

Current and Future Stem Cell Regulation: A Call to Action

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Abstract

The orthopedic sports medicine profession experienced a pivotal shift with the acceptance and application of the arthroscope. The next leap forward will hinge on the acceptance, application, and regulation of biologic therapies, and a sentinel event will be the US Food and Drug Administration approval of a stem cell technology. While the arthroscope was developed in the hands of our sports medicine mentors, the current history of biologics has been mostly written by basic scientists. The baby steps of these technologies have involved benchtop laboratory studies and preclinical animal trials, clearly illustrating great potential. Clinical progress has struggled forward but stalled. Regulatory constraints and our inability to establish safety and efficacy are the major hurdles, with disconnect between the basic scientist, clinician, and regulatory bodies to blame. While the development of the arthroscope was barely influenced by governmental regulation, this will control and model the future of stem cell technologies. With current legislation before Congress concerning stem cell regulation, the next steps are dependent upon the clinician's understanding and participation in this regulation.

The 2 cardinal properties of stem cells are the ability to self-renew and the ability to differentiate into distinctive end-stage cell types. The work of Caplan¹ captured our early attention, with cells cultured from bone marrow differentiating into a number of different cell types

of orthopedic interest. Our latest attention has been captured by the additional abilities of these cells to mobilize, monitor, and interact with their surrounding environment.²⁻⁴ In response to their environment, stem cells are able to release a broad spectrum of macromolecules with trophic, chemotactic, and immunomodulatory potential, which allows them to participate in injury response, tissue healing, and tissue regeneration.⁴ These cells are innate to the body's monitoring, maintenance, repair, and stress response systems.^{2,4-11} Basic science and animal studies have illustrated the potential of cells with stem potential regardless of their environment/source of harvest.

Where Can We Get Stem Cells?

Cells with stem properties are present in many environmental niches, including the bone marrow, peripheral circulatory system, adipose tissue, synovial tissue, muscle tissue, and tendon tissue.¹²⁻¹⁵ A number of cell types with stem properties populate the bone marrow niche, including hematopoietic stem/progenitor cells (HSPC), perivascular stromal cells (PSC), endothelial stem cells (ESC), and immature cells with qualities like embryonal stem cells termed very small embryonal-like stem cells (VESL).^{12,15-19} All of these cells have stem properties and have been shown to differentiate to tissues of orthopedic interest. The interplay, interaction, and potential of these cell types is complex and incompletely understood.^{12,15-19} When bone marrow is aspirated for culturing purposes, it is unclear which cell line produces the plastic-adherent multipotent cells grown in culture, which are often referred to as mesenchymal stem cells (MSCs). Researches propose that HSPC and/or VESL circulate peripherally in small numbers but leave the bone marrow in certain mobilization instances and are important for the monitoring and maintenance of the majority of tissues in our bodies.^{5,16} Current clinical utilization of these

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cell types by the orthopedic community primarily utilizes point-of-care bone marrow aspiration and concentration, while the hematology oncology community mobilizes cells from the bone marrow to the blood stream with pharmaceutical agents and harvests cells via apheresis. Bone marrow aspiration produces variable numbers of stem cells, with studies ranging from 1 stem cell per mL of tissue collected to 300,000 stem cells per mL of tissue collected.²⁰ Mobilization and apheresis can produce large volumes of peripheral blood-derived cells with 600,000 HSPC per mL and 2.32 million PSC per mL of tissue collected.²¹

In adipose tissue, cells adherent to the abluminal side of blood vessels known as pericytes also carry stem qualities. Aspiration and processing of adipose tissue can access these stem cells, producing a product often referred to as stromal vascular fraction (SVF). Processing of lipoaspirate to create stromal vascular fraction requires mechanical or enzymatic processing. This also produces variable numbers of stem cells, with quantitative studies ranging from 5000 to 1.5 million stem cells per mL of tissue collected.²⁰ Similar to adipose-derived stem cells, synovial-derived and muscle-derived stem cells also require mechanical or enzymatic processing. For applications where it is believed that a large number of cells is necessary, investigators often utilize culturing techniques for all sources with the exception of mobilization and apheresis harvest. As clinicians, 3 challenges have proven more important than which cell type to utilize: 1) patient-care logistics regarding collection and application; 2) the undefined dose-response curve regarding stem cell treatments; and 3) evolving government/community regulation.

Regulation of Stem Cell Therapies

The regulation of stem cell technologies is a double-edged sword for development. While loose regulation encourages clinical application and experimentation, patient safety and efficacy concerns are raised, and a technology's worth is not proven before clinical application. Tight regulation temporarily hampers progress, yet ensures the proof of safety and efficacy prior to widespread implementation. Within the United States, the Food and Drug Administration (FDA) has tightened regulation, established precedent, and intervened in the ability of clinicians to utilize stem cell therapies in humans, through "warning letters," "untitled letters," and industry guidance documents.²²⁻³⁰

The FDA categorizes stem cell therapies as human cells, tissues, and cellular- and tissue-based products (HCT/Ps). Section 361 of the Public Health Safety (PHS) Act established and outlined the authority of the FDA to regulate low-risk HCT/Ps in order to prevent the introduction, transmission, and spread of communicable disease. Section 361 provided standards for safety without requiring preclinical development. The FDA established 4 principles to determine the risk of HCT/Ps: the extent of manipulation involved in manufacture, the metabolic activity/autologous nature of the product, whether the product represents a tissue combined with another product, and whether the product is utilized in a fashion homologous with its original function (**Figure 1**). If a product/therapy meets requirements around all 4 of these principles, then it is deemed a low-risk product and regulated under Section 361 alone. If a product/therapy does not meet requirements

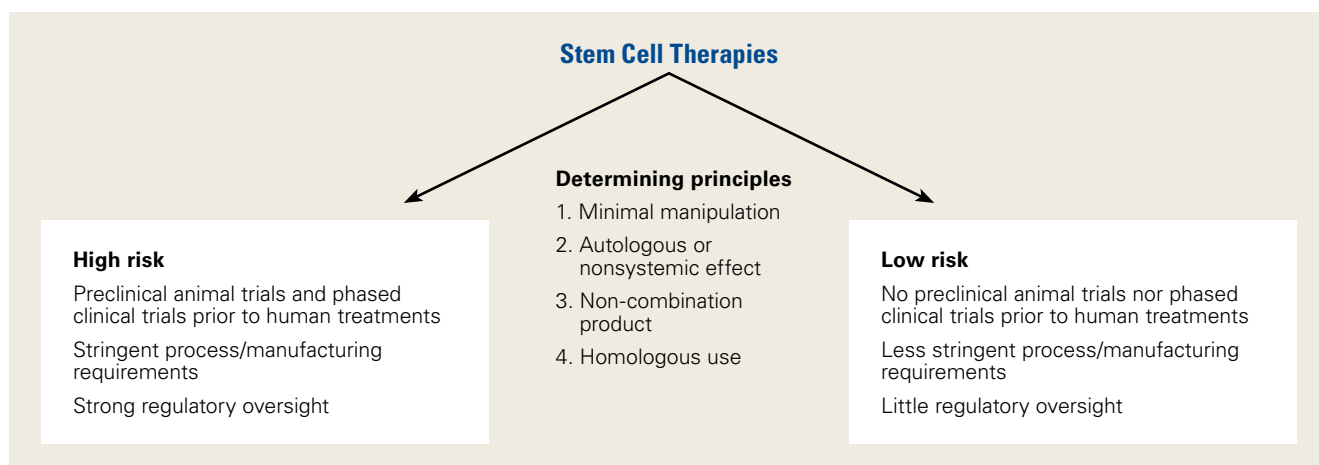


Figure 1. The US Food and Drug Administration determines the risk of therapies considering the principles of minimal manipulation, autologous/nonmetabolic mechanism, non-combination product, and homologous use.

around all 4 of these principles, then the FDA regulates the product/therapy under additional codes including Section 351 of the PHS Act. Section 351 outlines a developmental process including preclinical animal trials, phased clinical study, and premarket review by the FDA prior to offering the product/treatment in clinical practice. The developmental process requires investigators and/or industry developers to initiate an Investigational New Drug (IND) program whose end goal is to present data from all developmental study and obtain a Biologic License Application (BLA) approval to market the product.²²⁻²³ To establish safety and efficacy, the traditional IND program involves a preclinical animal study, a small pilot human study (Phase I), a small initial randomized controlled trial (Phase II), followed by a large multicenter randomized controlled trial (Phase III) (**Figure 2**). The FDA has recognized little to no stem cell treatments as products regulated by Section 361 alone. Additionally, the FDA has established precedent regarding allograft stem cells, cells obtained from fat harvest, amniotic/placental products, and cultured cells, suggesting that these products are not low risk and require an IND pathway outlined in Section 351.²⁴⁻³⁰

Bone Marrow Aspiration

Surprisingly, the FDA has not moved to regulate the point-of-care use of bone marrow aspirate or platelet-rich plasma and has labeled these as “not HCTPs.” The stem cell concentration of bone marrow aspirate is technique-dependent, declines with age, and has been found to be an important factor for clinical benefit.³¹ While it is possible to aspirate from multiple sites, posterior iliac crest harvest produces the highest stem cell yield.³²⁻³⁴ Hernigou and colleagues³⁵⁻³⁶ have outlined safe zones for trocar placement and illustrated that strong aspiration with small-volume syringes, 10-mL syringes, optimizes stem cell harvest. Additionally, studies by Hernigou and colleagues^{31,37-38} involving tibial nonunion, avascular necrosis of the femur, and augmentation of rotator cuff repair are guideposts to clinicians utilizing bone marrow aspirate.

Amniotic Stem Cell Technologies and Adipose-Derived Stem Cells

While some argue that there is regulatory confusion around amniotic/placental-derived tissues and adipose-derived products, the FDA has clearly established precedent establishing these as products requiring Section 351 development.²⁶⁻²⁹

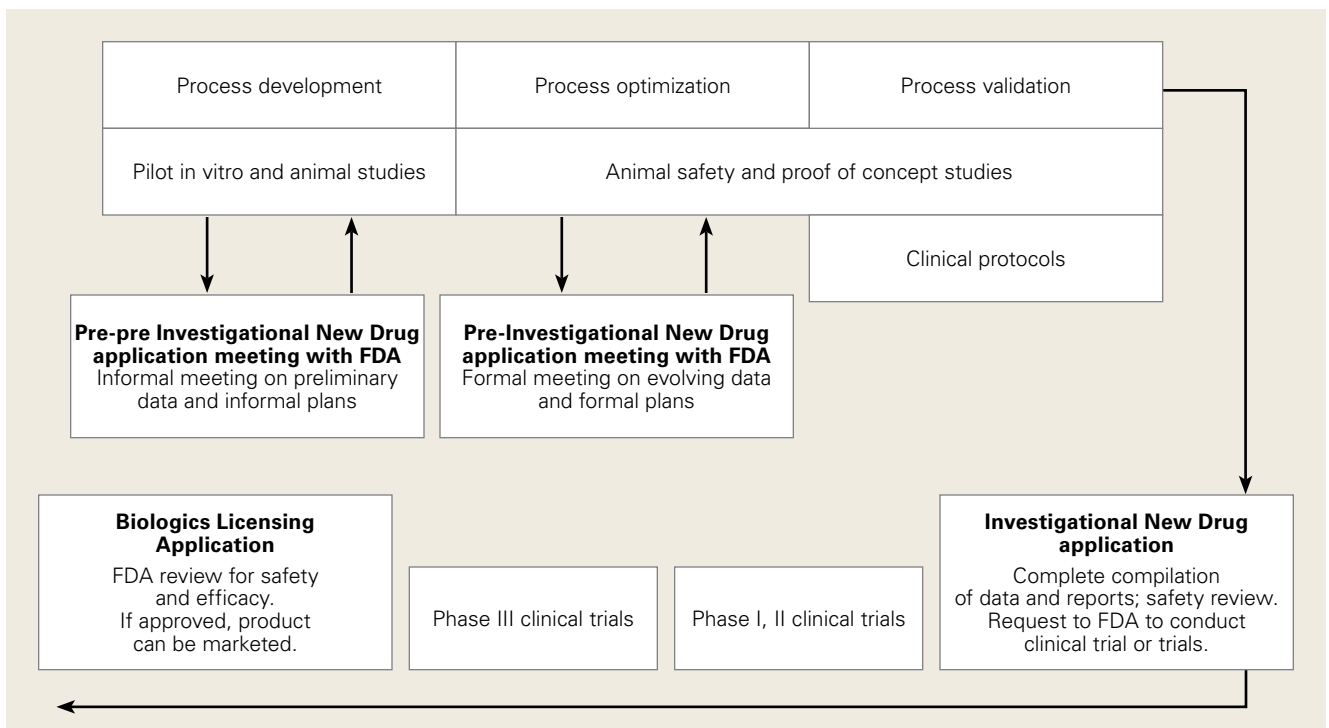


Figure 2. The 351 pathway for product development. Adapted from Anz AW, Hackel JG, Nilssen EC, Andrews JR. Application of biologics in the treatment of the rotator cuff, meniscus, cartilage, and osteoarthritis. *J Am Acad Orthop Surg.* 2014;22(2):68-79. Abbreviation: FDA, Food and Drug Administration.

Companies are marketing products derived from perinatal byproducts, yet there are multiple FDA letters suggesting that these are not products regulated solely under PHS Act 361 because they do not meet the criteria of homologous use and are not autologous.^{28,29} Use of these products places risk upon the clinician and the patient. Some argue that adipose-derived stem cell products are 361 products. While the FDA has approved devices for the mechanical processing of lipoaspirate, they have established precedent suggesting that they consider orthopedic applications nonhomologous and any processing that “alters the original relevant characteristics of adipose tissue relating to the tissue’s utility for reconstruction, repair, or replacement” as more than minimal manipulation.^{26,27} The FDA originally planned an open forum for discussion with clinicians and industry for April 2016. This open forum was delayed due to the volume of interest, and a workshop has been planned for Fall 2016.

Future Regulation of Stem Cell Technologies

While many countries have mirrored the FDA with tight regulatory mechanisms, a few countries have established modern regulatory mechanisms aimed at the promotion of conscientious development, including South Korea, Japan, and England. For example, in 2014 Japan labeled stem cell technologies as “regenerative medicine products,” setting them apart from pharmaceuticals, and implemented a new approval system allowing early observed commercialization with reimbursement after less stringent safety and efficacy milestones.²² The observed commercialization lowers time and financial

hurdles for development while still requiring the proof of the technology’s worth. Countries that have effected change have positioned themselves to be pioneers in this emerging field.

In March 2016, the Reliable and Effective Growth for Regenerative Health Options that Improve Wellness (REGROW) Act of 2016 (S. 2689 / H.R. 4762) was introduced into the United States Congress. This bipartisan, bicameral legislation was introduced, read twice, and referred to subcommittee. Its goal is to reduce barriers and accelerate development of biologic therapies while keeping the frame work set forth under Sections 351 and 361 of the PHS Act.³⁹ Similar to the pathway in Japan, the REGROW Act would establish a conditional approval pathway that would ensure products are safe and effective while also evolving the regulatory pathway towards progress (**Figure 3**). Development would still require an IND application after preclinical animal study. However, after safety was established with human Phase I data and preliminary evidence of efficacy with Phase II data, patients could be treated with the investigational therapies and reimbursement collected for a limited period of time (5 years) prior to a large Phase III human clinical trial. Patients treated with the new therapy would be monitored closely. All results would be reported to the FDA in a BLA. This change in legislation would lower but not remove regulatory hurdles necessary for development.

Conclusion

The future of stem cell treatments hinges upon the creation of new favorable regulatory mechanisms

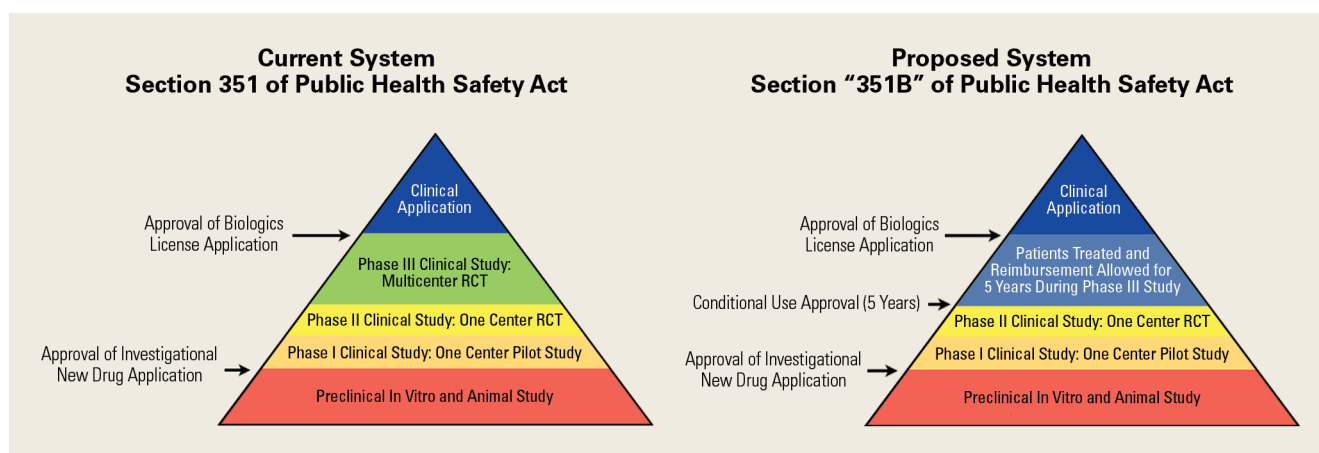


Figure 3. The REGROW Act proposes the addition of section “351B” to the Public Health Safety Act. The additional section would create an expedited review and approval process. The traditional process would remain in place with the addition of a conditional 5-year approval phase, during which the treatment of patients and reimbursement of therapies would be allowed during Phase III development.

Abbreviation: RCT, randomized controlled trial.

that will promote clinical application while ensuring that safety and efficacy milestones are reached. Clinical researchers require freedom to develop these technologies while protecting patients and ensuring the validity of treatments. The coordination of research and regulatory affairs on a global level is necessary focusing on the harmonization of guidelines, regulations, and mechanisms for simultaneous adoption in different countries. The global orthopedic community has made strides regarding the science of stem cell technologies; it is time for us to initiate progressive change regarding regulation so that we can determine what is effective clinically.

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