Chapter 10
Regulation of Regenerative Medicine Products

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Abstract Cellular therapies have moved to the forefront based upon promising results from clinical trials using both chimeric antigen receptor T lymphocytes to treat leukemia and other cell types to restore structure and function to tissues that have been damaged by disease or physical injury. The pace at which these treatments have evolved has posed a regulatory challenge to agencies, such as the Food and Drug Administration (FDA). This chapter describes how a specific regulatory strategy was developed and how it has evolved in response to the demand for these new therapies.

Keywords Extracellular matrix · Regenerative medicine · Cellular therapies · Regulatory authority · Food and Drug Administration · FDA guidance · GDraft guidance · Good manufacturing practices · GMP manufacturing · Investigational new drug application · Minimally manipulated · More than minimally manipulated

10.1 Introduction

For many years, it has been proposed that cellular therapies could provide cures for otherwise untreatable diseases. These claims were based on two concepts. The first was that a specific immune response could be engineered to destroy diseased target cells. The second was based on the concept that all cells evolved from stem and progenitor populations, which could be expanded and differentiated ex vivo or in vivo to produce a population that could be used to elicit a regenerative or corrective effect in the recipient. Clinical proof of principle was provided by bone marrow transplantation, in which functioning immune and blood-forming systems could be restored in cancer patients treated with myeloablative chemo/radiotherapy. This therapy has achieved the status of practice of medicine and is not regulated by the

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FDA. Subsequently, different cell sources, new in vitro cell manipulations, and novel indications have proliferated. This has posed a problem to the international regulatory agencies as to what laws should govern this area. In the following sections, the evolution of specific regulations is reviewed together with how they have been recently streamlined to increase patient access.

10.2 Regulatory Authority

In the United States, the responsibility for regulation of drugs, foodstuffs, cosmetics, animal feeds, etc. falls to the FDA. These regulations are published in Title 21 of the Code of Federal Regulations (CFR), which is available online. On an ongoing basis, the FDA monitors developments in their area of responsibility and determines whether they require regulation. If so, the initial approach is to decide whether there are pre-existing regulations that could be applied to the new issue. Cellular therapy products are regulated as pharmaceuticals, and as such, there were some existing laws that were deemed to be relevant. There were, however, obvious differences between exiting regulated small molecule drugs and biological therapeutics that required specific attention. The problem was identifying these differences and developing a consistent regulatory strategy that would address them.

The method by which this is achieved is often through a survey of what new products are being developed. This may be followed by publication of draft guidances, which suggest a regulatory strategy that may be adopted and how compliance could be achieved. Stakeholders in the field have the opportunity to submit comments to the FDA. These will be officially reviewed and may result in changes to the proposed strategy. Eventually, the FDA will produce a final guidance document, and subsequently the contents may appear in the regulations published in the CFR.

This process was adopted when the FDA reviewed developments in cellular therapies. The data gathering stage consisted of a variety of meetings held between the FDA and stakeholders. At these, the stakeholders could propose regulatory strategies, outline needs and problems, and indicate how they believed the field would evolve. In parallel, the FDA introduced Annual Establishment Registration. This requires facilities involved in preparation of cellular therapy products to register with the FDA and indicate the activities they perform, e.g., collection, processing, distribution, etc., and the types of cellular products involved, etc. This provides ongoing data on how the field is developing and whether new cellular products and practices are emerging.

Based upon an extensive review of the field, the FDA identified existing regulations that could be applied. These included the requirement to evaluate the new product under an Investigational New Drug (IND) approval [1]. The IND mechanism requires submission of data on the rationale for the treatment, preclinical studies to support this rationale, how the product will be manufactured and tested, and design of the clinical trial, to include patient numbers with inclusion and exclusion criteria, doses to be evaluated, stopping rules, statistical analysis methods, etc.

An IND study requires that the test product is manufactured under current good manufacturing practices (GMP). This is a system that ensures that the cells are prepared using a controlled, auditable, reproducible procedure that results in a safe and potentially effective product. GMP regulations have been in place for other types of therapeutics for many years and can be found in Parts 200 and 600 of Title 21 of the CFR (the electronic version of the current CFR is available online at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.

Having made the decision, the FDA then had to address how the IND and GMP mechanisms would be applied to living therapeutics.

10.3 Risk-Based Regulations

There are a number of issues that arise quickly when trying to implement existing regulations to cellular products. These are living entities with inherent variability that are then subjected to ex vivo manipulation, possible long-term storage, shipment to treatment centers, and additional manipulation before patient administration. It would be very difficult to develop a single regulatory strategy that could be applied to a potentially very wide range of product types. The FDA elected to use a risk-based approach. This evaluated the potential degree of risk to the donor, the risks posed by ex vivo manipulation, and the risks to the intended recipient. Using this system, it was possible to implement two regulatory strategies; however, to do so, the risks needed to be specified. The major risks are outlined in Table 10.1 for somatic cell therapy products. Products defined as posing high risk would follow the existing GMP/IND mechanism and are referred to as Type 351 products. Lower-risk products (Table 10.1) would be subject to new regulations. These were named good tissue practices (GTP) and are described in 21 CFR Part 1271 and described in an FDA guidance [2] and cover Type 361 products. They regulate minimally manipulated products, which immediately raises the question of how this term is defined.

Table 10.1 Major factors used to classify high- and low-risk cell therapy products

Low-risk (Type 361 products) Good tissue practice regulations	High-risk (Type 351 products) Good manufacturing practice regulations
Simple collection procedure, e.g., peripheral blood draw	Complex collection procedure, e.g., surgical procedure required
Minimal manipulation of cells ex vivo, e.g., • Plasma reduction • Red cell removal • Selective removal of cells	More-than-minimal manipulation of cells ex vivo, e.g., • Ex vivo cell culture • Genetic modification • Activation of cells
No change to relevant or biological characteristics of the cells	Changes to relevant and/or biological characteristics of the cells
No combination of cells with another article	Combination with another article or device
Homologous use	Nonhomologous use

For structural tissue, it is defined as processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement, and, for cells or nonstructural tissues, it is processing that does not alter the relevant biological characteristics of tissues. This would appear to put many regenerative products under the GTP regulations; however, this is not always true. The FDA was requested by stakeholders to provide a clearer definition of manipulation, and in 2006, it published the "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update" [3]; this described a request for designation process, by which the investigator could ask for an official manipulation designation on their particular processing. There is an associated Guidance for Industry and FDA: "How to Write a Request for Designation (RFD)" [4]. This document did not specifically define what in vitro procedures would constitute more-than-minimal manipulation, and so this issue continued to be debated. In parallel, there was controversy on the term "homologous use," which is a requirement for regulation under GTP. Many investigators felt that GTP regulations covered use of bone marrow or adipose-derived cells implanted in different tissues to achieve different functions. The FDA argued that homologous use only included applications where the cells were expected to perform the same function at the sites of collection and administration. This interpretation was still questioned, and to try to resolve both of these areas of contention, the FDA in December 2017 [5] published the "Guidance for Industry and Food and Drug Administration Staff—Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use." This guidance aims to provide clear definitions for both minimal manipulation and homologous use.

In general terms, more-than-minimal manipulation, for the purposes of this article, covers ex vivo culture, genetic manipulation, and cell activation, some or all of which are used when preparing cells for regenerative applications. In turn, depending on the origin of the cells and their final application, the cells or tissues may be for homologous or nonhomologous use. As a result, most early-phase regenerative medicine protocols are regulated under the IND mechanism and employ product manufacturing under GMP, rather than GTP regulations (Table 10.1).

10.4 GMP Manufacturing

Many academic institutions contemplating opening Phase 1 clinical trials of a regenerative medicine product may be unfamiliar with GMP regulations. A full description of the requirements is outside the scope of this article, but reviews are available [6, 7]. Not all components of full GMP are required for Phase 1 studies. The FDA Guidance "CGMP for Phase 1 Investigational Drugs" provides a summary of the expectations [8]. These include policies and procedures that cover staff, quality control, facility and equipment, control of components, manufacturing and records, laboratory controls, packaging, labeling, distributing, and recordkeeping. Recognizing that cell therapy products differ from traditional small drug

pharmaceuticals, in 2013 the FDA issued a Guidance [9] specifically relating to cellular and gene therapy products: "Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products", which provided important supplementary information.

The IND application contains the Chemistry, Manufacturing and Control (CMC) section, which describes in detail the origin, manufacturing, testing, labeling and distribution of the product, and the facility in which it is to be manufactured. Luckily, there is an excellent FDA Guidance [10] on how the CMC should be written and formatted, "Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)". There is a parallel Guidance [11], which provides the same information for gene therapy products, "Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)". These documents streamline writing of the CMC section, and should be followed closely when preparing information for IND submission.

10.5 Extracellular Matrix (ECM) Regulation

This volume discusses the types and properties of ECMs and how they exert their beneficial effects. This chapter addresses the regulation of ECM and how it is evolving. Therapeutic products that consist of cells plus a matrix [12, 13], or scaffold, are regulated as combination products, and assignment falls under the FDA Office of Combination Products. The designation as a combination product can be disputed using the request for designation mechanism described earlier. Additional information can be found in a recent final guidance "Classification of Products as Drugs and Devices & Additional Product Classification Issues" [14]. Combination products are specifically intended to be used together, and both components are required to mediate the therapeutic effect. Jurisdiction as to which part of the FDA (the Center for Biologics Evaluation and Research (CBER) or the Center for Devices and Radiological Health (CDRH)) the combination product is assigned and is determined by its primary mode of action. In some cases, two applications may be required. Table 10.2 shows the information that will be requested on the cell and scaffold components. The variety and properties of ECM are continually evolving, making it difficult to describe a single common regulatory strategy for all. The most recent development has been signing into law of the twenty-first Century Cures Act in 2016, which is designed to accelerate the development and review of novel medical products [15]. It also established new expedited product development programs: (i) the Regenerative Medicine Advanced Therapy (RMAT) [16] and (ii) the Breakthrough Devices program. RMAT designation is intended for regenerative medicine therapies that are required to treat, modify, reverse, or cure serious or life-threatening diseases or conditions where there is preliminary clinical evidence that the therapy has the potential to address unmet medical needs. RMAT designation is

Table 10.2 Information required by FDA on combination products

Cells	Scaffold (Device)
Source (auto, allo) Donor eligibility, master cell bank testing	Starting materials Material selection, design, and fabrication Biocompatibility
Cell processing GMP compliance, in-process testing	Design and properties Mechanical and physical
Release testing Safety, identity, purity, potency Cell number	Manufacturing and testing Resorption profile, design control, performance Sterility assurance, quality system regulations, device GMP
Cells + Device	
Dose response, cell growth, cell function, cell-scaffold interactions	
Final product	
Safety, potency, durability, cell fate, structural and biomaterial decomposition	

This table is based on information presented by MH Lee, Office of Cellular, Tissue, and Gene Therapies, CBER, FDA, at the 2nd Annual Symposium on Stem Cell Strategies, Best Practices and Regulatory Considerations, San Francisco, CA. September 2010

obtained by filing a request with CBER or by including the request in the IND application. Since many regenerative therapies involve the use of a device as part of a combination product, the FDA subsequently issued a draft guidance "Evaluation of Devices used with Regenerative Medicine Advanced Therapies" [17]. It is important to note, however, that this guidance specifically states that the "FDA does not consider scaffolds combined with a cellular product to be within the scope of this Guidance." The rationale is that the scaffold would not generally be considered solely "a device used in the delivery of RMAT," because it provides more than a delivery function, and that "both the scaffold and the cellular product are typically necessary for the RMAT to achieve its intended purpose."

In spite of an evolving regulatory landscape, the FDA has approved a number of scaffolds and combination products. These include autologous cellularized scaffolds, CorMatrix ECM, and hydrogels, such as polyethylene glycol (PEG) or polyethylene oxide (PEO), which is a biocompatible and hydrophilic polymer approved for several biomedical applications (12).

10.6 Interacting with the FDA

The best approach when seeking regulatory approval for an ECM/cell product is to obtain advice from the FDA early in the process. In 2017, the FDA published a procedural draft guidance "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products" [18]. This summarizes the types of meetings that can be held with the agency. The most important are the types A, B, and C meetings. Initial contact should be made through a Type C meeting. This is described as

"any meeting other than a Type A, Type B, or Type B (end of production) meeting regarding the development and review of a product." It offers the IND sponsor the opportunity to obtain regulatory feedback on an IND study under early development. The normal procedure is to contact the FDA to request a Type C meeting (often referred to as a pre-pre-IND meeting) and provide them with a list of issues that require clarification. This is usually done by outlining the proposed action to be taken, e.g., we proposed to assess product functionality using the following assay, will that be acceptable? The meeting takes place by conference call between the investigators and selected FDA staff. Careful notes should be taken of the proceedings, and it is advisable to follow up with an e-mail or letter to the FDA outlining your understanding of the points that were raised. This advice is invaluable in clarifying how the IND will be written, the product manufactured and tested, and the studies designed.

Type B meetings occur subsequently. These are used as the "official" pre-IND meetings and are held shortly before the IND application is submitted. They provide an opportunity to briefly present points where clarification from the agency is required. The format is the same as described above for the Type C meeting, and an outline of what is to be discussed should be submitted to the agency in advance. Type B meetings can also be used to discuss other issues, e.g., risk evaluation. Type A meetings are used for dispute resolution, follow-up after regulatory action, etc.

Before holding a meeting with the FDA, it is advisable to become familiar with the various draft and final guidances that have been published. These allow an investigator to get an overview of current thinking on regulatory strategies. Some of the most valuable guidances are listed in Table 10.3. All are accessible from the FDA website at http://www.fda.gov/. It is also possible to subscribe to the CBER website to automatically receive notification of new information.

10.7 Summary

Recent successes achieved by cellular therapies for leukemia, and in regenerative medicine applications, have caught the public interest. As a result, there has been increasing pressure on the FDA to develop new regulatory approaches to accelerate the evaluation and approval of these treatments. For the investigator wishing to implement a clinical trial using a new cellular product, this poses a challenge, since the existing regulatory approach has taken some time to evolve and continues to do so. The concepts of "manipulation," "homologous use," and "combination products," all of which affect the regulatory pathway, have been long debated, and their final definitions were only recently resolved. We now face additional mechanism to improve the evaluation and approval process. This chapter aims to provide a "snapshot view" of where the field is currently and how it may evolve in the future. Given rapid developments in ECM biology, cardiac cell therapy science and indications, and governmental regulations, it is impossible to hit such a rapidly moving target

Table 10.3 Selected FDA guidances

Guidance	Subject	Date
Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products: Draft Guidance for Industry	Description of types of meeting that can be held with the FDA	December 2017
Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products—Draft Guidance for Industry	Making changes to the chemistry, manufacturing, and control section of an approved IND	December 2017
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue- Based Products: Minimal Manipulation and Homologous Use—Guidance for Industry and Food and Drug Administration Staff	Clarification of definitions of homologous use and manipulation	December 2017
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies: Draft Guidance for Industry	Evaluation of combination products in regenerative medicine	November 2017
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions	Mechanisms for accelerated approval of regenerative medicine products	November 2017
Current Good Manufacturing Practice Requirements for Combination Products: Final Guidance for Industry and FDA Staff	GMP regulations for manufacturing combination products	January 2017
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products	Difference between designs for cell and gene therapy clinical trials and those for small molecule drugs	June 2015
Preclinical Assessment of Investigational Cellular and Gene Therapy Products: Final Guidance	Types of preclinical data required for cell and gene therapy IND applications	November 2013
Process Validation: General Principles and Practices: Guidance for Industry	Design of validation studies	January 2011
Potency Tests for Cellular and Gene Therapy Products: Guidance for Industry	Types of potency tests that can be used for cell and gene therapy products	January 2011
Cellular Therapy for Cardiac Disease: Guidance	Overview of considerations for product manufacturing, testing, delivery, and clinical trial design	October 2010
Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs): Guidance for Industry and FDA Reviewers	Template for writing somatic cell therapy product CMC section	April 2008
Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	Template for writing gene therapy product CMC section	April 2008

(continued)

Table 10.3 (continued)

Guidance	Subject	Date
CGMP for Phase 1 Investigational Drugs: Guidance for Industry	Minimal GMP requirements for manufacturing products for use in a Phase 1 clinical trial	July 2008
Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice: Guidance for Industry	Sterile manufacturing for products that cannot be terminally sterilized	September 2004

accurately. The reader is strongly advised to keep abreast of scientific and clinical developments and to use FDA resources to determine the best way to translate these into early-phase clinical trials.

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