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Original Article

Considerations for Tissue-Engineered and Regenerative Medicine Product Development Prior to Clinical Trials in the United States

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Tissue-engineered and regenerative medicine products are promising innovative therapies that can address unmet clinical needs. These products are often combinations of cells, scaffolds, and other factors and are complex in both structure and function. Their complexity introduces challenges for product developers to establish novel manufacturing and characterization techniques to ensure that these products are safe and effective prior to clinical trials in humans. Although there are only a few commercial products that are currently in the market, many more tissue-engineered and regenerative medicine products are under development. Therefore, it is the purpose of this article to help product developers in the early stages of product development by providing insight into the Food and Drug Administration (FDA) process and by highlighting some of the key scientific considerations that may be applicable to their products. We provide resources that are publically available from the FDA and others that are of potential interest. As the provided information is general in content, product developers should contact the FDA for feedback regarding their specific products. Also described are ways through which product developers can informally and formally interact with the FDA early in the development process to help in the efficient progression of products toward clinical trials.

Introduction

Tissue engineering has been defined as "the application of principles and methods of engineering and life sciences toward fundamental understanding of structure–function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue functions."[1] This field involves the development of substitutes for the repair or regeneration of tissue or organ function and has led to a broad range of technologies. Product development faces many scientific challenges and often is the result of multidisciplinary efforts, including a wide variety of approaches from physical and biological sciences and of people from bench scientists to clinicians. Of special importance to such innovative and complex products is the development of the knowledge database and of new techniques to ensure that they are safe for use in clinical trials to test clinical effectiveness. It is the intent of this article to provide an overview of the Food and Drug Administration (FDA) process and a general understanding of the scientific and regulatory considerations in the United States that are relevant in the development of tissue-engineered and regenerative medicine (TE/RM) products.

The criteria that the FDA uses to evaluate the safety and effectiveness of medical products can be found in publically available sources. There are statutes that are passed by the Congress and signed by the President (Food, Drug, and Cosmetic Act [FDCA],[2] Public Health Service Act [PHSA][3]), regulations that are written by the agency (Code of Federal Regulations [CFR][4]), guidances that are recommendations/guidelines from the agency's interpretation of the regulations, and voluntary standards from established standards organizations that the FDA recognizes. Statutes and regulations are legally binding requirements, whereas guidances and standards serve as nonbinding recommendations. Guidance documents are, however, important publications in that they clarify the agency's current thinking related to regulatory issues and procedures. In general, product developers may elect to use alternate approaches that still comply with existing laws and regulatory requirements. Within the arena of TE/RM, guidances and standards are available, both of which are product specific and are related to broader issues of preclinical testing, manufacturing issues, and clinical

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trial design. These are provided as references throughout this article.

FDA's review process for investigational products is based on an understanding of the science inherent in the product, is structured by regulations, and is intended to parallel prudent product development (Fig. 1). The assessment of any specific product is dependent on the characteristics of that product, preclinical studies designed to support the use of the product, and the proposed clinical trial design. As many potential TE/RM products are still in the developmental phase, this article will primarily focus on providing information to help product developers recognize and overcome the challenges in the early stages of development of clinical products. Of particular importance for those considering clinical studies in the near future are the need to (1) recognize and identify the appropriate regulatory pathway(s) early in development, (2) acquire early feedback from the FDA through informal interactions with the agency, (3) know the relevant regulations and guidance documents, and (4) consider early in development the questions that will be asked at the clinical phase. The changes in product design and manufacturing are inevitable and require foresight and planning as well.

The information in this article will be presented in the following manner. First, a brief overview of three regulatory categories of products (human tissues, biologics, and devices) and statutes, regulations, and guidances that are relevant to TE/RM are provided. Some generic examples of products that span multiple categories are included for illustration. Second, key aspects of the preclinical assessment of the product are described. Special attention is paid to cell–scaffold constructs which form the basis for many TE/RM products and introduce a unique combination of issues for the individual components and for the assembled product. Lastly, a description of the relevant standard organizations and of programs that the FDA has in place to interact with the public are included to provide additional ways to acquire information that are relevant to specific products.

Regulation of Human Medical Products

Broadly defined, human medical products include those that are regulated by the FDA as human drugs, tissues, biological products, and medical devices, those regulated by other agencies, and unregulated products. It should be first noted that there are some human medical products that are not regulated by the FDA. Vascularized organs are regulated by the Health Resources Services Administration, which oversees the transplantation of vascularized human organ transplants such as kidney, liver, heart, lung, and pancreas. Also excluded from FDA jurisdiction are minimally manipulated bone marrow for homologous use and not combined with a FDA-regulated article, blood vessels recovered with organs for use in organ transplantation, and some secreted or extracted human proteins.

FIG. 1. The big picture: product development process. BLA, biologic license application; IDE, investigational device exemption; IND, investigational new drug; PMA, premarket approval.

TE/RM products may be regulated by the FDA under several different pathways because they often contain components from different product categories (Fig. 2). The characteristics and intended use of the product determine which statutes and regulations may apply. As it is important for product developers to be familiar with the various pathways and the rules that may apply to their product, the following section will discuss each briefly. A more extensive discussion of the regulatory pathways for these products can be found elsewhere.[5]

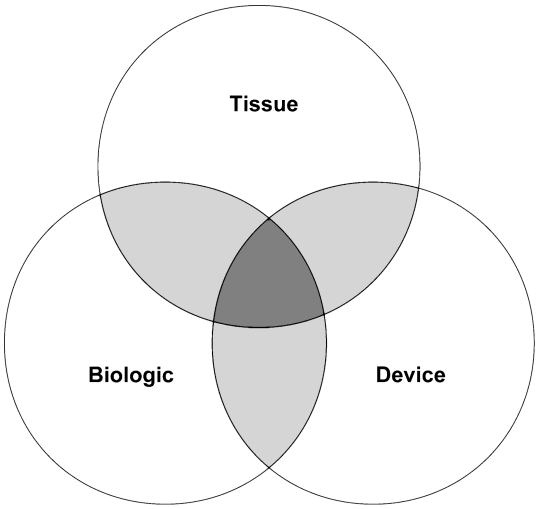

FIG. 2. The different product pathways that intersect for combination products developed by tissue-engineered and regenerative medicine. Some examples of products that combine elements of biologic, device, and tissue can be found on the publically available list of recommendations from the Tissue Reference Group[6] and updates from the Office of Combination Products.[7]

Human medical products regulated by the FDA

Tissues. Human tissues (and cells) are commonly used for the repair, reconstruction, replacement, or supplementation of a recipient's tissues; however, utilization is sometimes limited by availability (i.e., human leukocyte antigen match requirements) and/or complications, such as donor site morbidity and immune rejection. Tissues can be autologous or allogeneic (or xenogeneic) in source and are routinely used as components for TE/RM applications. Human tissues fall under the broader biologic product category of human cells, tissues, and cellular and tissue-based products (HCT/Ps) and are regulated by the FDA using the Tissue Rules. These rules went into effect on May 25, 2005 and are under Section 361 of the PHSA which focuses primarily on the prevention of infectious disease transmission in products containing human cells or tissue. This tiered, risk-based approach to regulating HCT/Ps is published as 21 CFR Part 1271 and covers establishment registration and product listing,[8,9] donor eligibility,[10] and current good tissue practices.[11] Current good tissue practice requirements address the methods, facilities,

and controls used for manufacturing HCT/Ps to prevent the introduction, transmission, and spread of communicable disease. Table 1 describes the four criteria that are used to determine if HCT/Ps are regulated solely under Section 361 of the PHSA and 21 CFR Part 1271. No premarket approval (PMA) is required for these lower risk "361 products." Those tissues that do not meet all the criteria listed in 21 CFR Part 1271.10(a) are regulated under Section 351 of the PHSA and relevant parts of the FDCA for biological products and/or medical devices. In these cases, the HCT/P regulations supplement the other requirements such as good manufacturing practice (GMP) and quality systems regulations (QSR) that are already in place for products regulated as drugs, devices, and/or biological products. Tissue-specific FDA guidances are available.[12]

Biological products. Biological products are defined in Section 351(i) of the PHSA to include "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product that are applicable to the prevention, treatment, or cure of a disease or condition of human beings." Biological products are critically different from conventional, chemically synthesized drugs in that they are derived from living sources, are complex mixtures that are not readily characterizable, may be heat sensitive, and have increased susceptibility to microbial contamination. The provisions of PHSA Section 351 for biological products provide a legal framework that accommodates these inherent features (21 CFR Parts 610s). Biological products that meet the definition of HCT/Ps are also subject to 21 CFR Part 1271 for prevention of infectious disease transmission. It should be noted that the FDCA provisions for drugs also apply to biological products. These include the requirements for GMP (21 CFR Parts 210 and 211) and for labeling. FDA guidances that provide the agency's current thinking on issues related to regulation and biological product development are available.[13]

Table 1. Determination of 361 Classification of Human Cells, Tissues, and Cellular and Tissue-Based Products

An HCT/P is regulated solely under Section 361 of the PHS Act and the regulations in Part 1271 if it meets all of the following criteria:

- The HCT/P is minimally manipulated;
- The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P;
- Either:

(i) the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or

(ii) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and

(a) is for autologous use,

(b) is for allogeneic use in a first-degree or second-degree blood relative, or

(c) is for reproductive use.

HCT/P, human cells, tissues, and cellular and tissue-based products; PHS, Public Health Service.

Medical devices. A medical device is defined in Section 201(h) of the FDCA as "an instrument, apparatus, etc., that is intended for use in the diagnosis or treatment of disease or is intended to affect the structure or any function of man or other animals and which does not achieve its primary intended purposes through chemical action and is not dependent upon being metabolized for the achievement of its primary intended purposes." The Medical Device Amendments to the FDCA in 1976 established the requirement for PMA/clearance and categorized devices into three risk-based classes. The design controls necessary for each class type was introduced later by the FDA Modernization Act of 1997. The lowest risk class, class I, requires only General Controls whereas higher risk classes II and III require additional Special Controls and QSR. QSR refers to a Design Control system that is a processing control analogous to GMP for drugs and biological products. It should be noted that many innovative technologies found in TE/RM are often classified as class III and reach the market via a PMA application. For PMAs, the product is evaluated to ensure that the product is safe and effective and displays consistent performance characteristics. For the lower risk classes, classes I and II, another regulatory mechanism, 510(k) or Premarket Notification, exists for products that are similar to those already marketed, usually called a predicate device. 510(k) clearance is evaluated only for substantial equivalency. 21 CFR Part 800 further describes device-related regulations. A list of relevant databases from the Center for Devices and Radiological Health (CDRH) and the guidance memoranda ("Blue Book Memos") from the Office of Device Evaluation of CDRH are publically accessible.[14,15]

Combination products. Regulation of combination products by the FDA has evolved over the last decade. An Office of Combination Products (OCP) was established on December 24, 2002, with broad regulatory and oversight responsibilities during the collaborative review process of combination products. Additional information can be found on the OCP website.[16] Briefly, a combination product is composed of two or more components that would normally be regulated under different authorities (i.e., drug–device, device–biologic, drug–biologic, and drug–device–biologic). Notably, the definition of combination products, as defined in 21 CFR 3.2(e) 2–4, is broad enough to include not only those products that are physically or chemically combined but also those components that are copackaged or packaged separately but have labeling that requires use with another component to achieve the intended use, indication, or effect. Although jurisdiction decisions can frequently be obtained informally for novel or complex products, there is a formal process in place for the jurisdiction of combination products based on determination of the primary mode of action (PMOA) through which the product achieves its therapeutic effect. In cases of multiple modes of action, a single PMOA that provides the most important therapeutic action or

provides the greatest contribution to the overall therapeutic effect is scientifically identified. The PMOA analysis is used to determine which of the three centers that regulate human medical products (Center for Biologics Evaluation and Research [CBER], Center for Drug Evaluation and Research, and CDRH) at the FDA take the lead in the review process. The regulatory pathway most appropriate for the product is ultimately determined by the lead center. Irrespective of the lead center's designation and regulatory pathway selection, the combination products are typically reviewed using a team of reviewers from all necessary centers with the expertise to ensure product safety and efficacy.

Note on xenogeneic products

The limited supply of human organs for transplantation has led to the use of cells and organs from animal sources. Xenotransplantation is broadly defined as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live cells, tissues, or organs from a nonhuman animal source or human body fluid, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs."[17] These notably include human cells previously cultured *ex vivo* with live nonhuman feeder cells or animal antigen-presenting cells and extracorporeal perfusion of a patient's blood or blood component through an intact animal organ or isolated cells contained in a device for liver failure. Xenogeneic tissue sources pose a number of regulatory challenges including the potential risk of transmission of zoonotic diseases and the introduction of new pathogenic entities to the public. United States Public Health Service Agencies, including the FDA, the National Institutes of Health, the Centers for Disease Control and Prevention, and the Health Resources Services Administration, have collectively published a guideline on this topic.[17] FDA has also provided more specific advice regarding xenotransplantation product development and production, and xenotransplantation clinical trials in a guidance.[18] It should be noted that acellular products of xenogeneic origin (e.g., porcine heart valves) do not meet the FDA definition of "xenotransplantation products" and are regulated as biological products or medical devices.

Note on jurisdiction and regulatory pathway

Often, it is not immediately apparent to product developers to which category a specific product belongs. There are several ways through which FDA's input can be obtained. A general understanding of product jurisdiction can be gained by review of past decisions made by the Tissue Reference Group (TRG)[6] and the OCP.[7] The TRG, established in 1997, serves as a single reference point for questions to the three FDA centers regulating human medical products or to OCP about HCT/Ps. The TRG considers questions from the product developers and makes recommendations about jurisdiction related to HCT/Ps. Questions typically include whether HCT/Ps will be regulated as a 361 tissue, a biological product, or a device, and which center will lead the review process. Informal communications are also possible with the center's jurisdictional officers and with the OCP for clarifications on jurisdiction and regulatory pathway that may be appropriate for their products. There is also a formal mechanism in place to request a decision that is legally binding.[19]

General Considerations for TE/RM Products Prior to Initiation of Clinical Studies

Many of the TE/RM products in the market or currently under development are products in which cells are combined with a biomaterial scaffold. The scaffolds serve as the matrix that provides support for the growth of new tissue. These products pose novel challenges that may have significant bearing on how clinical products are developed. The most challenging aspect for a cell–scaffold combination product arises from the fact that the product combines distinct components that are customarily developed under disparate manufacturing and regulatory approaches. Further, these products are not defined solely by components alone because product assembly and cell–scaffold interactions also influence the characteristics of the final product. In evaluating cell–scaffold products, it is useful to distinguish which tests need to be conducted on individual components prior to assembly and which are most relevant after product assembly. A unique consideration to this product class is that they may not be in their final form when administered to patients, as *in vivo* remodeling can occur. This unusual situation may preclude complete functionality testing and may require more extensive preclinical proof-of-concept (POC) studies and *in vivo* safety data to serve as a basis for reliance that any potential construct failures are addressed prior to clinical trials.

In this section, we identify some overarching analytical elements that may be important when developing products for clinical study. The specific requirements for safety and effectiveness of a specific TE/RM product may vary depending on the type of product and its intended clinical use. Figure 3 is a useful flowchart of the main characterization and safety considerations that are of potential concern for each of the two main components, cell and scaffold, individually and in combination. We also provide examples of product performance characteristics thought to be unique to these products, which may consequently affect development

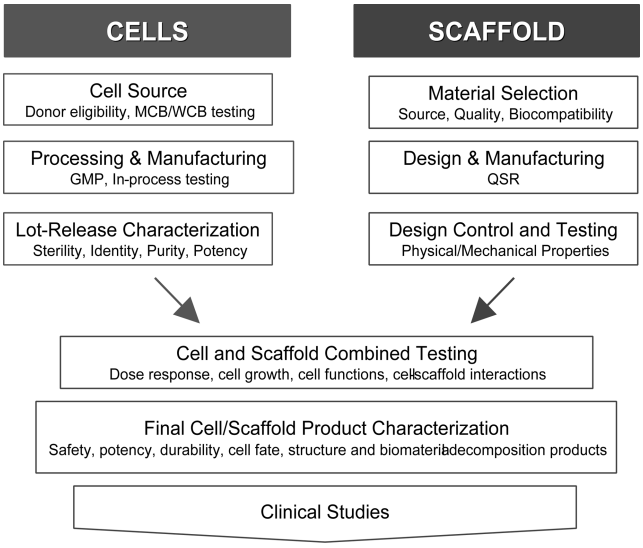

FIG. 3. Safety and effectiveness considerations for a cell–scaffold combination product. GMP, good manufacturing practice; MCB, master cell bank; QSR, quality systems regulation; WCB, working cell bank.

and regulatory considerations. To some extent, the individuality and uniqueness of these products often necessitate a case-by-case approach to identify and prioritize risks and develop methods to mitigate them. Thus, it is beneficial to be aware of these types of issues and it is strongly encouraged that one should engage in early dialog with the FDA to reach clarification for his/her specific product.[20]

Chemistry, manufacturing, and controls

Testing and characterization of scaffold. There is a wide variety of matrix materials that may serve as scaffolds. The scaffolds may consist of biologic materials such as carbohydrates, proteins, peptides, and nucleic acids; synthetic materials such as polymeric or inorganic materials (ceramic and metallic); or processed tissue derived from human or animal sources. Material selection, design, and fabrication contribute to defining the scaffold parameters that in turn define the functional properties of the final product. Important aspects in understanding the safety and performance of TE/RM products include the biocompatibility of the scaffold/matrix components (e.g., source, purity, and contaminates), physical properties, resorption kinetics (applicable to synthetic biodegradable or natural matrices), and sterility.

Broadly defined, biocompatibility is a property that implies the absence of adverse interactions between the material and the tissue. Biocompatible materials should not, either directly or through the release of their material constituents, produce adverse local or systemic effects. Based on years of clinical experience with medical devices, biocompatibility assessments consider parameters such as chemical composition (including additives, dyes, and coatings), the manufacturing processes, component sterilization methods, and the extent of contact/exposure in the body. One of the FDA guidances[21] contains recommendations on how to apply International Organization for Standardization (ISO) 10993 for FDA products. Other FDA guidances (depending on clinical use)[22,23] may further clarify the applicability of these tests. It should be noted that the tests suggested are only a framework for the selection of analyses and it is up to the product developer to provide rationale for the selection and/or waiving of tests performed for their product. It is also important to consider when new scientific approaches are needed to test their product and consider retests when changes in aspects of device composition, processing, physical configuration, and/or intended use imply that this is appropriate.

In general, standard biocompatibility tests for implanted medical devices or TE/RM scaffolds include cytotoxicity, sensitization, irritation, intracutaneous reactivity, systemic toxicity, subchronic/chronic toxicity, carcinogenicity, genotoxicity, and implantation (duration and migration). Depending on scaffold characteristics and intended use, additional tests, such as those for hemocompatibility, specific target organ toxicity, and reproductive and developmental toxicity, may be necessary as well. Ultimately, testing for each device should consider the nature of materials used, toxicological activity, bioavailability, and published literature. For instance, it may not be necessary to conduct all of the suggested tests if the material has a long history of safe use.[24–28] However, the usage of the material in novel applications may warrant additional testing.

The physical characteristics of the scaffold ultimately determine its functional properties and its general manufacturability. As such, it is important to have sufficient testing to determine the parameters that are critical for scaffold function and to ensure that they are consistently reproduced in products. Some of these physical parameters of importance to scaffolds include mass, volume, density, and porosity. Appropriate mechanical testing for tensile/compressive strength, elastic/flexural modulus, fixation strength, fatigue, and abrasion should be considered as well. The properties that should be tested can be refined using the intended clinical use for the scaffold/final product. For instance, the requirements for scaffold performance are different if it is meant to be weight-bearing, resorbable, or replacing/augmenting existing tissue. Product developers may wish to refer to the appropriate American Society for Testing and Materials International (ASTMi), ISO, and United States Pharmacopeia (USP) standards for how testing for physical properties should be performed. Sufficient samples (intralot and interlot) should be tested to provide reasonable assurance of product consistency. In addition, early consultation with the appropriate FDA staff may have great value in identifying/resolving the methods and tests that should be considered for any specific product.

Many scaffolds for TE/RM applications are designed to degrade or resorb after implantation to allow tissue regeneration to occur *in vivo*. This is commonly achieved using synthetic polymers such as poly(glycolide/L-lactide) and polydioxanone, or natural matrix materials such as collagen and hyaluronic acid that degrade or resorb *in vivo*. The resorption profile of the biomaterial should be properly characterized, including the kinetics of cell ingrowth, mechanism/pathway of decomposition (hydrolytic and enzymatic), and the degradation products that are generated/cleared from the body. The resorption profile of the final sterilized product, as demonstrated with appropriate *in vitro* and/or *in vivo* testing, should be consistent with its intended use. The appropriate testing for performance as a function of time, kinetics of mechanical failure, and the potential for acute/chronic inflammation (from wear or degradation products) should be considered as well. The existing FDA guidances for biodegradable polymer implant devices,[27] sutures,[28] surgical meshes,[22] and resorbable bone fillers[29] may serve as useful starting points for other scaffolds.[30]

Sterility plays a central role in determining the safety of the final product. Sterilization of the scaffold is a special process requiring controls and validation because it is often not possible to detect microorganisms by simple inspection, and testing every item through culturing is not practical. Therefore, sterility assurance procedures are employed by product developers through design and validation of sterilization, process control, and continual monitoring. For typical medical devices, terminal sterilization is viewed as the final manufacturing step that is subject to QSR and audits/inspection by the FDA. Some traditional techniques used industrially for medical devices include steam, dry heat, ethylene oxide, and ionizing radiation and there are FDA guidances[31–33] and American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI)/ISO standards[34–36] that describe the sterility assurance levels for products as a function of different risk levels of intended use.

Although terminal sterilization may be useful for some robust, synthetic scaffolds, the traditional techniques generally cannot be applied to biological scaffolds that are more sensitive to the sterilization conditions. Also, the possibility of

viral transmission from the source material becomes an additional concern and viral inactivation and removal methods should be considered. Some common methods include heat, acid/NaOH, detergents/organic solvents, radiation, chemicals, precipitation, and filtration. Sterility assurance for biological scaffolds may be achieved through validation of the source material (herd/animal source/maintenance) and the application of appropriate in-process controls and testing to achieve aseptic processing conditions.[22,37]

Testing and characterization of cellular products. Cell products pose complex manufacturing challenges, and as such, product characterization takes on a greater importance. These challenges include the variability and complexity of the cells, potential for contamination, need for sterile processing, limitation on amount of product, and challenges to product distribution. Manufacturing controls contribute to product safety and effectiveness; however, the cellular component will likely undergo testing for safety and quality just prior to assembly onto the scaffold. This may be conducted through a combination of in-process testing and process validation. Manufacture and testing of the cellular components used in the final cell–scaffold product should include test methods and parameters currently followed for somatic cell therapy products. Characterization of product properties such as sterility, identity, purity, and potency are so important to assuring the safety and efficacy of biological products and so these have been incorporated into regulations by the FDA (see 21 CFR 610). Cellular components should be shown to be free of microbiological contamination and to be of sufficient identity, purity, and potency. Product developers can refer to a guidance[38] that discusses these considerations in more detail.

Biological products are generally not amenable to terminal sterilization. As such, selection of source material and reagents used in product manufacture and the maintenance of aseptic culture and processing techniques are vital to meeting safety requirements.[39,40] For the raw materials/reagents used for product manufacture, qualification programs commonly include documentation of the reagent characteristics (e.g., source, supplier, grade, and concentration) and/or source (country of origin, closed herd, and quality of animal) for animal-derived materials. It should be noted that an important part of product manufacture is also the removal of problematic reagents, such as beta-lactam antibiotics and animal-derived reagents, from the final product and may require validation and/or product testing. In general, the appropriate combination of in-process testing of components during the manufacture and of release testing after product manufacture also plays an important role in ensuring consistency of product sterility and quality from lot to lot.

Note on master/working cell banks

When feasible, establishment of a cell banking system becomes a practical way to manage the necessary donor, in-process, and release testing requirements in an organized, hierarchical manner.[40,41] Cell banks are most commonly used with allogeneic cells capable of culture expansion and cryopreservation. The testing that is common at the master cell bank and working cell bank levels includes the following: (1) master cell bank—*in vitro*, *in vivo*, human/animal virus testing (endogenous and adventitious), bacterial, fungal, mycoplasma, and endotoxin, and cell characterization including identity, purity, activity, and tumorigenicity; (2) working cell bank—*in vitro* adventitious virus testing, bacterial, fungal, mycoplasma, endotoxin, and limited identity testing. Autologous therapies and limited production lots to treat one patient do not usually use a cell banking system.

Microbial contamination is a central safety issue for biological products. The standard tests for sterility are based on 14-day cultures and must include aerobic/anaerobic bacteria and fungi. Testing for mycoplasma is also important for cells obtained from culture. The tests described in 21 CFR 610.12 or USP <71>,[42] or alternative methods that are properly qualified, can be used. The manufacturing step at which any microbiological testing is performed and the sample on which the test is performed should be selected to allow maximum assay sensitivity. It should be noted that the use of antibiotics in the culture media may mask contamination and may necessitate additional bacteriostasis and fungistasis data to ensure product sterility. Lastly, an important consideration for TE/RM products is the short shelf-life of the cell component, and so quicker tests for sterility may be needed. Rapid release of product after 48–72 h culture may be possible under certain conditions[43]; a draft FDA guidance on rapid microbiological methods is now available for public comment.[44]

Identity is an important aspect of cell characterization, because it allows the developer to distinguish the product from other products processed in the same facility and thereby ensure accurate product labeling. Cell source is a primary consideration in determining identity for cellular products. This typically includes donor information, the cell type, the tissue from which it is derived, and the method used to collect the cells (e.g., surgery, mobilization, and device). It should be noted that there are different requirements for autologous and allogeneic cell sources and that pooling of cells from multiple donors is generally restricted (21 CFR 1271.220(b)). More detailed information on donor eligibility, screening, and testing can be found in the FDA guidance on HCT/P products[9] and the FDA website on tissue safety.[45] Identity is also useful for tracking the status of the cell component through various cell processing steps (e.g., cell selection, irradiation, and storage) that are necessary for cell sourcing. These steps may alter the characteristics of the cells significantly and/or increase the potential for product mix-up.

Purity refers to the freedom from extraneous material in the finished product, whether or not harmful. This includes residual contaminants (cells, reagents, DNA, and protein) and pyrogens/endotoxin.[46–49] For endotoxin, the acceptable limits have been established and are dependent on the intended route of administration for the product (e.g., parenteral vs. intrathecal). Other cell parameters such as cell number (minimum and maximum) and viability are also useful for determining purity and product dosage. Although the specifications for these are also application dependent, some recommendations are provided in a FDA guidance.[38]

Potency has been defined in the FDA regulations as the specific ability or capacity of the product to affect a given result (21 CFR 610.10). In practice, the potency of a single entity cellular product is often demonstrated by either a direct measurement of specific biological activities or an indirect measurement of relevant surrogate characteristics. An

example of the latter case would be an analytical method that is correlated to the functional activity of the product. Therefore, it follows logically that potency measurements should be expected to correlate with the intended biological activity or function in preclinical animal models and clinical outcomes. In cases where it is not possible or feasible to develop a single assay that encompasses all of these elements, a matrix of multiple assays (Assay Matrix) that is correlated to product function may be useful. FDA has recently published a draft guidance for comments on the subject of potency for cellular and gene therapy products[50] which may be relevant to TE/RM products.

The assays for cell characterization are identified and refined throughout the product development process. Some of the more complex assays often present challenges because of limited information on the product and its mechanism of action. These issues should be considered early in product development and may require the development of multiple assays simultaneously. A minimalist approach to product characterization early in development limits knowledge of your product and may hamper development in the long term. Special attention should be paid to cellular parameters that affect clinical efficacy, demonstrate product integrity and stability, and can be used in comparability studies.

The cell characterization parameters also serve as metrics, an another important function that is used to validate product stability and help define shelf-life.[51–54] Stability includes measures of sterility, identity, purity, potency, and integrity and testing is required for Investigational New Drug (IND) submission (21 CFR 312.23(a)(7)(ii)). This type of validation may be needed for both in-process (e.g., cryopreservation and holding steps) and final product (e.g., time prior to administration and shipping) testing. The data generated should be at appropriate times and conditions and should minimally cover the time period proposed for the clinical trial, including the method, sampling times, temperature, and assays. It should be noted that the stability data are used to support final formulation and shelf-life at later clinical phases. The product characterization data are also useful in the latter stages to demonstrate product comparability after manufacturing changes.

Testing and characterization of cell–scaffold constructs. In general, one of the main obstacles in the clinical development of cell–scaffold products is the development of appropriate *in vitro* and *in vivo* testing and characterization methods. This is a direct consequence of the unique set of characteristics that many of these products share. These include (1) complexity in three-dimensional structure, (2) heterogeneity in composition, (3) small manufacturing lot sizes (sometimes a "lot size of 1"), and (4) expected remodeling of the product after implantation. These complexities result in manufacturing challenges that may lead to inconsistency in the characteristics of the final product and also hinder the full characterization of the final clinical product because of sampling and testing issues. Moreover, the final product specifications determined through *in vitro* testing may not provide predictive information about clinical safety and efficacy of the product because of remodeling of the cell–scaffold construct *in vivo*. All of these factors can contribute to product failure during clinical studies and should be considered as a part of product development.

When the final cell–scaffold product is manufactured, safety and efficacy of the product are reasonably assessed using a combination of both *in vitro* and *in vivo* tests for characterization and performance. Many of the important parameters that may be measured for the final combination product using *in vitro* methods mirror those for the individual components. These may include sterility, mycoplasma, pyrogenicity/endotoxin, product dimensions, identity, purity, and viability of the cell population in the scaffold. Depending on the regulatory pathway that is appropriate, a demonstration of product potency and/or performance will also be necessary. In some instances, cell potency may also be appropriately regarded as a component of "product performance." The complex nature of TE/RM products will likely necessitate the development of the aforementioned matrix approach for potency, based on a complimentary array of assays and tests. In considering assays to characterize a cell–scaffold product, attention should be paid to include testing that can reliably predict the stability of the final cell–scaffold construct *in vivo* after implantation. These products raise unique considerations in product stability: (1) the cells have the potential to migrate out of the scaffold to the host tissue and (2) the interaction of the cells and matrix is likely to be altered as the scaffold material undergoes biodegradation/resorption. Therefore, relevant tests addressing such types of post-implantation potency and/or performance are often needed with these products and should be considered early in product development.

Although the discussion thus far has been general to any cell–scaffold product, it is emphasized that product performance and/or potency issues are specific to both product type and the intended use. For example, a cell–scaffold product indicated for vascular grafts may require biomechanical testing to assess the ability of the product to tolerate repeated accesses without leaking and/or withstand a certain burst pressure. On the other hand, a cell–scaffold product indicated to regenerate a topical tissue by replacement may involve testing to address water permeability function or gas exchange function of the construct. For a cell–scaffold product indicated for repairing cartilage, the most pertinent requirement may be for the final construct to be capable of forming cartilage tissue or supporting a certain compressive/shear load. For more specific recommendations to individual products, product developers may look for guidances that may be applicable to their product and refer to related standards from standards organizations such as the ASTMi, International Conference on Harmonization, ISO, and USP (Table 2). It is important to note that not all standards are formally recognized by the FDA and that product developers may wish to contact FDA for more detailed information regarding the applicability of a particular standard to their product.

Note on animal studies

Animal studies are an important component of assessing the safety of musculoskeletal TE/RM products prior to human clinical trials. When developing an animal model to be used to demonstrate a POC and product performance, and/or to identify toxicity of the cell–scaffold product, it is important to take both the characterization of the product and its ultimate clinical use into account.[55] In some cases,

Table 2. Selected Standards of Potential Relevance to Tissue Engineering and Regenerative Medicine Products[a]

Standard	*Title*
ASTM F 2027	Standard Guide for Characterization and Testing of Raw or Starting Biomaterials for Tissue-Engineered Medical Products
ASTM F 2064	Standard Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Products Application
ASTM F 2150	Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products
ASTM F 2211	Standard Classification for Tissue-Engineered Medical Products
ASTM F 2212	Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue-Engineered Medical Products
ASTM F 2312	Standard Terminology Relating to Tissue-Engineered Medical Products
ASTM F 2315	Standard Guide for Immobilization or Encapsulation of Living Cells or Tissue in Alginate Gels
ASTM F 2347	Standard Guide for Characterization and Testing of Hyaluronan as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
ASTM F 2603	Standard Guide for Interpreting Images of Polymeric Tissue Scaffolds
ASTM F 2383	Standard Guide for Assessment of Adventitious Agents in Tissue-Engineered Medical Products
ASTM F 2386	Standard Guide for Preservation of Tissue-Engineered Medical Products
ASTM F 2450	Standard Guide for Assessing Microstructure of Polymeric Scaffolds for Use in Tissue-Engineered Medical Products
AAMI/ISO 13022	Tissue-Engineered Medical Products—Application of Risk Management to Viable Materials of Human Origin Used for the Production of Medical Products
ASTM F 2103	Standard Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
ASTM F 2451	Standard Guide for *In Vivo* Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage
USP 31:2008	Nonresorbable and Resorbable Surgical Suture
ASTM F 0754	Standard Specification for Implantable Polytetrafluoroethylene Polymer Fabricated in Sheet, Tube, and Rod Shapes
ISO 10993	Biological Evaluation of Medical Devices
ASTM F 1609	Standard Specification for Calcium Phosphate Coating for Implantable Materials
ASTM F 1088	Standard Specification for Beta-Tricalcium Phosphate for Surgical Implantation
ASTM F 2149	Standard Test Method for Automated Analyses of Cells—The Electrical Sensing Zone Method of Enumerating and Sizing Single-Cell Suspension
ASTM F 2739	Standard Guide for Quantitating Cell Viability Within Biomaterial Scaffolds
ASTM F 1983	Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications
AAMI/ANSI/ISO 7198	Cardiovascular Implants—Tubular Vascular Prostheses
AAMI/ANSI/ISO 5840	Cardiovascular Implants—Cardiac Valve Prostheses
ISO 14160	Sterilization of Single-Use Medical Devices Incorporating Materials of Animal Origin—Validation and Routine Control of Sterilization by Liquid Sterilants
AAMI/ANSI/ISO 13408	Aseptic Processing of Health Care Products
AAMI/ANSI/ISO 11138	Sterilization of Health Care Products—Biological Indicators
AAMI/ANSI/ISO 11137	Sterilization of Health Care Products—Radiation
AAMI/ANSI/ISO 11135	Sterilization of Health Care Products—Ethylene Oxide

[a]It should be noted that although standards are useful starting points in the absence of product-specific guidance(s), product developers are strongly encouraged to contact the Food and Drug Administration for product-specific considerations.

AAMI, Association for the Advancement of Medical Instrumentation; ANSI, American National Standards Institute; ASTM, American Society for Testing and Materials; ISO, International Organization for Standardization; USP, United States Pharmacopoeia.

choosing a relevant animal model of disease/injury or animal species may not be straightforward. It should be noted that there is no default animal species for this task (rodent, nonrodent species, nonhuman primate, or multiple species may be used). Therefore, scientific justification should be provided for the animal models that are chosen and the chosen models should relate to the overall product development. Similarly, nontraditional animal models may also be appropriate with the understanding that these models require validation for the type of disease/injury and for any inherent variability. It is important to understand the limitations of the species/model as well. Some of these include availability, size, sex/age, housing needs, cost, Animal Care and Use Committee concerns, potential nonanimal alternative test methods, technical feasibility, historical/baseline data, and statistical limitations.

For preclinical animal study results to directly support clinical use, the clinical product in its final formulation rather than an equivalent product is recommended whenever possible. A POC study in an animal model of disease can sup-

plement other nonclinical studies (including nonanimal studies) performed during product development and should be designed to provide substantial evidence supporting the feasibility of the product. Therefore, the study should be designed to provide morphological outcome data (e.g., *in vivo* differentiation of cells and integration of implanted construct) and functional outcome data (e.g., total integration of the cell–scaffold construct as a fully functioning tissue). At least a subset of the animal studies conducted in support of clinical trials should also be designed to provide a safety assessment of the product, although a substantial amount of safety data can be gleaned from studies designed for other purposes, if appropriate safety endpoints are incorporated in the study design. Postmortem analysis of, for example, local inflammatory response for an allogeneic cartilage repair/replacement product and scar formation for vessel or hard tissue graft could be some endpoints relevant to product safety. Finally, as with all cellular products, it is important to consider what the appropriate approach is regarding an assessment of the tumorigenic potential for cell–scaffold products and regarding determination of the fate of implanted cells (e.g., survival, trafficking, differentiation, and proliferation).

Methods for Learning More About FDA Review of Products

Pre-IND/preinvestigational device exemption interactions

The preinvestigational meetings were created to provide product developers with an opportunity to engage in open communication with the FDA and to discuss the content of future investigational (IND/investigational device exemption) submissions. By providing background information and specific questions, it is possible to obtain nonbinding feedback from the agency, regarding a wide range of issues including product safety issues, necessary preclinical studies, and the design of the clinical studies. These meetings are particularly useful for discussing innovative combination products, as clarifications of regulatory requirements may be provided as well. These preinvestigational meetings also allow the FDA to become familiar with the product and to identify/develop the necessary regulatory framework to allow efficient review of investigational applications prior to submission. FDA guidances that describe the meeting procedures in more detail are available.[56,57]

Guidances/public summary of licensed products

A list of all guidances from the three FDA centers that regulate human medical products can be found on their respective websites.[13,14,58] These represent the agency's current thinking on a wide range of issues. Most guidances of specific relevance to TE/RM can be found at the websites for CBER and CDRH. In the absence of a guidance for a specific product area or regulatory question, other related guidances that are currently available often serve as the best starting point. Also of use is the publically available information on licensed or approved products. Examples include CBER's Summary Basis of Approval[59] and CDRH's Summary of Safety and Effectiveness Data packages.[60] These files typically include useful information on licensed products such as manufacturing and controls information, summary of preclinical and clinical studies, and the recommendation from the relevant advisory committee/panel.

Advisory committee/panel meeting transcripts

Advisory committees/panels consist of scientific experts that the FDA uses to obtain outside advice on issues of interest to the FDA and complement the internal review process. Topics addressed may be product specific or generally applicable to a range of products. These experts are asked to review data and make recommendations on product or clinical issues such as the adequacy of data in applications, benefits and risks of products, design of clinical trials, and recommendations regarding postmarket studies. There are 30 advisory committees and 18 advisory panels (for medical devices) that are divided along product areas. Some advisory committee and panel meetings of potential interest to developers of TE/RM products are shown in Table 3. The transcripts from advisory committee meetings are publically available on the web.[61–63]

Standards' activities for tissue engineering

The word "standards" can have many different meanings ranging from a laboratory specific physical standard, an international physical standard, or written standards that represents consolidated results of science, technique, and experience. For this article we will concentrate on the potential application of written standards that were developed by voluntary standards development organizations (SDOs). This type of standards includes those in terminology, guides, test methods, performance standards, specifications, and technical reports. The use of standards for TE/RM products (sometimes known as tissue-engineered medical products [TEMPs] in SDO parlance) may help to facilitate product design and performance as well as improve time to market. Two SDOs that have been active in the TE/RM arena are the ASTMi and ISO.

ASTMi standards for TEMPs are developed in Committee F04 on Medical and Surgical Materials and Devices.[75] The standards developed by this committee help to ensure the safety and efficacy of medical devices and their components. The committee is composed of 22 technical subcommittees

Table 3. Selected Advisory Committee Meetings on Topics Related to Tissue-Engineered and Regenerative Medicine Products

- Orthopedics Panel for Carticel (March 1997)[64]
- Dermagraft, Graftskin (Apligraft) PMA Review (January 1998)[65]
- Examination of Risks Posed by Different Types of Xenotransplantation Products (January 2000)[66]
- Hematopoietic Stem Cells for Hematopoietic Reconstitution (February 2003)[67]
- Allogeneic Islet Cell Therapy for Diabetes (October 2003)[68,69]
- Somatic Cell Cardiac Therapies (March 2004)[70,71]
- Somatic Cell Therapies for Joint Surfaces (March 2005)[72,73]
- Potency Measures for Cell, Tissue, and Gene Therapies (February 2006)[74]

PMA, premarket approval.

(SCs) which maintain jurisdiction of over 250 standards. These SCs include five primary areas of focus: resources, orthopedic devices, medical and surgical devices, tissue-engineered products, and computer-assisted surgical systems. TEMP standards focus on materials needed in, and practices and methods for, the development and application of TEMPs. This committee coordinates with the ISO Technical Committee (TC) 150 on Implants for Surgery to ensure harmonization and avoid duplication of efforts in standard development.

ISO is a nongovernmental, international organization that develops consensus standards in collaboration with both the public and private sector.[76] Standards for tissue engineering are developed in TC 150 SC 7 (Tissue-Engineered Medical Devices) and in TC 194 (Biological Evaluation of Medical Devices). TC194 SC 01 is responsible for tissue product safety and within SC 01 are four working groups (WG); WG 01 Risk Assessment, Terminology and Global Aspects; WG 02 Sourcing Controls, Collection, and Handling; WG 03 Elimination and/or Inactivation of Viruses and Transmissible Spongiform Encephalitis Agents; and WG 04 Transmissible Spongiform Encephalitis Elimination.

Although the details of FDA participation in SDO activities vary according to center and product area, FDA encourages use of appropriate consensus standards during product development.[77] It may be prudent to check with FDA staff, or the CBER and CDRH websites, regarding the applicability of a particular standard to the specific area of product development.

Agency Efforts to Promote Tissue-Engineered Products

Commissioner's fellowship program

An example of FDA's desire to accelerate the introduction of novel medical products, including tissue-engineered products, into medical practice is the recently initiated Commissioner's fellowship program.[78] This program, which began in October 2008, currently has 50 fellows with expertise in professions ranging from scientists, engineers, physicians, to veterinarians working on many different laboratory research, regulatory policy, and review projects based on issues throughout the FDA. Each fellow is mentored by a FDA senior scientist preceptor from one of the various FDA centers. The fellows undergo a combination of coursework that provides instruction in all aspects of the FDA and regulations and practical working experience through a regulatory science project. Two of the fellows in the first class were selected to work jointly in both CBER and CDRH on projects related to regenerative medicine. These fellows have identified three specific aims that include (1) providing expertise in the area of tissue engineering to expand the knowledge base of the FDA, (2) promoting collaboration between the various centers to address regulatory issues related to combination products, and (3) identifying both internal and external resources to aid and educate both reviewers and external stakeholders in regenerative medicine regulation. An example of a new initiative included the establishment of a monthly regenerative medicine seminar series for FDA staff to learn recent advances in regenerative medicine from both agency personnel and external experts.

Multiagency tissue engineering strategy

FDA's participation in the Multiagency Tissue Engineering Science (MATES) Interagency WG stands as another example of FDA's desire to accelerate the introduction of tissue-engineered products into medical practice by coordinating and integrating, wherever possible, its actions with the scientific/medical activities of other federal agencies involved in tissue engineering. MATES (which was organized under the auspices of the Subcommittee on Biotechnology of the National Science and Technology Council in the Office of Management and Budget) serves as a focal point for sharing information on tissue engineering activities within the federal government.[79] In 2007, MATES issued a strategic plan[80] that identified the overarching strategic goals for tissue science and engineering and the role federal agencies could take in advancing this field. FDA's involvement in MATES has also improved the quality and efficiency of scientific activities within the agency by leveraging scientific and medical expertise within the federal government for public workshops[81,82] and FDA Advisory Committee meetings[74] as well as information sharing of technology assessments and funding proposals.

Conclusion

TE/RM provides innovative therapies that hold great promise to addressing unmet medical needs. It is precisely the innovative nature of these products that also result in many scientific challenges for ensuring that the therapies are safe and effective. From a technical point of view, this is related to the complexity of (a) manufacturing and control of a three-dimensional cell–scaffold construct and (b) the lack of established *in vitro* and *in vivo* testing and characterization techniques that are appropriate for these combination products. For successful product development to occur, the first goal may be to gain control of this complex, heterogeneous, and dynamic product during manufacture. Some general questions that product developers should ask during development include the following: (1) What questions need to be asked for testing of final products or their components? (2) At what stage of product assembly is the most accurate information obtained? (3) What are the key product parameters? (4) What testing methods are currently available and what methods need to be developed or standardized? (5) What important functional information can be obtained during the different stages of the product in animal and humans? Product developers may increase their chances of achieving clinical products by developing and refining new product manufacturing and characterization techniques early in their process. It is also equally important to take advantage of the various informal routes of communication possible with the FDA to obtain early and most up-to-date feedback from the agency regarding their specific product to ensure efficient progression of their products toward clinical trials in the United States.

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Appendix:

Table of Commonly Used Acronyms

Acronym	*Full term*	*Acronym*	*Full term*
510(k)	Premarket Notification	OCBQ	Office of Compliance and Biologics Quality (CBER)
AAMI	Association for the Advancement of Medical Instrumentation	OCP	Office of Combination Products
ACUC	Animal Care and Use Committee	OCTGT	Office of Cellular, Tissues, and Gene Therapies (CBER)
ANSI	American National Standards Institute	ODE	Office of Device Evaluation (CDRH)
ASTM	American Society for Testing and Materials	OSEL	Office of Science and Engineering Laboratories (CDRH)
BLA	Biologic license application	PHS	Public Health Service
CBER	Center for Biologics Evaluation and Research	PHSA	Public Health Service Act
CDC	Centers for Disease Control and Prevention	PMA	Premarket approval (application)
CDER	Center for Drug Evaluation and Research	PMOA	Primary mode of action
CDRH	Center for Devices and Radiological Health	POC	Proof-of-concept
CFR	Code of Federal Regulations	QSR	Quality system regulation
CGTP	Current good tissue practices	SAL	Sterility assurance level
FDA	Food and Drug Administration	SBA	Summary basis of approval
FDCA	Food, Drug, and Cosmetics Act	SC	Subcommittee
FR	Federal Register	SDO	Standards Development Organizations
GMP	Good manufacturing practice	SIS	Supplemental information sheet
HCT/Ps	Human cells, tissues, and cellular and tissue-based products	SSED	Summary of safety and effectiveness data
HRSA	Health Resources and Services Administration	TC	Technical Committee
ICH	International Conference on Harmonization	TE/RM	Tissue-engineered and regenerative medicine
IDE	Investigational device exemption (application)	TEMPs	Tissue-engineered medical products
IND	Investigational new drug (application)	TE-STG	CBER–CDRH Cross-Center Tissue Engineering Specialty Task Group
ISO	International Organization for Standardization	TRG	Tissue Reference Group
MATES	Multiagency Tissue Engineering Science	USP	United States Pharmacopeia
MCB	Master cell bank	WCB	Working cell bank
MOA	Mode of action	WG	Working group
NIH	National Institutes of Health		
OC	Office of Compliance (CDRH)		