Adrian P. Gee *Editor*

Cell Therapy

cGMP Facilities and Manufacturing

Second Edition

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Preface

Cellular and gene therapies are now producing very promising results and even potential cures. This has resulted in a dramatic increase in the number of academic institutions and biotechnology companies involved in the field. Many of these are engaged in conducting early phase clinical trials, which necessitates the use of facilities that comply with current Good Manufacturing Practices (cGMP) to prepare the therapeutic products. For those new to these regulations, it can be intimidating knowing how to start to design, build and run a cGMP-compliant facility. The purpose of this book is to update our original publication "Cellular Therapy: cGMP Facilities and Manufacturing" published in 2009. This book grew out of the Production Assistance for Cellular Therapy (PACT) contract program supported by the National Heart Lung and Blood Institute (NHLBI) of the U.S. National Institutes of Health. The second volume is also supported by the NHLBI and marks the termination of the third version of PACT.

In this updated and expanded volume, we provide basic advice to those manufacturing products for early phase clinical trials on the approaches used by a variety of facilities and individuals to comply with the regulations. This information is primarily intended for academic facilities and smaller or start-up biotechnology firms. It covers international governmental regulations for cellular therapies, the design and qualification of new facilities, operational activities, such as cleaning, environmental monitoring, equipment qualification, validation and document generation and management. It also discusses the roles played by professional accreditation organizations, standards and governmental agencies and funding organizations.

Our aim is to provide a repository of information that can be easily accessed and a listing of individuals whom the reader can contact to discuss the topics covered. Since much of the information contained is based upon governmental regulations it is strongly suggested that the reader keep abreast of current requirements whenever implementing any of the suggestions in this volume.

The editor would like to thank all of the authors for their contributions, especially during the time of the COVID-19 pandemic! They were all a joy to work with and simplified my task enormously. I would especially like to thank Laarni Ibenana and Lisa Davis of Emmes for their help in manuscript management and

organization and Lis Welniak of NHLBI for her support of the book. My gratitude is also owed to all my colleagues at the Baylor College of Medicine Center for Cell and Gene Therapy in Houston for their help and encouragement.

As I near retirement, I should like to dedicate this volume to all those with whom I have had the pleasure of working and collaborating over the last 40 years. They have made my time in this area both enjoyable and stimulating. It has been incredible to see the evolution of these new treatments and I shall continue to monitor their progress with fascination.

Houston, TX, USA Adrian P. Gee

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Part I
Regulatory

Regulation of Cellular Therapy in the United States

Nicole Fisher, Laarni Ibenana, Ashraf El Fiky, and Robert Anderson

1 Introduction

In the United States, the Food and Drug Administration (FDA), a federal agency within the Department of Health and Human Services, is responsible for regulatory oversight of cell therapy products. The FDA is organized into centers that report to the FDA Commissioner, each with jurisdiction for products by class. The FDA centers most relevant to the oversight of cell therapies are the Center for Biologics Research and Evaluation (CBER) and the Center for Devices and Radiological Health (CDRH). This chapter discusses the framework under which the FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) and discusses applicable requirements. 21 CFR 1271, applicable to all HCT/Ps, is discussed in detail, including donor eligibility requirements and current good tissue practices (cGTPs).

2 Regulatory Authority for Oversight of Cellular Therapy Products

The legislative framework under which the FDA operates is shaped by federal laws, including the Food, Drug, and Cosmetic (FD&C) Act of 1938 [1] and the Public Health Service (PHS) Act of 1944 [2], which were enacted by Congress under the authority of the United States Constitution. Both the FD&C Act and the PHS Act, along with other permanent laws in the United States, are codified in the *United States Code* (U.S.C.); the laws promulgating the FD&C Act begin at 21 U.S.C. 301, and the PHS Act starts at 42 U.S.C. Based on the laws established through the

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FD&C Act and the PHS Act, the FDA issues regulations in accordance with the Administrative Procedure Act [3], which permits public input through a "notice and comment rulemaking" process [4]. FDA regulations are found in Title 21 of the Code of Federal Regulations (CFR). Proposed rules and the mechanisms by which the public may submit comments are published daily in the Federal Register. The FDA reviews and assesses each comment received by the public prior to the issuance of the regulation, or final rule, via the Federal Register. The Federal Register notice not only contains the language of the regulation, but it also contains a preamble, which includes relevant background information and the FDA's responses to the comments received from the public. The preamble of a final rule provides insight into the FDA's thinking on regulations. The FDA shares their current interpretation of the regulations through guidance documents. The FDA issues guidance documents in accordance with the Good Guidance Practice regulation, 21 CFR 10.115, which specifies that guidance documents are not legally binding. A searchable list of all available FDA guidance documents is available through the FDA's website [5], and a list of guidance documents applicable to cellular therapies is included at the end of this chapter.

3 Brief History of Cell Therapy Regulations

The FDA first defined somatic cell therapy products in 1993 as "autologous (i.e., self), allogeneic (i.e., intraspecies), or xenogeneic (i.e., interspecies) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo, to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries" [6]. In the same Federal Register notice in 1993, the FDA announced how it would apply the existing statutory framework, applicable at the time to other therapeutic products, to human cell therapy products, i.e., cell therapy products would be regulated as drugs, biologics, and/or medical devices and would be subject to regulations promulgated under both the PHS Act and the FD&C Act. In response to reports that communicable diseases such as HIV and hepatitis were being transmitted via transplanted human tissue, the FDA issued an interim rule [7] to address the immediate need to implement additional oversight of these products to protect public health. The interim rule, which required donor screening and testing of human cellular and tissue-based products, was promulgated under Section 361 of the PHS Act [42 U.S.C. 264], which authorizes the creation and enforcement of regulations deemed necessary to prevent the introduction, transmission, or spread of communicable diseases. In 1997, the final rule was issued as 21 CFR 1270 [8]. The same year, the FDA issued their Proposed Approach to Regulation of Cellular and Tissue-Based Products [9] to provide a unified and comprehensive regulatory approach to the regulation of HCT/Ps, with the goal of protecting public health while minimizing the regulatory burden required for innovative products to reach the market. Under the risk-based approach, lower-risk products meeting certain criteria would

be regulated under Section 361 of the PHS Act and would be required to comply with 21 CFR 1271, but would not require premarket approval. Higher-risk products would be regulated as drugs, devices, and/or biological products under Section 351 of the PHS Act [42 U.S.C. 262] and the FD&C Act. These products would be subject to the applicable regulations in 21 CFR, including Part 1271 and good manufacturing practices (cGMPs) in 21 CFR 210 and 211, and would require premarket approval.

The FDA published three final rules, which comprise 21 CFR 1271, to promulgate the tiered approach to the regulation of HCT/Ps [10]:

- "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing" [11]
- "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" [12]
- "Current Good Tissue Practice for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products; Inspection and Enforcement" [13]

Part 1271 became fully effective on May 25, 2005, and provided the basis for the regulation of all HCT/Ps and is the sole regulation applicable to Section 361 HCT/Ps. The good tissue practice final rule [13] changed the definition of "tissue" in §1270.3(j) to render Part 1270 applicable only to tissue recovered before May 25, 2005; however, in December 2020, the FDA published a proposed rule to revoke Part 1270 because it is unlikely that any tissue recovered prior to May 25, 2005, remains available for implantation [14].

FDA oversight of HCT/Ps continues to evolve with scientific innovation. The expedited development of innovative regenerative medicine therapies, including HCT/Ps, was one area of focus in the 21st Century Cures Act (Cures Act) passed in 2016 [15]. As part of the comprehensive policy framework implemented to support the expedited development of regenerative therapies, the FDA published four guidance documents (included in the list at the end of this chapter). Two of the guidance documents provide further interpretation on the requirements of Part 1271, and one guidance discusses the expedited development of Regenerative Medicine Advanced Therapy (RMAT) products [16]. The Cures Act amended Section 506 of FD&C Act to include RMAT designation for a cell therapy, therapeutic tissue engineering product, and human cell and tissue product, intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition. RMAT designation does not apply to products regulated solely under Section 361 of the PHS [17]. RMAT designation and accelerated approval pathways available for RMAT products are discussed later in this chapter.

4 Definition of HCT/P

HCT/Ps are defined in § 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." Examples of HCT/Ps listed in § 1271.3(d) include the

bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following items do not meet the definition of HCT/P:

- Vascularized human organs for transplantation or blood vessels recovered with an organ, as defined in 42 CFR 121.2, which are intended for use in organ transplantation and labeled "For use in organ transplantation only"
- Whole blood or blood components or blood derivative products subject to listing under Parts 607 and 207
- Secreted or extracted human products, such as milk, collagen, and cell factors (except semen)
- Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow)
- Ancillary products used in the manufacture of HCT/P
- Cells, tissues, and organs derived from animals other than humans
- In vitro diagnostic products

5 Determining Statutory Authority Applicable to an HCT/P

Under the tiered, risk-based approach to the regulation of HCT/Ps, the FDA implemented criteria to determine which HCT/Ps are to be regulated under the authority of Section 361 of the PHS Act. Section 361 HCT/Ps do not require premarket approval and are subject only to the regulations in 21 CFR 1271. Per § 1271.10(a), an HCT/P is regulated only under Section 361 of the PHS Act if it meets all of the following criteria:

1) The HCT/P is minimally manipulated.
2) The HCT/P is intended for homologous use only (as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent).
3) 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).
4) Either:
    a) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function.
    b) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function and:
        i) Is for autologous use

ii) Is for allogeneic use in a first-degree or second-degree blood relative; or
iii) Is for reproductive use

Figure 1 illustrates the application of the criteria in § 1271.10(a) to determine if an HCT/P is a 361 product.

The guidance document "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" [18] provides insight and examples regarding the FDA's interpretation of the definitions "minimal manipulation" and "homologous use." Key points from the guidance document are described below.

5.1 Minimal Manipulation

Minimal manipulation is defined in § 1271.3(f) as follows:

- For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissues utility for reconstruction, repair, or replacement
- For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues

Therefore, in order to apply the definition, one must first determine if the HCT/P in question is structural tissue or cells/nonstructural tissue, based on the characteristics in the donor (i.e., before any recovery or processing steps). The guidance describes structural HCT/Ps as "those that physically support or serve as a barrier or conduit, or connect, cover, or cushion" and provides the following examples: the bone, skin, amniotic membrane and umbilical cord, blood vessel, adipose tissue, articular cartilage, nonarticular cartilage, and tendon or ligament. Cells or nonstructural tissue that have "metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions" are considered cells/nonstructural HCT/Ps; examples provided in the guidance include reproductive cells/tissues, cord blood, lymph nodes/thymus, parathyroid glands, peripheral nerve, and pancreatic tissue.

Additional terms included in the definition of minimal manipulation, such as "original relevant characteristics" and "relevant biological characteristics," also need to be considered when applying the criteria. For structural tissue, "relevant" tissue characteristics are those traits that contribute significantly to the tissue's ability to reconstruct, repair, or replace, and "original" applies if the trait was present in the donor. The guidance cites the following examples of the relevant characteristics of structural tissues: strength, flexibility, cushioning, covering, compressibility, and response to friction and shear. The meaning of "relevant biological characteristics" for cells/nonstructural tissue is similar to "relevant" for structural tissue in that it refers to traits in the donor that play a role in the cell or tissue's function (e.g., differentiation, proliferation potential, and metabolic activity).

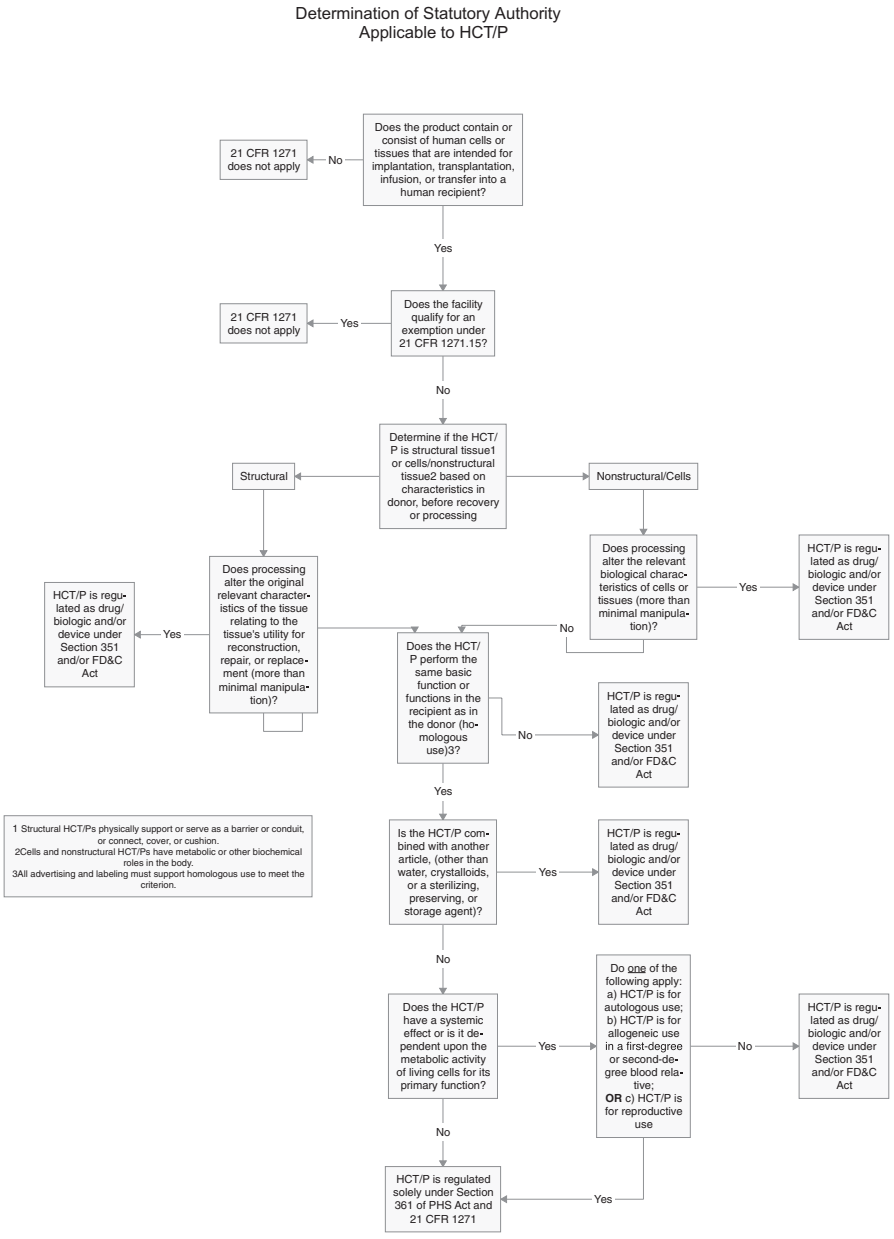

Fig. 1 Flowchart depicting application of criteria in 21 CFR 1271.10(a) to determine statutory authority applicable to an HCT/P

5.2 Homologous Use

Homologous is defined in § 1271.3(c) as "repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." The recipient cells/tissue do not need to be identical to the donor cells/tissue to meet the definition. The guidance further defines "repair," "reconstruction," "replacement," and "supplementation." To meet the "same basic function or function" part of the definition of homologous use, any of the basic functions (i.e., those that are well understood and commonly ascribed to the HCT/P) expected in the recipient must be a basic function in the donor. An HCT/P may still meet the definition of the "same basic function" even if it is used in a different location in the recipient.

Another key component of the criteria related to homologous use is the manufacturer's intent for use, as reflected by the labeling, advertising, and other circumstances surrounding the distribution of the product, including written or oral statements by the manufacturer or its representatives. If any of these refer to nonhomologous uses, the HCT/P would not meet the criterion.

If the HCT/P does not meet the criteria in § 1271.10(a), and the establishment that manufactures the HCT/P does not qualify for any of the below exceptions in § 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under the FD&C Act and/or Section 351 of the PHS Act. These products, discussed in more detail later in this chapter, are subject to 21 CFR 1271, additional regulations in 21 CFR specific to drugs, biological products, or medical devices, and are subject to premarket review [10].

Per § 1271.15, the following entities are exempt from the requirements in Part 1271:

- Establishments that use HCT/Ps solely for nonclinical scientific or educational purposes.
- Establishments that remove HCT/Ps from an individual and implant the HCT/P into the same individual during the same surgical procedure.
  - For additional information regarding this exemption, refer to the Guidance Document "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception" [19].
- Carriers that accept, receive, carry, or deliver HCT/Ps as part of their usual business as a carrier.
- Establishments that do not recover, screen, test, process, label, package, or distribute, but only receive or store HCT/P's solely for implantation, transplantation, infusion, or transfer within the same facility.
- Establishments that only recover reproductive cells or tissue for immediate transfer into a sexually intimate partner of the donor.
- An individual that only recovers HCT/Ps under contract with a registered establishment and sends recovered HCT/Ps directly to the registered establishment.
  - Note: the individual is exempt from registration and listing; however, regulations pertaining to the manufacturing step(s) performed are still applicable.

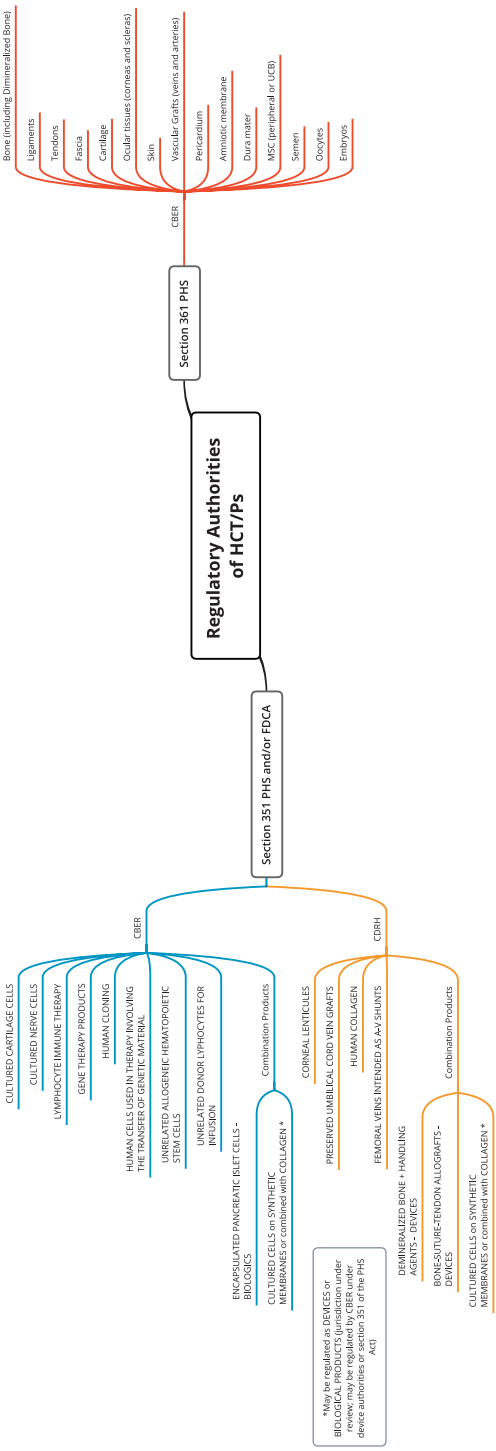

Fig. 2 List of product types, separated by FDA center responsible for review, considered Section 361 HCT/Ps or HCT/Ps regulated under Section 351 and/or the FD&C Act

Figure 2 illustrates the types of HCT/Ps that may be regulated under Section 361 (if all criteria are met) and those that the FDA considers to be regulated as drugs, biologics, and/or devices [20]. Section 361 HCT/Ps are regulated under CBER. As discussed in more detail in the section "Requirements for HCT/Ps Regulated as Drugs, Biologics, and/or Medical Devices," HCT/Ps regulated as drugs, biologics, and/or devices are regulated under CBER or CDRH. Combination products (i.e., those with multiple constituent parts that are drugs, biologics, and/or devices) are assigned to an FDA center based on their primary mode of action [21]. HCT/P combination products are typically assigned to either CBER or CDRH. The FDA has several mechanisms to assist with classification and/or center assignment, including the pre-RFD (informal) and RFD (formal) processes, discussed below.

6 Classification and Jurisdiction Assistance

The FDA offers several mechanisms by which a manufacturer of an HCT/P may obtain a recommendation or decision regarding classification and/or jurisdiction.

1) The TRG Rapid Inquiry Program (TRIP) is a temporary program operating as part of the FDA's Tissue Reference Group (TRG). The TRG was created as specified in the 1997 Proposed Approach document and is further described below. When the TRIP was originally announced, it was effective from June 12, 2019, to December 31, 2019. The FDA has announced several extensions of the program and, most recently, announced in July 2020 that the program would be extended through March 31, 2021 [18]. At the time of publication of this chapter, it was not clear if the program will be extended past that date. Through TRIP, manufacturers may obtain a nonbinding assessment regarding the regulation of their specific HCT/P. Requests should be submitted via email for each HCT/P and should contain the information specified on the TRIP website. The FDA aims to respond with their assessment within 1 week [22].
2) The TRG is another mechanism by which a manufacturer may obtain a nonbinding recommendation regarding the application of the criteria in § 1271.10(a) to a specific HCT/P, including which FDA center will have primary jurisdiction. The TRG is composed of three representatives from CBER and three from CDRH, including the product jurisdiction officer at each center. Representatives from the Office of Combination Products (OCP) and from the Office of the Chief Counsel attend the meetings. Submissions to the TRG may be sent via mail, email, or fax and should contain the information specified on the TRG website. The TRG aims to respond within 60 days; however, if the manufacturer does not agree with the agency's recommendation, they may submit a Request for Designation (RFD) or pre-RFD as described below [23, 24].
3) An RFD may be submitted to the OCP to obtain a formal decision regarding the classification of an HCT/P, including which FDA center will have primary jurisdiction. 21 CFR 3.7 contains the information required for an RFD, and addi-

Table 1 Applicability of 21 CFR 1271 to Section 361 HCT/Ps

21 CFR 1271 Subpart	Applicability to 361 HCT/Ps
Subpart A – general provisions	Applicable to all 361 HCT/Ps
Subpart B – procedures for registration and listing	Applicable to all 361 HCT/Ps
Subpart C – donor eligibility	Applicable to all 361 HCT/Ps
Subpart D – current good tissue practice	Applicable only to nonreproductive 361 HCT/Ps
Subpart E – additional requirements for establishments described in 21 CFR 1271.10 (reporting and additional labeling requirements)	Applicable only to nonreproductive 361 HCT/Ps
Subpart F – inspection and enforcement of establishments described in 21 CFR 1271.10	Applicable to all 361 HCT/Ps

tional information on the process can be found in the April 2011 guidance document "How to Write a Request for Designation (RFD)" [25]. The Agency aims to respond within 60 days.

4) A pre-RFD may also be submitted to obtain a nonbinding, informal feedback on the classification of the HCT/P, which FDA center will have primary jurisdiction, and/or for advice regarding the preparation of the RFD. Additional information can be found in the February 2018 guidance document "How to Prepare a Pre-Request for Designation (Pre-RFD)" [26]. The Agency aims to respond within 60 days.

7 HCT/Ps Regulated Solely Under Section 361 of the PHS Act

As described above, if an HCT/P meets all of the criteria included in § 1271.10(a), it is subject only to regulation under Section 361 of the PHS Act. Section 361 HCT/Ps are regulated by the CBER and must comply with the regulations in Part 1271, as shown in Table 1 subparts E and F, which are only applicable to 361 HCT/Ps and are discussed below. Subparts B through D, which also apply to HCT/Ps regulated as drugs, biologics, or devices, are discussed in greater detail later in this chapter under the section "Requirements of 21 CFR 1271 Applicable to All HCT/Ps, Including Registration and Listing, Good Tissue Practices, and Donor Eligibility Determination."

7.1 Reporting [21 CFR Subpart E]

Reporting of adverse reactions and deviations is required for nonreproductive 361 HCT/Ps.

7.1.1 Adverse Reaction Reports [§ 1271.30(a)]

An adverse reaction is defined in § 1271.3(y) as "a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response." Situations in which the HCT/P is one of several possible causes of the issue, or those in which the relationship between the issue and the HCT/P is "unlikely" (yet still possible), would meet the definition of an adverse reaction [27].

Under § 1271.350(a), any adverse reaction involving a communicable disease related to an HCT/P made available for distribution must be investigated. The adverse reaction must be reported to the FDA if it:

- Is fatal
- Is life-threatening
- Results in permanent impairment of a body function or permanent damage to body structure
- Necessitates medical or surgical intervention, including hospitalization
- Includes an action related to the treatment or prevention of communicable disease or infection that is not routinely expected after the administration of an HCT/P [27]

It is important to note that if the adverse reaction does not involve communicable disease transmission (e.g., graft failure), it does not need to be reported to the FDA [27]. Adverse reactions required to be reported to the FDA must be submitted using an FDA Form 3500A within 15 calendar days of initial receipt of the information. The 2016 guidance document "Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely under Section 361 of the Public Health Service Act and 21 CFR Part 1271" [28] contains detailed recommendations for investigating and reporting complaints of adverse reactions and includes instructions on how to complete the Form FDA 3500A for these products.

7.1.2 Reports of HCT/P Deviations [§ 1271.30(b)]

An HCT/P deviation is defined in § 1271.3(dd) as "an event (1) that represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination or (2) that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination."

Under § 1271.350(b), all HCT/P deviations related to a distributed HCT/P must be investigated, and deviations related to a core cGTP requirement ([§ 1271.150(b)], described below) must be reported to the FDA within 45 days of discovery using Form FDA 3486. The report should contain a description of the HCT/P deviation; information relevant to the event and the manufacture of the HCT/P involved; and information on all follow-up actions that have been or will be taken in response to

the HCT/P deviation (e.g., recalls). Refer to the 2017 guidance document "Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271" [29] for additional information.

7.2 Additional Labeling Requirements [21 CFR Subpart E]

In addition to the labeling requirements in §§ 1271.55, 1271.60, 1271.65, and 1271.90, which pertain to donor eligibility determination and quarantined HCT/Ps, the labeling requirements described in this section apply to nonreproductive 361 HCT/Ps.

Each HCT/P made available for distribution must be labeled clearly and accurately [§ 1271.370(a)] with the following information per § 1271.370(b):

- Distinct identification code affixed to the HCT/P container and assigned in accordance with § 1271.290(c) as described under "good tissue practices".
- Description of the type of HCT/P.
- Expiration date, if any.
- Warnings required under §§ 1271.60(d)(2), 1271.65(b)(2), or 1271.90(c), if applicable and physically possible.
  - If there is not sufficient space on the label, the warnings must accompany the HCT/P instead.

The following information must either appear on the HCT/P label or accompany the HCT/P per § 1271.370(c):

- Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution
- Storage temperature
- Other warnings, where appropriate
- Instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases

7.3 FDA Inspections and Enforcement Actions [21 CFR Subpart F]

The FDA will conduct inspections under 21 CFR 1271.400(a) in order to determine compliance with the applicable requirements of Part 1271, which may include, but is not limited to, an assessment of the establishment's facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers, and controls required to be maintained under Part 1271. Inspections may be conducted with or without prior notice but typically occur

during normal business hours, and the frequency of inspection is at the agency's discretion [10].

Based on the inspection or other available information, the FDA may take enforcement action(s) to prevent the introduction, transmission, or spread of communicable diseases. Possible advisory, administrative, and judicial actions for Section 361 HCT/Ps include untitled letters, warning letters, orders of retention/recall/destruction or order of cessation of manufacturing, or prosecution [20].

7.3.1 Enforcement Discretion

As described above, if an HCT/P does not meet the criteria § 1271.10(a), the product is considered a drug, device, and/or biological product under the FD&C Act and/or Section 351 of the PHS Act and is subject to premarket approval, in addition to the requirements discussed later in this chapter. To allow manufacturers time to determine if they need to submit an Investigational New Drug (IND) application or a marketing application and to prepare the application, the FDA announced its plan to exercise enforcement discretion in the 2017 guidance document "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" [18]. In the 2017 guidance, the FDA stated that over a period of the subsequent 36 months, ending in November 2020, the agency would exercise enforcement discretion provided that the use of the HCT/P was not associated with reported safety concerns or potential significant safety concerns. In July 2020, the FDA updated the guidance to extend the enforcement discretion period through May 31, 2021. It is not clear at the time of publication if the enforcement discretion period will be extended again.

The enforcement discretion focuses on products with high-risk routes of administration, such as intravenous, intraocular, or central nervous system injection/infusion and aerosol inhalation, and those that are intended for nonhomologous use, particularly those intended to be used for the prevention or treatment of serious and/or life-threatening diseases [18]. The FDA has issued over 15 untitled letters and warning letters during the enforcement discretion period [30].

8 Requirements for HCT/Ps Regulated as Drugs, Biologics, and/or Medical Devices

HCT/Ps that do not meet the criteria in § 1271.10(a) for regulation under Section 361 of the PHS Act are regulated as drugs, devices, and/or biological products under the FD&C Act and/or Section 351 of the PHS Act. Section 351 of the PHS Act defines a biological product 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 a disease or condition of human beings."

HCT/Ps regulated under Section 351 of the PHS Act also meet the definition of drugs and/or devices under the FD&C Act. Section 201(g) of the FD&C Act defines a drug as:

> (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C) …

Section 201(h) of the FD&C Act defines a device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

HCT/Ps that meet the definition of biological drug products are regulated at the FDA by CBER under Section 351 of the PHS Act and the FD&C Act. These HCT/Ps are subject to regulations promulgated under both Acts, including 21 CFR 210 and 211 (cGMPs), 21 CFR Parts 600-680 (the Biological Product Regulations), and 21 CFR 1271 (Registration and Listing, Donor Eligibility, and cGTPs) [31].

HCT/Ps that meet the definition of device are regulated by CDRH under the FD&C Act. As discussed above, products with more than one constituent drug, device, and/or biological part are considered combination products, which are assigned to a lead FDA center based on their primary mode of action [21]. HCT/P combination products are typically assigned to either CBER or CDRH; refer to Fig. 2. Note that this chapter focuses on the requirements for HCT/Ps regulated as biologics. Regulations applicable to devices include, but are not limited to, 21 CFR 801 (Labeling), 21 CFR 807 (Registration and Listing), 21 CFR 807 Subpart F (Premarket Notification), 21 CFR 814 (Premarket Approval), 21 CFR 812 (Investigational Device Exemption), and 21 CFR 820 (Quality System Regulation). The FDA's website [32] should be consulted for comprehensive information regarding the regulation of medical devices.

8.1 Biologic Product Licensing

Biological drug products are required to be licensed under Section 351 of the PHS Act; the licensing provisions are included in 21 CFR 601. Form FDA 356h contains the required information for a Biologics License Application (BLA), which is a

comprehensive data package containing data demonstrating that the product meets prescribed requirements of safety, purity, and potency. Briefly, the BLA includes applicant information, product/manufacturing information, data from preclinical studies, data from clinical studies, and labeling [33]. Refer to the section entitled "Special Considerations for Cord Blood" for information specific to BLAs for cord blood.

Per 21 CFR 601.2(d), the FDA will issue the license if it determines that "the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products." A product's effectiveness for its intended uses must be demonstrated as part of the statutory requirement for potency [21 CFR 600.3(s)] [6]. The biological drug product must comply with the conditions of licensure in the FDA-approved BLA, along with the Biologics regulations [21 CFR 600-680] to ensure the product is safe, pure, potent, effective, and appropriately labeled [31]. As this chapter does not discuss the Biologics regulations in-depth, the relevant regulations should be referenced for specific requirements. Figure 3 contains a timeline of HCT/P approvals.

8.2 Investigational New Drug Application Regulations

In order to generate the safety and effectiveness data needed for a BLA, the product is studied in human clinical trials under an Investigational New Drug (IND) application in accordance with the regulations in 21 CFR 312.

The list below contains the IND content required per 21 CFR 312.23; however, the IND application is discussed in greater detail in a subsequent chapter.

- Form FDA 1571
- Table of contents
- Introductory statement and general investigational plan
- Investigator's brochure
- Clinical protocol
- Chemistry, manufacturing, and control information
- Pharmacology and toxicology information
- Previous human experience
- Additional information, as relevant

The clinical trial cannot be initiated until the IND is in effect, and an IND must be in effect for the product to be lawfully shipped for use in the clinical trial(s). An IND goes into effect 30 days after it is received by the FDA (unless FDA notifies the sponsor otherwise) provided the sponsor also complies with the requirements in 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards). Per 21 CFR 312.42, the FDA may place an IND on clinical hold at any time. A clinical hold is issued to delay the start of a proposed clinical study or suspend conduct of an ongoing study. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the

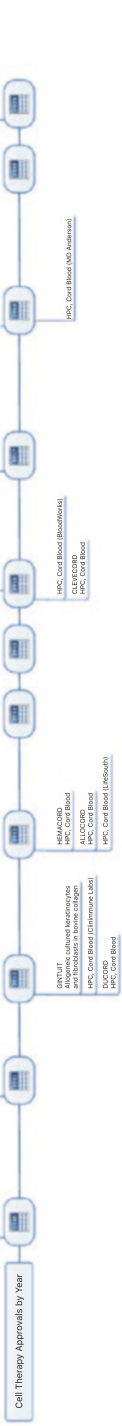

Fig. 3 Approval timeline of licensed HCT/Ps

investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by the FDA in the interest of patient safety. The grounds for a clinical hold are specified in 21 CFR 312.42(b) and include:

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.
- The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND.
- The investigator brochure is misleading, erroneous, or materially incomplete.
- The IND does not contain sufficient information required under § 312.23 to assess the risks to the subjects of the proposed studies.
- The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility.
- The (Phase 2 or 3) plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

Typically, the basis for hold is related to patient safety risks or the IND does not contain sufficient information. A few examples of scenarios in which a clinical hold may be issued include a product with a potentially hazardous impurity profile, inadequate preclinical animal data to support the proposed clinical trial, or inadequate safety assessments during the clinical trial [34]. Imposition of the study hold may be initially communicated via telephone or other rapid method by the end of the 30-day review. A written explanation of the clinical hold issues will be sent to the sponsor within 30 days of the notification of clinical hold. The sponsor must submit a complete response to all deficiencies; refer to the guidance document "Submitting and Reviewing Complete Responses to Clinical Holds" [35]. The FDA will review the responses within 30 days of receipt; however, the investigation may not resume until notification is received from the FDA [34].

Additional requirements including investigational product labeling and responsibilities of sponsors and investigators are outlined in 21 CFR 312. Refer to the section entitled "Special Considerations for Cord Blood" for information specific to INDs for cord blood.

8.3 Current Good Manufacturing Practices

Because biologic products are a subset of drugs, they are also subject to cGMPs as described in 21 CFR 210 and 21 CFR 211. The cGMPs govern the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to ensure that it meets the requirements for safety, identity, strength, quality, and purity [21 CFR 210.1(a)]. 21 CFR 210.1(b) states that

failure to comply with the requirements in Part 211 means that the product is considered adulterated under Section 501(a)(2)(B) of the FD&C Act and subject to regulatory action.

Part 211 contains the following subparts:

- Subpart A – general provisions
- Subpart B – organization and personnel
- Subpart C – buildings and facilities
- Subpart D – equipment
- Subpart E – control of components and drug product containers and closures
- Subpart F – production and process controls
- Subpart G – packaging and labeling control
- Subpart H – holding and distribution
- Subpart I – laboratory controls
- Subpart J – records and reports
- Subpart K – returned and salvaged products

HCT/Ps must also comply with cGTPs in 21 CFR 1271, Subparts C and D. According to § 1271.150(d), if Part 1271 conflicts with a requirement in Part 210 or 211, the regulations more specifically applicable to the product in question (i.e., 21 CFR 1271) will supersede the more general [13].

There is significant overlap between the cGTPs and cGMPs, and, in many cases, both sets of requirements require the same manufacturing practice; however, several requirements of the cGTPs would not be included in routine cGMP practice (e.g., predistribution shipment, audits, prohibition on pooling, tracking, etc.). In addition, there are cases in which a corresponding cGMP requirement partially covers a cGTP requirement (e.g., the quality program requirement in § 1271.160) [27]. The more specific regulations (i.e., cGTPs) are discussed in this chapter; refer to "Requirements of 21 CFR 1271 Applicable to All HCT/Ps, Including Registration and Listing, Good Tissue Practices, and Donor Eligibility Determination." However, it is important to note that HCT/Ps regulated as biological drug products must also comply with cGMPs in Parts 210 and 211.

8.4 Donor Eligibility and Good Tissue Practices

Under 21 CFR 210.1(c), HCT/Ps regulated as biological drug products are subject to the donor-eligibility and applicable cGTPs, both of which are described below under "Requirements of 21 CFR 1271 Applicable to All HCT/Ps, Including Registration and Listing, Good Tissue Practices, and Donor Eligibility Determination."

8.5 Registration and Listing

Registration and listing requirements for HCT/Ps regulated as biological drug products are discussed below under "Requirements of 21 CFR 1271 Applicable to All HCT/Ps, Including Registration and Listing, Good Tissue Practices, and Donor Eligibility Determination."

8.6 Enforcement Actions

HCT/Ps regulated as biological drug products are subject to inspection and enforcement actions under both the PHS and FD&C Acts. CBER's Compliance Program Guidance Manual 7345.848 [31], summarized in this section, describes FDA's approach to conducting inspections of establishments involved in the manufacture of HCT/Ps regulated as biological products.

To ensure compliance with applicable regulations and conditions in the FDA-approved BLA, a cGMP-focused inspection is conducted at least biennially (or more frequently, if determined to be necessary). Prelicense inspections are performed for new biological products seeking a license, and pre-approval inspections are performed as part the approval process for significant changes to a biologics license application. As part of their risk-based approach to inspection, the FDA has identified three critical elements (standard operating procedures, training, and records) and seven key systems (quality, facilities/equipment, materials, production, packaging/labeling, laboratory control, donor eligibility). A Level I inspection covers the three critical elements and at least four of the key systems, including the quality system and production system. A Level II inspection covers the three critical elements, the quality system, and one additional key system on a rotating basis. Level I inspections are conducted for the initial inspection of an establishment; establishments under a Consent Decree of Permanent Injunction or under a Notice of Intent to Revoke; for follow-up inspections to verify an establishment's implementation of corrective action after regulatory action has been taken; establishments that have implemented significant changes since the prior inspection; or establishments whose previous two inspections were Level II. Level II inspections are conducted for establishments with a satisfactory history of compliance; establishments for which one of the two previous biennial inspections was Level I; or when inspection preparation procedures did not reveal significant safety or quality trends. Possible enforcement actions include untitled letters, warning letters, license revocation or suspension, seizure, injunction, and prosecution [31].