



Veterinary Medicine and the Law

Regulatory considerations related to stem cell treatment in horses

Gary L. Yingling and Karl M. Nobert

Horse owners, veterinarians, and the equine industry in general are constantly searching for new and more effective treatments for injured horses. Stem cell treatment may offer such an alternative to current treatments, and initial reports¹ suggest that stem cell treatment may be effective for a variety of injuries, including tendon and ligament injuries, in horses and may shorten recovery times and reduce the overall risk of further injury. Not surprisingly, therefore, the use of stem cell treatment in horses has gained considerable ground in recent years.

To date, neither the US FDA nor the USDA, the federal agencies responsible for regulation of veterinary treatments and products containing cellular and tissue material, has promulgated regulations specifically governing the practice of veterinary stem cell treatment in the United States. Nevertheless, current laws do provide these agencies the authority to exercise regulatory control over stem cell treatment, and it is possible to predict how equine stem cell treatment might be regulated in the future on the basis of how the FDA currently regulates human cellular and tissue products and veterinary drugs and how the FDA and USDA currently regulate veterinary biologics. The present article provides a brief overview of equine stem cell treatment, offers thoughts on how the practice may be federally regulated in the future, and analyzes the potential impact of such regulations on practicing veterinarians.

Introduction to Stem Cells

Stem cells are adaptable regenerative cells capable of transforming themselves into a variety of body cell types, including blood, heart, muscle, fat, bone, and cartilage cells.² In the United States, the discussion of stem cell treatment is currently overshadowed by the ongoing political debate over embryonic stem cell research. Initially, embryos were thought to be the only viable source of stem cells. More recent research, however, has shown that stem cells can be obtained from numerous sources, including bone marrow, blood ves-

sels, muscle, and fat tissue,² and these nonembryonic stem cells are currently being used to treat various injuries in horses from a number of disciplines, including racing, showing, and recreation.

In November 2005, the Executive Board of the AVMA approved a position statement supporting the study and use of stem cells in the treatment of veterinary injuries. Recognizing "the enormous impact that research on stem cells will have on ultimately leading to a potentially diverse array of clinical applications in veterinary and human medical care," the AVMA adopted a position fully supporting and encouraging "the ethical study and use of animal stem cells for the benefit of animal and human health."³

Overview of Equine Stem Cell Treatment

Equine stem cell treatment is promoted as a potentially viable alternative to traditional treatment options such as shock wave therapy and surgery. It is currently marketed as a treatment for tendon, ligament, joint, and bone injuries as well as for degenerative joint disease (osteoarthritis), osteochondrosis, and subchondral bone cysts.⁴⁻⁶ Equine stem cell treatment is also being evaluated as a potential treatment for cardiac disease, laminitis, chronic obstructive pulmonary disease (heaves), and some forms of cancers.⁴⁻⁶ Preliminary data^{1,7} suggest that the procedure is successful in about 70% of all cases. Because stem cells have the ability to regenerate and differentiate into site-specific cell types, stem cell treatment of tendon injuries is suggested to facilitate growth of stronger, more tendon-like tissue, rather than the scar tissue that normally appears with traditional treatments.⁸

Currently, there are 2 main types of equine stem cell treatment being offered and performed by veterinarians in the United States. The first involves stem cells harvested and concentrated from fat tissue; the second involves stem cells extracted and cultured from bone marrow. Both fat tissue and bone marrow have been shown to be viable sources of stem cells.⁸⁻¹¹ In addition, various companies are also exploring the use of stem cells extracted from the placenta, umbilical cord, and umbilical cord blood.

From Kirkpatrick & Lockhart Preston Gates Ellis LLP, 1601 K St NW, Washington, DC 20006.
Address correspondence to Dr. Nobert.

Stem cells extracted from fat tissue are currently being used to treat tendon and ligament injuries in horses.⁴ For this procedure, a small amount of fat tissue is harvested from the patient's tail head, inguinal, or pectoral region. The sample is then shipped by overnight mail to a laboratory, where the stem cells are extracted, processed, concentrated, and purified to produce a stem cell-based product suitable for autologous injection at the injury site. Generally, there is no cellular culturing, expansion, or engineering involved with this procedure, and the concentrated stem cell product is returned to the veterinarian for injection into the patient at the site of the injury.

Stem cells extracted from bone marrow have also been used for the treatment of tendon and ligament injuries.^{5,6} In this instance, the patient is sedated, local anesthetic is injected, and bone marrow (approx 30 mL) is extracted from the sternum or tuber coxa. The bone marrow sample is shipped by overnight mail to a laboratory for processing, where the stem cells are extracted and cultured. The stem cell-based product is then returned to the veterinarian for injection into the patient at the site of the injury.

Current Federal Regulation of Human Stem Cell Treatment

Human stem cell treatment and associated products are regulated by the FDA under the authority of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act.^{12,13} Stem cells can be regulated as biologics under FDA's own recently promulgated Human Cells, Tissues, and Cellular and Tissue-Based Products Regulations, or depending on their intended use, under the agency's drug or medical device regulations.¹⁴

By their very definition, human stem cells may be considered biologics. Biologics are regulated by the FDA's Center for Biologics Evaluation and Research. Formerly, a manufacturer of biologics was required to hold an approved Establishment License Application and a separate Product License Application before marketing a biologic in interstate commerce. This rule was changed by the FDA in October 1999 so that now a manufacturer is only required to hold a single approved Biologics License Application before introducing a product into interstate commerce.¹⁵ To obtain a Biologics License Application, a manufacturer must show that the proposed product is safe, pure, and potent and that the facility in which the product is manufactured, processed, packed, or held meets established quality control standards.¹⁵

In April 2006, the FDA published and implemented regulations governing the use of human cells, tissues, and cellular and tissue-based products in humans. These regulations defined such products as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."¹⁶ Examples include bone, ligament, skin, dura mater, stem cells, cartilage cells, and various other cellular and tissue-based products. The regulations include registration and listing requirements for establishments that manufacture and process such products; provisions discussing donor eligibility; current good tissue practices covering all stages of production, including harvesting,

processing, manufacture, storage, labeling, packaging, and distribution¹⁷; and other requirements intended to prevent the introduction, transmission, and spread of communicable diseases in humans.¹⁸ Factors considered in the regulation of these products include the degree of manipulation (ie, whether the product has been more than minimally manipulated), whether the product is intended for a homologous function, whether the product has been combined with noncellular or non-tissue components, and the product's effect or dependence on the body's metabolic function.¹⁹ For these purposes, the definition of minimally manipulated differs depending on whether the product is used as structural tissue, cells, or nonstructural tissue.²⁰ With regard to structural tissues, minimally manipulated 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." With regard to cells and nonstructural tissues, however, minimally manipulated means "processing that does not alter the relevant biological characteristics of cells or tissues." To determine which definition applies, the FDA evaluates each product's labeling, advertising, and indications.²¹

In those instances when cells, tissues, and cellular and tissue-based products have been only minimally manipulated, are intended strictly for homologous use, have not been combined with noncellular or nontissue substances, and do not depend on or have an effect on the body's metabolism, the manufacturer only needs to register with the FDA, submit a list of manufactured products to the agency, and adopt and implement procedures for the control of communicable diseases.¹⁹ If one or more of the factors has been exceeded, the regulatory status of the product changes and the product will also be regulated as a drug or device.²²

For products that are regulated as drugs, an investigational new drug application and an approved new drug application are required before marketing and sale in the United States.²³ An investigational new drug application notifies the FDA of prospective clinical testing and allows the test product to be shipped in interstate commerce. Approval of a new drug application requires a showing that the drug is safe and effective for its intended use and that the methods, facilities, and controls used for the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity.

Even if a particular cellular or tissue-based product is not considered a drug, it may be considered a medical device, which would require clearance by the FDA prior to marketing.¹⁹ The data required for premarketing approval are similar to those required to support a new drug application.

Current Federal Regulation of Veterinary Medicines and Biologics

The FDA regulates the drugs used by veterinarians to treat sick and injured animals. Less explicit than the rules governing human medicine, the rules applicable to veterinary medicine allow for greater regulatory interpretation, making it difficult to definitively determine how new treatments such as equine stem cell treatment will be regulated by the agency.

Veterinary cellular and tissue-based treatments and associated products are regulated by the USDA's Center for Veterinary Biologics under the Virus, Serum, and Toxin Act of 1913²⁴; the FDA's Center for Veterinary Medicine under the applicable provisions of the Food, Drug, and Cosmetics Act²⁵; or a combination of the two. The Center for Veterinary Biologics has regulatory authority over the interstate shipment of animal biologics, whereas the Center for Veterinary Medicine regulates the manufacture and distribution of food additives, drugs, and devices given to animals and the intrastate marketing and sale of animal biologics. Under these regulations, animal biologics are defined as products prepared from animal tissues or fluids or from microorganisms that are used for the prevention or treatment of disease in animals; they include vaccines, serums, toxins, and analogous products.²⁶ In instances when an animal biologic shipped in interstate commerce also qualifies as a new animal drug, it will be regulated by both agencies. To date, neither agency has issued regulations specifically governing veterinary stem cell treatment.

How Equine Stem Cell Treatment May Be Federally Regulated in the Future

Given the current regulation of veterinary biologics and animal drugs, it is likely that if equine stem cell treatments and associated products are considered biologics, then they will be regulated by the USDA, requiring company registration and both facility and product licenses. However, if they are considered to be animal drugs rather than biologics, then they will likely be regulated by the FDA, requiring submission and approval of a new animal drug application.

The Virus, Serum, and Toxin Act requires all veterinary biologics produced in or imported into the United States to be safe and effective for the diagnosis, prevention, and treatment of animal diseases.²⁶ They must be pure, safe, potent, and effective and must be produced at a USDA-approved establishment.²⁶ Domestic veterinary biologics manufacturers are required to have a valid Veterinary Biologics Establishment License for the production facility and a separate Veterinary Biologics Product License for each product marketed and sold.²⁶ Foreign manufacturers may export veterinary biologics to the United States provided that they have US-based legal representatives holding valid Veterinary Biologics Product Permits to import these products into the United States for general distribution and sale.²⁷

The FDA's Center for Veterinary Medicine regulates the manufacture and distribution of food additives and drugs given to animals under the applicable provisions of the Food, Drug, and Cosmetic Act and is responsible for ensuring that medicated feeds and animal drug products are safe and effective for their intended use and that food from treated animals is safe for consumption. Unless approved and properly labeled for its specific intended use, a new animal drug will be deemed unsafe and in violation of the Food, Drug, and Cosmetic Act.

Given the current regulation of human stem cell treatment and associated products, if federal regulatory agencies should decide to regulate equine stem cell

treatment in particular and veterinary stem cell treatment in general, it seems likely that the agencies will take a multifaceted regulatory approach that will take into account factors such as degree of manipulation, intended use, composition, and metabolic interaction and divide veterinary stem cell treatments and associated products into 2 categories: biologics and drugs. Under this hypothetical regulatory approach, manufacturers that do not exceed a particular regulatory threshold would only be required to obtain and possess valid establishment and product registration certificates and to adopt and implement safeguards to prevent the introduction, transmission, and spread of communicable diseases. In contrast, manufacturers that exceed this threshold would be subjected to a greater degree of regulatory scrutiny and, potentially, required to obtain agency approval through a new animal drug application before going to market.

In general, it seems likely that treatments involving only the harvesting, concentration, and reinjection of autologous stem cells would not exceed the regulatory threshold and would only be required to comply with the registration provisions of the Virus, Serum, and Toxin Act. However, equine stem cell treatments and associated products exceeding this hypothetical regulatory threshold would likely be treated as drugs and would be regulated by the FDA's Center for Veterinary Medicine. This would include equine stem cell treatments that involve rigorous culturing and processing of harvested stem cells.

Legal Considerations for Companies Offering Equine Stem Cell Treatments

Companies offering equine stem cell treatment will be faced with the dilemma of deciding whether they are clinical investigators studying an investigational product or simply laboratories supporting the practice of veterinary medicine. If they are clinical investigators, they will need to file investigational new animal drug applications before shipping their stem cell-based products in interstate commerce and will be required to comply with all FDA-mandated guidelines applicable to the processing, manufacturing, packaging, labeling, and storage of veterinary cellular and tissue-based products. If they are merely laboratories supporting the practice of veterinary medicine, they would be exempt from FDA regulations as they currently exist. Either way, these companies may face a legal battle in the courts with the FDA or USDA over how these treatments should be regulated.

In deciding how to proceed, companies will need to carefully consider 2 points. First, in human medicine, limited use of unapproved drug products by state-licensed physicians is allowed, so long as the products are not distributed in interstate commerce, but the FDA does not provide the same autonomy with respect to the practice of veterinary medicine. If an unapproved equine stem cell-based product is marketed and used for a traditional drug function, the FDA may deem the product to be adulterated, exposing the laboratory and the practicing veterinarian to enforcement actions under the Food, Drug, and Cosmetics Act.²⁸

Second, the decision in *Grand Laboratories Inc v Harris* exposed the complex interplay between the USDA and FDA.²⁹ The case involved a South Dakota corporation, Grand Laboratories that manufactured and marketed animal biologics solely for intrastate sale and use in South Dakota. Thus, when the FDA sought to inspect Grand Laboratories' facility, it was denied access by the company, who questioned FDA's jurisdictional authority to inspect a biologics manufacturer. In response, the FDA argued that it had the right to inspect the South Dakota facility because animal biologics are drugs under the Food, Drug, and Cosmetics Act. Although the district court disagreed with the FDA and held that animal biologics are not drugs, the decision was reversed by the Eighth Circuit Court, which found that in some cases, animal biologics are drugs and, therefore, subject to the regulatory jurisdiction of both the USDA and the FDA. Thus, it is possible that, notwithstanding any veterinary practice exemption argument, the FDA may still be permitted to inspect the facilities of stem cell companies that identify themselves as laboratories supporting the practice of veterinary medicine, even if all they do is process samples to produce stem cell-based products intended for re-injection into the horse from which the sample came. Importantly, once the FDA has the authority to inspect a facility, it can be argued that the agency has the jurisdiction to regulate the facility's products.

Implications for Veterinarians Prescribing Equine Stem Cell Treatment

Considering its current experimental nature, it is possible that until its regulatory status is clarified, equine stem cell treatment would be treated in the same manner as complementary and alternative veterinary medical practices such as acupuncture, chiropractic therapy, aromatherapy, and nutraceutical therapy. Veterinarians practicing complementary and alternative veterinary medicine are held to the same standards as those practicing traditional veterinary medicine and have an obligation to protect the safety and well-being of their patients and to ensure that the treatments they provide are safe and effective. Under this interpretation, a veterinarian who offered equine stem cell treatment would have to be properly trained, obtain owner consent before proceeding with treatment, comply with all applicable state-specific regulations, and act in an ethical manner.³⁰

Given stem cell treatment's current nontraditional status, it will be particularly important for any equine practitioner recommending the treatment to have a thoughtful discussion with the horse owner about the potential hazards and risks associated with the procedure before proceeding. Owner consent should be obtained in a manner that is easily understood by a reasonable person and should include a comprehensive discussion of the various diagnostic and treatment options available, the potential risks involved, and the prognosis.³¹ For veterinarians working with companies identifying themselves as clinical investigators, this documented owner consent will be particularly important because the procedure will be deemed investigatory and the data collected may be used to support a future new animal drug application.

Several equine veterinarians in the United States are already offering equine stem cell treatment as an alternative to traditional treatment options. Yet, veterinary drugs are considered unsafe and adulterated unless approved, labeled, and used in accordance with a particular or intended use.³² Similarly, veterinary biologics are deemed unsafe unless registered with the appropriate agency. The Food, Drug, and Cosmetic Act does not provide for extralabel use in the practice of veterinary medicine as it does in the practice of human medicine.³³ Thus, unless the product is registered as a biologic or is the subject of an approved new animal drug application and is used in accordance with its approved indications, a veterinary stem cell-based product may be considered adulterated, in which case, its use would be a violation of federal law, subjecting the practicing veterinarian to the risk of FDA enforcement action.

So long as the FDA exercises its enforcement discretion to not take action, the regulatory risks faced by practicing veterinarians prescribing stem cell treatment are probably quite low. Should the FDA, however, decide that stem cell-based products and treatments are unapproved new animal drugs or unregistered new animal biologics and decide to exercise its enforcement authority against the industry and its providers, then there is a potential risk that veterinarians offering equine stem cell treatment could be charged with violating the Food, Drug, and Cosmetic Act.

In sum, stem cell treatment is a new technology with a vast number of potential future therapeutic applications. Provided that serious safety issues do not arise and the treatment is marketed as research and not as a proven veterinary drug treatment, it seems unlikely that the FDA will exercise its enforcement authority and take action against veterinarians currently doing research in the field.

Conclusion

Published reports^{34,35} suggest that substantial scientific achievements have been made in the field of equine stem cell treatment. Marketed for the treatment of tendon, ligament, and other joint injuries, equine stem cell treatment may offer horse breeders, trainers, and owners an alternative to current treatments.

To date, neither the USDA nor the FDA has promulgated regulations or published guidance specific to the practice of equine stem cell treatment or veterinary stem cell treatment in general. We are also unaware of any regulatory enforcement actions being taken by either agency against companies or veterinarians offering stem cell treatment. Thus, it appears that neither agency has deemed the practice to be an enforcement priority. However, as veterinary stem cell treatment becomes more popular and is used with greater frequency in the future, it is possible that one or both of these agencies may take steps to regulate the industry and the practice. If this happens, equine stem cell treatment and its associated products could be regulated as biologics, requiring registration with the USDA, or drugs, requiring FDA approval.

References

1. King M. Stem cell therapy. *The Horse* 2006;Jun. Available at: www.thehorse.com. Accessed Apr 10, 2008.
2. US Department of Health and Human Services, National Institutes of Health Web site. Stem cell basics: what are adult stem cells? Available at: stemcells.nih.gov/info/basics/basics4. Accessed Apr 10, 2008.
3. AVMA Web site. Position statements: stem cells. Available at: www.avma.org/issues/policy/stem_cells.asp. Accessed Apr 10, 2008.
4. Vet-Stem Web site. Available at: www.vet-stem.com. Accessed Apr 10, 2008.
5. Vet Cell Web site. Available at: www.vetcell.com. Accessed Apr 10, 2008.
6. Vet Biotechnology Web site. Available at: www.vetbiotechnology.com.au. Accessed Apr 10, 2008.
7. Pinock S. Stem cells in racehorses. *Scientist* 2005;19:34.
8. Salleh A. Stem cells may keep racehorses on track. *ABC Science Online* 2005;Nov 11. Available at: www.abc.net.au/science/news/stories/s1501332.htm. Accessed Apr 10, 2008.
9. Smith Thomas H. Health notes: stem cell therapy holds promise for injured tendons and ligaments. *Mid-Atlantic Thoroughbred* 2004;May:70–71.
10. Smith Thomas H. Stem cell therapy for repairing tendons and ligaments. *California Thoroughbred* 2004;Jun:51, 54, 55.
11. Clegg P. Stem cells—hope or hype? *Horse & Hound* 2005;Jul:12–13.
12. Federal Food, Drug, and Cosmetic Act, 21 USC §301–399.
13. Public Health Service Act, 42 USC §262, 264, 266.
14. Human Cells, Tissues, and Cellular and Tissue-Based Products Regulations, 21 CFR §1271.1–1271.440; Drug for Human Use, 21 CFR §300–369; Medical Devices, 21 CFR §800–898.
15. Public Health Service Act, 42 USC §262(a)(1)–(a)(2)(C).
16. 21 CFR §1271.3(d).
17. 21 CFR §1271.160–1271.320.
18. 21 CFR §1271.145–1271.320.
19. 21 CFR §1271.10(b).
20. 21 CFR §1271.3(f)(1)–(2).
21. 21 CFR §1271.10(a)(2).
22. 21 CFR §1271.20.
23. 21 USC §355.
24. Virus, Serum, and Toxin Act of 1913, 21 USC §151–158.
25. Food, Drug, and Cosmetic Act, 21 USC §354 (Veterinary Feed Directive Drugs); 21 USC §360b (New Animal Drugs); 21 USC §360ccc (New Animal Drugs for Minor Use and Minor Species); 21 USC §379j (Fees Relating to Animal Drugs).
26. 21 USC §151–158. See also *United States v Miami Serpentarium Laboratories Inc*, Food, Drug, Cosm L rep (CCH) [1982–83] Dev Trans Binder 38, 164 (SD Fla, 1982).
27. 21 USC §155.
28. 21 USC §355; 21 USC §360b.
29. *Grand Laboratories Inc v Harris*, 660 F2d 1288 (8th Cir, 1981).
30. AVMA Web site. AVMA guidelines for complementary and alternative veterinary medicine. Available at: www.avma.org/issues/policy/comp_alt_medicine.asp. Accessed Mar 20, 2008.
31. AVMA adopts policy on informed consent. *J Am Vet Med Assoc* 2007;230:1435.
32. 21 USC §360b(a)(1).
33. *United States v Evers*, 643 F2d 1043 (5th Cir, 1981).
34. Richardson LE, Dudhia J, Clegg PD, et al. Stem cells in veterinary medicine—attempts at regenerating equine tendon after injury. *Trends Biotechnol* 2007;9:409–416.
35. Herthel DJ. Enhanced suspensory ligament healing in 100 horses by stem cells and other bone marrow components, in *Proceedings. Am Assoc Equine Pract Annu Meet* 2001;47:319–321.