

Food and Drug Administration's Position on Commonly Injected Biologic Materials in Orthopaedic Surgery

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The use of biologically based therapies is becoming a popular less-invasive therapy for relieving pain and promoting tissue regeneration. The most commonly used biologics are autologous adipose-derived products, bone marrow aspirations, and platelet-rich plasma (PRP). Birth tissue is a common allogenic source of biologics, including umbilical cord, placental membranes, and amniotic fluid. Injected biologics, depending on the indication and how they are processed, formulated, delivered, and promoted, can be subject to different regulatory pathways. The aim of this review is to provide an overview of these products and procedures and educate the musculoskeletal community about the relevant current Food and Drug Administration (FDA) regulations.

Keywords: Food and Drug Administration; regulatory aspects; biologic injection; HCT/Ps; tissue rules

Biologic and regenerative medicine products are becoming more prevalent in the practice of medicine. “Stem cell” injection therapy, a misnomer, has emerged as a conservative “treatment gap” alternative for a wide range of conditions.^{10,12} Examples of autologous sources of biologics include adipose-derived products,²⁴ bone marrow aspirations,³¹ and platelet-rich plasma (PRP).¹⁸ Common allogenic sources of biologics include umbilical cord and placenta-derived products.²¹ The manufacturing, labeling/claims, and promotion of these products are regulated under the US Food and Drug Administration (FDA). It is important that the physician understand the government's regulatory role and current stance on these emerging biologic injections.

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FDA OVERVIEW

There are several different sections in the FDA, including 6 distinct centers with responsibility for regulating specific product areas. The agency has several administrative and program offices aimed toward its mission to protect and promote public health.⁴⁴ The center that is directly responsible for regulating biological products, including human cells, tissues, and cellular and tissue-based products (HCT/Ps), is the Center for Biologics Evaluation and Research (CBER).³⁸ CBER publishes ongoing guidance documents describing comprehensive requirements for industry, including current good tissue practices, donor screening, and donor testing requirements to prevent the introduction, transmission, and spread of communicable disease. The 1938 Food, Drug, and Cosmetic Act and the 1944 US Public Health Service Act (PHSA) provide the FDA with the legal framework to control clinical use and interstate commerce of these HCT/Ps.⁵³ The regulations related to these laws are contained in the 1997 Code of Federal Regulations (CFR).³⁹

The majority of HCT/Ps intended for injection, depending on the indication and how they are processed, formulated, delivered, and promoted, are regulated as defined by Sections 351 and 361 in 21 CFR 1271 of the PHSA. The less burdensome 361 pathway has no requirement for premarket approval (PMA). The 351 biologics pathway requires PMA: biologics license application (BLA). HCT/Ps also may fall into a device category that would require premarket clearance (510[k]) or PMA.

FDA TISSUE RULES

The structure of HCT/Ps is complex and often includes a complex combination of different cell lines, extracellular matrix proteins, growth factors, and cytokines. There is

significant variability in the final product composition based on the type of tissue used and the processing techniques. Because of this unique nature of HCT/Ps, the FDA implemented a 3-tiered, risk-based approach to the regulation in 2005.⁴⁷ This set of regulations, known as the “tissue rules,” is split into different tiers based on the degree of perceived risk to public health and regulatory concerns. This includes preventing transmission of communicable disease, preventing contamination of products, and preserving the integrity and function of these tissues. Different regulatory tiers provide varying degrees of regulatory oversight, preapproval, and standards under the authority of Section 361 of the PHSa.

These biologic HCT/Ps can be split into 3 different categories with increasing oversight (Table 1). Biologic products that the FDA considers to be low or minimal risk and are not regulated as HCT/Ps include “vascularized human organs for transplantation, whole blood and blood-derived products, and extracted human products such as collagen and bone marrow that are minimally manipulated, for homologous use and not combined with another article (except for the purpose of sterilizing, preserving, or storing).”⁵³ Additional products that are exempt from HCT/Ps oversight include autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping. These tissues cannot be combined with other articles and must be minimally manipulated and comply with homologous (intended) use. The FDA also considers a same-day surgical procedure as an exception to regulation in Part 1271 since the transplantation of one’s own tissues raises no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery.⁵³ Examples of procedures that are considered the same surgical procedure as listed by the agency include autologous skin grafting and coronary artery bypass surgery.⁵³ Good tissue practices must be followed for infection/contamination safety. Registration with the CBER is not required.

The next tier of products is considered to require minimal oversight and must comply with requirements specified under Section 361 of the PHSa. These do not require FDA premarket review or notification before they are marketed and sold.³⁹ To be considered a 361 product, the HCT/Ps must (1) be minimally manipulated (processing cannot alter the original relevant biological tissue characteristics), (2) be intended for homologous use only (same basic function in recipient and donor), (3) not be a combination product or combined only with such articles that “do not raise new clinical safety concerns with respect to the HCT/Ps,” and (4) have no systemic effect and not be dependent on the metabolic activity of living cells.⁵³ Registration of use with the CBER and annual reporting is required.

Finally, the highest tier of FDA oversight includes products that do not meet 361 requirements. These products are regulated under Section 351 of the PHSa and require complex preclinical animal trials, pharmacology, and toxicity studies before getting an investigational new drug (IND) application with the FDA to administer the biologic product

in phased human clinical trials. These studies require a completed and approved BLA before the product can be marketed.^{22,51} This category is much more restrictive.

FDA MEDICAL DEVICE REGULATION

Medical devices are common in the medical field and are currently used with biological products. The FDA classifies medical devices based on risk (Table 2). Class 1 devices are considered low risk, class 2 pose a moderate risk, and class 3 devices are high risk with the potential of harm or injury to patients.⁴⁶ Class 1 products (eg, tongue depressor) are typically exempt devices and do not require FDA clearance before market entry. A small subset of class 2 devices also qualify for exempt status, but most class 2 devices undergo the 510(k) pathway. Everything else falls into the class 3 PMA safety and effective pathway, the most rigorous regulatory review.⁴⁹

Before the medical devices can be marketed (sold) in the United States, they are required to be cleared or approved by the FDA.⁴⁰ There are major differences between these 2 distinctions. A cleared device means that it has undergone a 510(k) submission, where the FDA has reviewed and provided clearance. There are no requirements for 510(k) products to prove safety and efficacy because they need to prove substantial equivalence to a legally marketed device (predicate device). The strict device PMA classification and evaluation process is comparable to those required for drugs. PMA products need to demonstrate a higher standard of safety and efficacy. Device classification depends on the intended use of the device and the indications for use. Approved medical devices are typically reserved for class 3 medical devices that the FDA has approved through a PMA application or a humanitarian device exemption. During times of emergencies the FDA also reserves the right to approve new drugs or new indications for previously unapproved drugs and medical devices with an emergency use authorization.⁴³ This type of authorization was seen during the coronavirus 2019 (COVID-19) crisis to approve medical devices and therapeutics.

There is a separate category, the de novo pathway, for low- to moderate-risk devices that do not have a predicate device and are automatically classified into class 3 (new devices).⁸ The de novo pathway document is submitted to the FDA to reclassify the device with new classification/regulation. Medical device sponsors have 2 options to consider a de novo pathway. They can submit a 510(k) application to the FDA, and upon the feedback of “not substantially equivalent” (no predicate device), they can make a de novo request. Otherwise, sponsors can directly send a de novo application. During the submission process, sponsors need to characterize the risks to health and safety associated with the use of the device and how these risks can be minimized.⁴² However, since there is no existing product in a de novo submission, there are stricter regulatory safeguards. Once a device is approved through a de novo submission, it creates a predicate device that somebody else can use to do a 510(k).

TABLE 1
FDA “Tissue Rules”^a

Category	HCT/P That	Regulation	Examples
Exempt from HCT/Ps	<ul style="list-style-type: none"> Does not meet the definition of HCT/Ps (21 CFR 1271.3(d)) Exceptions include: <ul style="list-style-type: none"> Establishment that uses HCT/Ps solely for nonclinical, scientific, or educational purposes Same surgical procedure exception Carrier who accepts, receives, carries, or delivers HCT/Ps in the usual course of business as a carrier Establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within the facility 	<ul style="list-style-type: none"> Follow current good tissue practices (cGTPs) Follow the respective regulation that the tissue product falls under Regulated as a drug, device, and/or biological product under the act and/or Section 351 of the PHSA, and applicable regulations in Title 21, Chapter I Applicable regulations include, but are not limited to, 207.9(a)(5), 210.1(c), 210.2, 211.1(b), 807.20(d), and 820.1(a) 	<ul style="list-style-type: none"> Vascularized human organs for transplantations Whole blood and blood-derived products Extracted human products Same-day surgical procedure (autologous skin grafting, coronary artery bypass)
361 products	<ul style="list-style-type: none"> The HCT/P is minimally manipulated The HCT/P is intended for homologous use only 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; and either: <ul style="list-style-type: none"> The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and <ul style="list-style-type: none"> Is for autologous use; Is for allogenic use in a first-degree or second-degree blood relative; or Is for reproductive use 	<ul style="list-style-type: none"> HCT/P is regulated solely under Section 361 of the PHSA, and regulations in 21 CFR 1271 No premarket approval required Follow CGTPs Donor eligibility determination 	<ul style="list-style-type: none"> Bone (include demineralized bone) Tendons Cartilage Skin Pericardium Dura mater Embryos Ligaments Fascia Ocular tissue Vascular grafts (except preserved umbilical cord veins) Hematopoietic stem cells derived from peripheral or umbilical cord blood
351 products	<ul style="list-style-type: none"> Fail to meet criteria for 361 products Regulated as a drug, device, and/or biological product depending on the primary mode of action 	<ul style="list-style-type: none"> HCT/P is regulated under Section 351 of the PHSA Regulated under the Federal Food, Drug, and Cosmetic Act (FD&C) and applicable regulations CGTPs and current good manufacturing practices (cGMPs) Premarket approval, safety, and effectiveness Investigational new drug (IND) 	<ul style="list-style-type: none"> Cultured cartilage cells Cultured nerve cells Lymphocyte immune therapy Gene therapy products Human cloning Human cells used in therapy involving the transfer of genetic material Unrelated allogenic hematopoietic stem cells Unrelated donor lymphocytes for infusion

^aCFR, Code of Federal Regulations; FDA, Food and Drug Administration; PHSA, Public Health Service Act.

CURRENT BIOLOGIC INJECTION PRODUCTS

Platelet-Rich Plasma

PRP has seen increased interest and utilization in the past decade in a wide range of medical fields, including dermatology, orthopaedics, and aesthetic plastic surgery.^{4,14} PRP can generally be defined as a complex concentrated solution derived entirely from autologous whole blood and processed to concentrate platelets. There are no stem cells in PRP products, and the FDA’s definition of PRP requires that the blood be collected by a single, uninterrupted venipuncture; be centrifuged within hours of collection; and

contain at least 250,000 platelets per microliter.⁵⁹ In addition to the concentrated platelets, PRP contains a diverse compilation of other cells, proteins, cytokines, and growth factors. The concentration of these biomolecules significantly differs between PRP preparations, and there are currently no standardized preparation techniques. Platelet-poor plasma (PPP) is another product created when spinning down whole blood. As the name suggests, PPP contains almost no platelets, but has fibrinogen and growth factors without cellular components.¹

The underlying principle generally includes the following steps (Figure 1): (1) venous blood drawn into a sterile

TABLE 2
FDA Medical Device Classification^a

Class	Risk Level	Regulation	Examples
Class 1	<ul style="list-style-type: none"> • Low risk • 55% of devices 	<ul style="list-style-type: none"> • General controls for medical devices • Exempt from premarket notification (510(k)) • Exempt from medical device good manufacturing practices (GMPs) • No approval needed 	<ul style="list-style-type: none"> • Adhesive bandages • Tongue depressors • Crutches • Ankle braces
Class 2	<ul style="list-style-type: none"> • Medium risk • 40% of devices 	<ul style="list-style-type: none"> • General controls for medical devices • Premarket notification (510(k)) • De novo pathway • FDA clearance 	<ul style="list-style-type: none"> • Syringes • Pregnancy test kits • Platelet-rich plasma preparation kits • Lipoaspirate tissue processing system
Class 3	<ul style="list-style-type: none"> • High risk • 5% of devices 	<ul style="list-style-type: none"> • General controls for medical devices • Investigational device exemption (IDE) (if clinical studies are required) • Premarket approval (PMA) • FDA approval 	<ul style="list-style-type: none"> • Heart valves • Pacemakers • Hyaluronic acid • Implanted prosthetics

^aFDA, Food and Drug Administration.

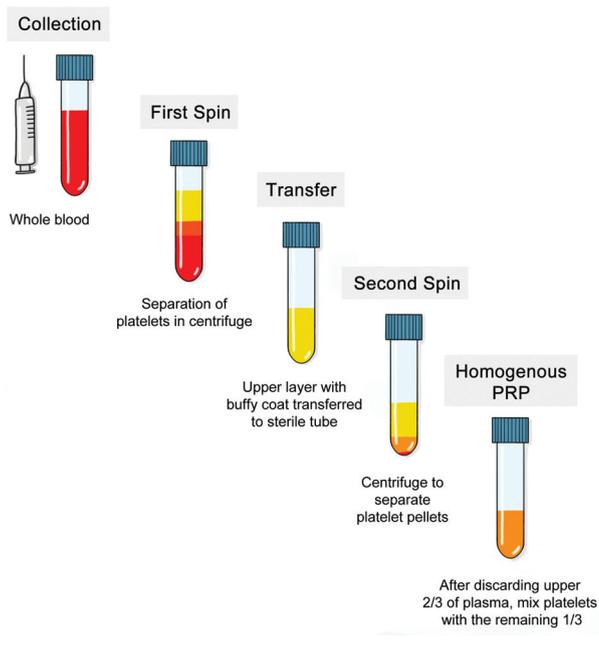


Figure 1. Platelet-rich plasma (PRP) preparation steps.

tube; (2) centrifugation to separate the sample into 3 layers: red blood cells, buffy coat (containing leukocytes and platelets), and plasma; and (3) separation and further centrifugation of the buffy coat and plasma before PRP application. Dozens of companies make and currently market PRP preparation devices with varying techniques.^{3,19}

PRP and PPP are biologic products under FDA definitions and are regulated by the CBER. However, as mentioned previously, the FDA considers “whole blood and blood-derived products” to be low or minimal risk and therefore they are not regulated as HCT/Ps.⁵² PRP preparation devices are considered medical devices and need to undergo a separate regulatory pathway before reaching the market.

PRP preparation devices are generally considered class 2 products, with most devices being cleared for use under the 510(k) device pathway. This pathway is a premarket submission made to the FDA for a medical device that is “substantially equivalent” and has a predicate device on the market already cleared by the FDA. A 510(k) pathway does not require any clinical evidence derived from randomized clinical trials, but it needs to comply with FDA established “general controls” and prove that the device is as safe and effective as the predicate device.⁶¹ In the case of PRP preparation devices, nearly all of these products have been approved as a 510(k) product designed to be used for the “safe and rapid preparation of autologous PRP from a small sample of blood at the patient point of care.”⁶ The indications for use of the PRP produced from these cleared devices are that it can be mixed with autograft and allograft bone grafts before an orthopaedic surgical site as deemed necessary by the clinical use,⁶⁴ mixed with bone graft materials to enhance handling properties,² or used to prepare a PRP gel for the management of cutaneous wounds.³⁵ An FDA clearance limits the marketing or promotion of the device beyond the specific indication for which it was cleared.

The use of PRP has not been indicated for any orthopaedic conditions. Therefore, the use of PRP for direct patient applications, such as injections, is considered “off-label use” (used for a treatment indication for which it was not officially cleared or approved).⁶⁰ This suggests that either a BLA or PMA approval or de novo 510(k) clearance is needed for PRP to be used in a clinical injection setting. BLA and PMA applications are required to demonstrate safety and efficacy in controlled randomized clinical trials. The de novo 510(k) requires more evidence for safety and efficacy when compared with traditional 510(k), but less than what is required for a PMA before reaching the market.

Bone Marrow

During a bone marrow aspiration procedure, bone marrow is commonly harvested by a needle aspiration procedure

from a patient's anterior or posterior iliac crest (among other possible bone sites) and injected as a point-of-service care event after centrifugation and concentration. Bone marrow aspirate contains growth factors and various types of blood cells, including hematopoietic stem cells; however, it has a low number of mesenchymal stem cells (MSCs), with only 0.01% to 0.001% of the harvested cells meeting International Society for Cellular Therapy MSC criteria.¹³ There are several bone marrow concentration devices used in orthopaedics. These devices are almost all FDA 510(k)-cleared devices and are regulated like the previously mentioned PRP devices. Bone marrow concentration devices have indications to produce concentrated bone marrow for diagnostic use only³⁹ or to be mixed with bone allograft or autograft.⁵⁵ There is no point-of-care concentrated bone marrow product that has been cleared by the FDA for clinical injection use. Just like PRP, concentrated bone marrow products used for direct patient applications, such as injections, are considered off-label use. Proper clinical data demonstrating safety and efficacy for any specific indication are needed.

There is an important distinction between a procedure involving harvesting bone marrow with isolation and expansion of cells (manipulated) before reimplantation, compared with the same-day nonmanipulated single bone marrow aspiration. The FDA has a clear stance that the isolating and expanding cell procedure is more than minimal manipulation of the cells and is regulated as a Section 351 product.³⁹ There have been warnings to consumers that this type of cell expansion procedure is not FDA approved and cannot be performed in the United States (outside of a registered clinical trial with a proper IND).⁴⁵ On February 4, 2014, the US Court of Appeals found that the "stem cell mixture" (isolated and culture expanded cells) used by Regenerative Sciences LLC (Regenexx) was defined as a drug or biologic product and fell within the regulations of a 351 product.³³ The court concluded that Regenerative Sciences violated federal laws regarding the manufacturing and labeling of drugs and biological products.³²

Autologous bone marrow products are considered to be exempt from HCT/P regulations only if they are "minimally manipulated, intended 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)."³⁹ The FDA considers bone marrow a source of hematopoietic progenitor cells (HPCs) whose relevant biological characteristics include forming and replenishing the lymphohematopoietic system.⁵³ The FDA stated in their 2018 guidance document that if the bone marrow is more than minimally manipulated, intended by the manufacturer for a nonhomologous use, or combined with another article with limited exceptions,⁵³ then it meets the definition of an HCT/P and is subject to the regulations in 21 CFR 1271.³⁹ There are currently no indications or approval by the FDA that bone marrow should be injected into the joint, making this use off-label.

Adipose

Adipose tissue contains more MSCs (approximately 2%) than bone marrow (less than 1% MSCs for concentrated bone marrow aspirations)⁶² and is easily accessible, leading many US businesses to promote adipose-derived autologous MSC interventions.²⁹ Lipoaspiration is performed to obtain fat tissue from harvesting sites, including the abdomen, hip, thigh, flank, and knee fat pad.¹⁶ This aspirate is then rinsed to remove excess blood, oil, and cellular debris. This tissue is then processed by several techniques categorized into 3 main groups: mechanical emulsification, mechanical separation, or enzymatic digestion. The goal for processing the fat tissue is to obtain a heterogeneous mixture of adipocytes, fibroblasts, erythrocytes, lymphocytes, macrophages, pericytes, mesenchymal stromal cells, and other cells,^{11,20} which is then administered by injection into patients.

Adipose tissue is not exempt from HCT/Ps rules like bone marrow and blood products and falls under the purview of either a 351 or 361 product. The FDA has released a series of guidance documents to help medical professionals understand the regulatory aspects of adipose tissue. Although these "draft guidances" are not official regulations, they represent the current position of the FDA and give an opportunity for public comments and time for the industry to adjust to compliance. They provide useful insight into the FDA's perspective on certain topics, including the regulation of specific biologic products.

The most recent draft guidance released in 2017 provides clarification on the same-day surgical procedure exemption, minimal manipulation, and homologous use for adipose tissue-based products.⁵³ In this document, the FDA defines adipose tissue as a type of structural tissue, with its primary function to "provide cushioning and support for other tissues."⁵³ This is an important distinction because it limits processing techniques that might alter the original characteristics of adipose to provide support and cushioning. Additionally, the draft guidance clearly states and defines that preparing stromal vascular fraction products by "enzymatically digesting, mechanically disrupting, etc. would also be considered more than minimally manipulated," since these processes break down adipose cells and structural components.⁵³ This guidance document states that the use of HCT/Ps from adipose tissue for the treatment of a degenerative, inflammatory, or demyelinating disorder would generally be considered nonhomologous use. This includes musculoskeletal conditions such as arthritis or tendinitis, since regeneration and anti-inflammation effects on articular cartilage or tendon are not considered a structural function of adipose tissue. Products that stray from these guidelines would be considered a 351 product, a category 3 product that requires strict regulatory oversight for patient use and marketing.

There currently are no FDA-approved adipose-derived stem cell medical products, but there are several medical devices that are 510(k) cleared and, like PRP, are used off-label. There are many existing 510(k)-cleared premarket notifications^{34,48,50,56} for adipose processing systems

that are based around a process to harvest and clean adipose tissue for surgical use, unrelated to any proposed specific procedure or treatment. This lack of indication has not stopped the use of adipose injections as “stem cell treatments.” This type of off-label use has attracted the attention of the FDA, which is trying to protect patients from unproven treatments. The FDA has recently sent warning letters and has legally challenged companies that have harmed patients, including a Florida doctor who injected enzymatically digested autologous adipose “stem cell products” into the eyes of 3 patients with age-related macular degeneration.⁵⁸ This intravitreal injection led to severe visual loss after the injection and total blindness a year after the procedure.¹⁷

Placental Products

Placental membranes, parts of human placenta, and umbilical cord tissue are rich sources of MSCs that are fetal in origin. These cells are reported to have higher proliferative capacity and greater expansion potential, and they do not suffer the age-related issue of senescence.²¹ There are several parts of the placenta and its derivatives, including placental membrane amnion and chorion, amniotic fluid, umbilical cord, and cord blood, that have all been studied for use as an injectable regenerative treatment.²⁶ This is different from using placenta tissue to serve as a covering or barrier. Taken together, these gestational tissues are finding applications in a multitude of potential therapies.

The FDA states in their in their latest (2017) guidance document that if a manufacturer “grinds and lyophilizes amniotic membrane and packages it as particles,” it is considered to be more than minimally manipulated, since the processing alters the primary function of the tissue to serve as a cover or barrier.⁵³ These processed tissues for injection use are considered to be 351 products⁵³ including unrelated cord blood for hematopoietic reconstitution for certain disorders. Therefore, companies using injectable placenta products should pursue an IND/BLA license. In the same guidance document, the FDA gave clinics or medical practitioners up to 36 months or until November 2020 to comply with changing regulations.⁵⁷ (Between the time this article was written and revised, the FDA published a new guidance document in July 2020.⁵⁴ The only substantive change to this guidance was to revise the FDA’s enforcement discretion period. This period has been extended from November 30, 2020, to May 31, 2021, allowing manufacturers more time to prepare IND and marketing applications. This change is warranted under the unique circumstances of the COVID-19 epidemic, slowing/stopping clinical trials.) Since then, several companies have filed for IND applications and are conducting clinical trials with their injectables.^{9,14}

The most commonly used placenta-derived product to date is cord blood cells. The FDA does not regulate cord blood stored for personal use or its use in first- or second-degree relatives.⁴¹ However, cord blood that does not fit these 2 criteria meets the definition of a “drug” and a “biological product” and is regulated under the stringent rules

of Section 351. There are currently 8 FDA-approved cord blood products, all with replacement indications for patients with disorders affecting the hematopoietic system that are acquired or result from myeloablative treatment, a high-dose chemotherapy regimen.³⁷

The other placental products are all classified as HCT/ Ps and fall under the regulation of 21 CFR 1271 Section 361. The most crucial distinction between the regulations for these products concerns whether they are produced with minimal manipulation and intended for homologous use. The FDA guidelines state that the amniotic membrane’s original relevant characteristics include serving a barrier function.⁵³ Currently, companies have amniotic membrane products for indications of a physical barrier in wound care and ocular surface reconstruction. All these products are regulated by the FDA under 21 CFR 1271 Section 361 without requirement for PMA or clearance, except for Prokera, which is a combination of amnion with a plastic ring for ocular applications and was cleared as a 510(k) device.³⁶ For instance, Grafix, a cryopreserved placental membrane from Osiris, has “limited to the homologous use as a wound cover” in its indications for use.²³ A company cannot use the amniotic membrane to claim wound healing, to support bone regeneration, or even to reduce inflammation since these are nonhomologous uses.⁵³ The FDA has not formally indicated an opinion on the other placenta products. These placenta products are typically donated or stored in biobanking companies that need to comply with FDA requirements for transplanted tissues: donor screening, testing for infectious diseases, and current good tissue practice regulations.²⁷ Since these tissues are for allogenic transplantation, the FDA wants to minimize the risk of contamination and transmission of infectious diseases.

OFF-LABEL INJECTIONS OF BIOLOGIC MATERIAL

As these rapidly expanding treatments are coming to market, the issue of “off-label treatments” is currently at issue. While off-label treatments are not FDA approved, they are not illegal and are commonly used in medical practice. In a 2006 investigation, there was an estimated “150 million off label mentions (21% overall)” among sampled medications.²⁸ The current regulatory framework provides significant flexibility and allows physicians and healthcare providers to prescribe drugs or devices for ethical off-label use in the best interest of the patient.⁶³ Medical practitioner evaluation, patient discussion and education, and documentation of use and efficacy are appropriate.⁵ However, most off-label use is not backed by sound scientific evidence and could lead to dangerous outcomes.^{7,15}

CONCLUSION

At this point, there are many clinics that provide and promote these biologic injections to patients, often for financial gain.²⁵ Scientific evidence is lacking for clinical

efficacy, further compounding the lack of regulatory approval to use these products by the FDA. Multiple studies have called for the careful use of these products and the establishment of level 1 studies, randomized controlled trials, to support their current clinical use.^{5,28,30}

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