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Review Article

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A study on the US FDA Regulatory requirements for Stem Cell Based-Products

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Abstract

Purpose: To thoroughly investigate the regulatory structure implemented by the U.S. Food and Drug Administration (FDA) for products derived from stem cells. As regenerative medicine advances, it is essential to comprehend the FDA's function in safeguarding the safety, effectiveness, and quality of these therapies.

This research utilizes a thorough method to explore the regulatory requirements set by the U.S. Food and Drug Administration (FDA) for stem cell-derived products. The approach combines qualitative analysis, document review, and case study assessment to evaluate the FDA's regulatory structure and its influence on the advancement and authorization of regenerative treatments.

Results and discussion: This research examine the U.S. FDA's regulatory framework for stem cell-derived products, including combination products. It clarifies the distinctions between Section 361 and Section 351 HCT/Ps based on criteria like minimal manipulation and homologous use. The article discusses various regulatory pathways, emphasizing the need for Investigational New Drug (IND) and Biologics License Applications (BLA). Additionally, it explores the regulation of stem cell combination products, which may involve devices or drugs. The FDA's strategy for regulating stem cell-based products demonstrates a dedication to finding a balance between innovation and patient protection. Although important advancements have been achieved in creating explicit guidelines and enforcement strategies, persistent challenges in product characterization, manufacturing processes, and international cooperation need ongoing focus.

Keywords: Combination Products; Stem Cell-Based Products; HCT/P; CBER; OCP; IND; BLA; Public Health Service

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1. Introduction

The United States Food and Drug Administration (FDA) plays a vital role in overseeing the development, approval, and regulation of stem cell-derived products. These encompass a range of therapies, including cell-based treatments, tissue engineering, and gene therapies, designed to address various medical challenges. Given the complex nature and potential of regenerative medicine, the FDA's regulatory framework is designed to ensure the safety, efficacy, and quality of these innovative therapies.

This study seeks to investigate the FDA's regulatory requirements for stem cell-based products, analyzing the agency's strategy for ensuring safety and efficacy, the challenges faced, and the future implications for regenerative medicine.

1.1 Stem Cells Based Products

The U.S. Food and Drug Administration (FDA) describes stem cell-based products as human cells, tissues, or products consisting of cellular and tissue components (HCT/Ps) that include stem cells and are meant for implanting, transplanting, infusing, or transferring into a human patient. These products can originate from: Autologous sources, Allogeneic sources, or Xenogeneic sources.

Stem cell products can be broadly classified into two categories:

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) According to 21 CFR Part 1271.3(d): "HCT/P refers to items containing or consisting of human cells or tissues that are meant for implantation, transplantation, infusion, or transfer into a human recipient."

Stem cells are included in this classification when they are utilized for structural purposes (such as tissue repair) or for cellular functions (like regenerative treatment).

Biological Products (for stem cells that are more than minimally manipulated)

Stem cell products are considered biological products under Section 351 of the Public Health Service (PHS) Act

- They are intended for non-homologous use,
- They are combined with other materials (such as drugs, scaffolds, devices),
- Or they produce systemic effects and depend on the metabolic activity of living cells to function.

1.2 Regulatory Structure

The regulations are divided into two distinct categories, with section 351 covering drugs, devices, and biological products, while section 361 pertains to HCT/Ps and the prevention of communicable diseases. The regulations for HCT/Ps are outlined in Part 1271, which covers various aspects such as donor eligibility, manufacturing standards, procedures for clinical trials, and labeling of products, among other elements. Any products that fulfil all the criteria specified in 1271.10 must secure FDA licensure and approval. On the other hand, if a product fails to meet the standards set forth in 1271, it will fall under the regulations specified in Section 351 of the PHS Act and the FD&C Act. (1-2) The use of the 21 CFR Part 1271 product has been demonstrated in Figure 1 via a flowchart.(3)

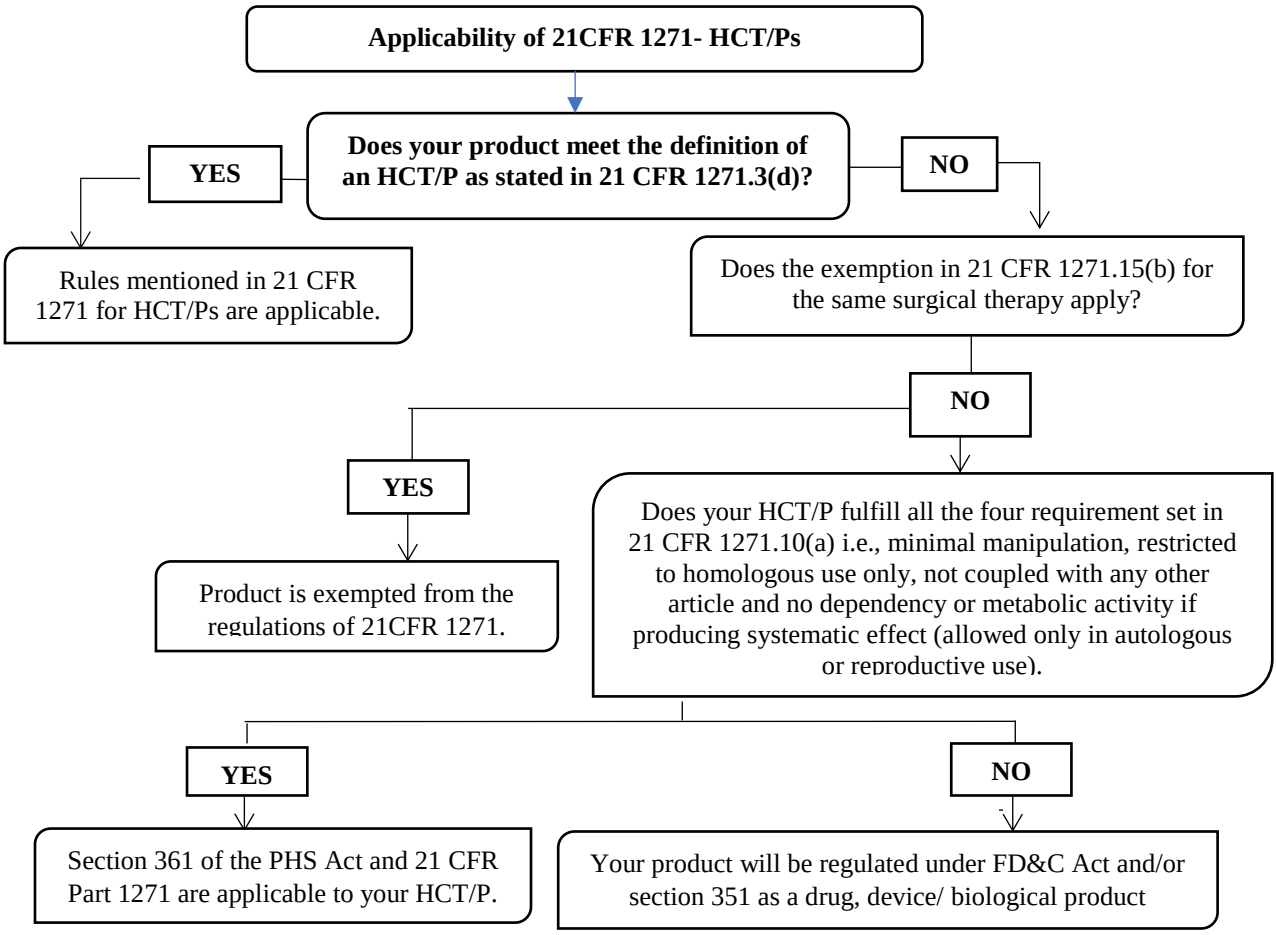

Figure 1. Flowchart depicting the relevance and exceptions of 21 CFR 1271 (3)

The FDA has introduced expedited initiatives for regenerative medicines to promote innovation and address unmet medical needs. These initiatives provide a fast-tracked process for the development and approval of cutting-edge products in a timely fashion. As a result, regenerative medicines receive a designation that makes them eligible for accelerated approval or priority review. (4) Table 3 presents the different programs in a comparative format.

2. US FDA Regulatory Requirements for Stem Cell based Products

2.1 Regulatory Considerations and Product Classification

In the United States, the regulation of cell therapy products is specified by certain sections of the CFR, which include IND regulations (21 CFR 312), biologics regulations (21 CFR 600), and cGMP (21 CFR 211).Federal regulations related to cellular therapy are categorized under two sections of the PHS Act, known as "361 products" and "351 products." The FDA has determined that cells or tissues used for therapeutic purposes, along with the processing guidelines for 361 products, are regulated by Good Tissue Practice. (7)

An HCT/P is only governed by section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria (21 CFR 1271.10(a)):

a. The HCT/P is only subject to minimal manipulation;

The HCT/P is intended solely for homologous use, as evidenced by labeling, advertising, or other indications of the manufacturer's purpose;

Table 1. Regulatory tools and Expedited programs for HCT/Ps by USFDA

Program	Eligibility Criteria	Nature of Program	Benefits	FDA Response timeline	When to submit
Fast Track Designation	In order to potentially address unmet medical needs, both clinical and non-clinical data are needed. A drug must be designed to treat a serious medical condition.	Designation	facilitated growth accelerated review and develop-ment Rolling review	A request must be made within 60 calendar days after receipt	it should be completed before the pre-BLA or pre-NDA meeting. This request may be included with the IND application or submitted as an amendment to the IND. (4-5)
Breakthrough Designation	• Preliminary clinical data is essential to demonstrate a significant improvement over existing treatments, with one or more clinically meaningful endpoints. • The drug must aim to address a serious condition.	Designation	• All benefits of fast track designation will apply. • There will be intensive FDA guidance on effective drug development. • Senior management will be involved as per the organization's commitment.	Within 60 calendar days of receipt request	The request should be submitted no later than the end-of-phase 2 meeting and can be included with the IND application or submitted as an IND amendment.
Regenerative Medicine Advanced Therapy	Preliminary clinical data must be provided to establish clinical significance. The product intended should treat, modify, reverse, or cure a serious condition and meet an unmet medical need.	Designation	• All advantages of fast track • Initial engagement with the FDA according to section 505(g)	Within 60 calendar days of receipt request	Prior discussions with the reviewing division regarding the potential for accelerated approval during the development phase.
Accelerated Approval	• The medication must be aimed at treating a serious condition. It must demonstrate a significant improvement over existing treatments. • It should show an influence on a clinical endpoint that can be assessed before irreversible morbidity or mortality (IMM).	Approval Pathway	Approval may be granted based on a surrogate endpoint that predicts the drug's clinical benefit.	Not specific	The request can be made alongside the original BLA, NDA, or efficacy supplement.
Priority Review Designation	The medication must be aimed at treating a serious condition. It should provide a meaningful enhancement in safety or effectiveness OR Any supplement requesting a labeling change due to a 505A report following a pediatric trial OR a drug qualified for treating infectious diseasesOR Any application or supplement for a drug submitted using a priority review voucher.	Designation	Reduced review timeline for marketing application (6 months instead of the usual 10-month standard review).	CBER must respond within 60 calendar days upon receiving the original BLA, NDA, or efficacy supplement.	
Orphan Designation	Intended for a rare disease or condition affecting 200,000 individuals (or a larger subset designated as orphan) in the United States, or where the costs of developing and producing the drug in the U.S. cannot be recouped through sales.	Designation	Offers 7 years of market exclusivity, a tax credit for qualified clinical trials, and an exemption from drug user fees.	The FDA will assess the request and provide a decision within 90 days of receipt.	Before submitting a marketing application, sponsors are allowed to seek designation at any point during the drug development phase. (6)
Revocation of Designation	If a product no longer meets the specific qualifying criteria for the designation, the designation may be withdrawn later in the product development process (20)				

b. The creation of the HCT/P does not involve combining cells or tissues with any other substances, except for water, crystalloids, or agents used for sterilization, preservation, or storage, provided that the addition of water, crystalloids, or these agents does not pose new clinical safety concerns regarding the HCT/P; and

c. Either:

i. The HCT/P does not display a systemic effect and does not depend on the metabolic function of living cells for its primary purpose; or

ii. The HCT/P does demonstrate a systemic effect or relies on the metabolic activity of living cells to achieve its main function.

If an HCT/P fails to meet the criteria outlined in 21 CFR 1271.10 (a), and the manufacturing facility is not eligible for any of the exceptions specified in 21 CFR 1271.15,(8) then the HCT/P will be classified as a drug, device, and/or biological product under the FD&C Act, in addition to section 351 of the PHS Act (42 U.S.C. 262), along with applicable regulations, including 21 CFR Part 1271, which will require a premarket review.

Minimal Manipulation: As specified in 21 CFR 1271.3(f), minimal manipulation is defined in the following manner,

a. For structural tissue, any processing that maintains the original essential characteristics relevant to its use in reconstruction, repair, or replacement;

b. For cells or nonstructural tissues, any processing that preserves the essential biological characteristics of the cells or tissues.(9)

Homologous Use: Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) states that an HCT/P must be intended solely for homologous use, as shown by its labeling or advertising, to be governed by section 361 of the PHS Act and Part 1271 regulations. Homologous use, as defined in 21 CFR 1271.3(c), involves repairing, reconstructing, replacing, or supplementing a recipient's cells or tissues with an HCT/P that serves the same essential function in the recipient as it does in the donor.(10)

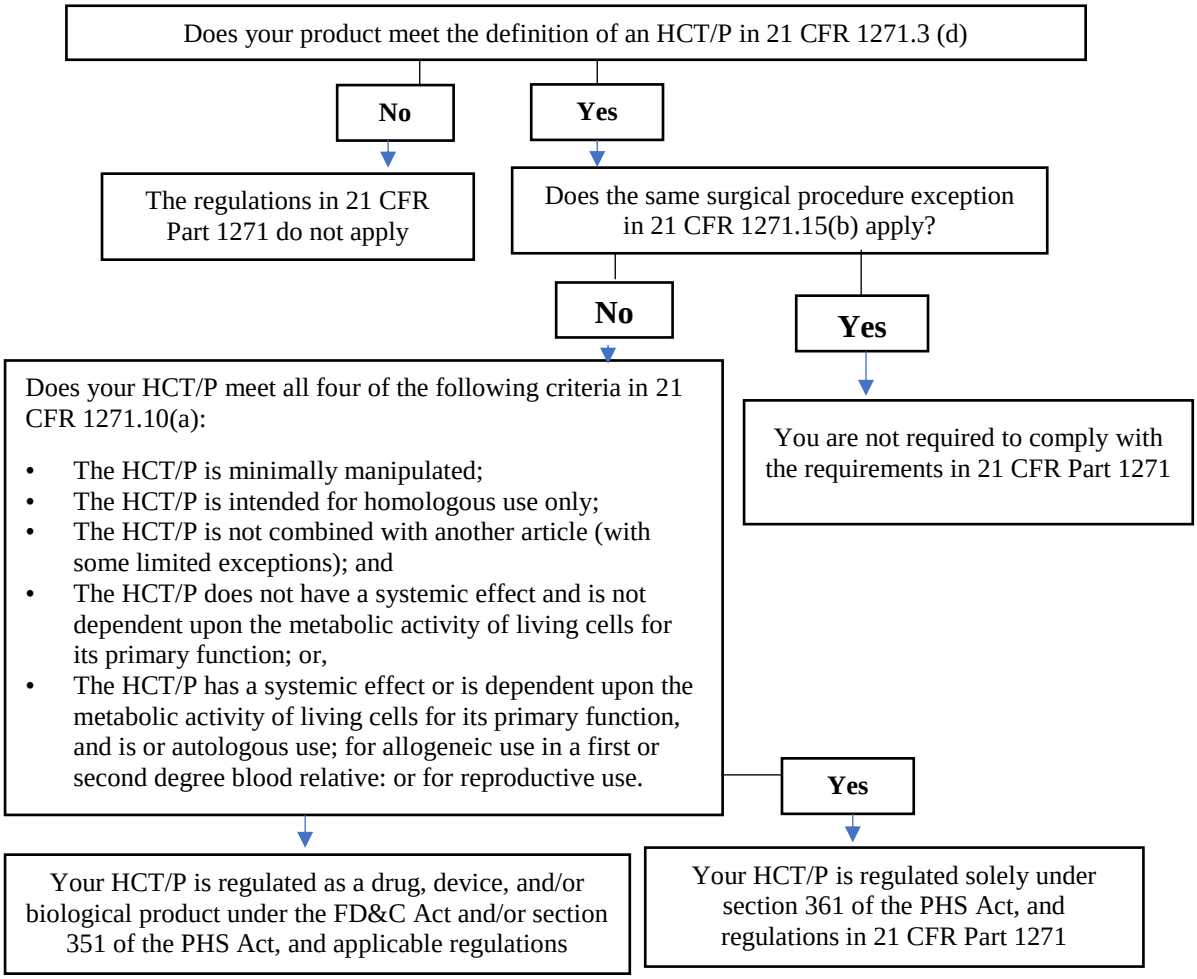

Figure 2. The flowchart above shows how manufacturers and healthcare providers should apply the criteria in 21 CFR 1271.15(b) and 1271.10(a) for HCT/Ps:(8)

2.2 Premarket Approval Process

2.2.1 IND (Investigational New Drug Application)

After preclinical studies assess the pharmacological properties and acute toxicity of new biological compounds in animals, the sponsor must obtain FDA approval to start human clinical trials by submitting an IND application.(11)

Under the Food, Drug, and Cosmetic Act, sponsors of biologics are required to file this application before administering products to humans. The IND sponsor, which can be an academic institution, government agency,

pharmaceutical company, or other entity, is responsible for the initial clinical trials.(12)

An IND application typically becomes effective 30 days after submission to the FDA, which uses this time to review it for safety concerns.(13) The evaluation focuses on safety issues, with preclinical study details helping the sponsor assess clinical trial safety.(14-16) During this period, the sponsor and FDA hold several meetings. The clinical investigation phase can last up to 12 years, with only 20% of tested compounds likely to show clinical effectiveness and safety. (17-18)

2.3 Application Review process of IND

2.3.1 Clinical Trials

- After a review by CDER or CBER, the application is sent to the document control center, which manages the application review process.
- Subsequently, an acknowledgment letter is generated for the applicant, and a project manager is designated to oversee the NDA review process.
- The CD is responsible for distributing several copies of the IND to various divisions for evaluation.
- The project manager performs an initial screening of the applications, which may be rejected if they fail to satisfy specific criteria.
- If any problems arise, a deficiency letter is issued to the applicant.(19-21)

Table 2. Phases of Clinical Trials

PHASE	FOCUS	PARTICIPANTS	DURATION
1	safety	20-100 volunteers	Months
II	efficacy	100-500 patients	Months to years
III	Safety & efficacy	1000-5000 patients	Years to decade
IV	Safety surveillance	Post approval surveillance	ongoing

2.4 NDA (New Drug Application)

To market a new drug or biologics product, it's necessary to submit an NDA or BLA application. The NDA is the process used by the CDER for drug product marketing, while the BLA is utilized by the CBER for biologics products. This situation can be confusing since some biological products receive approval through an NDA, while others are granted approval through a BLA. The evaluation and endorsement of an NDA focus on the product's safety and efficacy, based on comprehensive clinical trial reports.(22-25)

A pre-NDA meeting takes place between the sponsor and the FDA to go over the NDA's content and format. The main objective of the NDA is to obtain permission to market both the drug and biologics.(12, 26-27)

The NDA involves a specialized review team comprised of highly qualified specialists. This review team will determine whether to approve or reject the NDA.(17, 28)

2.4.1 NDA Review Process

a) The Central Document Room of CBER initially manages the application administration process, including stamping and dating (24, 29)

b) The status of user fees is determined, and details regarding user fees coverage are sent to the regulatory information management staff.

c) The CDR is tasked with distributing different copies of the NDA to various divisions for their evaluation.

d) Following this, an acknowledgment letter is sent to the applicant, and a project manager is appointed to oversee the NDA review process.

e) The project manager conducts the initial screening of the application, which may be rejected for certain reasons.

f) The FDA review team will gather for a meeting at 45 days to decide whether to accept or reject the application (19,30)

2.5 Biologics License Application (BLA):

The BLA is governed by 21 CFR 600 – 680 and serves as a request for permission to introduce a biologic product into interstate commerce (21 CFR 601.2). It typically pertains to vaccines, allergenic drugs, and gene therapies.(31)

2.5.1 Requirements for BLA:

- The FDA evaluates the market eligibility of biologics through the submission of a BLA. Although a BLA is similar to a NDA, it has its own intricate set of requirements. Determining whether an applicant included all essential information and presented it in an acceptable format according to the applicable regulations can be quite challenging.(32)
- While a BLA submission comprises various components, the main requirements are outlined in Form FDA 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use.(33) The checklist illustrated in the figure 3 acts as a general guide and reminder of the information that should be incorporated in a BLA; however, applicants must understand that specific and distinct details will be required depending on the particular type of BLA.(32)

2.5.2 Biologics License Application Process:

Vaccines and biologics typically follow same developmental pathway as pharmaceuticals.

The sponsor required to submit all non-clinical data to the FDA in case of an IND, and if the FDA does not respond within 30 days, the study under the IND can proceed. The sponsor may initiate clinical trials.For each phase of a clinical trial, the sponsor must evaluate the results and decide whether to move forward to the next phase.

Once the clinical trial data is finalized, the sponsor needs to conduct a pre-approval meeting. After submitting BLA to the FDA, the agency assembles a review team and assesses within the first 60 days of submission whether to

accept or deny the application. When applying for a BLA, the manufacturer must submit an application to the Director of the CBER at the FDA, using the prescribed forms, along with data from both nonclinical and clinical studies to demonstrate the safety, purity, and potency of the biological product. The US FDA also examines the production methods of the biological product.(34)

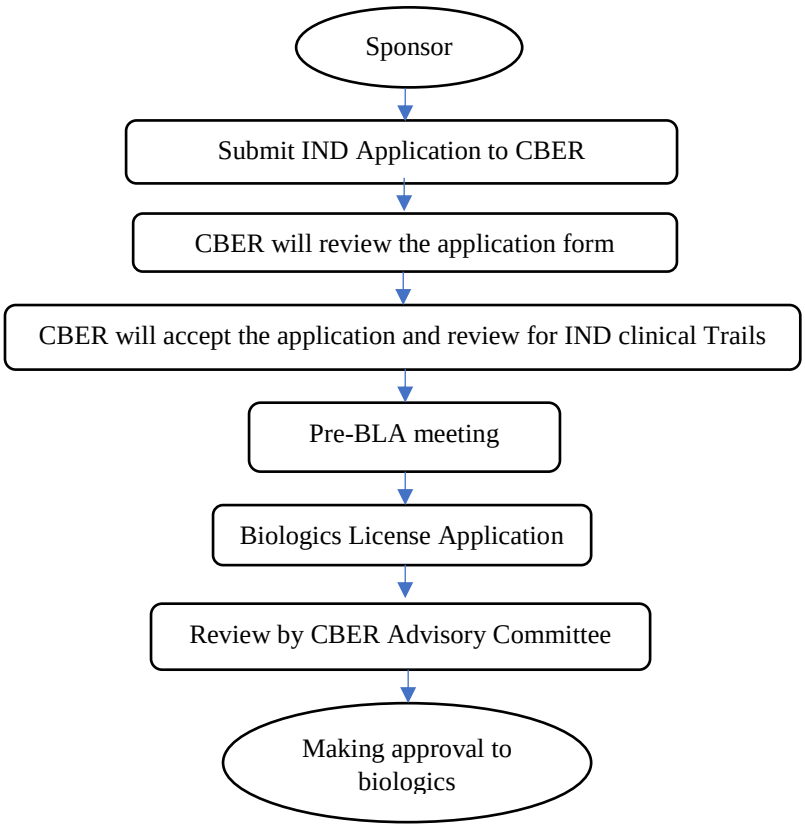

Figure 3. Biologics License Approval Process (35)

2.6 FDA Review Process

Upon submission of BLA, the FDA begins review process. This process initiates with a preliminary 60-day review period during which the FDA determines if the application is adequately complete enough to allow for a thorough review. If the application is deemed complete, the FDA will 'file' it and assign a Prescription Drug User Fee Act date, indicating the target date for the FDA to complete its review.

Around the midpoint of the review cycle, generally in the fifth month for standard reviews, the FDA communicates a mid-cycle update to the sponsor. As the review process approaches its end, a late-cycle meeting occurs between the FDA and the sponsor. This meeting allows for discussions regarding any unresolved application issues, examination of proposed labeling, and conversations about potential post-marketing obligations or commitments. Throughout the review process, the FDA also conducts pre-approval inspections of manufacturing sites to confirm compliance with current Good Manufacturing Practices (cGMP).

The guidelines for cGMP are elaborated in various segments of the Code of Federal Regulations (CFR), which consist of 21 CFR Parts 210, 211, 600, 606 and 820.

2.7 FDA Decision and Post-Approval Phase

After the review process is finalized, the FDA will either deliver an approval letter or a complete response letter. If the product is granted approval, the sponsor can proceed with its launch; nevertheless, their responsibilities are not complete. Post-approval duties entail performing any necessary post-marketing studies, submitting ongoing safety reports to the FDA, and ensuring compliance with current Good Manufacturing Practices.

2.8 Post-Marketing

Table 3. The criteria for PMS regarding stem cell products in the US

Framework	Guidelines
Main guidelines for the PMS of CGTP	• Guidance directed at the industry: post-marketing studies and clinical trials - the application of Section 505(0)(3) of the Federal Food, Drug, and Cosmetic Act • REMS: The FDA's consideration of statutory elements in deciding when a REMS is warranted • Guidance for industry on long-term follow-up post-administration of human gene therapy products guidance

Tools for PMS	• REMS • Adverse reaction reporting • Product labeling • PMR and PMC • PSUR
Submission of PSUR	Every three months for three years after the approval of the drug, and then annually
Mandatory PV requirements	• Monitoring of adverse events • Regular and additional pharmacovigilance • PMR • Spontaneous reports
Optional PV requirements	• PMC • Plan for risk minimization actions

2.9 Approved Cellular and Gene Therapy Products

Table 4. Approved cellular and gene therapy products (36-54)

PRODUCTS	MANUFACTURER
ALLOCORD® (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center
CLEVCORD (HPC, Cord Blood)	Cleveland Cord Blood Center
HEMACORD (HPC, Cord Blood)	New York Blood Center, Inc.
DUCORD (HPC, Cord Blood)	Duke University School of Medicine
HPC, Cord Blood	ClinImmune Labs
HPC, Cord Blood	MD Anderson Cord Blood Bank
HPC, Cord Blood	LifeSouth Community Blood Centers, Inc.
HPC, Cord Blood	Bloodworks
BREYANZI® (lisocabtagene maraleucel)	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
KYMRIAH™ (tisagenlecleucel)	Novartis Pharmaceuticals Corporation
YESCARTA® (axicabtagene ciloleucel)	Kite Pharma, Inc.
TECARTUS™ (brexucabtagene autoleucel	-
ABECMA® (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company
PROVENGE® (sipuleucel-T)	Dendreon Corporation
GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)	Organogenesis Inc.
LAVIV® (azficel-T)	Fibrocell Technologies, Inc.
MACI®	Vericel Corporation

Under the current FDA policies, there are at least two methods by which physicians can provide patients with stem cell products that are more than minimally manipulated. The first method is through the FDA's expanded access program for investigational drugs and biological products for treatment use, provided that these products are still being tested in clinical trials and that granting expanded access will not disrupt ongoing clinical investigations. The FDA permits clinicians to charge for the costs directly associated with expanded access and for administrative expenses. (53) The second method involves the off-label prescribing of stem cell products that have been approved by the FDA. Off-label prescribing is based on the belief that the FDA does not have the authority to oversee medical practice and the assumption that physicians can be relied upon to exercise their professional judgment in deciding how to treat their patients. (54)

3. Conclusion

The regulatory framework set forth by the US FDA for stem cell-derived products provides a comprehensive approach to ensuring the safety and efficacy of these innovative therapies. This study highlights the importance of understanding and complying with FDA regulations to successfully launch stem cell-based products in the market. By effectively maneuvering through the complex regulatory landscape, manufacturers can confirm that their products meet the necessary standards for safety, purity, and potency, ultimately benefiting patients and fostering progress in the realm of regenerative medicine.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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