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Regulatory Considerations of Orthobiologic Procedures

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KEYWORDS

• PRP • MFAT • SVF • BMAC • Birth tissue products • FDA

KEY POINTS

- Platelet-rich plasma (PRP) is not considered a human cellular-based product (HCT/P) and is regulated as blood-derived product under 21 CFR 640.
- Bone marrow products that undergo minimal manipulation for homologous use and are not combined with another article are not considered an HCT/P; regulation is similar to PRP.
- Nano fat, fat grafts, and microfragmented adipose tissue that do not alter tissue microarchitecture are regulated as HCT/Ps and are under moderate regulation; they do not require premarket approval (PMA) by the FDA.
- Bone marrow aspirate concentrate that is altered beyond centrifugation and concentration and adipose-derived products that are enzymatically or mechanically digested are under strict regulation; they require PMA by the FDA
- Birth tissue products are not permitted for use for orthopedic purposes outside of research with an investigational new drug application.

INTRODUCTION

Regenerative medicine is a rapidly growing field of novel therapies used in the treatment of musculoskeletal conditions. Despite growing experience among providers and developing evidence, the field continues to be under researched. Even so, some research can be associated with inflated expectations of regenerative capabilities and the ability to treat unmet medical needs.[1–3] Although this has stimulated growth in legitimate and appropriate research discussion, the growing enthusiasm has also permitted more exuberant and at times inappropriate information for both providers and patients. This information can potentially harm patients while also

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threatening research progress in the field, necessitating a stringent need for regulation.[4] These regulatory, ethical, scientific, and clinical concerns are the primary aim of this article .

The Necessity for Federal Regulation

The United States holds the largest number of stem cell clinics globally.[5] Hundreds of these clinics directly market unproven stem cell-related therapies to consumers. These unproven treatments without appropriate testing, manufacturing standards, and clinical supervision have several inherent risks.[1,6] Yet, despite these risks, the direct-to-consumer industry for these unproven stem cell clinics is growing, with marketing strategies targeting orthopedics/sports conditions, neurologic conditions, and cosmetic/antiaging/sexual conditions.[7]

Food and Drug Administration Regulations of Human Cells, Tissues, and Cellular-Based Products

Several regulations by the Food and Drug Administration (FDA) have been developed over time to enhance the discretion of these products and encourage the proper study of evidence-based treatments. In 1997 the FDA proposed a centralized plan for regulation, which eventually became the Title 21 Code of Federal Regulations Part 1271 (21 CFR 1271).[8,9] This policy, in use today, defined what is known as human cells, tissues, and cellular-based products (HCT/Ps).

The FDA defines HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." All HCT/Ps must pass Part 1271. This parameter addresses the primary constraints of structural versus nonstructural tissue, minimal manipulation, the homologous purpose of the product, and its autologous versus allogeneic properties.

In defining minimal manipulation, the FDA separates structural tissue from nonstructural tissue. For structural tissue, this 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. In nonstructural tissue, minimal manipulation is described as processing that does not alter the relevant biological characteristics of cells or tissues.[9] Examples of structural versus nonstructural tissues are displayed in **Table 1**.

Beyond minimal manipulation, it is necessary to determine the homologous use of the product. Homologous use is defined by the FDA as the 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 (CFR 1271.3(c)).[9] This may include identical cells and tissues, or cells and tissues that are not identical but perform one or more of the same basic functions.[10] If the HCT/P performs multiple functions, the basic functions that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor. Basic functions should be understood and not require study to prove that it is basic to the donor.

Finally, the product must be deciphered as allogeneic or autologous. All allogeneic products intended for stem cell use fail regulation under 21 CFR.10. These products cannot have a systemic effect or be dependent on the metabolic activity of living cells for their primary function.

The FDA has sent warning letters for noncompliance with homologous use mandates and minimal manipulation rules to companies such as Liveyon, Genetech, R3, and Cord for Life, among others. Despite warning letters and enforcement actions, unproven stem cell clinics still exist that continue to market these interventions.[11]

Table 1
Examples of structural and nonstructural tissues

Structural Tissue	Nonstructural Tissue
Bone	Reproductive cells or tissues
Skin	Cord blood
Amniotic membrane	Amniotic fluid
Blood vessels	Bone marrow aspirate
Adipose tissue	Lymph nodes
Articular cartilage	Parathyroid glands
Nonarticular cartilage	Peripheral nerve
Tendons and ligaments	Pancreatic tissue

Tiers of Human Cells, Tissues, and Cellular-Based Products Regulation

HCT/Ps are regulated in tiers based on the degree of perceived risk to public health. The tier-based approach is addressed in the "tissue rules" under the communicable disease authority of the Public Health Service (PHS) Act (42 US .C. 264). These regulations define those HCT/Ps that do not require premarket approval (PMA) and registration, manufacturing, and reporting steps that must be taken to prevent the introduction, transmission, and spread of communicable diseases. The PHS Act is the authority on which the FDA has relied for CFR Part 1271.[12]

There are two primary tiers of regulation that address minimally invasive orthopedic procedures in the PHS Act, Sections 351 and 361. Those HCT/Ps under Section 361 do not require PMA by the FDA. To qualify as an HCT/P that is regulated under Section 361, the tissue product must meet all three criteria defined in CFR 1271.10. This includes a tissue product that has a homologous purpose, autologous usage, and minimal manipulation of tissue. HCT/Ps that do not meet these criteria fall under the regulation of Section 351 of the PHS Act. These products are regulated as a drug, device, or biologic product that requires PMA.[13] To obtain PMA, a product must meet an additional level of regulation. New drugs require an investigational new drug (IND) approval and must comply with good manufacturing practice regulations.

There are cases where a biologic or establishment may qualify for an exception to criteria defined in part 1271. These exceptions are in CFR 1271.15(b), which states "you are not required to comply with the requirements of this Part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure." For this to apply, the HCT/P still must be autologous, implanted in the same surgical procedure, and the HCT/P must remain in its original form, that is, with minimal manipulation of tissue. Cell isolation, expansion, activation, or enzymatic digestion do not fall under this category and are not allowed.[13]

DISCUSSION

Regenerative Medicine and Orthobiologics

The conservative management for various orthopedic injuries, such as tendinopathy, ligamentous injuries, and osteoarthritis, has evolved with orthobiologics. Most of the biologics used within the clinical settings are autologous and include platelet-rich plasma (PRP), bone marrow aspirate (BMA), and adipose-derived stem cells (ASCs). Other allogeneic sources, however, have also been trialed and include birth tissue products such as the umbilical cord, placental tissue, and amniotic fluid.[13] These products are used in purported antiinflammatory usage but are unsure about their

ability to regenerate poorly healing tissues such as articular cartilage, tendons, and ligaments.[14] The regulations related to these individualized biologics vary and specific considerations should be considered when implementing them into common practice based on FDA HCT/P regulations.

Platelet-rich plasma

PRP is a biologic product defined as a portion of the plasma fraction of autologous blood with an elevated platelet concentration above the baseline to the concentration of 1,000,000 platelets per microliter.[15] The product is obtained from the blood of patients and is processed through a method of centrifugation. The FDA's definition of PRP stipulates that preparation requires a single, uninterrupted venipuncture to be centrifuged within hours of collection.[9] This definition constitutes PRP as a blood-derived product that is regulated under 21 CFR 640 and does not fall under the definition of an HCT/P per the 21 CFR 1271.[9]

There is substantial variability in PRP preparations, conceivably due to differences in patients' daily platelet levels, procurement methods, concentration mechanisms, and other exogenous factors.[14] Many of these may originate from specific device differences. PRP is regulated through the device that is used to manufacture it, and these devices have been brought to market via the 510(k) pathway.[16–18] The 510k pathway clears products that are substantially equivalent to an already cleared predicate device.[19] For PRP, the device is a platelet and plasma separator that produces the PRP. Through this pathway, PRP receives FDA clearance to be used in a variety of orthopedic conditions. Clearance, however, is not synonymous with FDA approval and PRP for musculoskeletal conditions is considered "offlabel" use.[16]

Bone marrow aspirate

Bone marrow-based stem cell therapies emerged as a promising biologic tool due to the presence of pluripotent mesenchymal stem cells (MSCs) and growth factors. These cells via paracrine and autocrine pathways decrease cell apoptosis and inflammation, activate cell proliferation and differentiation, and induce angiogenesis.[20,21] The aspiration of bone marrow is most often taken from the iliac crest, and aspirate volume depends on the processing system and the goal of treatment. The BMA can then be concentrated into BMA concentrate (BMAC) to result in a product with a higher concentration of nucleated bone marrow cells compared with BMA.[13,20] This concentrated product is subject to FDA regulation.

Autologous bone marrow products are not considered HCT/Ps if they undergo only minimal manipulation, are for homologous use, and are not combined with another article (except water, crystalloids, sterilizing agent, preserving agent, or storage agent). Bone marrow is considered a nonstructural tissue and the relevant biological characteristics cannot be altered to be considered minimally manipulated. This includes the differentiation and activation state, proliferation potential, and metabolic activity. If a manufacturer performs cell selection on a mobilized peripheral blood apheresis product to obtain a higher concentration of hematopoietic/progenitor cells for transplantation, the product is considered minimally manipulated and is not regulated under the 21 CFR 1271 as an HCT/P. By this, the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristics to repopulate the bone marrow.[12] It should be noted that the injection of BMAC for orthopedic indications is considered offlabel use.[13]

In contrast to BMAC products that have only undergone minimal manipulation and are intended for homologous use, bone marrow that has been altered beyond centrifugation and concentration is more tightly regulated. The FDA is clear that isolating

and expanding cells after bone marrow aspiration is not within minimal manipulation. Any cell expansion is controlled within the jurisdiction as a 351 Product (drug or biologic product) requiring PMA.[9,13]

Adipose tissue-derived products

ASC therapies for orthopedic conditions have come to the forefront of biological treatments given promising preclinical and clinical data from animal and human studies.[22–25] Adipose tissue is rich in MSCs, and its extraction has an excellent safety profile with easy accessibility and a self-replenishing abundance.[26,27] To extract adipose, the tissue is aspirated via tumescent liposuction either from the abdomen, hip, thigh, or infrapatellar fat pad. It can then be processed by a few different methods. In one method, the fat either undergoes mechanical emulsification or enzymatic digestion to obtain a liquefied heterogeneous suspension of a multitude of cells, referred to as stromal vascular fraction (SVF). The alternative is for the fat to be progressively reduced in size, eliminating residue and blood elements, via rinsing, resizing, and reshaping the fat without digestive enzymes. This occurs with microfragmented adipose tissue (MFAT), nano fat, or with a fat graft/fat transfer.[13,28,29] Each adipose-derived tissue product is subject to different regulations by the FDA.[13,28]

SVF involves processing by enzymatic digestion and/or isolation of cellular components. Owing to the processing required for the preparation of the ASCs in SVF, the use of SVF-derived stem cell injections does not qualify as minimally manipulated tissue. Therefore, it is regulated as a 351 Product (strict regulation and oversight as a drug, device, or biological product for patient use and marketing).[13] MFAT, nano fat, and fat grafts/fat transfers, in contrast, may be evaluated separately given the mechanism of action. Specifically, if these treatments and devices only process fat through steps of rinsing, sizing, cleansing, or shaping the tissue to facilitate removal of debris, the cell and tissue microarchitecture are preserved as "such HCT/P" and are considered minimally manipulated.[30,31] MFAT, nano fat, and fat grafts/transfers, when used in this manner, are minimally manipulated, autologous, and used within a single procedure. These devices have also been cleared by the FDA for homologous use as cushioning and support for other tissues. They are not, however, indicated to treat orthopedic and musculoskeletal conditions at this time. Still, they do qualify for the same surgical procedure exemption under CFR 1271.15(b) and with that, clinical application off label may be permitted with proper discussion and informed consent from the patient. Any adipose-derived products beyond this, including SVF, require PMA and the use of an IND.

Birth tissue products

In theory, birth tissue products, such as umbilical and amniotic cells, are a potent source of MSCs with high proliferative capacity and expansion potential. The cells contain antiinflammatory cytokines such as interleukin (IL)-1RA and IL-10 in addition to factors that upregulate anabolic pathways such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor.[32,33] The cells and fluid also upregulate tissue inhibitors of metalloproteinase, which can halt the progression of certain disease processes[34,35] and contain hyaluronic acid and proteoglycans for lubrication and reduction of shear forces.[36,37] It should be noted that on delivery and injection of the cells per the manufacturer's suggestions, there are no actual live cellular products.[38]

There are limited data suggestive of effective and positive outcomes for orthopedics sports indications.[13,39] The FDA regulates these products under the umbrella of an HCT/P. Under this regulation, the lyophilization and packaging of amniotic membrane

tissue as particles is considered more than minimal manipulation as it alters the original relevant characteristics of the HCT/P.[40] The original relevant characteristics, in this case, would be considered the integration of the amniotic membrane as a barrier, generally including the tissue's physical integrity, tensile strength, and elasticity. The use of MSCs from birth tissue products is not accepted by the FDA.

In 2017, the FDA outlined a framework for the regulation of regenerative medicine products and outlined the intent to exercise enforcement discretion until November 2020 for certain regenerative medicine products. This was regarding the IND and PMA requirements to give manufacturers time to determine what requirements apply and effectively engage with the FDA. During the period of enforcement discretion, products, mostly related to birth tissue products, were allowed to be used in the clinic setting to demonstrate safety and efficacy. The period of enforcement discretion was extended until May 2021. After this time, many amniotic fluid and membrane injectables were withdrawn from the market due to noncompliance with the FDA regulations for minimal manipulation and the failure to properly investigate the product or obtain an IND.[41] Several companies engaged with the FDA and regenerative medicine advanced therapy designations were obtained with ongoing studies for a few of these products. None have been approved for any orthopedic use and at this time they cannot be used in the clinic setting unless they are a part of a research trial with an IND from the FDA.

Future directions

Clinicians who use orthobiologics need to be aware of the shifting environment. The FDA regulations and enforcement have responded to the growth of unproven stem cell clinics and placed multiple regulations on products, with the hope that it will allow the field to grow safely and effectively. These regulations are always subject to change, and it is prudent to be cognizant of current protocols and recommendations for clinical practice. There exists a need to navigate the clinical environment with a standard of care and best practice statement that mirrors the current regulations by the FDA. This recommendation statement should define specific nomenclature, laws, and licensure limitations. The American Medical Society of Sports Medicine has addressed this gap with its most recent statement on the responsible use of regenerative medicine and orthobiologics in sports medicine.[42] This comprehensive position statement aids in moving clinicians and regulatory bodies. Through this, future research is encouraged to establish protocols for the field that may develop into the standard of care for practitioners.

SUMMARY

Many fraudulent stem cell clinics market unproven treatments, which consumers and physicians need to be aware of. The best way to address these ethical, legal, and scientific issues is to understand the current landscape of orthobiologics and be aware of the current FDA guidelines. It is only through this understanding that legitimate research can be performed to continue to advance the field.

CLINICS CARE POINTS

- The Food and Drug Administration (FDA) regulates minimally manipulated fat transfers, stromal vascular fraction (SVF), and birth tissue products under the Title 21 Code of Federal Regulations Part 1271. This specifically defines human cells, tissues, or cellular or tissue-based products (HCT/Ps).

- HCT/Ps must define whether a product is structural or nonstructural, minimally manipulated, used for a homologous purpose, and whether it is autologous or allogenic.
- Autologous platelet-rich plasma and bone marrow aspirate concentrate with minimal manipulation are not considered an HCT/P and are regulated as blood-derived products under 21 CFR 640.
- Bone Marrow Concentrate that undergoes alteration beyond centrifugation and concentration is considered more than minimal manipulation, which would be regulated as a 351-product requiring premarket approval (PMA).
- SVF is regulated as a 351 product and cannot be used outside of an IND, as enzymatic or mechanical digestion is considered beyond minimal manipulation.
- Nano fat, fat grafts, and micro-fragmented adipose tissue that do not alter tissue microarchitecture are regulated as HCT/Ps and are under moderate regulation; they do not require PMA by the FDA.
- All mesenchymal stem cells from birth tissue products are now classified as a 351 product requiring PMA and currently should not be used in clinics outside of the company's IND.
- Physicians can use any legally available product off label, according to their clinical judgment, but the marketing materials can only reflect onlabel claims.

DISCLOSURE

K. Mautner is a speaker and consultant for Lipogems.

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