the means by which a product achieves its intended therapeutic effect, i.e., drug, biologic, or device mode of action. Since combination products have more than one identifiable mode of action, the primary mode of action is the single mode that provides the most important therapeutic action of the combination product. The most important therapeutic action is that mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. The Final Rule also describes an algorithm that the agency will use to assign a product to a center when it cannot determine with reasonable certainty which mode of action provides the most important therapeutic effect. The Final Rule requires a sponsor to base its recommendation of the center with primary jurisdiction for its product by using the definition and, if appropriate, the assignment algorithm. This framework is based on: assessment of the product as a whole; its intended use and effect; consistency with assignment of similarly situated products; and safety and effectiveness issues.[11]

Moreover, the assignment of certain single-entity products often may not be readily apparent because of the incorporation of novel technology or other features. Therefore, it is important for product sponsors to understand and demonstrate the product's underlying mode ("mechanism") of action, i.e., does it "act like" and meet the statutory definition of a drug, biologic, or device.

To assist product sponsors in determining the classification and subsequent regulatory jurisdiction of their combination product, the OCP publishes jurisdictional updates of decisions rendered on selected classes of products. The OCP selects product classes to be subjects of jurisdictional updates based on its perception of the current level of interest in the jurisdictional issue, the extent to which the class of products can be clearly described, and the extent to which the existence and description of the class of products has been made public, and other related factors.

PRODUCT PREMARKET SUBMISSIONS

Understanding the requirements behind the FDA's approval process for a given product is important for sponsors in their development of a comprehensive product development plan and

strategies leading from discovery science and conceptual studies to the clinic and market. Strategies should include appropriate and meaningful investigational (pre-clinical and clinical) studies to demonstrate safety and effectiveness as well as efficient scale-up and manufacturing processes that result in a product of given specifications in a reproducible and consistent manner. A sponsor should develop such strategies very early in the product development process, i.e., following proof-of-concept studies from their research, in order to save time, control costs, and maximize efficiency of the entire process.

Investigational Studies

The FD&C Act requires demonstration of safety and effectiveness for new drugs and devices prior to introduction into interstate commerce. The PHS Act requires demonstration of safety, purity, and potency for biological products before introduction into interstate commerce. Consequently, premarket clinical studies must be performed under exemptions from these laws. For drugs and biologics, which are considered drugs under the FD&C Act, the application for the exemption is an Investigational New Drug (IND) application (21CFR312). The application for exemption of a device is an Investigational Device Exemption (IDE) (21CFR812).

The contents of IND and IDE applications are similar.[2] Applications will include a description of the product and manufacturing processes sufficient for an evaluation of product safety, and preclinical studies that have been designed to assess the product's risks and potential benefits. The IND and IDE applications contain a proposal for a clinical protocol, which describes the indication being treated, proposed patient population, patient inclusion and exclusion criteria, treatment regimen, study end points, patient follow-up methods, and clinical trial stopping rules. Both IND and IDE investigations require Institutional Review Board (IRB) approval before they may commence. Although IND and IDE requirements are somewhat different (e.g., in cost recovery and device risk assessment areas), the FDA applies comparable standards of safety and effectiveness for either type of application. When the FDA determines that there is sufficient information to allow a clinical investigation to proceed, the IND or IDE exemptions are approved.

The first clinical studies conducted under the IND or IDE applications are often clinical trials involving a small number of individuals (e.g., phase 1/feasibility studies) designed primarily to assess product safety. If these earlier studies indicate reasonable safety, phase 2

studies may be developed to investigate proper and safe dosing and potential efficacy. Phase 3/pivotal studies utilize well-controlled clinical trial designs that support a determination of safety and effectiveness and lead to an application to the FDA for premarket approval of the product.

There may be situations in which the first study under an IND or IDE will not be a phase1/feasibility study.[2] For example, this may occur when there is sufficient clinical experience to establish the safety of a product after use outside the US or in a different patient population. The FDA may review data from clinical studies performed outside the US in the IND/IDE process and/or in an application for marketing approval. The agency strongly recommends that the sponsor meets with FDA staff to discuss the clinical protocol, study results, statistical analyses, and applicability of the data to a US population before submitting the premarket submission, i.e. Biologics License or Premarket Approval application (BLA/PMA).

The importance of appropriate preclinical studies and commensurate investment in research and development to success in achieving product approval for market cannot be over-emphasized. *In vitro* bench studies and *in vivo* models designed to elucidate and demonstrate the product's mechanism of action have a direct bearing on the determination of a product's mode of action or primary mode of action of a combination product and whether the product meets the statutory definition of a drug, biologic, or device and, thus, determination of the appropriate regulatory path.

Potential benefits of appropriate investment in the pre-clinical development program may include: more rapid progress through phase 1 clinical trials; improved patient selection criteria that may result in enhanced response rates and/or fewer adverse events; clinical trial designs that provide statistically relevant data with fewer patients or over a shorter time period, and enhanced understanding of the incorporation of novel therapies into the current standard of care.[12]

Premarket Submissions

According to the laws and regulations governing commercial distribution of human medical products, there are several different types of product premarket submissions determined by the product's FDA classification. In general, the type of submission will depend on the type of product; i.e., drug, biologic or device.

Engineered tissue products, cell therapies, and other regenerative medicine products regulated as biologics will require review and approval of a BLA that demonstrates the safety and effectiveness of the product before it may be marketed commercially. If it is regulated as a device, a PMA demonstrating safety and effectiveness must be approved, or a premarket notification [510(k)] must receive clearance. In order to obtain 510(k) premarket clearance, the sponsor must demonstrate substantial equivalence of the device to a legally marketed predicate device.

Special Product Designations and Submissions

The FD& C Act recognized that there may be situations where the demand for new medical products may be such that the cost of obtaining marketing approval for a product may be prohibitive in view of the small size of the intended population.[10] To reduce the possibility that a cost-benefit analysis applied to product development for rare diseases will result in no available therapy, the FDA is authorized to grant special consideration and exceptions to reduce the economic burdens on developers of products under such conditions. As a result, the FDA may be petitioned to grant a Humanitarian Device Exemption (HDE) for certain devices (FD&C Act, 520m) or to recognize certain drugs or biologics as orphan drugs (FD&C Act, 525, et. seq.)

A Humanitarian Use Device (HUD) is a product that may be marketed under an exemption for treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals per year in the US. A HDE exempts a HUD from the effectiveness requirements for devices if certain criteria are met (FD&C Act, 529(m)(1), as amended February 1998). Several engineered skin constructs have been approved for market under the HUD designation.

Orphan drugs are those intended to treat a disease or condition affecting fewer than 200,000 individuals in the US for which there is little likelihood that the cost of developing and distributing it in the US will be recovered from sales of the drug in the US. The orphan drug designation was established through an amendment to the FD&C Act by the 1982 Orphan Drug Act. An orphan drug is defined to include biologics licensed under Section 351 of the PHS Act. Under certain conditions, the FDA has authority to grant marketing exclusivity for an orphan drug in the US for a period of seven years from the date the drug is approved for clinical use. Other benefits to sponsors include: grant support for clinical trials; tax credits for clinical

research expenses; and waiver of the prescription drug filing fee.[10] A sponsor must file a petition for orphan drug designation before any application for marketing approval.

Post Market Surveillance

Post market surveillance for therapeutic engineered tissues and other products of regenerative medicine is an important area of consideration. Manufacturers, user facilities, and health care professionals should report adverse events through the FDA MedWatch process. Post marketing studies may be necessary when: a sponsor seeks a change in product labeling; studies are a condition of the FDA approval; or such studies are necessary to protect the public health or to provide safety and effectiveness data.[2] Additionally, post market surveillance of a device introduced into interstate commerce after January 1, 1991, may be required if it is: intended for use in supporting or sustaining human life; presents a potential risk to human health; or is a permanent implant, whose failure may cause serious, adverse health consequences or death (Section 522, FD&C Act).

REVIEW OF PRODUCT PREMARKET SUBMISSIONS

Advances in tissue engineering and regenerative medicine research have led to potential therapeutic products for many different medical conditions characterized by organ and/or tissue damage. As indicated, the products may provide either a structural/mechanical or metabolic function. To date, products have been developed either as *in vitro* engineered tissue constructs for implantation, cell therapies for *in vivo* delivery, or *ex vivo* systems. Representatives of these products are in different stages of development. First generation products targeted to skin and the musculoskeletal system have been approved for use in the US (Table 1), while many others are under either preclinical investigation or regulatory evaluation.

Since many of the products may consist of more than one component, i.e., biomolecule, cell/tissue, and/or biomaterial, they are considered combination products. A determination of the product's primary mode of action dictates the jurisdictional authority for the product and the primary reviewing center, i.e., CDER, CBER, or CDRH. However, regardless of the product's designation, review of any regulated product considers four basic elements, i.e., product manufacture, preclinical (laboratory and animal model) testing, clinical performance, and

product labeling in order to determine safety and effectiveness in support of the manufacturer's claim of intended use.

Table 1. FDA-Approved Human Cellular- and Tissue-Based Products (HCT/Ps)

Skin Applications			
Product	**Sponsor**	**Intended Use**	**Approval**
Apligraf (Viable Allogeneic Fibroblasts/ Keratinocytes On Type-1 Bovine Collagen)	Organogenesis Inc.	Standard therapeutic compression for treatment of non-infected partial and full-thickness skin ulcers	1998-Device (PMA)
Dermagraft (Cryopreserved Dermal Substitute; Allogeneic Fibroblasts, Extracellular Matrix, Bioabsorbable Scaffold)	Advanced Tissue Sciences, Inc.	Treatment of full-thickness diabetic foot ulcers	2001-Device (PMA)
Composite Cultured Skin (Viable Allogeneic Fibroblasts/ Keratinocytes On Collagen Matrix)	Ortec International, Inc.	Adjunct to standard autograft procedures for covering wounds and donor sites after surgical release of hand contractions in Recessive Dystrophic Epidermolysis Bullosa patients	2001-Device (HDE)
Dermagraft (Cryopreserved Dermal Substitute; Allogeneic Fibroblasts, Extracellular Matrix, Bioabsorbable Scaffold)	Smith and Nephew Wound Management	Treatment of wounds related to Recessive Dystrophic Epidermolysis Bullosa	2003-Device (HDE)

Musculoskeletal Applications			
Product	**Sponsor**	**Intended Use**	**Approval**
Carticel (Autologous Cultured Chondrocytes)	Genzyme Corporation	Repair of femoral condyle caused by acute or repetitive fracture	1997-Biologic (BLA)
OP-1 Implant (Recombinant Human Osteogenic Protein (rh OP-1), Type-1 Bovine Bone Collagen Matrix)	Stryker Biotech	Alternative to autograft in recalcitrant long bone non-unions	2002-Device (PMA)
InFUSE Bone Graft/ LT-Cage Lumbar Tapered Fusion Device (Recombinant Human Bone Morphogenetic Protein-2, Type-1 Bovine Bone Collagen, Titanium Alloy Cage)	Medtronic	Spinal fusion for degenerative disc disease	2002-Device (PMA)

OP-1 Putty (Recombinant Human Osteogenic Protein (rh OP-1), Type-1 Bovine Bone Collagen Matrix, Putty Additive – Carboxymethyl Cellulose Sodium)	Stryker Biotech	Alternative to autograft in compromised patients requiring revision posterolateral lumbar spinal fusion for whom autologous bone and bone marrow-harvest are not feasible or expected to promote fusion	2004-Device (HDE)
GEM 21S™ (Growth Factor Enhanced Matrix) (Recombinant Human Platelet Derived Growth Factor, Synthetic Beta Tricalcium Phosphate)	Biomimetic, Pharmaceuticals, Inc.	Treatment for periodontally-related defects: intrabony defects; furcation defects; gingival recession associated with periodontal defects.	2005-Device (PMA)

Regulatory evaluation is conducted on a case-by-case basis and, the sponsor is responsible for providing evidence of the product's safety and effectiveness. As indicated, product safety and effectiveness are evaluated with respect to the product's manufacture and clinical performance, as applicable, as well as the manufacturer's claim of intended use, i.e., the patient population to be treated and the product's role in the diagnosis, prevention, monitoring, treatment, or cure of a disease or condition. For engineered tissue and regenerative medicine products as well as other human medical products, issues of product manufacture include, among others: cell/tissue, biomaterial, and/or biomolecule sourcing, processing, and characterization; detection and avoidance of adventitious agents; product consistency and stability; as well as quality control/quality assurance procedures. Other important considerations include evaluation of the preclinical data, e.g., toxicity and immunogenicity testing for local/systemic and acute/chronic responses, as well as assessment of *in vivo* remodeling. Collecting data on product performance in humans requires insight into clinical trial design, e.g., patient entry criteria, assessment criteria and study endpoints, study conduct, and subsequent data analyses.

At the request of the sponsor of a new drug or biologic, the FDA will facilitate the development and expedite the review of such a drug or biologic if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. The development program for such a drug or biologic is designated a fast-track development program and may apply special procedures such as

accelerated approval based on surrogate end points, submission and review of portions of an application, and priority review to facilitate its development and expedite its review.[2]

For devices, PMAs, PMA Supplements, and 510(k) applications may also undergo expedited review.[2] In general, applications dealing with the treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions may be candidates for expedited review if: the device represents a clear, clinically meaningful advantage over existing technology; the device is a diagnostic or therapeutic modality for which no approved alternative exists; the device offers a significant advantage over existing approved alternatives or; availability of the device is in the best interests of patients. Granted expedited review status means that the marketing application will receive priority review before other applications. When multiple applications for the same type of device have also been granted expedited review, the applications will be reviewed with the priority according to their respective submission due dates.

HUMAN CELLS, TISSUES, AND CELLULAR- AND TISSUE-BASED PRODUCTS

With the recognition that an important segment of the products that it regulates often arises from applications of new technology, such as those of tissue engineering and regenerative medicine approaches, and that the product applications may pose unique and complex questions, the FDA has devoted considerable resources since the early 1990's to the regulatory considerations of what have been termed human cellular-and tissue-based products (HCT/Ps). In February 1997, the FDA proposed a comprehensive tier-based approach for regulation of these products with the level of product review proportional to the degree of risk. On May 25, 2005, the final piece of this regulatory framework was put in place when the Current Good Tissue Practice for Human Cell, Tissues, and Cellular-and Tissue-Based Product Establishments: Final Rule (the CGTP Rule) became effective.[10,13] Two earlier final rules, one providing for establishment registration and the other establishing processes for donor screening had already set out significant portions of this framework. Publication of the CGTP Rule completed the set of regulations proposed in 1997 and issued in proposed or interim form since 2001 to implement the FDA's framework for regulation of HCT/Ps.

Defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient, HCT/Ps include: skin;

musculoskeletal tissue (bone and ligaments); ocular tissue (especially cornea); heart valve allografts; dura mater; hematopoietic stem and progenitor cells derived from peripheral and cord blood; reproductive tissue; cellular therapies; and combination products consisting of cells/tissue with a device and/or drug (such as cells on a natural or synthetic matrix).

The agency recognized the need for regulatory oversight of these products in the late 1980s and early 1990's because of a number of concerns. First, documented evidence of communicable disease transmission to recipients from infected donor tissue presented a primary public health concern. Second, the rapid growth of the industry with development of new applications and technologies for processing human cells and tissues, coupled with increased demand and international commerce presented different issues. Finally, voluntary standards established by certain organizations had not been followed uniformly, since they are not legally enforceable. These factors, together with public demand for safe products, compelled the agency to effect appropriate solutions.

The tenets of the tiered risk-based approach initially outlined by the agency have been maintained in the CGTP Rule. Essentially, products meeting certain criteria, so-called "kick-down" factors, would be regulated solely under provisions of Section 361 of the US PHS Act (361 Products) and would not be required to undergo premarket review. All others not meeting the kick-down factors would be regulated under existing drug, biologics, and device regulations, in addition to the new regulations addressing the incorporation of living biological materials into the finished product (Figure 3).

The kick-down factors include: minimal manipulation of the source tissue through the processing stage; homologous use; freedom from combination with another article, except a sterilizing, preserving, or storage agent, water, and crystalloids; and absence of intended systemic effect or dependence upon the metabolic activity of living cells (except in cases of autologous use, use in first or second degree blood relatives, or reproductive use). Those HCT/Ps not meeting these criteria would be regulated under the FD&C Act as drugs, biologics, or devices. The risk-based approach is tiered, i.e., stratified, to provide the appropriate type and level of regulation based on a product's characteristics, with a platform of minimal requirements for all cells and tissues and additional requirements when necessary for product safety and effectiveness.

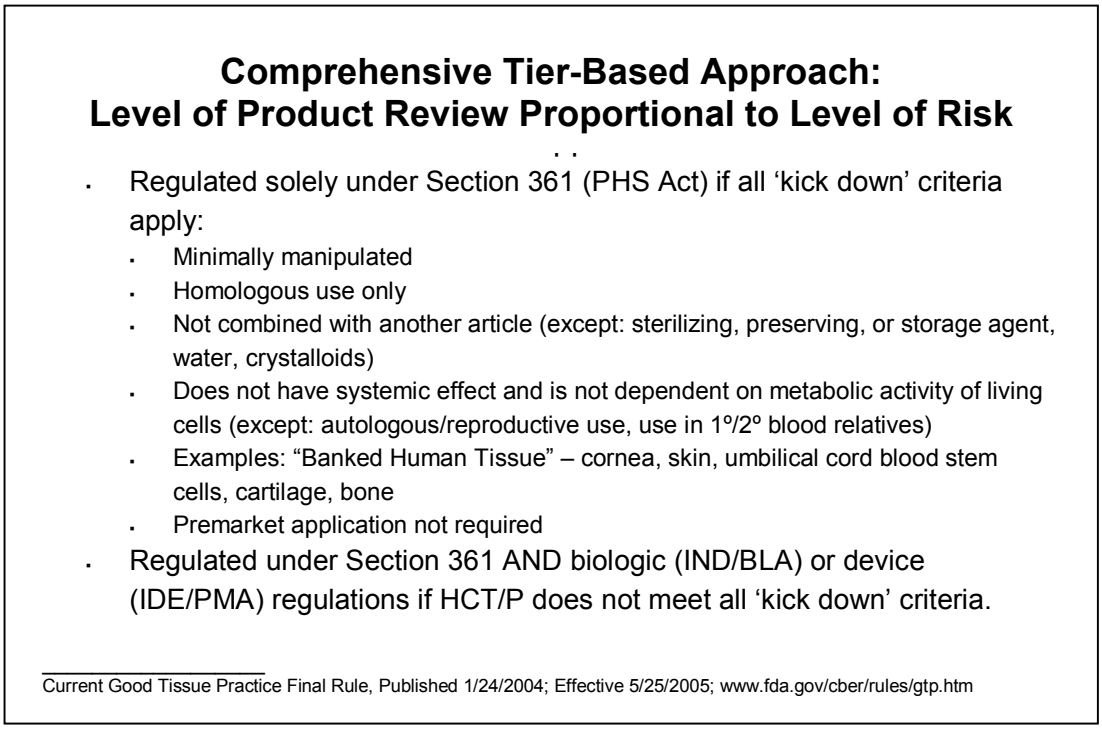

Figure 3. FDA Regulatory Framework for Cells, Tissues, and Human Cellular and Tissue-Based Products.

The FDA's OCP has received several RFD's requesting a determination of whether or not certain HCT/Ps will be regulated solely as 361 Products based on the manipulation the product undergoes during processing. As a result, on September 20, 2006, OCP and CBER jointly issued "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update" (http://www.fda.gov/cber/gdlns/minimaljur.htm) to improve the transparency of FDA's jurisdictional determination by providing additional information about classification and assignment of HCT/Ps regulated as 361 Products. The guidance discusses FDA's current thinking on the meaning of the term "minimally manipulated" as it applies to structural tissue.

The CGTP rule defines minimal manipulation for structural tissue as "processing that does not alter original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. A tissue characteristic is "original" if it is present in the tissue in the donor and is "relevant" if it could have meaningful bearing on how the tissue performs when utilized for reconstruction, repair, or replacement. A characteristic of structural tissue would be relevant when it could potentially increase or decrease the utility of the original

tissue. In addition, all the potential positive and negative effects of altering a particular characteristic of the tissue on its subsequent utility, i.e., changing the characteristic, could improve or diminish the tissue's utility. Once FDA determines, based on review of the information and data submitted, that processing has altered an original characteristic of a structural tissue, and that the characteristic is relevant, the agency considers the tissue to be more than minimally manipulated and not eligible for regulation solely as a 361 Product. In such a case, the structural tissues would be regulated as a drug, device, or biological product under the FD&C Act and/or Section 351 of the PHS Act.

The FDA Tissue Reference Group (TRG) with representatives from CBER, CDRH, Office of Chief Counsel, and OCP make initial recommendations on several issues pertaining to HCT/Ps, including whether a product may be regulated solely as a 361 Product. The TRG's recommendations may be appealed through the RFD process B21CFR(Part 3).

The CGTP requirements cover all aspects of production, including: cell and tissue recovery; donor screening and testing; processing and process controls; supplies and reagents; equipment and facilities; environmental and labeling controls; storage conditions; product receipt; predistribution shipment and distribution; advertisement and deviation reporting; and tracking form donor to product consignee. Each establishment of the affected industry must develop and maintain a quality program covering all these requirements and take measures to report and track any product-related adverse event. The CGTP Rule also grants additional provisions to the FDA, including inspection authority, control of imports, and enforcement authority.

Two recently identified cases of serious violations of safety requirements pertaining to tissue recovery prompted the agency to take actions to stop the operations. In addition, FDA published a guidance on September 13, 2006 intended to ensure that companies involved in any or all steps in recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and screening or testing of cell or tissue donors are aware of their regulatory responsibilities, and that FDA will act as needed to ensure that tissue establishments are in full compliance with the applicable requirements. In addition, if a manufacturer enters into a contract, agreement, or other arrangement with another establishment to perform any steps in the manufacturing process, the manufacturer must ensure that such an establishment also complies with applicable CGT/Ps.

In addition, on August 30, 2006, FDA announced the establishment of the Task Force on Human Tissue Safety as part of the agency's efforts to strengthen its regulation of HCT/Ps. Led by senior FDA staff, the Task Force's main priority is to assess the effectiveness of implementation of the CGT/Ps and to identify whether any additional steps are needed to further protect public health while assuring the availability of safe products. The Task Force will continue to work with professional and trade associations to support their ongoing efforts to assure quality oversight of manufacturing operations and product safety. Charged with developing an action plan and, where necessary, propose changes to existing policies, the Task Force will generate recommendations and report on how the agency can immediately implement its action plan.

Thus, predictable regulatory requirements serve to support innovation in technology and the industry and to minimize elements of uncertainty in the product development process. Since many, if not all, engineered tissues and regenerative medicine products will be, most likely, human cell or tissue-based and/or combination products, the CGTP Rule, PMOA Final Rule, and recent guidances, serve to clarify the regulatory requirements for such products and to demonstrate the FDA's commitment for facilitating the development process for these products while, at the same time, maintaining the public confidence in safe, effective medical products for the marketplace.

SCIENCE INVESTMENT AND PRODUCT DEVELOPMENT

Federal investment in basic biomedical science is expected to lead to an overall improvement in public health. However, as observed and reported by the FDA in its March 2004 report, "Challenges and Opportunity on the Critical Path to New Medical Products" (Critical Path Report) that expectation is not being fulfilled, and there is a discontinuity from basic research to application.[14]

Data, based on ten-year trends showed that, while there has been an increase in research spending by federal government agencies, such as the National Institutes of Health, and industry, there has been a concomitant decrease in major drug and biological product submissions to the FDA. This is also true for devices, although not to as great an extent.

The FDA's analysis of this pipeline problem has led to the conclusion that the current medical product development path is becoming increasingly challenging, inefficient, and costly. To address these concerns, the FDA launched the Critical Path Initiative to identify the most pressing obstacles in the path and in technology translation. With publication of the Critical Path Report, the FDA framed the challenge as the shortage of modern tools to enable effective and efficient assessment of the safety and effectiveness of new medical products. Since then, the FDA has worked with FDA staff and external stakeholders to identify the most important challenges and to create the Critical Path Opportunities List as an outline of its strategy to overcome them.

While a number of issues and opportunities have been identified, certain common themes have emerged. The primary concerns are: clinical trials and biomarker development. There is a need to improve clinical trials and outcomes assessment generally. Accelerating the development and regulatory acceptance of biomarkers or other surrogate markers is perceived as an approach for their use in characterizing the product as well as in measuring outcome(s) for both preclinical and clinical studies. Other areas identified include: bioinformatics; manufacturing and scale-up generally, i.e., moving from laboratory bench studies to a manufacturing process with appropriate system design controls to assure a consistently reproducible, stable product; and progress in evaluating products developed through tissue engineering approaches. In addition, development of therapies for specific at-risk populations, such as pediatrics, with better extrapolation methods and best practices in clinical trial design was felt to be especially important. It was noted that a key hurdle inhibiting innovation in tissue engineering is the difficulty in sufficiently characterizing the finished product to enable development of meaningful quality controls and product release specifications. For example, conventional techniques for evaluating cell characteristics cannot be applied to these products since they may also include matrix materials and other components. Consensus on how to assess engineered tissue products and ensure manufacturing consistency would provide developers the predictability needed to fulfill the technology's full potential.

The initiative will continue as a formal process for continued input from all stakeholders and will be helpful to those engaged in research on engineered tissues as well as regenerative medicine and ensuing product development. The FDA published the Critical Path Opportunities

List and the full Critical Path Opportunities Report on May 16, 2006 (http://www.fda.gov/oc/initiative/ criticalpath).[15]

An important contribution to one major goal of the Critical Path Initiative is publication by the agency on September 29, 2006 of "The Final Guidance: Quality Systems Approaches to Pharmaceutical Current Good Manufacturing Practices (CGMP) Regulation". The guidance incorporates a set of formalized practices and procedures to ensure the quality of human and veterinary drugs and human biological drug products during manufacturing and embraces the current requirements for ensuring manufacturing quality known as CGMP regulations. The guidance incorporates modern quality principles into FDA's approach to manufacturing and encourages industry adoption of new technological advances and integrated quality systems to help produce drugs and biologics more efficiently. The guidance is intended to provide manufacturers with the ability to make technology improvements more readily with appropriate regulatory oversight.

PERSPECTIVES AND FUTURE DIRECTIONS

Strategic investment in science, engineering, and allied disciplines is a critical determinant for advancing both basic and translational research in organ/tissue replacement, repair, restoration, and regeneration towards products for the clinic and marketplace. However, to achieve successful product commercialization and market penetration, research strategies must be based on sound market analysis and demonstrated clinical need and with a product development plan in place to attract the needed funding support from the financial communities and approval from product regulatory and reimbursement authorities. Understanding the product regulatory process and specific points to consider for engineered human cellular- and tissue-based engineered and regenerative medicine products will help companies in development of their overall commercialization strategy. Moreover, since low reimbursement rates can often be the single greatest impediment to product acceptance by end users in the healthcare environment, attention to cost recovery issues and their relationship to clinical and economic outcomes is equally important.[16] All these determinants are interdependent and must be considered by companies in developing a sound product development strategy and business plan, since uncertainties in any one determinant can have a profound effect on the entire commercialization pathway.

The challenges for the tissue engineering community are multifold. For example, sponsors should consider the important determinants in the product regulatory path such as: the nature of the product, its manufacture and classification, i.e., tissue or product, its mode (mechanism) of action or primary mode (mechanism) of action if a combination product, and overall therapeutic approach; and preclinical *in vitro* bench studies and small as well as large animal models and clinical strategies to assess safety and effectiveness, such as selection of appropriate outcome measures and assessment tools/methods. The sponsor's claim of intended use and whether the product will provide incremental or substantive therapeutic benefit compared to the standard of care will be important for end-user and market acceptance, and, ultimately, cost reimbursement. The time to clinic and market will be dependent on the product's classification and subsequent submission and review of sponsor-generated data. For example, an orphan drug or humanitarian use device will have a relatively shorter regulatory timeline than a product regulated under existing authorities as a drug, biologic, or device.

To advance the science and minimize the variables in engineered tissue and regenerative medicine systems, understanding the mechanisms and control processes in normal as well as diseased or damaged human organs and tissues will continue to be a necessary prerequisite for design of novel research strategies focused on applications for tissue repair, restoration, regeneration and replacement. In this context and to advance the science the following should continue to be examined: operative mechanisms in cell and developmental biology; interactions of engineered tissue constructs with the host and remodeling by the *in vivo* environment; and acute/chronic as well as local/systemic sequelae of either reparative or regenerative approaches through appropriate preclinical large animal and clinical monitoring studies. Progress in biomaterials science such as: the development of matrix materials, including biodegradable materials, customized for the cell(s) and application of interest; advances in manufacturing and scale-up techniques such as development of tissue-customized bioreactors designed to stimulate cultured tissue by developmentally relevant signals[3] and; process system design, as well as outcomes assessment tools such as non-invasive *in vivo* monitoring of implanted engineered tissues will be important for translating science to products.[5]

In general, more research should be targeted toward understanding the signals that regulate cell differentiation[3] and to utilizing cells with the appropriate cues to predictably form different types of functional tissue[17] *in vivo*. The NIH-sponsored "Workshop on Tissue

Engineering: The Next Generation," held May 2-4, 2005 articulated the challenges ahead and emphasized that inquiry into the understanding of fundamental biology associated with tissue regeneration is essential for the development of biomimetic approaches to controlling tissue formation, cell function, and differentiation using factors involved in normal tissue development and function.[3] Moreover, the scientific and technological gaps between developmental biology and tissue engineering[6] must be identified and addressed. It is envisioned that a quantitative, systems approach; modern methods for the analysis of cell behavior such as on-line imaging and molecular assays; and modeling of biological processes will, most likely, guide the overall effort in tissue engineering for the next decade.[6]

Adult stem cells have the potential to revolutionize research in tissue engineering and regenerative medicine systems because of their unique capacity to self-replicate and differentiate into different phenotypes. These cells have been harvested from different types of tissues, such as bone marrow, skeletal muscle, adipose, and placenta[18], and more recently, from amniotic fluid.[19] While adult stem cells from different tissue sources have been utilized in tissue engineering and there has been much progress in understanding and utilizing their tissue regenerative properties, many challenges remain before stem-cell based engineered tissue constructs will be available for therapeutic use. Among others, there is a need for greater understanding of stem cell biology at the molecular level and engineering advances in scaffold design with micro- and nano-scale technology. Maintaining the regenerative capacity of stem cells during *in vitro* amplification by utilizing culture conditions that more closely mimic cell-cell and cell-matrix interactions in the stem cell niche will, most likely, retain the proliferative and differentiation capacity of stem cells for longer periods of time. In addition, further insight into receptor ligand interactions will be helpful in directing fate decisions between self-renewal and differentiation along a specific lineage.[18]

Ultimately, the challenge for the tissue engineering and regenerative medicine community is to continue advances in the science while maintaining awareness of the product regulatory environment in the US and abroad and to be an active voice for articulating the important issues in order to maintain a productive dialogue with the regulatory agencies and consumers so that engineered tissues and regenerative medicine products find their proper place in the clinic and market. The FDA Liaison Meeting held on April 28, 2006 between representatives from recognized tissue engineering and regenerative medicine centers in the US

and Canada and FDA staff is such a dialogue. The meeting focused on sharing information on the scientific and regulatory issues of technology applications and development in the field.

CONCLUSION

The FDA's approach to regulation of human cellular- and tissue-based products and combination products as well as other evolving initiatives are indicative of the agency's commitment to providing the appropriate regulatory oversight for products generated from novel technology, such as tissue engineering and regenerative medicine approaches. It is expected that the FDA will continue to build on these initiatives and on the cooperative approaches across the appropriate FDA Centers and the Office of the Commissioner in its regulatory oversight so that: questions from manufacturers/sponsors are addressed early on in product development; product regulatory jurisdiction questions are addressed in a timely manner and; the product premarket review process becomes more transparent and simplified. This is especially important since the pursuit of new and different research directions focused on tissue and organ regeneration, such as the apparent shift toward the use of stem cell technology,[20] will lead to the development of new and different products, posing unique product-specific issues (Figure 4).

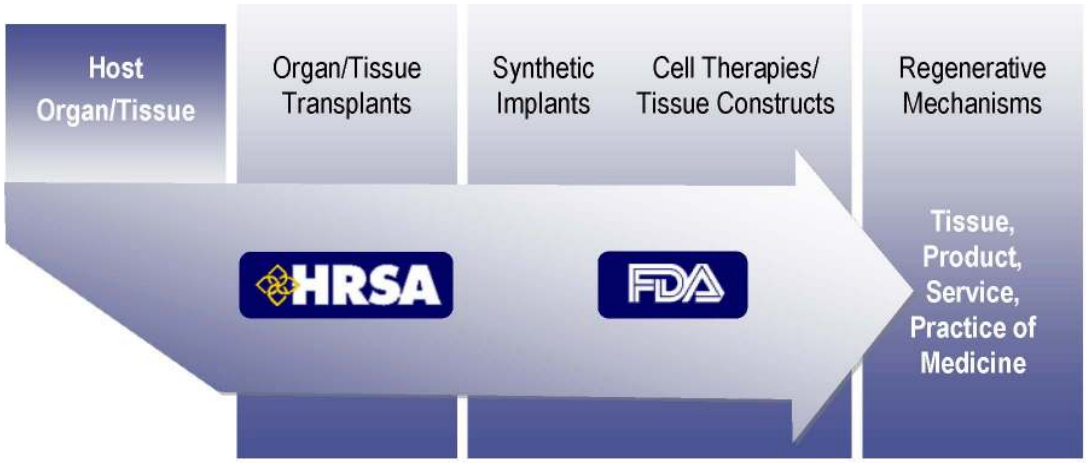

Figure 4. US Regulatory Oversight for Tissue Repair, Restoration, Replacement, or Regeneration: An Evolving Continuum.

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