

Regulatory and Ethical Aspects of Orthobiologic Therapies

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Orthobiologic therapies show significant promise to improve outcomes for patients with musculoskeletal pathology. There are considerable research efforts to develop strategies that seek to modulate the biological environment to promote tissue regeneration and healing and/or provide symptomatic relief. However, the regulatory pathways overseeing the clinical translation of these therapies are complex, with considerable worldwide variation. The introduction of novel biologic treatments into clinical practice raises several ethical dilemmas. In this review, we describe the process for seeking approval for biologic therapies in the United States, Europe, and Japan. We highlight a number of ethical issues raised by the clinical translation of these treatments, including the design of clinical trials, monitoring outcomes, biobanking, “off-label” use, engagement with the public, marketing of unproven therapies, and scientific integrity.

Keywords: orthobiologics; biologics; regulation; oversight; regeneration

The term “musculoskeletal regeneration” is widely considered to encompass therapeutic solutions for musculoskeletal conditions that harness the benefits of biology to improve healing, reduce pain, improve function, and provide an environment for tissue regeneration.³⁸ Tools to facilitate musculoskeletal regeneration include drugs, surgical intervention, physical and electromagnetic stimuli, and biologics. Orthobiologics are biological substances derived from the body that are used to treat musculoskeletal disease, injury, and disability, focusing on the growth, replacement, and repair of cells, organs, and tissues specific to the health needs of patients.³⁰

The potential application of regenerative therapies spans the breath of orthopaedics, using approaches such as cell transplantation, gene transfer, and tissue engineering.³¹ These strategies differ significantly from most mainstream treatments in orthopaedic practice, as they aim to treat the underlying cause of the disease with the goal of augmenting the native biological repair processes, preferably at an earlier stage of the disease progression. Despite enormous promise, most orthobiologic approaches remain at a very early step along the road to widespread application. Culture-expanded autologous and allogeneic cell therapies and gene therapies have all entered human clinical trials, with many patients already treated with current Good Manufacturing Practice–produced musculoskeletal regenerative approaches.^{7,63,64} While many regenerative

interventions remain in preclinical phases of research, the number of clinical studies is expected to increase rapidly in the near future.

Despite research advances, there is growing concern about the increasing number of centers that are marketing stem cell–based interventions directly to consumers, making unwarranted claims, or performing risky biologic procedures.³⁵ Such centers and their associated providers have been known to recommend, prescribe, or deliver so-called regenerative preparations, in many cases marketed as “stem cells,” without sufficient data to support their true content, safety, and efficacy.^{27,44} Although the progress of promising investigational therapies should not be thwarted, clinicians and regulators have a duty to protect the public from the risks associated with unproven and uncharacterized therapies.^{32,33}

An appreciation of the regulatory environment of orthobiologics and the ethical dilemmas that they raise is central to developing future strategies to support legitimate translation. However, the regulatory environment can appear both convoluted and cumbersome, with considerable worldwide variation. As such, there is a pressing need for these aspects to be deciphered and presented in a logical and accessible form. In this narrative review, we describe the current regulatory environment of orthobiologics and describe the process for seeking approval for biologic therapies using the United States, Europe, and Japan as examples of global variation. We highlight a number of ethical issues raised by the clinical translation of these treatments, including the design of clinical trials, monitoring of outcomes, biobanking, “off-label” use, engagement with the

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public, marketing of unproven therapies, and conflicts of interest.

CURRENT REGULATORY ENVIRONMENT OF ORTHOBIOLOGICS

Regenerative therapies are regulated by national or regional regulatory authorities, such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada, Australian Therapeutics Goods Administration, or Japan's Pharmaceuticals and Medical Devices Agency. There is significant geographic variation in these regulatory processes. The European Union (EU), United Kingdom, United States, and Japan have been central in fostering the development of biologic therapies. In this section, we outline and compare key features of the regulation of biologic therapies in the United States, Europe, and Japan that may affect the development and clinical use of novel regenerative therapies.

There are a number of regulatory processes and challenges to overcome in the journey from scientific concept to approval of new regenerative treatments. The first step in this pathway is to accurately define the product, as this will determine how it is classified by the regulatory authority of each country and dictate the subsequent regulatory pathways that this product must follow.²³ In the United States, Europe, and Japan, there is a broad legal framework covering a wide range of chemical and biological sub-categories. Correct classification of the product will influence the regulatory guidelines that apply.

Regulatory Oversight in the United States

The agency that governs the use of orthobiologics in the United States is the FDA. As part of the federal Food, Drug, and Cosmetic Act (1938)³² and the Public Health Services Act of 1944 (PHS)³², the FDA oversees the Code of Federal Regulations (CFR), and Part 1271 Title 21 applies to the use of human cells, tissues, and cellular and tissue-based products (HCT/Ps).³² Additionally, in 2017, the FDA published a comprehensive guidance¹⁹ to improve stakeholders' understanding of the regulatory criteria for human biologic therapies in the United States, and while these are nonbinding, they reflect the FDA's current thinking on CFR Part 1271. As part of this framework, the FDA provided finalized guidance on how preparations should be classified. HCT/Ps encompass most novel orthopaedic

regenerative products and are defined as products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.³⁰

The utilization of orthobiologics and the process by which some new biologic products become approved treatments in the United States is complex. Before embarking on clinical trials, an investigator must understand the regulatory framework and if the HCT/P requires premarket approval and, thus, an Investigational New Drug (IND) application toward a Biologics License Application (BLA) or an investigational device exemption application for device products.

The FDA employs a tiered approach to the regulation of HCT/Ps based on their assessment of patient risk and public safety.⁶⁰ The first group comprises products that are considered of lowest risk and require no HCT/P oversight (Table 1). A second grouping comprises products that are considered lower risk and are regulated under Section 361 of the PHS, with a further grouping of products that are considered higher-risk products that are regulated under Section 351. Additional regulatory pathways for Regenerative Medicine Advanced Therapies (RMAT), 510(k) and premarket approval devices, and other biologic products have been incorporated into this framework.

Products in the first group are those considered to be low risk and, although still regulated as HCT/Ps, do not require Premarket Approval (PMA) /Biologics Licence Application (BLA).⁵ Examples include whole blood, blood-derived products, bone marrow, human organs for transplantation, and extracted human products such as collagen. These biologic agents must be minimally manipulated, used in a homologous fashion, and not combined with any other agents. Platelet-rich plasma (PRP) and bone marrow aspirate concentrate are the most widely used products under this classification. Physicians who use these products need to follow current good tissue practices.^{58,59}

The second grouping, comprising lower-risk products, falls under Section 361 of the PHS, and those HCT/Ps require only minimal oversight.^{5,67,68} For an HCT/P to be regulated under Section 361, the product must (1) be "minimally manipulated," (2) intended for homologous use, (3) not a combination product, and (4) have no systemic effects. These category 2 lower-risk products are not subject to formal premarket approval before marketing but do require (1) registration with the FDA, (2) donor screening and testing, (3) good tissue practices and labeling,

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TABLE 1
Summary Interpretation of FDA Classification and Regulatory Oversight for Orthobiologics^a

Product Category	HCT/P Oversight	Examples
Category 1 (lowest-risk product)	None	PRP and BMAC equipment, fat grafts
Category 2 (low-risk product)	Section 361	Cellular bone matrix, demineralized bone
Category 3 (higher-risk product)	Section 351	Cultured chondrocytes, amniotic products, cultured mesenchymal cells, adipose-derived stem cells

^aBMAC, bone marrow aspirate concentrate; FDA, United States Food and Drug Administration; HCT/P, human cells, tissues, and cellular and tissue-based product; PRP, platelet-rich plasma.

(4) adverse event reporting, and (5) postmarket inspection and enforcement. Central to this is the concept of “minimal manipulation” of biologic products. Such manipulation is characterized as only slight modifications of cells or tissues, with preservation of the product’s inherent biological properties.⁶¹ Examples include centrifugation, cutting, antibiotic treatment, gamma irradiation, ethylene oxide sterilization, lyophilization, and cryopreservation. Widely used examples in current clinical practice include demineralized bone without handling agents, cellular bone matrix, and autologous chondrocytes. Producers of Section 361 products need to comply with current good tissue practices, register their establishment with the FDA, provide a list of HCT/Ps produced each year, and label these products in accordance with FDA guidelines.⁶¹

HCT/P products that do not meet the above criteria are regulated under Section 351 as higher-risk products, and a BLA is required to certify the “safety, purity, and potency” of a preparation.⁶⁸ “More than minimal manipulation” is defined as processing that alters the biological characteristics of cells or tissues, and the FDA would include activation, encapsulation, genetic modification, or expansion of cells or tissues under this umbrella. Other examples of more than minimal manipulation include enzymatic degradation, the addition of chemical or biological elements to a product, and mechanical emulsification. Examples include cultured cartilage cells, cultured mesenchymal stem cells, and enzyme-digested fat or stromal vascular fraction. While the Section 351 designation was created to ensure patient safety, obtaining premarket approval is complicated, costly, and time-consuming. The PMA process begins with preclinical studies conducted using animal models to demonstrate safety, confirm mechanism of action, and assess efficacy. An IND application can then be made before launching phase 1 clinical trials overseen by the local institutional review board and a BLA, toward formal premarket approval.⁶⁴ These processes are costly, and marketing cannot begin until the product is approved. Successful phase 1 trials are followed by phases 2 and 3 trials in larger numbers of patients to seek stronger safety and efficacy data, which are then included with IND as part of a New Drug Application. Even after formal approval of the marketing application, postapproval studies may still be mandated by the FDA. Given that the Section 361 classification offers more flexibility, most commercial products have targeted the 361 designation.

The RMAT designation, introduced in 2016 as part of the 21st Century Cures Act, is a special designation for

products intended to treat serious or life-threatening conditions.² This pathway mandates preliminary evidence that the product may address unmet clinical needs.⁶¹ RMATs may follow a pathway that allows sponsors to essentially skip phase 3 and gain premarket approval after phase 2. The recent designation of osteoarthritis (OA) as a “serious condition” has enabled a number of products with preliminary data supporting symptomatic and functional improvement in the setting of OA to follow this fast-track pathway.^{34,60}

Products exempt from Section 351 or 361 oversight are considered on an individual basis, with 1 outcome being considered via the so-called 510(k) medical device pathway. This pathway allows FDA clearance for medical devices that represent substantial equivalence to preexisting devices in the market.^{14,56} In the case of PRP, the original predicate device is a platelet and plasma separator that produces PRP that is intended to be mixed with bone graft materials to enhance handling properties,⁵⁷ or in the case of PRP gel, to “maintain moisture in a wound.” A system for producing microfragmented adipose tissue has been cleared by the 510(k) premarket notification pathway for substantial equivalence to existing medical lipoplasty suction systems.⁵⁵ At this time, it is not clear whether future orthobiologic preparations will be regulated this way.

Regulatory Environment in Europe

Many aspects of the regulatory environment in the EU mirror those in the United States. In the EU, biologic therapies are regulated by the EMA. European policy is largely guided by policy European Community (EC) No. 1394/2007 and the Human Cells and Tissues Directive (2004/23/EC).²³ This framework outlined the concept of advanced therapy medicinal products (ATMPs). ATMPs include gene therapy products, somatic cell products, or tissue-engineered products that are more than minimally manipulated or used in a nonhomologous fashion. The EMA defines more than minimal manipulation as processes through which “biological characteristics, physiological functions or structural properties are altered in a way intended to be used for repair, replacement or regeneration.” Similar to the US system, processes such as centrifugation, irradiation, or antibiotic addition are not considered more than minimal manipulation.

The process by which a biologic product reaches the bedside is analogous to the US system. Preclinical studies are performed under International Conference on Harmonisation

of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. To begin clinical trials, a clinical trial authorization is required and is granted at a national level. After completion of clinical trials (phases 1-3), EU-led procedure must then be followed, with a Marketing Authorization Application required to reach commercialization. For the final approval of ATMPs, there are 2 committees within the EMA that scrutinize the scientific justification for product approval: the Committee for Advanced Therapies and the Committee for Medicinal Products for Human Use (CHMP). The former is responsible for assessing the quality of the clinical trials in defining the safety and efficacy of ATMPs and making a recommendation on whether the ATMP should be approved, with the CHMP responsible for making the final decision on the use of each ATMP. However, after an ATMP is approved at a European level for use, it is then dependent again on individual member states providing provisions to implement these biologic therapies, thus leading to further heterogeneity even within Europe.⁶

Orthobiologics that do not fulfill the definition of an ATMP are regulated via separate legal documents published by the EU. The clinical use of PRP is regulated under Directive 2001/83/EC.¹⁷ This directive is then adopted by each member country and adapted by the national committees. As the directive has not been translated into a Europe-wide law, individual countries have interpreted the document to suit their specific requirements. Another biologic agent regulated separately from ATMPs is demineralized bone, which falls under the European Directive 2004/23/EC.

There are several routes for bypassing the main EU regulatory pathway. The “hospital exemption” clause within EC No. 1394/2007 allows for the nonroutine administration of ATMPs manufactured and prescribed within the same member state to individual patients.⁶² While the hospital exemption creates a loophole in the regulatory system, analogous to the “same surgical procedure exemption” in the United States, exempt products may still be regulated on a national level and must be manufactured in accordance with good clinical practice guidelines. Conditional marketing authorizations may also be granted by the CHMP for products aimed at treating or preventing serious debilitating or life-threatening diseases. These criteria are as follows: the product must address an unmet need, the benefit-risk balance of the product is positive, and the benefit to public health of the products’ immediate availability on the market outweighs the risks due to need for further data.¹⁵

Autonomy of Individual EU Countries. While ATMPs are centrally regulated by the EMA, individual member countries maintain substantial autonomy in allowing different preparations. As such, significant heterogeneity remains in the handling of ATMPs between countries. In the United Kingdom, the regulatory structure follows the same central structure as the EU. The Medicines and Healthcare products Regulatory Agency (MHRA) oversees the manufacturing and importation of centrally approved ATMPs. While hospital exemptions are possible in the United Kingdom, they are scrutinized by the British

General Medical Council (GMC) under the Medical Act of 1983.⁵³ The accountability resulting from the GMC oversight is thought to be the reason why the United Kingdom has relatively fewer stem cell therapies performed outside of the research sector than other countries have. Despite also following EMA guidelines, Italy has made significant national changes to be more permissive of cell therapies outside of the clinical trial setting.

Effect of Brexit. After Brexit, the UK MHRA regained full responsibility for the regulation of ATMPs. Classification of ATMPs remains aligned with the EMA, but the process of development, through to marketing and the final approval of an ATMP for clinical use, is now carried out at a national level, and ATMPs are assessed in a similar approach to the licensing of a new medication. The United Kingdom is the European leader for ATMP research, with 44% of all EU ATMP registered and accredited research facilities in 2017.⁵⁴ This is largely because of a large academic field predominantly focusing on the early stages of clinical research. However, none of the current EU-approved and -licensed therapies are manufactured in the United Kingdom.⁵² The disparity in research and manufacturing capabilities may prove troublesome after Brexit. The MHRA is held in high regard by the EMA, as it provides the vast majority of leading scientific experts within the field of ATMPs to committees where decisions are made regarding European ATMP policies. The MHRA is also reliant on the EMA to progress with ATMP research, as the United Kingdom often cannot provide the required number of patients to investigate the use of ATMPs in particularly rare diseases. As such, both agencies hope that close relationships will remain after Brexit.⁵²

Present Legislation for Regenerative Medicine in Japan

There has been considerable recent change to regulation in Japan. In 2013, the Japanese government submitted the 2 acts relating to regenerative medicine including orthobiologics: one is the Act on Safety of Regenerative Medicine, and the other is the Pharmaceuticals and Medical Devices Act.⁴³ The Act on Safety of Regenerative Medicine obligates hospitals to notify the Ministry of Health, Labour and Welfare (MHLW) of their regenerative treatment plans, which in turn must be reviewed by a special committee certified by the MHLW.²⁹ In addition, hospitals are requested to use the biological components prepared at certified processing facilities to manufacture specific cellular products used in clinical regenerative treatments. Regenerative treatments are divided into 3 categories based on the risk of the biologic products and different procedures. In July 2021, the number of certified processing facilities had reached 3115, and the MHLW had been notified of 4330 treatment protocols.²⁵ To date, orthobiologic treatments have been carried out in >450 hospitals, and the number of patients who received regenerative treatment including orthobiologic therapies has reached >50,000.²⁶ Under this act, 16 medical institutions have been ordered to suspend regenerative treatment,

and one medical institution received an improvement order. Furthermore, one of the doctors at one of these medical institutions has been convicted of violating the act. With respect to safety, 2 deaths that are considered to be related to treatment have been reported, and improvement measures and safety guidelines are being considered. Via this act, the Japanese government has been able to closely monitor the implementation status of regenerative medicine in Japan.

The Pharmaceuticals and Medical Devices Act of 2013, which is the revised version of the Pharmaceutical Affairs Law, defines the category of regenerative medical products related to regenerative medicine or gene therapy.⁴² As regenerative medical products are usually heterogeneous and contain living cells, a long duration of follow-up is required to evaluate the safety and effectiveness of the treatments. Therefore, a conditional/time-limited approval system was established to facilitate the early clinical application of regenerative medical products. This system is anticipated to facilitate the determination of more suitable conditions for regenerative medical products and is a type of adaptive licensing system that has been used to enhance product accessibility to patients. In this system, acute adverse effects can be identified from short-term investigations, and the long-term safety is evaluated in the postmarketing surveillance of a registry of all patients. To further ensure the maintenance of safety measures, it is clearly stated that doctors should provide patients with a thorough explanation of all procedures and obtain prior informed consent. Doctors are also obliged to keep complete records on the use of regenerative medical products. In addition, regenerative medical products are to be included under the heading of the Relief Services for Adverse Health Effects. A further revision included the generation of a new standard (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) for manufacturing management and quality control in the industry to secure the quality and safety of the products. The changes to the regulatory framework for regenerative medical products may facilitate research and development and contribute to the safety of regenerative medicine. In fact, 7 products including orthobiologics have already been approved since the legislation was enacted.

ETHICAL ISSUES IN CLINICAL TRANSLATION OF ORTHOREGENERATIVE THERAPIES

All treatment decisions across medicine should be considered in the context of the 4 *prima facie* principles of medical ethics: beneficence, nonmaleficence, autonomy, and justice.³ “*Prima facie*” means that the principle is binding unless it conflicts with another moral principle—if it does, we have to choose between them.²⁰ Respect for autonomy is the moral obligation to respect the autonomy of others insofar as such respect is compatible with equal respect for the autonomy of all potentially affected.²⁰ Beneficence and nonmaleficence are often considered together and aim at producing net benefit over harm. Justice is often regarded as being synonymous with fairness and can be summarized as

the moral obligation to act on the basis of fair adjudication between competing claims.²⁰ Orthobiologic therapies raise considerable ethical quandaries, many of which are unique. Our ability to navigate these issues is made more challenging by our current limited understanding of these novel treatments. Being a gatekeeper to these treatments carries significant responsibility, and both clinicians and scientists should not shy away from the difficult logistical and ethical challenges that arise. A select number of these challenges are summarized below.

Clinical Trial Design

As in all areas of medicine, the use of orthobiologics should be based on evidence demonstrating both safety and efficacy. Randomized controlled trials (RCTs) constitute the hallmark of evidence-based medicine and form the basis for translating research data into clinical practice.^{49,50} These types of studies are even more important in the field of orthobiologics, where multiple variables can significantly alter outcomes and preclude the scientific world from having a clear answer to several questions about their use, efficacy, and safety. Spieth et al⁵⁰ summarized important concepts and recommendations regarding design, conduct, and reporting of RCTs that can improve the quality of the trial. First, clinically relevant endpoints should be defined a priori, and an unbiased analysis and report of the study results should be performed. Specifically, for biologic therapies, selection of a placebo or control group should be carefully considered. Placebo-control groups play a critical role in the development of new therapies and in establishing a “null” baseline upon which a proposed intervention must demonstrate improvement to substantiate clinical use. For example, the administration of an intra-articular saline placebo injection has been reported to yield a statistically and clinically meaningful improvement in functional outcomes up to 6 months after the injection in patients with knee OA.⁴⁸ Furthermore, in the comparison of experimental treatment with standard care, preplanned interim analyses during an ongoing RCT can aid in maintaining clinical equipoise by assessing benefit, harm, or futility, thus allowing a decision on the continuation or termination of the trial.

A structured study design and performance as indicated in the Consolidated Standards of Reporting Trials statement should be employed as well as registration in a public trial database, reporting on significant and nonsignificant results.⁴⁹ Importantly, potential conflicts of interest and funding sources should be disclosed in study reports or publications. In summary, well-powered and executed RCTs are warranted to determine the real effect of biologics in the field of orthopaedics. Remaining is the ethical issue of utilizing substances with very low morbidity or side effects in the absence of RCTs when a minimally important clinical difference indicates their use may provide patients with some relief and offer treatment options before approval.

Monitoring Outcomes and Registries

As clinicians, it is our responsibility to monitor the outcomes and complications of treatments we provide.

Consequently, it remains essential to collect accurate and meaningful data. This necessity highlights the importance of establishing standardized outcome collection systems, ideally in the form of prospective cohorts, that could serve as orthobiologic patient registries.¹² These organized systems may then use observational study approaches to collect uniform data, including clinical (patient characteristics, disease characterization, and patient-reported outcome measures) and biologic therapy specifics. Additionally, data on complications and adverse events need to be collected. Biologic interventions including cell therapies can remain biologically active for long periods and thus may present risks with long latencies. Collection of these data will allow the evaluation of specified outcomes for a given population defined by a disease, ailment, exposure, or treatment. Such registries will then serve multiple predetermined goals across different venues, including scientific, clinical, or policy purposes, and represent “real-world evidence” as prescribed by the FDA’s 21st Century Cures Act.²⁸ This will allow a better understanding of the musculoskeletal diseases we are treating and the clinical efficacy or cost-effectiveness of orthobiologic treatments, and most importantly, it will allow us to monitor safety and harm. The successful implementation of scientifically valid, cost-effective, and scalable data outcome collection systems will be required via a highly collaborative effort.^{13,30} Finally, the output from these unbiased orthobiologic registries will be high-quality evidence that clinicians and patients greatly need to become available in a timely and cost-effective manner. As a result, product and treatment approvals may be accelerated in a manner complementary to ongoing RCTs. This evidence will then have the potential to improve outcomes and determine the value of care by determining if and which orthobiologic treatments are to become standard of care.

Biobanking Cells and Tissues

A crucial aspect of the success of an orthobiologic registry in disseminating knowledge and innovation will be determined by its ability to characterize and register the biologic therapies delivered.¹² In addition to collecting clinical aspects of the orthobiologic therapy, such as type, frequency, volume, location, and indication, among other features, there is a critical need to further understand the specifics of these therapies.^{36,39,46} The heterogeneity in different biologic formulations is likely to be associated with variation in clinical outcomes.^{11,45} However, clinical and imaging outcomes must be captured and correlated with the composition to provide insight into the key drivers of biologic activity and clinical efficacy of a given treatment. Economics limit the rigor of investment in point-of-care qualitative and quantitative characterization. However, biorepositories can be established to collect, process, and store biospecimens to support current and future efficiently targeted investigations.

A biorepository requires standardized systems to procure, process, transport, and bank a specific biological sample to enable later measurement of the cellular, proteomic, and transcriptomic content and biologic activity. Just as

important, biospecimens must be linked to quantitative clinical data related to patient factors, disease state, sample source and processing, and the success of care (objective clinical outcome). Appropriate infrastructure and incentives will be required to motivate both physician and patient participation in clinical baseline data, sample collection, analysis, and outcome reporting. Rigorously designed biorepositories have the potential to be a powerful and generalizable tool for rigorous assessment biologic therapies in musculoskeletal medicine.

Clearance, Approval, and Off-Label Use

It is important to consider the difference between the terms “clearance” and “approval,” which are not interchangeable. For example, FDA clearance allows PRP to be used for a wide range of different orthopaedic indications.^{31,37,68} However, clearance is not synonymous with approval for a specific indication.⁴ As such, most of the PRP treatments offered for musculoskeletal indications are considered off-label use, which transfers liability from the manufacturers of the device to the individual providing it.^{21,57} Similarly FDA clearance of microfragmented adipose tissue systems does not infer a robust evidence basis for use in a range orthopaedic applications.

While off-label treatments are not FDA approved, it is important to understand that their use is not necessarily improper or illicit. Indeed, off-label prescriptions account for roughly half of all prescriptions written today,⁶⁵ and the off-label use of certain drugs is well accepted within medical standards.⁶⁶ However, it is equally important to understand that off-label use is often not supported by sound scientific evidence. This has the potential to expose patients to ineffective care and unnecessary risks and drive up health care costs.⁶⁵

Nevertheless, off-label use presents distinct challenges for biologic interventions. Depending on the jurisdiction, some biologic interventions are not authorized for a specific use because of exemption from regulation. This can limit physicians’ access to reliable information on validated uses. In addition, the complex biological characteristics of these therapies and our limited clinical experience with many of them present uncertainties about long-term safety and effectiveness. Physicians should therefore exercise particular care when applying biologic interventions off-label. As a rule, off-label use should be offered only when supported by high-quality evidence or in situations consistent with current scientific knowledge, local legal and institutional regulations, and the standards of the international medical community.²⁴ In all cases, patients must be made aware in advance when off-label use has not been evaluated for safety and/or efficacy with respect to their specific medical condition.

Public Engagement and Trust

Patients exhibiting pain and/or dysfunction because of orthopaedic pathology may rely on their primary care provider or orthopaedic surgeon to offer biologic options for symptom modification. Patients have implicit trust in their health care

provider to present treatment recommendations that are low risk and efficacious. All licensed practitioners are governed by their respective regional and medical professional rules of ethical behavior when utilizing these therapies. For example, the American Academy of Orthopaedic Surgeons mandates standards of professionalism, which state that “it is the obligation of the orthopaedic surgeon to present a fair and honest representation of services and the goals, alternatives, expectations and risks associated with these services.”¹ The UK GMC’s Good Medical Practice states that a good doctor will “maintain trust in you and the profession by being open, honest and acting with integrity.”⁵¹ Unfortunately, since the field of orthobiologics is relatively new, most health care providers never received education on this subject during their training, and thus they must rely on self-education. While PubMed provides easy access to published peer-reviewed studies, it is a daunting task to keep current. To facilitate provider and patient education, a number of academic groups, including the Biologic Association (an international group of musculoskeletal societies that collaborate to speak with a unified voice about the responsible use of orthobiologics), have developed educational resources that are freely available on their website (<https://www.thebiologicassociation.com>). Despite this, there appears to be a lack of formal training or certification in orthobiologics, and the level of expertise and background knowledge in providers varies. It is only when the health care provider is appropriately educated that he or she can present orthobiologic options in an ethical and legal manner and both earn and preserve the trust of their patients.

Marketing of Unproven Treatments

The unwitting public is subjected to a variety of methods for marketing orthobiologics. Regulations regarding ethical and legal advertising vary by country. For example, the European Parliament 2006/114/EC Directive “confer(s) upon the courts or administrative authorities’ powers enabling them to require the advertiser to furnish evidence as to the accuracy of factual claims of advertising.”¹⁶ In the United States, the Federal Trade Commission truth-in-advertising laws state that “an ad must be truthful, not misleading, and when appropriate, backed by scientific evidence.”¹⁸ In a 2020 study by Kingery et al,²⁷ the authors identified 896 practice websites in the United States and found that 96% of them contained statements of misinformation. Examples include “This is a curative treatment. You can literally grow new joint tissue. Once your joint is healed, it is healed” and “The oldest research to date shows that 100% of recipients who benefited from stem cell therapy were still pain free 4 years later.” While clinics in the United States have been prosecuted for making unsubstantiated claims, they often reappear with the same owners under a different name using another orthobiologic. In 2019, Health Canada issued a policy position paper that informed Canadians that all cell therapies are regulated as drugs and present risk to the recipient, and “therapeutic interventions pursued on the basis of anecdotal evidence that are ultimately proved ineffective or harmful when studied in well-controlled trials are common.”²² Despite

legal authority, the administrative burden of policing the marketing content of rogue stem cell clinics exceeds the manpower of enforcement agencies. This tips the responsibility to clinicians and health care organizations to protect patients via education and awareness.

Conflicts of Interest

Conflicts of interest represent circumstances in which professional judgments or actions of a clinician or medical researcher may be influenced by a secondary interest, such as financial gain or career advancement.⁴⁷ The secondary interest may be financial or nonfinancial, and the bias may be conscious or unconscious. Conflicts of interest can threaten professional, patient, and public trust in clinical care and research.

A strong partnership between scientists, physicians, and industry is integral to the development of biologic treatments for patients. Interactions with industry representatives can occur in the office and at professional meetings, ideally leading to collaborations for clinical research and in the development of new treatments. While partnerships can offer important opportunities to advance medical knowledge, they can also introduce bias. In a qualitative evaluation of orthopaedic surgeons’ attitudes to orthobiologics via serial interviews, Niemannsburg et al⁴¹ reported considerable concerns among experts that the role of industry in surgical research and clinical practice causes conflicts of interest that could negatively affect the integrity of researchers and the scientific validity of clinical studies.^{9,69} The issues raised by studies evaluating bone morphogenetic protein, for example, indicate that conflicts of interest can lead to both underreporting of adverse events and methodological flaws in clinical trial design.^{8,10} Conflicts of interest can also arise from other parties, such as universities, government agencies, and funding bodies.⁴⁰ More attention to identifying and managing nonfinancial conflicts is required in the future.

Effective means of identifying and managing conflicts are an important element in successfully achieving the goals of research and ensuring that patients receive the most appropriate treatments. Current strategies typically rely on disclosure and are centered around the individual researcher or clinician. However, this approach has substantial limitations, and increased focus on process-oriented steps and outcome-oriented strategies has been advocated.⁴⁷

CONCLUSION

Orthobiologics show significant promise in improving outcomes for patients with a wide variety of musculoskeletal pathologies. There is considerable worldwide variation in the regulatory pathways that must be followed. Navigating these complex pathways is challenging for both scientists and clinicians. Understanding the regulatory pathways as well as the logistical and ethical factors involved in the clinical translation of orthobiologic therapies will better equip clinicians as they seek to offer their patients the best chance of recovery while keeping them safe.

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