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Challenging the FDA's Authority to Regulate Autologous Adult Stem Cells for Therapeutic Use: Celltex Therapeutics' Partnership with RNL Bio, Substantial Medical Risks, and the Implications of *United States v. Regenerative Sciences*

Katherine Drabiak-Syed

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CHALLENGING THE FDA'S AUTHORITY TO
REGULATE AUTOLOGOUS ADULT STEM
CELLS FOR THERAPEUTIC USE:
CELLTEX THERAPEUTICS' PARTNERSHIP
WITH RNL BIO, SUBSTANTIAL MEDICAL
RISKS, AND THE IMPLICATIONS OF *UNITED
STATES V. REGENERATIVE SCIENCES**

Katherine Drabiak-Syed†

ABSTRACT

This Article examines the convergence of three corporations that have attempted to capitalize on translating emerging research into clinical procedures by manufacturing and facilitating the process for patients to obtain mesenchymal stem cell (MSC) injections. Although the Food and Drug Administration (FDA) has asserted its authority to regulate somatic cell therapy products like MSCs under the Public Health Service Act and the Food, Drug, and Cosmetic Act, some manufacturers have attempted to circumvent FDA regulation through various mechanisms and argue that their products do not fall within the definition of a biological product or drug. However, scientific knowledge of using MSCs for clinical therapy remains in its infancy, and MSCs pose a number of serious risks to patients. This Article focuses on the development of Celltex, a company based in Sugar Land, Texas that manufactures and facilitates the injection of autologous MSCs; RNL Bio, a company that licenses its operations technology to Celltex; and Regenerative Sciences, a company based in Broomfield, Colorado that was recently involved in litigation with the FDA. Corporate circumvention of intended regulatory oversight exposes patients to potentially inefficacious products that could contribute to serious medical injuries such as viruses, myocardial infarction, cancer, or death.

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† Law & Bioethics Policy Consultant, Indiana University Center for Bioethics. I would like to thank the faculty and staff at the Indiana University Center for Bioethics for their support of this Article and acknowledge Professor Leigh Turner's extensive investigative research as inspiration for examining the potential effects of circumventing intended regulations relating to emerging research in regenerative medicine.

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INTRODUCTION

Over the past few years, a growing number of companies have started to offer patients purported treatment for various diseases and conditions using autologous adult stem cells (ASCs) for non-homologous purposes—specifically mesenchymal stem cells (MSCs) derived from the patient's own adipose tissue.¹ This Article examines the convergence of three corporations that have attempted to capitalize on translating emerging research into clinical procedures by manufacturing and facilitating the

1. This Article will refer to non-blood stem cells (mesenchymal) derived from an individual and prepared for use in that same individual (autologous) and intended to serve a different medical purpose (non-homologous).

process for patients to obtain mesenchymal stem cell (MSC) injections.² The FDA has asserted its authority to regulate somatic cell therapy products, including MSCs, under the Public Health Service Act (PHSA) and the Food, Drug, and Cosmetic Act (FDCA), but some manufacturers have attempted to circumvent FDA regulations through various strategies—namely, by arguing that their products do not fall within the definition of a “drug” so the corporation need not follow the requirements set forth in the FDCA prior to advertising the product for treatment purposes. This Article examines: (1) the development of Celltex, a company that manufactures and facilitates the injection of autologous MSCs; (2) RNL Bio, the company that licenses its operations technology to Celltex; and (3) recent litigation between the FDA and Regenerative Sciences.

ASCs are unspecialized multi-potent cells that are capable of renewing themselves through cell division and differentiating into different types of cells.³ Unlike pluripotent cells, which are capable of differentiating into all tissues of the patient, ASCs are more limited in their ability to differentiate.⁴ They can be derived through sources such as bone marrow, muscle, skin, and teeth; more recently, scientists have begun extracting and isolating them from adipose tissue.⁵ Despite ASCs’ anticipated potential for clinical therapies, the scientific community is just beginning to understand their efficacy and safety.⁶ In addition to uncertain benefit, the manipulation and injection of stem cells poses a number of risks arising from inherent properties of the cells and the method of manufacture.

Part I of this Article describes the development of Celltex and its connection to Texas Governor Rick Perry and outspoken physician and Celltex co-founder Dr. Stanley Jones. This section explores Celltex’s connection to RNL Bio and describes the initial media coverage relating to Celltex’s practices. Part II provides an overview of sections of the PHSA and the FDCA pertaining to the manufacture of MSCs and describes FDA guidance that explicitly states the agency’s intention to

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2. All reference to ASCs or MSCs in this Article refer specifically to autologous ASCs that are used for non-homologous purposes.
 3. *NIH Stem Cells Basics*, NIH, <http://stemcells.nih.gov/info/basics/basics1.asp> (last updated Apr. 28, 2002).
 4. Mary A. Chirba & Stephanie Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine*, 7 J. HEALTH & BIOMED. L. 233, 234 (2011).
 5. *Id.* at 235.
 6. See generally Phanette Gir et al., *Human Adipose Stem Cells: Current Clinical Applications*, 129 PLASTIC & RECONSTRUCTIVE SURGERY 1277 (2012); Bettina Lindroos et al., *The Potential of Adipose Stem Cells in Regenerative Medicine*, 7 STEM CELL REVIEWS AND REPORTS 269 (2011).

regulate MSCs and adipose stem cells as somatic cell therapy products within the framework of biological products and drugs. Part III discusses the current scientific research examining potential clinical uses of ASCs and summarizes the numerous and potentially severe risks associated with autologous ASC injections for non-homologous use, where the injected stem cells are intended to differentiate and restore and repair other areas of the brain or body. Part IV provides an overview of Celltex's business practices and product claims. It discusses concerns raised by bioethicists and the media and also describes the FDA's recent findings during a facility inspection. Part V describes why Celltex's business arrangement with RNL Bio raises additional concerns and summarizes allegations against the company's subsidiary as set forth in a recent lawsuit connected to the subsidiary's business practices in Los Angeles, California. Part VI summarizes recent litigation in which the FDA asserted its authority under the PHSa and the FDCA to regulate Regenerative Sciences' practices of manufacturing and facilitating the injection of MSCs to patients. This non-binding precedent is significant because it affirms that the FDA has appropriately set forth regulations to classify types of ASCs and has the authority to regulate MSCs under the PHSa and the FDCA. Finally, Part VII explores the implications for physicians performing the injections and examines regulations set forth by the Texas Medical Board, professional standards, and Texas state law.

I. THE RISE OF ASCs IN TEXAS: DR. STANLEY JONES, GOV. RICK PERRY, CELLTEX THERAPEUTICS, AND RNL BIO

In the past few years, both local and national media have reported on the development of initiatives to advance ASCs for treatment purposes in Texas. In May 2010, an orthopedic surgeon named Dr. Stanley Jones traveled with his wife, Kathi Jones, a registered nurse and owner of a medical spa, to Kyoto, Japan to undergo ASC infusions administered by RNL Bio, a company based in Seoul, South Korea.⁷ Five months later, the company reported in a press release that Dr. Jones experienced complete recovery from his autoimmune arthritis.⁸

Jones, a personal friend of Texas Governor Rick Perry, stated that he felt compelled and "moved by his faith" to call on Perry for his

7. Andrea Vasquez, *Perry Watch: Perry's Back Surgery Included Experimental Stem Cell Therapy*, HOUS. CHRON.: TEXAS ON THE POTOMAC (Aug. 4, 2011), <http://blog.chron.com/txpotomac/2011/08/perry-watch-perrys-back-surgery-included-experimental-stem-cell-therapy>.

8. *Id.* For sake of clarity, references to RNL include RNL Bio and RNL Life Sciences (now Human Biostar).

support to permit commercializing ASC procedures in Texas.⁹ In addition to the close relationship between Jones and Perry, Celltex co-founder David Eller contributed a substantial amount to Perry's election campaign.¹⁰ In July 2011, Texas newspapers and online media outlets widely reported that Jones performed an infusion of autologous MSCs by injecting the cells into Perry's back and bloodstream as a treatment for Perry's existing back injury.¹¹ Weeks after Perry received the injections, he contacted the Texas Medical Board (the Board) at Jones' behest, requesting that it promulgate rules to ensure that physicians would be permitted to perform stem cell infusions.¹² Around the same time, Texas State Representative Rick Hardcastle, who also received MSC infusions from Jones, sent a letter to the Board. A month prior to Perry's injection in the summer of 2011, Rep. Hardcastle introduced legislation to create a stem cell bank in the state and wrote to the Board that he did not intend to create "onerous and unnecessary regulations to impede the practice and research of physicians in regards to the use of investigational agents."¹³

The amount of publicity around Perry's injections attracted the attention of *Nature*, which began publishing articles on the use of ASCs in Texas and FDA regulations relating to the practice. Perry continued to publicly acclaim his infusions and expressed his hope that "Texas [would] become the world's leader in the research and use of adult stem cells" and "lead the nation in advancing adult-stem-cell research that will treat diseases, cure cancers, and ultimately, save lives."¹⁴ Despite Perry's claims, *Nature* reiterated that the FDA has not approved such ASC treatments because it regulates cells that undergo more than minimal manipulation during the cell culturing process.¹⁵ In the past few years, manufacturers and clinics in the United States have begun

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9. Emily Ramshaw, *Perry's Adult Stem Cell Treatment Was Doctor's First Attempt*, TEX. TRIB. (Aug. 4, 2011), <http://www.texastribune.org/2011/08/04/perrys-stem-cell-treatment-was-doctors-first-attem>.
 10. Emily Ramshaw, *Key Players Drive Texas Medical Board Stem Cell Rules*, TEX. TRIB. (Feb. 9, 2012), <http://www.texastribune.org/texas-health-resources/texas-medical-board/key-players-drive-texas-medical-boards-stem-cell-r>.
 11. *Id.*; Emily Ramshaw, *Perry, Allies Lay Groundwork for TX Stem Cell Industry*, TEX. TRIB. (Aug. 4, 2011), <http://www.texastribune.org/2011/08/04/perry-allies-lay-groundwork-tx-stem-cell-industry>.
 12. Letter from Rick Perry, Governor of Texas, to Irvin E. Zeitler, Jr., Chairman, Texas Medical Board (July 25, 2011), *available at* <http://freepdfhosting.com/a30d34c191.pdf>.
 13. Ramshaw, *supra* note 10; David Cyranoski, *Texas Prepares to Fight for Stem Cells*, 477 NATURE 377, 378 (2011).
 14. Cyranoski, *supra* note 13, at 377.
 15. *Id.* at 378.

circumventing FDA regulations in various ways: by sending patients overseas for the injections (RNL Bio and RNL Life Sciences); asserting that the manufacture and injection of ASCs falls within the practice of medicine (Regenerative Sciences and Stanley Jones); or arguing that MSCs do not fall within the regulatory definition of “drugs” overseen by the FDA (Regenerative Science and Celltex).¹⁶ Specifically, manufacturers such as Celltex argue that the process of culturing and preparing the stem cells does not constitute the manufacture of a biological drug, so the process stands outside the scope of FDA’s regulatory authority.¹⁷

In December 2011, Celltex opened its doors for business to manufacture and facilitate the process for individuals seeking to receive stem cell injections.¹⁸ Founded by Jones and Eller, Celltex uses technology licensed from RNL Bio to process stem cells.¹⁹ Several months later, *Nature* published another article describing Celltex’s company practices, whereby Celltex coordinates with local physicians to remove a patient’s adipose tissue that Celltex then processes, cultures, and expands to produce mesenchymal stem cells over a period of three weeks.²⁰ Celltex charges patients an estimated twenty to thirty thousand dollars for monthly MSC injections, of which coordinating physicians receive five hundred dollars per injection.²¹ One Houston-based physician, Dr. Jamshid Lofti, has worked with Celltex to administer ASC injections manufactured by Celltex to more than twenty people for diseases such as multiple sclerosis and Parkinson’s disease.²² According to Lofti, patients generally receive three injections over several months.²³ He claims that most of his patients report improvement, although he acknowledges the limitations of anecdotal evidence in medicine.²⁴

16. *Id.*

17. *Id.*

18. David Cyranoski, *Stem-Cell Therapy Takes Off in Texas*, 483 NATURE 13, 13 (2012).

19. *Id.*

20. Leigh Turner, *Celltex Makes Bold Marketing Claims Despite Significant Manufacturing Problems Found During FDA Inspection*, HEALTHIN THE GLOBAL VILLAGE (Aug. 7, 2012), <http://www.healthintheglobalvillage.com/2012/08/07/Celltex-makes-bold-marketing-claims-despite-significant-manufacturing-problems-found-during-fda-inspection>.

21. Cyranoski, *supra* note 18, at 14. According to Lofti’s information, if Celltex pays him \$500 per injection, patients generally receive at least three injections, and he has “treated” more than 20 patients, Celltex has paid Lofti at least \$30,000 from December 2011 to March 2012.

22. *Id.* at 13.

23. *See id.*

24. *Id.* at 14.

Problematically, Lofti and Jones have dismissed any risks arising from undergoing MSC injections.²⁵ Lofti echoed Perry's praise of ASCs, asserting that they could be "a panacea, from cosmetics to cancer" and that "the worst case scenario is that [the ASC treatment] won't work."²⁶ Similarly, months before Celltex opened, when Jones discussed Perry's injections with the media, Jones claimed that ASC injections had "no side effects" and that pharmaceutical drugs posed more risks to patients. He did acknowledge, however, that ASCs might not work for everyone.²⁷ Scientific literature in this area not only demonstrates the presence of risks potentially arising from using ASCs in clinical therapy but also shows the severity and nature of those risks, including transmitting viruses or endotoxins, inducing a potentially fatal immune reaction, creating tumors within the body, and differentiating inappropriately and leading to pulmonary emboli or myocardial infarctions.²⁸ Jones' statements are especially worrisome because he is both a co-founder of Celltex and has administered injections to at least two patients (Perry and Hardcastle). Accordingly, it is uncertain whether and how he discussed the risks of the procedure with his patients. There are questions of how accurately Celltex represents risks to patients in general.

Bioethicists, scientists, and the FDA responded to emerging information of Celltex's business practices, the promises of ASCs' potential, and the disclosure of potential risks. George Daley, the Director of the Stem Cell Transplantation Program at Harvard Medical School, has explained the experimental nature of any treatment and how little the scientific community knows about ASCs.²⁹ He affirmed that patients who receive MSC injections are indeed exposed to risks from the cells, the conditions of their manufacture, and the procedure itself.³⁰ Furthermore, Daley and other stem cell scientists questioned why Celltex was charging patients substantial sums of money for procedures it could not prove were effective through FDA-regulated clinical trials.³¹ Bioethicist Leigh Turner took note and began authoring meticulous media updates on company practices and wrote a letter to the FDA thoroughly detailing numerous legal and ethical concerns.³² Rita Chappelle, a spokesperson for

25. See *id.*; Ramshaw, *supra* note 9.

26. Cyranoski, *supra* note 18, at 14.

27. Ramshaw, *supra* note 9.

28. See *infra* Part IV.

29. Cyranoski, *supra* note 18, at 14.

30. *Id.*

31. *Id.*

32. Letter from Professor Leigh Turner, Univ. of Minn. Ctr. for Bioethics, to Dr. Karen Midthun, Director, Ctr. for Biologics Evaluation and Res., Food and Drug Admin. (Feb. 21, 2012), available at <http://freepdfhosting.com/46b331a006.pdf> [hereinafter "Turner Letter"].

the FDA's Center for Biologics Evaluation and Research, affirmed that if a manufacturer processes the cells for expansion, this constitutes more than "minimal manipulation" and would subject the manufacturer to FDA regulation.³³ A former reviewer at the Center alleged that "if Perry was treated in the United States, it was clearly in violation of FDA regulation."³⁴

II. FDA REGULATION OF ASCS

A. *Regulation of Human Cell and Tissue Products (HCT/Ps)*

Under the Public Health Service Act (PHSA), the FDA regulates human cell and tissue products (HCT/Ps), which refers to articles "containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."³⁵ According to the FDA, the goal of the regulations is "to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products."³⁶ These regulations are designed to prevent contamination and communicable disease³⁷ rather than to ensure safety and efficacy. They impose several requirements such as registering the HCT/Ps with the FDA and promulgating standards for Good Tissue Practice, including monitoring the procedures, facilities, processing equipment, and supplies and reagents used in the manufacturing process.³⁸ Under the HCT/P system Section 1271, the FDA classifies different types of human cells, tissues, and cellular and tissue-based products into categories for regulation based on the public health risks they pose: (1) products not subject to HCT/P regulations, (2) HCT/Ps regulated under Section 361 of the PHSA, and (3) products posing the most risk that are to be regulated stringently as a biological product or drug.³⁹

In 2006, the FDA replaced a single word in its definition of HCT/Ps, substantially changing its official application.⁴⁰ Previously, the regulation defined HCT/Ps as "articles containing or consisting of human cells or

33. Cyranoski, *supra* note 18, at 14.

34. Cyranoski, *supra* note 13, at 378.

35. 21 C.F.R. § 1271.3(d) (2012).

36. Human Cells, Tissues, and Cellular and Tissue-Based Products, 66 Fed. Reg. 5447 (Jan. 19, 2001) (codified at 21 C.F.R. pts. 207, 807, & 1271).

37. See 21 C.F.R. § 1271.145 (2012); Barbara von Tigerstrom, *The Food and Drug Administration, Regenerative Sciences, and the Regulation of Autologous Stem Cell Therapies*, 66 FOOD & DRUG L.J. 479, 485 (2011).

38. 21 C.F.R. § 1271.150 (2012).

39. *Id.* §§ 1271.1, 1271.150; Chirba & Garfield, *supra* note 4, at 250.

40. 21 C.F.R. § 1271.3(d) (2012) (changing the phrase "another human recipient" to "a human recipient"); Chirba & Garfield, *supra* note 4, at 253.

tissues that are intended for implantation, transplantation, infusion, or transfer into *another* human recipient.”⁴¹ The FDA replaced the word “another” with “a,” which formally included autologous products within the classification of HCT/Ps.⁴² Scholars have debated this agency action, arguing that the FDA failed to provide the sufficient notice and comment generally required for rulemaking. Others maintain that the FDA repeatedly announced its intention to regulate both allogenic (stem cells derived from one individual and used in a different individual) and autologous therapies (stem cells derived from one individual and used in that same individual) in previous guidance documents, and therefore this change merely updated the regulations to reflect the new HCT/P risk classification system.⁴³ However, manufacturers such as Regenerative Sciences have recently used this particular modification as a basis to challenge the FDA’s authority to regulate ASCs even under the less onerous HCT/P framework.⁴⁴ The FDA has since stated this change merely represented an interpretative rule to clarify existing regulations and constituted a procedural rather than substantive change, and therefore the agency did not need to abide by notice and comment procedures.⁴⁵

The first category in Section 1271 lists products that the FDA does not regard as human cell- or tissue-based products subject to this regulation, such as human organs for transplantation, whole blood, and bone marrow.⁴⁶ Section 1271 states that the FDA does not consider a product to be an HCT/P under the regulation if the product is only “minimally manipulated” and is intended for homologous use. In other words, a product is not subject to the regulations set forth in the HCT/P system if the manufacturing and processing of the cells does not alter the cells’ relevant biological characteristics and the cells will serve the same biological function in the donor and recipient.⁴⁷

Section 361 of the PHSA provides the FDA with authority to regulate the second category of products in the HCT/P system. The FDA will not regulate the HCT/P solely under Section 361, subjecting any of the following circumstances to more stringent regulation as a drug or biologic: (1) if the manufacturing and processing alters the relevant biological characteristics of the cells; (2) if the cells are intended to serve a different biological function after transfer to the recipient; or (3) if the

41. See Chirba & Garfield, *supra* note 4, at 253–54.

42. *Id.* at 254.

43. *Id.*; von Tigerstrom, *supra* note 37, at 488–89.

44. See *infra* Part VII.

45. Chirba & Garfield, *supra* note 4, at 266–67.

46. 21 C.F.R. § 1271.3 (2012); Chirba & Garfield, *supra* note 4, at 250; von Tigerstrom, *supra* note 37, at 485.

47. von Tigerstrom, *supra* note 37, at 485.

manufacture of the HCT/P involves the combination of the cells with another article that is not an agent intended to sterilize, preserve, or store.⁴⁸

B. Regulation under the PHSa and the FDCA

If the product does not meet all the requirements set forth in Section 1271, the FDA will regulate it as a “biological product” under Section 351 of the PHSa or as a “drug” under the FDCA, which requires stricter regulation than a Section 361 product.⁴⁹ Under the FDCA, a manufacturer must show its drug is both “safe” and “effective” prior to moving the drug in interstate commerce.⁵⁰

A “biological product” is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”⁵¹ A biological product manufacturer must (1) obtain a biologics license to deliver the product into interstate commerce; (2) demonstrate to the FDA that the product is safe, pure, and potent; (3) abide by contemporary good manufacturing practices (cGMPs); and (4) submit post-market studies and clinical trial information.⁵²

Under the FDCA, a “drug” refers to an article that is “intended for use in the diagnosis, cure, mitigation, or prevention of disease,” or an article that is “intended to affect the structure or any function of the body of man or other animals.”⁵³ The intended use refers to the manufacturer’s objective intent, which can be determined from labeling claims, advertisements, or written or oral statements by the manufacturer or its representatives.⁵⁴ Jurisprudence in this area has held that the definition of the word “drug” should be read as widely as possible and that its scope should not be limited to products commonly referred to as drugs.⁵⁵ Once the FDA determines that a product is a drug, the manufacturer is

48. See Human Cells, Tissues, and Cellular and Tissue-Based Products, 66 Fed. Reg. 5447 (Jan. 19, 2001) (codified at 21 C.F.R. pt. 207, 807, & 1271).

49. See Suzan Onel et al., *Cultured Stem Cells for Autologous Use: Practice of Medicine or FDA Regulated Drug and Biological Product?*, K & L GATES 1 (Sept. 19, 2011), http://www.klgates.com/files/Publication/93fd6a2d-ef3a-4259-b20a-8abb1d1ffbce/Presentation/PublicationAttachment/4fe18eca-fa06-465c-a52f-8e4cf7ddb80e/FDA_Alert_Cultured_Stems_Cells_091911.pdf.

50. See Chirba & Garfield, *supra* note 4, at 243.

51. 42 U.S.C. § 262(h)(i) (2012).

52. *Id.* § 262(a).

53. 221 C.F.R. § 201.128 (2012); von Tigerstrom, *supra* note 37, at 484 (quoting 21 U.S.C. §§ 321(g)(1)(B), 321(g)(1)(C) (2006)); Chirba & Garfield, *supra* note 4, at 245.

54. 221 C.F.R. § 201.128; Chirba & Garfield, *supra* note 4, at 245.

55. Chirba & Garfield, *supra* note 4, at 246.

subject to the FDA's pre-marketing requirements designed to ensure the drug's safety and efficacy, which includes submitting a new drug application or an investigational new drug application (IND), undergoing investigational drug studies approved by an institutional review board (IRB), complying with cGMPs, and conducting clinical trials.⁵⁶

C. FDA Guidance and Application to ASCs

In the 1990s, the FDA promulgated guidance that classified MSCs and adipose stem cells as somatic cell therapy products (autologous, allogeneic, or xenogeneic living cells, which have been manipulated, processed, or expanded) and excluded them from the list of HCT/PS that the FDA intended to regulate solely under Section 361.⁵⁷ During its revision of the regulations pertaining to HCT/PS in 2001, the FDA stated in its rulemaking preamble that the agency did “not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation,” announcing that it intended to regulate such ASCs within the framework of biological products and drugs.⁵⁸ Indeed, guidance on the FDA's website clarifies that “human somatic cell therapy products include autologous or allogeneic cells that have been propagated, expanded, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries” and are subject to regulation as a biological product and or drug.⁵⁹ In January 2012, the FDA issued a Consumer Health Information Guide, cautioning consumers to make sure that any stem cell treatment they consider has been approved by the FDA or is subject to a current protocol submitted to the FDA to ensure that the stem cells are safe, effective, and have undergone adequate and well-controlled clinical

56. *Id.* at 247, 252; Onel et al., *supra* note 49.

57. GUIDANCE FOR HUMAN SOMATIC CELL THERAPY AND GENE THERAPY 7–8 (1998), *available at* <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm081670.pdf>; REGULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS), SMALL ENTITY COMPLIANCE GUIDE 4 (2007), *available at* <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062592.pdf>; *Revised Instructions for Listing Other HCT/PS on Form 3356 or in eHCTERS*, FDA, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/ucm146772.htm> (last updated May 5, 2009).

58. Human Cells, Tissues, and Cellular and Tissue-Based Products, 66 Fed. Reg. 5,447, 5,457 (Jan. 19, 2001) (codified at 21 C.F.R. pts. 207, 807, 1271).

59. *Revised Instructions*, *supra* note 57.

trials.⁶⁰ Accordingly, the FDA must also oversee the manufacturing process to assure the products' safety, purity, and potency.⁶¹

Despite the FDA's clarity that MSCs constitute biological products and drugs, some manufacturers have attempted to challenge the FDA's interpretation of the enabling statutes in the PHSA and the FDCA.⁶² Two companies—Regenerative Sciences and Celltex—have recently challenged the FDA's regulation of ASCs as biological products and drugs.⁶³ These challenges are especially worrisome based on the emerging science of ASCs, uncertainties about their safety and efficacy, and the inherent risks posed by ASC injections.

III. RISKS OF ASCs IN SCIENTIFIC LITERATURE

Scientific literature discussing the clinical applications of ASCs for regenerative medicine lends support to the FDA's position that expanding and processing the cells constitutes more than minimal manipulation and that the FDA must regulate ASCs as biological products and drugs. Literature reviews note that we are in the process of developing an understanding of the safety and efficacy of using ASCs.⁶⁴ Scientists have only begun to conduct clinical trials in the past few years, and the published data that is currently available often originates from uncontrolled studies or studies monitoring only a limited number of patient outcomes.⁶⁵ As of August 2012, only seventy autologous adipose stem cell therapy studies have been or are currently in the process of being conducted in human trials worldwide.⁶⁶ These studies examine the use of MSCs derived from adipose cells to treat diseases ranging from congestive heart failure to multiple sclerosis to autism.⁶⁷ Notably, most of the discussions regarding regulatory considerations presume that ASCs for

60. *FDA Warns About Stem Cell Claims*, FDA, <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM286213.pdf>.

61. *Id.*

62. Chirba & Garfield, *supra* note 4, at 257; von Tigerstrom, *supra* note 37, at 482-86.

63. Regenerative Sciences sets forth additional arguments that are outside the scope of this Article. *See Celltex Responds to Media Reporting in FDA Visit: Company Pioneering Regenerative Medicine Services Invited FDA to Inspect Lab*, CELLTEX THERAPEUTICS (June 27, 2012), <http://www.celltexbank.com/Celltex-responds-to-fda-visit/> (last visited Sept. 1, 2012); von Tigerstrom, *supra* note 37, at 485-86.

64. Gir et al., *supra* note 6, at 1279; Lindroos et al., *supra* note 6, at 269.

65. *Id.* at 270.

66. A search for the term "adipose stem cell therapy" on the NIH Clinical Trials website in August 2012 yielded seventy studies. *Basic Search*, CLINICAL TRIALS, <http://www.clinicaltrials.gov/ct2/search>.

67. *See id.*

use in clinical therapies are subject to FDA regulation as a biological product and drug and would require the manufacturer to comply with GMPs, file appropriate forms, and conduct clinical trials.⁶⁸

Clinicians can obtain adipose (fat) tissue from liposuction aspirates, and scientists next isolate and extract the ASCs and then apply induction factors including chemicals and growth serum to expand the ASCs in culture medium over a period of several weeks.⁶⁹ Both the culture medium and the choice of growth serum affect how the cells grow and differentiate as well as the overall health and quality of the cells.⁷⁰ Processing the ASCs in growth serum enables their survival and offers the cells protection from cytotoxic agents.⁷¹ Because fetal bovine growth serum (FBS) is rich in growth factors and stimulates protein secretion in the cells during their proliferation,⁷² most studies have used FBS as the choice of growth agent. The FDA has approved MSCs cultured using FBS for clinical trials in the United States during Phase I trials, but some regulatory agencies would require xeno-free or serum-free media during later phase studies or in the application of clinical therapy.⁷³

The process of expanding and culturing stem cells can change the biological characteristics of the ASCs.⁷⁴ That is, each division of the cell creates the possibility of problematic mutations, and the mechanisms that ordinarily correct these changes may not function adequately during the in vitro process.⁷⁵ Accordingly, this observation means that ASCs cannot be treated as minimally manipulated and cannot be regulated solely under Section 361.⁷⁶ Research has also demonstrated the increasing genetic instability of cells connected to the amount of time left in culture, showing that too much time expanding in culture can alter the genetic composition of cells.⁷⁷ Scientific literature has concluded that this particular risk warrants extensive pre-clinical studies to determine safety and efficacy and subsequently recommends monitoring the genetic

68. See Gir et al., *supra* note 6, at 1280.

69. Lindroos et al., *supra* note 6, at 273, 275–77.

70. *Id.* at 275, 277; see Carla Herberts et al., *Risk Factors in the Development of Stem Cell Therapy*, J. TRANSLATIONAL MED., Mar. 2011, at 1, 6; Chandana Tekkatte et al., “Humanized” Stem Cell Techniques: *The Animal Serum Controversy*, 2011 STEM CELLS INT’L [doi: 10.4061/2011/504723 at 3] (2011).

71. Tekkatte et al., *supra* note 6 at 3.

72. Lindroos et al., *supra* note 6, at 279.

73. Lindroos et al., *supra* note 6, at 279, 284; Tekkatte et al., *supra* note 70 at 3, 10.

74. Herberts et al., *supra* note 70, at 6.

75. *Id.*

76. See 21 C.F.R. § 1271.3(f) (2012).

77. Lindroos et al., *supra* note 6, at 284.

stability of cells during the manufacturing process and following injection.⁷⁸

In addition to the intrinsic risks involved in the expansion process, the choice of growth serum and other adventitious agents both influences the cells' ability to proliferate and poses additional risks.⁷⁹ Human cells that are exposed to xenogenic products (foreign substances) originating from cell culture reagents may transfer xenogenic antibodies into the recipient once the cells are injected.⁸⁰ Literature has widely acknowledged risks specifically from using FBS, such as activating immune responses, with reports of anaphylactic shock or Arthus-like immune reactions in patients following introduction of cells grown in FBS media.⁸¹ FBS also poses the risk of transferring numerous viruses, bacterial infections, prions, and even currently unidentified zoonoses (cross-species diseases).⁸² Additionally, the serum could potentially become contaminated with yeast, fungi, and endotoxins, some of which are impossible to remove from the serum.⁸³ Although processing can remove most of the FBS prior to clinical use, trace bovine proteins may remain sufficient to trigger an immune response and some contaminants (such as viruses, prions, and nanobacteria) are impossible to remove.⁸⁴

Notably, Jeong Chan Ra of RNL Bio has published on the safety and potential risks of MSCs for therapeutic human use using FBS as a growth factor.⁸⁵ Ra's article asserts that RNL's methodology "completely removed" FBS from cultured MSCs.⁸⁶ These specific methodology and research claims are critical because Celltex advertises numerous claims on its website relating to the company's use of RNL Bio's methods for processing the ASCs it facilitates for patient injection.⁸⁷ Celltex does not advertise its specific methods for ASC expansion or clarify on its website material its choice of growth serum.

78. *Id.*

79. Tekkatte et al., *supra* note 70, at 10.

80. Lindroos et al., *supra* note 5 at 279.

81. Tekkatte et al., *supra* note 70, at 3.

82. Lindroos et al., *supra* note 6, at 279.

83. Tekkatte et al., *supra* note 70, at 2.

84. *Id.* at 2, 10.

85. Jeong Chan Ra et al., *Safety of Intravenous Infusion of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Animals and Human*, 20 STEM CELLS & DEV. 1297, 1306 (2011).

86. *Id.* at 1298.

87. See Tekkatte et al., *supra* note 70, at 4–8; Sven Kinzbach & Karen Bieback, *Expansion of Mesenchymal Stem/Stromal Cells under Xenogenic-Free Culture Conditions*, 129 ADVANCES IN BIOCHEMICAL ENG'G/BIO TECHNOLOGY 33 (2013).

Based on the risks described above, scientists have begun to examine the possibility of using either xeno-free serum or serum-free culture conditions.⁸⁸ However, such xeno-free and culture-free media have not yet been shown to be safe or effective.⁸⁹ Some scientists in this area have proposed creating autologous serum derived from the intended patient, but studies have not been able to confirm cells' ability to differentiate, proliferate, or show consistent growth in autologous serum.⁹⁰ As discussed above, too much time in culture can create genetic instability in the cells, so the culture formula must be able to expand the cells within this anticipated maximum in vitro time period.⁹¹ Recent studies have also suggested that autologous serum may not serve as an effective medium when it is derived from older individuals because preliminary studies have shown it interferes with MSCs capacity to proliferate and differentiate.⁹² Furthermore, autologous serum derived from human blood poses additional risks that would require further investigation prior to human clinical application.⁹³

ASCs also pose a number of clinical risks related to tumor growth once the ASCs are injected. Inherent properties of stem cells are similar to cancer cells: they have a long life span, they are resistant and can replicate over extended periods of time, and they are controlled by similar growth regulators within the body.⁹⁴ Scientific literature widely cites the risk of tumor formation as one of the most difficult obstacles to using ASCs in clinical therapies.⁹⁵ If cells are kept too long in culture and undergo chromosomal alterations, some studies have found this increases their risk of tumorigenicity.⁹⁶ Injection of ASCs also poses the risk of bystander tumor formation where the injected cells can affect the growth of existing previously undetected tumor cells within the body.⁹⁷

The literature recognizes several other distinct concerns that pose a risk to clinical use of ASCs. Scientists still do not fully understand the

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88. Francisco dos Santos et al., *Toward A Clinical-Grade Expansion of Mesenchymal Stem Cells From Human Sources: A MicroCarrier-Based Culture System Under Xeno-Free Conditions*, 17 *TISSUE ENG'G PART C: METHODS* 1201 (2011); Tekkatte et al., *supra* note 70, at 3, 10.
89. *See generally* Kinzebach & Bieback, *supra* note 84; Tekkatte et al., *supra* note 70, at 4–8.
90. Tekkatte et al., *supra* note 70, at 4–8; Lindroos et al., *supra* note 6, at 280.
91. Lindroos et al., *supra* note 6, at 280.
92. Herberts et al., *supra* note 70, at 8–9.
93. Tekkatte et al., *supra* note 70, at 4–8.
94. Herberts et al., *supra* note 70, at 4–5.
95. *Id.* at 6; Gir et al., *supra* note 6, at 1279.
96. Herberts et al., *supra* note 70, at 6.
97. *Id.* at 7.

mechanism that controls ASCs' migration, but research shows that the migration of cells to particular parts of the body could influence their biological properties and growth, and the risks that unengrafted cells pose to the recipient cells are unknown.⁹⁸ It is also generally unknown how many cells are needed for clinical benefit, which poses the dilemma of choosing how many cells to administer during the injection. If the injection contains too few cells, it may lack efficacy, but if it contains too many cells, they may migrate inappropriately throughout the body or form cell aggregates that could cause pulmonary emboli or infarctions.⁹⁹ Animal models have shown that injected MSCs could also differentiate into unwanted cell types such as osteocytes and adipocytes, which can cause calcification or ossification in the heart potentially leading to a myocardial infarction.¹⁰⁰

The manufacturing process and methods can pose extrinsic additional risks if the final product injected into the patient has been contaminated or lacks purity. Literature in this area describes in detail each of the cGMPs manufacturers must follow, such as quality controls, processing controls, and cell viability and phenotype testing.¹⁰¹ The manufacturer must closely monitor the processing to ensure that the cells have not inappropriately proliferated and changed genetic structure and that the cells have expanded sufficiently to yield the appropriate number of expanded cells.¹⁰² Close oversight of environmental controls, equipment monitoring, and checking supplies and reagents is necessary to prevent contamination and ensure that the final product is safe for use and that it has the appropriate ingredients and potency.¹⁰³ Failing to adhere to cGMPs means that the product may not only lack the characteristics it claims to have—genetically similar sufficient amount of ASCs—but it may also contain genetically mutated cells or inappropriate adventitious agents or pose a threat of contamination from bacteria or viruses.¹⁰⁴

The risks discussed above relate not only to potential contamination or inadequate processing but also stem from the intrinsic and clinical characteristics of using ASCs, which requires extensive studies examining safety and efficacy to mitigate potential risks in clinical application. The amount and severity of these risks, as well as the lack of knowledge of how to control their occurrence, lends support to the FDA's classifica-

98. *See id.* at 9.

99. *See id.*

100. *Id.*

101. Lindroos et al., *supra* note 6, at 279.

102. *Id.*

103. *See Drug Applications and Current Good Manufacturing Practice (cGMP) Regulations*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm> (last updated Sept. 7, 2012).

104. *See* Lindroos et al., *supra* note 6, at 279; Herberts et al., *supra* note 70, at 8.

tion of MSCs as biological products and drugs. That is, even under the most carefully controlled manufacturing process, MSCs pose a number of significant risks including transmitting viruses or endotoxins, inducing a potentially fatal immune reaction, creating tumors within the body, and differentiating inappropriately, which could lead to pulmonary emboli or myocardial infarctions. Should a manufacturer fail to closely monitor and regulate the manufacturing process, the injection of MSCs poses additional and entirely distinct risk factors and potential complications to the recipient.

IV. CELLTEX THERAPEUTICS

A. *Red Flag: Professor Turner's Letter to the FDA*

The existence of these risks as well as the minimization or denial of such risks in the media by Celltex raises serious concerns about business practices that expose patients to potentially serious harm. For the first several months of operation, Celltex's company practices, including statements by Jones, were reported through media accounts, and the company's policies and procedures were publicly unknown. But these key pieces of information were clear: Governor Perry openly advocated for the procedure; Jones minimized and outright denied its risks; physicians such as Jones (and later Lofti) reported that they performed injections; the FDA unambiguously classified MSCs as biological drugs; and scientific literature explained the significant risks posed by the procedure. Bioethics media such as the Center for Genetics and Society took note and began reporting on and questioning the implications of "emerging science commercialized as medicine" and posing questions about Celltex's informed consent process based on Jones and Lofti's comments to the media.¹⁰⁵ Prior to the public knowledge that Lofti performed additional procedures, bioethicist Professor Leigh Turner began a campaign to investigate Celltex's practices.¹⁰⁶ In February 2012, Turner sent a lengthy and detailed letter to the Director of the Center of Biologics Evaluation and Research at the FDA enumerating eight specific concerns about Celltex's practices, such as the lack of evidence to demonstrate the safety or efficacy of injections Celltex was administering, Celltex's relationship with RNL Bio, allegations that RNL Bio's injections caused deaths in Korea, and concerns relating to informed consent.¹⁰⁷

105. Pete Shanks, *Stem Cell Fraud Is the Real Issue In Texas*, BIOPOLITICAL TIMES (Mar. 2, 2012), <http://www.biopoliticaltimes.org/article.php?id=6099>; Pete Shanks, *Rick Perry, Glenn McGee and Selling Texas Stem Cells*, BIOPOLITICAL TIMES (Feb. 16, 2012), <http://www.biopoliticaltimes.org/article.php?id=6078>.

106. Turner Letter, *supra* note 32.

107. *Id.*

Celltex responded with a letter from its legal counsel asserting Turner's "allegations" in the letter to the FDA were false.¹⁰⁸ The letter further maintained that Celltex "is duly registered with the FDA as a Section 361 facility" because it is a lab that merely "processes stem cells at the behest of independent physicians who diagnose and prescribe to *their* patients."¹⁰⁹ Lastly, the letter assured the FDA that "Celltex's process ensures that cells are genetically identical to the original and free from any contaminants."¹¹⁰ This short letter set forth strong claims. First, despite its method of processing the MSCs using twelve supplies and reagents over a period of weeks, Celltex considers its product to fall within Section 361 regulation involving no more than minimal manipulation and entailing minimal risk. Celltex did not address how it satisfies the additional criteria requiring that the product will be used in a homologous manner, which is also required for the FDA to regulate it as a Section 361 product. Second, it asserted that Celltex's manufacturing procedures are so meticulous and advanced as to promise what the scientific literature has considered a serious obstacle—ensuring enough time in culture and choosing effective adventitious agents for sufficient expansion but stopping proliferation prior to chromosomal deviations.

B. FDA Inspection of Celltex

In April 2012, the FDA performed a facility inspection of the Celltex lab over a period of two days. Turner and reporters at *The Houston Chronicle* sought public release of the inspection report through the Freedom of Information Act.¹¹¹ The FDA's 483 report¹¹² made news headlines based on the number of deficiencies in Celltex's processing and manufacturing procedures.¹¹³ Among the seventy-nine violations, the

108. Letter from Jonathan Emord & Andrea Ferrenz, Emord & Associates, PC, to Dr. Karen Midthun, Dir., Center for Biologics Evaluation and Research, FDA (Mar. 9, 2012), *available at* http://www.circare.org/info/stemcell/emord_fda_20120309.pdf.

109. *Id.*

110. *Id.*

111. Todd Ackerman, *FDA Report Faults Houston Stem-Cell Company*, HOUS. CHRON., June 25, 2012, <http://www.chron.com/news/houston-texas/article/FDA-report-faults-Houston-stem-cell-company-3661778.php>.

112. *See Inspection Observations*, FDA, <http://www.fda.gov/iceci/EnforcementActions/ucm250720.htm> (last updated Nov. 16, 2012) ("During an inspection, [Office of Regulatory Affairs] investigators may observe conditions they deem to be objectionable. These observations, are listed on an FDA Form 483 when, in an investigator's judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA's requirements.").

113. Ackerman, *supra* note 111; David Cyranoski, *US Drug Regulator Audits Texas Stem Cell Company*, NATURE NEWS BLOG (June 26, 2012),

report found that Celltex failed to validate processes to prevent contamination, to distinguish between components being quarantined or approved, to routinely calibrate and check the equipment, and to review quality processing systems.¹¹⁴ The company could not guarantee the sterility, uniformity, viability, or integrity of the cells.¹¹⁵ Thus, according to the inspection report, at best Celltex's manufacturing process could not guarantee that the cells would actually expand and be viable upon injection, and at worst, the cells prepared for injection could be contaminated. As discussed above, even if a laboratory exactly controls the manufacturing process during the expansion of MSCs, injecting MSCs poses significant risks to patients. Failure to comply with cGMPs exponentially increases the otherwise avoidable risks to the patient from injecting contaminated or unsterile cells.¹¹⁶ Perhaps most significantly, the inspection report classified Celltex as a biological drug manufacturer, which means the FDA classifies Celltex's laboratory process of expanding MSCs within the biological products and drug framework.

Celltex responded by claiming that the company invited the FDA to view how it is "pioneering" regenerative medicine services.¹¹⁷ Celltex maintains that the investigation was a routine one to check that its practices were in accordance with the good tissue practices governing Section 361 products.¹¹⁸ Celltex's first public response explained that the FDA's "observations" arose from a language barrier because the scientists and technicians working in the laboratory licensed through RNL Bio speak and document their work in Korean.¹¹⁹ Language barrier aside, Celltex assured the public that it processes stem cells in a sterile laboratory according to procedures to guarantee the cells' sterility, viability, and integrity.¹²⁰ Notably, even after the inspection report classified Celltex as a biological drug manufacturer, Celltex staunchly held the position in press releases that it is solely an HCT/P manufacturer regulated under Section 361.¹²¹ Celltex added: "Some media reports and

<http://blogs.nature.com/news/2012/06/fda-hammers-texan-stem-cell-company.html>.

114. Cyranoski, *supra* note 113.

115. *Id.*

116. Ed Silverman, *FDA Slams Stem Cell Company for Violation*, PHARMALOT.COM (June 27, 2012), <http://www.pharmalot.com/2012/06/fda-slams-stem-cell-company-for-violations>.

117. *Celltex Responds to Media Reporting on FDA Visit*, CELLTEX THERAPEUTICS (June 27, 2012), <http://www.celltexbank.com/Celltex-responds-to-fda-visit>.

118. *Id.*

119. *Id.*

120. *Id.*

121. *Id.*

social media chatter suggest that Celltex is somehow acting illegally or providing unapproved treatments. These statements are inaccurate . . . Celltex's process for reproducing adult mesenchymal stem cells is legal, and there is no requirement that the cells be approved or licensed."¹²² These statements not only ignored the deficiencies catalogued in the inspection report, but managed to directly challenge FDA regulatory definitions and guidance that clearly categorize expanded MSCs within the biological product and drug framework because they are more than minimally manipulated and intended for non-homologous use in patients.

C. Celltex Prepares to Challenge the FDA

Celltex's website was under construction until the summer of 2012, limiting the amount of information available to the public about the company's practices. Once Celltex operationalized its web presence, the company advanced several more claims relating to product safety and the company's research integrity, regulatory and legal compliance, technological leadership, and innovation in providing ASCs for therapeutic use.¹²³ Celltex's website contains the same press release that had been issued publicly after the FDA's inspection became public and continues to assert that the company is merely an HCT/P manufacturer regulated under Section 361.

Celltex claims that scientists have researched this field extensively and that ASCs have been used safely and successfully for over fifty years, arguing dozens of studies have demonstrated their safety.¹²⁴ Numerous literature reviews in the field of ASC research in fact find the opposite: there are a lack of published results demonstrating successful clinical applications of ASCs for therapy; clinical potential is uncertain; known risks are significant and potentially severe; and the limited clinical trials available have shown serious adverse events in some cases, which means more knowledge is needed to understand the biological mechanisms of ASCs and their long term safety.¹²⁵ Celltex's website does not address these points of general consensus in the literature but offers a link to a study published by Jeong Chan Ra of RNL Bio and his colleagues that discusses the safety of MSCs for therapeutic use.¹²⁶ The authors acknowledge the study's limitations, concluding that the small

122. *Id.*

123. CELLTEX THERAPEUTICS, <http://www.celltexbank.com/> (last visited Sept. 1, 2013).

124. *Company Overview*, CELLTEX THERAPEUTICS, <http://celltexbank.com/about/overview/> (last visited Sept. 1, 2013).

125. *See generally* Gir et al., *supra* note 6; Lindroos et al., *supra* note 6, at 284–85; *see* Herberts et al., *supra* note 70, at 11.

126. *See* Ra et al., *supra* note 85.

number of patients studied limited the ability to gauge the potential for adverse reactions or the potential recovery rate.¹²⁷

Celltex's website does not describe the specific methodology the laboratory uses during the expansion process or disclose the substance of each additional agent it uses during the manufacturing process. However, Ra and colleagues state that Celltex uses FBS as a growth agent.¹²⁸ As discussed above, FBS specifically poses numerous safety concerns, and even if processing can remove most of the FBS prior to clinical use, trace bovine proteins could remain sufficient to trigger an immune response and some contaminants (such as viruses, prions, and nanobacteria) are impossible to remove.¹²⁹ If Celltex is utilizing a xeno-free serum or serum-free media, the scientific literature specifically notes that research of these alternatives is still in nascent stages, and these methods for expansion have not been shown to be safe or effective.¹³⁰ Finally, any type of serum could become contaminated with yeast, fungi, and endotoxins, some of which are impossible to remove.¹³¹ Independent of methodology, the literature directly contradicts Celltex's claims relating to established knowledge of the safety and efficacy of using MSCs for therapeutic purposes.

In stark contrast to the FDA's findings during the facility inspection, Celltex has also asserted that it rigorously follows the "highest quality control standards," that "[n]o other corporation . . . does as much quality control," and that the company's quality assurance is unsurpassed.¹³² But rather than finding that Celltex employs the highest quality standards, the FDA concluded that it could not guarantee the uniformity, sterility, or viability of the cells the company manufactures.¹³³

Following Celltex's emergence on the web, Professor Turner posted an in-depth examination of Celltex's claims as compared to the FDA's 483 inspection report, linking each of Celltex's assertions point by point to the report.¹³⁴ Although Celltex claims that its cells are sterile, viable,

127. *Id.* at 1306.

128. *See id.* at 1298.

129. Tekkatte et al., *supra* note 70, at 2, 10.

130. Kinzebach & Bieback, *supra* note 87; Tekkatte et al., *supra* note 70.

131. Tekkatte et al., *supra* note 70, at 2.

132. *Highest Quality Standards*, CELLTEX THERAPEUTICS, <http://www.celltexbank.com/advantage/quality> (last visited May 20, 2013); *Banking Basics*, CELLTEX THERAPEUTICS, <http://celltexbank.com/benefits/basics> (last visited May 20, 2013).

133. FDA, INSPECTIONAL OBSERVATIONS: CELLTEX THERAPEUTICS CORPORATION (2012), *available at* <http://www.scribd.com/doc/98243777/DAL-DO-Celltex-Therapeutics-Corporation-Sugar-Land-TX-04-27-2012> [hereinafter INSPECTION REPORT].

134. Leigh Turner, *Celltex Makes Bold Marketing Claims Despite Significant Manufacturing Problems Found During FDA Inspection*, HEALTH IN THE

and intact, the 483 report shows that Celltex did not perform validation to ensure that the cells are viable, and it could not verify the final product.¹³⁵ Celltex also assures customers of its safety by asserting that it takes steps to prevent the parasites, toxins, fungi, or bacteria from contaminating the final product.¹³⁶ However, Turner noted that the 483 report stated that Celltex failed to conform for cGMPs during the manufacturing process and it lacked quality control and validation procedures designed to prevent contamination.¹³⁷ The FDA further found that Celltex failed tests for sterility and acceptable endotoxin levels and that it could not produce records of the destruction of cells that had previously failed this quality testing.¹³⁸ Similarly, the inspection report stated that bacteria and fungi exceeded acceptable levels and that Celltex did not produce the expansion flasks to the FDA to check for contamination. Although Celltex's procedures could not guarantee the viability, sterility, or safety of its cells, it continues to advertise to the contrary while charging patients \$20,000 to \$30,000 for potentially dangerous MSC injections.

In addition to scrutinizing Celltex's manufacturing process, Turner also questioned Celltex's licensing partnership with RNL Bio whereby RNL's lab technicians and scientists operate the Celltex laboratory. Turner maintains that Celltex's assertion that it is at the forefront of "biosafety" is incompatible with "the disturbing corporate practices" of RNL.¹³⁹ News headlines compiling RNL and its subsidiary's activities suggest that their business practices are potentially misleading at best, and at worst, have likely caused patient injury and at least one reported death.¹⁴⁰

V. RNL, STEM CELL TOURISM, AND *LEE V. HUMAN BIOSTAR*

To understand why Celltex's advertisement claims are problematic, it is important to discuss RNL Bio and its Korean operations as well as

GLOBAL VILLAGE (Aug. 7, 2012), <http://www.healthintheglobalvillage.com/2012/08/07/Celltex-makes-bold-marketing-claims-despite-significant-manufacturing-problems-found-during-fda-inspection>.

135. INSPECTION REPORT, *supra* note 133.

136. *Highest Quality Standards*, CELLTEX THERAPEUTICS, <http://celltexbank.com/advantage/quality/> (last visited May 23, 2013).

137. Turner, *supra* note 134.

138. INSPECTION REPORT, *supra* note 133.

139. Turner, *supra* note 134.

140. See David Cyranoski, *Korean Deaths Spark Inquiry*, 468 NATURE 485, 485 (2010); Kim Tae-jong, *Investigation Opens Over Stem Cell Treatments*, KOREA TIMES (Jan. 6, 2011), http://www.koreatimes.co.kr/www/news/nation/2011/04/117_79290.html.

a recent lawsuit against its subsidiary RNL Life Science (also called Human Biostar) operating in Los Angeles, California.

A. *RNL Bio: Seoul, Korea*

In November 2010, *Nature* picked up on a story in the *Korea Times* reporting an investigation into the practices of RNL Bio, which was manufacturing and facilitating the injection of ASCs to patients in its Seoul office.¹⁴¹ Because Korean law prohibits the injection of ASCs into patients, RNL sent patients to affiliated clinics in China and Japan to receive the injections for a fee ranging from \$9,000 to \$27,000.¹⁴² In fact, Stanley Jones reported that he and his wife Kathi received their injections in Japan.¹⁴³ According to reports by the *Korea Times*, RNL advertised that “a person who could not wake up can walk after the injection” and maintained that the injections would rejuvenate patients’ skin and body functions to that of a person decades younger.¹⁴⁴ The amount of patients to whom Celltex provided injections is unclear. CEO Jeong Chan Ra reported to the media in 2010 that RNL had organized 4900 customers for its medical tours since its opening three years prior.¹⁴⁵ However, in the company’s regulatory filing with the Korean Financial Supervisory Service, Ra cited a substantially higher number of 8000 patients.¹⁴⁶ *Korea Times* suggested that the discrepancy in the number of patients may have arisen from RNL providing the injections illegally in Korea.¹⁴⁷ RNL officials, however, explained the 3000-patient difference arose because patient names may overlap or were omitted, and Ra denies facilitating any injections in Korea.¹⁴⁸ *Korea Times* also alleged that RNL was suspected of providing free or reduced-rate ASC injections to politicians, celebrities, and powerful figures as a means of bargaining for relaxed industry regulations.¹⁴⁹ Notably, Turner has highlighted Celltex’s similar affiliation with powerful figures such as Gov. Perry and

141. Kim Tong-hyung, *Questions Continue over RNL's Stem Cell Handling*, KOREA TIMES (Nov. 15, 2012), http://www.koreatimes.co.kr/www/news/biz/2010/11/133_76356.html; Cyranoski, *supra* note 140, at 485.

142. Kim Tae-jong, *Investigation Opens Over Stem Cell Treatments*, KOREA TIMES (Jan. 6, 2011), http://www.koreatimes.co.kr/www/news/nation/2011/04/117_79290.html.

143. Vasquez, *supra* note 7.

144. Bae Ji-sook, *Hospitals Caught Offering Illegal Stem Cell Treatments*, KOREA TIMES (Nov. 7, 2010), http://www.koreatimes.co.kr/www/news/nation/2011/11/117_75911.html.

145. Tong-hyung, *supra* note 141.

146. *Id.*

147. *Id.*

148. *Id.*

149. *Id.*

Rep. Hardcastle and pointed out these individuals' similar efforts to change the legal landscape in Texas.¹⁵⁰

Around this time, the media and the Korean Ministry of Health and Welfare began to investigate complaints from patients and reports of the deaths of two patients who received ASC injections from RNL Bio coordinated by its Korea office in 2008.¹⁵¹ One patient, a seventy-three-year-old man, received a treatment in Japan and died from a pulmonary embolism two months later; the second patient failed to awaken after receiving anesthetic during his injection procedure in China.¹⁵² Another patient came forward claiming he developed cancer several weeks following injections to "treat" his diabetes.¹⁵³

RNL Bio has vehemently denied that its injections caused, or could even contribute to, such injuries and deaths. In a press conference in Seoul, Ra argued that "[t]here has been no scientific evidence reported here or elsewhere that stem cell injections can be the cause of cancer or cardiovascular disease. In fact our studies with the Seoul National University suggest that stem cell injections rather help suppress such conditions."¹⁵⁴ Ra also asserted that facilitating injections for patients through other countries is inevitable, stating, "If our client asks for the stem cell treatment, we must give them what they want."¹⁵⁵

In stark contrast to Ra's characterization, the scientific literature reviews discussed above conclude that both of the harmful outcomes constitute a risk from receiving the injections based on limited knowledge of clinical applications of ASCs for therapy and the intrinsic characteristics of stem cells. Literature widely cites the risk of tumor formation as one of the largest obstacles to using ASCs in clinical therapies.¹⁵⁶ The scientific community is also unsure how many cells to inject to produce clinical benefit without exposing a patient to risks like pulmonary emboli or infarctions.¹⁵⁷ MSCs can also differentiate into unwanted cell types, which can cause calcification or ossification in the heart, potentially leading to a myocardial infarction.¹⁵⁸ Accordingly, literature supports the claims that the patients' MSC injections could have, or did, contribute to cancer development and death.

150. Turner Letter, *supra* note 32.

151. Tong-hyung, *supra* note 141; Cyranoski, *supra* note 140, at 485.

152. Cyranoski, *supra* note 140, at 485.

153. Tong-hyung, *supra* note 141.

154. Kim Tong-hyung, *Concerns Grow Over Stem Cell Therapies*, KOREA TIMES (Oct. 26, 2010), <http://www.koreatimes.co.kr/www/news/include/print.asp?newsIdx=75215>.

155. *Id.*

156. See Herberts et al., *supra* note 70, at 6; Gir et al., *supra* note 6, at 1279.

157. See Herberts et al., *supra* note 70, at 9.

158. *Id.*

The International Cellular Medicine Society (ICMS), an international non-profit organization dedicated to the advancement of stem cell treatments without governmental regulatory oversight, conducted an investigation into the patient deaths.¹⁵⁹ ICMS concluded that the injections likely triggered the death of one patient, but for the other patient the cause of death was unknown.¹⁶⁰ These findings, however, should be strongly scrutinized. ICMS promotes its agenda of providing autologous ASC treatments as the practice of medicine outside the scope of regulation, which means that significant problematic findings could hinder its goal of forgoing regulatory approval.

ICMS also concluded that “[n]o evidence was found to suggest that inaccurate information caused either patient to give consent to medical procedures that they otherwise would not have given” and that the evidence suggests that “both patients were provided sufficient information to give appropriate informed consent, and both did give consent.”¹⁶¹ Based on Ra’s characterization of benefits and risks in his media statements, this finding seems inaccurate. Ra inflated the promises of MSC injections and denied MSC injection risks against consensus in scientific literature. These failures fundamentally prevent a patient from making an informed decision and uncannily echo Jones’ statements to the media while promoting Celltex’s MSC injections. Scholars have noted deep conflicts of interest and questioned whether ICMS can impartially determine risks to patients or accurately report adverse events while holding strong ties to corporations that profit from permitting injections.¹⁶²

Currently, the Ministry of Health and Welfare is investigating these claims along with whether RNL Bio’s practices comply with the requirements of the Korean Food and Drug Administration (KFDA).¹⁶³ As in the United States, the KFDA is still considering how to address the manufacturing and selling of MSCs with reference to the current framework for drugs.¹⁶⁴ Although the KFDA would prohibit the sale and use of MSCs for treatment without its approval, such regulation would only apply if the MSCs are sold to and injected in patients in Korea.¹⁶⁵

159. *International Cellular Medicine Society Releases Findings on Stem Cell Patient Deaths*, INT’L CELLULAR MED. SOC’Y (Dec. 13, 2010), <http://www.cellmedicinesociety.org/home/news/press-releases/318-international-cellular-medicine-society-releases-findings-on-stem-cell-patient-deaths>.

160. *Id.*

161. *Id.*

162. von Tigerstrom, *supra* note 37, at 498-500.

163. Tong-hyung, *supra* note 141

164. *Id.*

165. *Id.*

RNL Bio and Ra's conduct is highly problematic. Based on Ra's statements to the *Korea Times* and regulatory requirements set forth in Korean regulation, RNL Bio structured its corporate practices specifically to circumvent the KFDA's regulatory requirements designed to oversee the manufacture, sale, and use of ASCs through a number of practices, including facilitating injections in other countries. As in the United States, these regulations are designed to assess potential risk of a product intended to treat disease and require the manufacturer to show the product's safety and efficacy precisely because unregulated use of the product poses an unsatisfactory level of risk to patients. Ra's public statements assume that the procedure constitutes an appropriate risk-benefit calculation, which contradicts the consensus of the scientific literature. Further, it is doubtful whether patients understand that the general scientific community does not support Ra's statements and that the injections pose such significant risks. Shirking corporate responsibility by adopting a consumer demand model is not only inappropriate but has likely resulted in actual harm to patients for which Ra denies any responsibility. For each of these reasons, Turner and other bioethicists have questioned RNL Bio's business entanglement with Celltex and the company's specific claims relating to its reputation.

B. RNL Life Sciences: Los Angeles, California

In 2009, RNL Bio expanded and opened the subsidiary RNL Life Sciences' corporate office in Los Angeles, California.¹⁶⁶ RNL operates from an office in the Koreatown Galleria shopping mall that provides print and video testimonials showing happy and satisfied patients who received the MSC injections.¹⁶⁷ RNL then coordinates an interstate and international process for obtaining, manufacturing, and injecting MSCs. According to *Nature*, patients visit an affiliated clinic in Los Angeles to undergo a procedure to remove adipose tissue that is sent to RNL's Maryland lab for technicians to isolate mesenchymal cells.¹⁶⁸ The RNL Maryland lab sends the mesenchymal cells to Seoul for culturing.¹⁶⁹ RNL then recommends that patients travel to affiliated RNL clinics in China to receive their injections.¹⁷⁰ Jane Shin, a "stem-cell" consultant with RNL Life Sciences, stated that 10,000 patients worldwide have paid for MSC injections, including 130 from the United States.¹⁷¹ Based on these figures, RNL and its subsidiaries have collected a total income of at least \$75 million (a very conservative minimum estimate) from patients since

166. Cyranoski, *supra* note 140, at 485.

167. *Id.*

168. *Id.*

169. *Id.*

170. *Id.*

171. *Id.*

it opened for operation.¹⁷² Of these patients, some have received injections for serious conditions such as Parkinson's disease, kidney failure, and diabetes, while RNL Life Sciences estimates that half of patients sought facial injections for anti-aging rejuvenation purposes.¹⁷³

RNL appears to have learned from previous media statements and has carefully tempered and crafted its representations of corporate services to the media. According to Jin Han Hong, President of RNL Life Sciences, RNL does not offer therapy but merely offers isolation and banking services.¹⁷⁴ Hong also claims RNL does not guarantee the efficacy of the product, stating "we note the potential but we don't make promises."¹⁷⁵ Hong also openly disagrees with the KFDA's classification of ASCs as drugs, defending their practice and arguing that the MSCs RNL cultures and expands are "just part of the patient's body."¹⁷⁶ However, both the FDA and scientific literature classify ASCs outside the scope of products that are merely part of the human body based on the level of manipulation and non-homologous use of the injected cells.

C. *Lee v. Human Biostar*

Former customers of RNL Life Sciences have claimed that the company engaged in "unconscionable deceptive advertising" to promote its services.¹⁷⁷ In May 2012, six individuals led by Ben Hang Lee filed a lawsuit against Human Biostar (formerly RNL Life Sciences), Hong, and Ra, alleging seven separate causes of action: (1) fraud and intentional misrepresentation of fact; (2) negligent misrepresentation of fact; (3) false advertising; (4) unfair competition; (5) financial elder abuse; (6) negligence; and (7) breach of implied covenant of good faith and fair dealing.¹⁷⁸ The plaintiffs allege that they attended workshops sponsored by RNL in Los Angeles where Hong claimed that the MSC injections would cure all their ailments, including diabetes, arthritis, high blood

172. RNL Bio reportedly charged patients in Korea \$9,000–27,000 for its services. RNL Life Sciences (now Human Biostar) charged patients in the US \$7,500–8,000 per injection and patients reportedly received one to two injections. If RNL and subsidiaries have provided injections to over 100,000 patients since beginning its operations, then it has collected anywhere from \$75 million to \$2.7 trillion from these patients. Tong-hyung, *supra* note 141.

173. Cyranoski, *supra* note 140, at 485.

174. *Id.*

175. *Id.*

176. *Id.*

177. See David Cyranoski, *Patients Seek Stem Cell Compensation*, NATURE NEWS BLOG (July 6, 2012), <http://blogs.nature.com/news/2012/07/patients-seek-stem-cell-compensation.html>.

178. Complaint for Damages, *Lee v. Human Biostar, Inc.*, No. BC485105 (Cal. App. Dep't Super. Ct. L.A. May 21, 2012), *removed*, No. 12-05668 (C.D. Cal. June 29, 2012) [hereinafter *Lee Complaint*].

pressure, back pain and insomnia, while reversing aging and restoring their body functions to that of their twenties and thirties.¹⁷⁹ According to the plaintiffs, Hong also assured them that the injections were “completely safe and risk free without any side effects or allergic reactions, since patient’s own cells are transplanted back to the same patient.”¹⁸⁰ Furthermore, the plaintiffs assert that Hong led them to believe that science has proven the MSC injections to be effective rather than experimental and that he charged \$7500 to \$8000 for each injection.¹⁸¹ The plaintiffs received either one or two injections.¹⁸² In the plaintiffs’ statement of facts, they allege that RNL marketed its product to them in Los Angeles and facilitated the process to receive injections in other countries such as Mexico, China, and even Korea, where regulations prohibit injecting MSCs.¹⁸³ Five of the six plaintiffs are over the age of sixty-five and allege that RNL represented the injections as a method of “turning back the clock” and “prevent[ing] future illness” for the elderly.¹⁸⁴ Believing these representations, plaintiffs sought treatment for their specific health conditions and claim that the MSC injections were ineffective or even contributed to additional suffering.¹⁸⁵

The plaintiffs also question how RNL managed the process of transporting and storing the cells prior to injection and claimed that despite the lengthy transportation of the MSCs, RNL failed to perform tests to ascertain the cells’ quality and freshness prior to injection.¹⁸⁶ They also questioned whether the individuals who performed the injections actually had the appropriate training and qualifications to perform the procedures.¹⁸⁷ These specific allegations open the possibility of the plaintiffs asserting RNL exposed them to additional risks based on its manufacturing and administration processes. If a corporation fails to closely monitor and regulate manufacturing, then the injection of ASCs poses additional and entirely distinct risks and raises potential complications for the recipient.¹⁸⁸ Further, if the clinical staff fails to inject the cells correctly

179. *See id.* at 5–6. It is interesting to note that although Jones has not set forth anti-aging claims for Celltex, he and his wife’s Persona Medical Spa could provide a future venue to offer highly lucrative MSC injections for cosmetic purposes.

180. Lee Complaint, *supra* note 178, at 6.

181. *See id.* at 7–8.

182. *Id.*

183. *See id.* at 7.

184. *Id.* at 6–7.

185. *See id.* at 8–9.

186. *See id.* at 9–10.

187. *Id.* at 10.

188. *See supra* Part IV.

during the procedure, improper administration may produce inappropriate differentiation or cellular migration contributing to tumor growth, emboli, or infarction.

The plaintiffs request a variety of remedies, including compensatory and punitive damages, injunctive relief, restitution, and disgorgement of profits.¹⁸⁹ In Count I, they allege that RNL knew that stem cell treatment is only in the experimental phase; that the injections have not been approved for use in the US; and there is a lack of scientific evidence demonstrating that the treatment would cure the plaintiffs' specific ailments, work to reverse aging, or prevent future illness.¹⁹⁰ The plaintiffs claim that RNL induced them to rely on the company's representations by concealing risk information.¹⁹¹ In Count III, the plaintiffs allege that RNL's acts and omissions constitute false and misleading advertising under California state law, deceiving the general public as well as injuring the specific plaintiffs.¹⁹² In Count IV, the plaintiffs request an injunction, claiming that RNL promulgated unfair, deceptive, untrue, or misleading advertising that constituted an unlawful, unfair, or fraudulent business practice.¹⁹³ The plaintiffs also invoke California law's specific protections against financial elder abuse based on the anti-aging claims of the MSC injections.¹⁹⁴ In Count VI, the plaintiffs assert that RNL owed to them a "duty of care to exercise reasonable skill and care in performance of their duties" and "knew or should have known that [a] failure to exercise [such] care" would harm the plaintiffs.¹⁹⁵ In this claim, the plaintiffs reference the transportation, storage, and injection of cells, alleging that RNL failed to exercise ordinary care in harvesting, culturing, growing, storing, transporting, and administering the cells.¹⁹⁶

Both the plaintiffs' claims and prayer for relief allege that RNL, Hong, and Ra created a business that intentionally misrepresents an experimental and unproven product to induce aging consumers or those with ailing health to purchase it as a miracle cure.¹⁹⁷ It further charges consumers thousands of dollars to undergo a risky procedure that may not work or could cause grave health complications including cancer or

189. Lee Complaint, *supra* note 178, at 16.

190. *Id.* at 10.

191. *Id.*

192. *Id.* at 12.

193. *Id.* at 12–13.

194. *See id.* at 5–6.

195. *Id.* at 14.

196. *Id.*

197. *Id.* at 5–6.

death.¹⁹⁸ The plaintiffs allege that RNL's injections were even more dangerous based on its negligent manufacturing and clinical practices. Accordingly, the plaintiffs request an injunction, disgorgement of profits, as well as exemplary and punitive damages.

D. Celltex's Adoption of RNL's Business Model

RNL's corporate practices in Korea and California raise a number of significant concerns and by association call into question Celltex's claims of technological leadership, innovation, and biosafety. Celltex has engaged in a number of practices similar to those of RNL. From its inception, Celltex enlisted Governor Perry to publicly promote MSC injections and lobby (with Jones), the Texas Medical Board for relaxed regulations within the state.¹⁹⁹ Similar to Ra and Hong, Perry and Jones have dismissed regulatory barriers to manufacturing and obtaining MSC injections.²⁰⁰ Jones and Eller structured Celltex in a manner to avoid requirements to demonstrate the product's safety and efficacy through clinical trials prior to patient use, adopting a consumer demand model that would permit consumers to obtain the most "cutting edge" technology. Celltex's website even replicates RNL's assertions that it merely offers expansion and banking services, which minimizes its powerful role of advertising and facilitating a risky medical procedure. Both RNL and Celltex charge patients a substantial sum for an unproven and potentially dangerous experimental therapy while targeting the aging, the ill, and even those seeking cosmetic procedures. It is possible that Jones may follow RNL's lead in marketing anti-aging cosmetic procedures and attempt to capitalize on this massive market by linking Celltex's services with his and his wife Kathi's medical spa. Jones has also echoed Hong's statements that MSCs are simply part of the patient's body, assuaging the public and potential consumers.²⁰¹ These statements mislead patients who may not understand the very significant risks inherent in injecting MSCs and the additional risks connected to a corporation's failure to adhere to cGMPs during product manufacturing. Both Ra and Jones lauded MSCs' efficacy while downplaying or denying the risks identified by a consensus of scientific literature.²⁰² Perhaps most concerning, these

198. Kim Tae-jong, *Investigation Opens Over Stem Cell Treatments*, KOREA TIMES (Jan. 6, 2011), http://www.koreatimes.co.kr/www/news/nation/2011/04/117_79290.html; Kim Tong-hyung, *Concerns Grow Over Stem Cell Therapies*, KOREA TIMES (Oct. 26, 2010), <http://www.koreatimes.co.kr/www/news/include/print.asp?newsIdx=75215>.

199. See Letter from Rick Perry, *supra* note 12.

200. Cyranoski, *supra* note 13, at 377.

201. Public Comments on Chapter 198. Unlicensed Practice, 37 Tex. Reg. 4929, 4930 (June 29, 2012) [hereinafter Public Comments].

202. Ramshaw, *supra* note 9; Kim Tong-hyung, *Concerns Grow Over Stem Cell Therapies*, KOREA TIMES (Oct. 26, 2010), <http://www.koreatimes.co.kr/www/news/include/print.asp?newsIdx=75215>.

business practices have produced corporate profits at the expense of exposing patients to unacceptable risk and allegations of grave consumer injuries. Exploring RNL's business model demonstrates the inappropriateness of Celltex's attempts to circumvent the FDA's clear regulatory guidelines for MSCs.

VI. THE FDA'S AUTHORITY TO REGULATE MSCS AS
BIOLOGICAL PRODUCTS AND DRUGS IN *UNITED STATES V.*
REGENERATIVE SCIENCES

At this time of writing, only one jurisdiction has examined how to interpret the FDA's regulations relating to the sale and manufacture of autologous MSCs in *United States v. Regenerative Sciences*. Regenerative Sciences is a company in Broomfield, Colorado that manufactures MSCs to treat a variety of orthopedic conditions in a procedure it called Regenexx.²⁰³ To create the MSCs, the company extracted and isolated cells in a patient's bone marrow, processed the cells with growth factors derived from the patient's blood and reagents and drug products, expanded them for several weeks in culture, and injected the MSCs into the patient at the site of injury.²⁰⁴ The treatment of two to four injection cycles reportedly cost \$7000 to \$9000.²⁰⁵

In July 2008, the FDA sent a letter to Regenerative Sciences informing the company that it classified Regenexx as a drug and biological product based on Regenerative Sciences' intent that the product would be used in the "diagnosis, cure, mitigation, treatment, or prevention of disease."²⁰⁶ The letter also stated that Regenerative Sciences must obtain a biologics license to introduce its product into interstate commerce and submit an IND application demonstrating Regenexx's safety and efficacy.²⁰⁷ Regenerative Sciences responded to the FDA's letter by asserting that Regenexx was neither a biological product nor a drug and argued that the procedure merely constituted the practice of medicine, which the FDA has no authority to regulate.²⁰⁸ The FDA performed a facility inspection in 2009 and again the next year. In its first inspection, the FDA found numerous violations of current good manufacturing

203. See Onel et al., *supra* note 49, at 2; Chirba & Garfield, *supra* note 4, at 236–37; von Tigerstrom, *supra* note 37, at 480.

204. *Id.*

205. *Id.*

206. Letter from Mary A. Malarkey, Dir., Office of Compliance & Biologics Quality, FDA, to Christopher J. Centeno, Med. Dir., Regenerative Sciences, Inc. (July 25, 2008), <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm091991.htm>.

207. *Id.*

208. von Tigerstrom, *supra* note 37, at 483.

practices.²⁰⁹ Prior to completing the inspection, Regenerative Sciences filed for a declaratory judgment and injunction to prevent the FDA from regulating Regenexx as a biological product and drug.²¹⁰ The court dismissed the action for ripeness because the FDA had not issued a final administrative action.²¹¹ In 2010, the FDA inspected Regenerative Sciences once more, again finding violations of cGMPs.²¹² In August 2010, the FDA announced its intention to seek an injunction preventing Regenerative Sciences from producing Regenexx because the company failed to make sufficient corrections to its manufacturing process.²¹³ When such an issue proceeds to litigation, courts generally defer to the agency's interpretation of the regulations, especially where it is the agency's area of expertise.²¹⁴

In district court litigation between the Department of Justice and Regenerative Sciences, Regenerative Sciences maintained that the manufacture and injection of MSCs constituted the practice of medicine, which is not within the FDA's authority to oversee.²¹⁵ The company further argued that the manufacture and injection of MSCs was outside the scope of the FDA's authority to regulate as either a biological product or drug or under Section 361.²¹⁶ Scholarly analysis of the case noted that FDA regulation does not infringe on the practice of medicine, but rather controls the products physicians use within the practice of medicine.²¹⁷

The FDA responded by reiterating the purpose of Section 361 and stressing the risks of contamination and infection posed by the processing of cells in culture.²¹⁸ The FDA's pleadings explained that the risk is two-fold because risks inhere based on both the products and reagents used during processing as well as the conditions of manufacture.²¹⁹ However, the FDA also asserted that expanding cells in culture

209. *Id.* at 482–83; Chirba & Garfield, *supra* note 4, at 259–60.

210. Chirba & Garfield, *supra* note 4, at 237.

211. *Id.*

212. *Id.* at 259–60.

213. *Id.* at 237-38; see *FDA Seeks Injunction Against Colorado Manufacturer of Cultured Cell Products*, FDA (Aug. 6, 2010), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm221656.htm>.

214. Chirba & Garfield, *supra* note 4, at 245; von Tigerstrom, *supra* note 37, at 486.

215. See Complaint at 16, U.S. Dep't of Justice v. Regenerative Sciences, 878 F.Supp.2d 248 (D.D.C. 2012).

216. von Tigerstrom, *supra* note 37, at 485–87.

217. *Id.* at 490.

218. *Id.* at 488.

219. See Chirba & Garfield, *supra* note 4, at 264–65.

constitutes more than minimal manipulation and changes their relevant biological characteristics, meaning the cells do not meet the definition for a Section 361 product but rather fall under the regulatory category of biological products and drugs.²²⁰ As the FDA explained,

culturing results in the selection and alteration of the original [cells] . . . because cells grow and respond to the tissue culture flasks and the composition of the media and other conditions under which they are grown [T]he remaining cells would expand in number and change so they are different from the original cells . . . [because] culturing causes changes in the proteins and the genes expressed by the cells, as well as changes in the shape of the cells.²²¹

In July 2012, the District Court for the District of Columbia examined whether and how the FDA may regulate MSCs in *United States v. Regenerative Sciences*.²²² The court rejected Regenerative Sciences' claim that the manufacturing and injection of MSCs merely constituted the practice of medicine because the FDA controls the availability and method of manufacturing drugs for use prescribing by physicians, even if this regulation affects how physicians practice medicine.²²³ The court reiterated the FDA's rationale for Section 361 regulation of HCT/PSs, finding that the FDA may regulate MSCs under Section 361 because autologous stem cells present a risk of spreading communicable disease.²²⁴ Importantly, the court held that the method Regenerative Sciences used to process the MSCs constitutes more than minimal manipulation, which placed them under the FDA's authority to regulate as biological products and drugs.²²⁵ Regenerative Sciences described the manufacturing process as "involv[ing] many steps, including selective culture and expansion of a multitude of different types . . . of cells using plastic flasks, additives and nutrients, and environmental conditions such as temperature and humidity, to determine the growth and biological characteristics of the resulting cell population."²²⁶ The manufacturing process changed the biological characteristics of the cells, resulting in

220. von Tigerstrom, *supra* note 37, at 486.

221. *Id.* (quoting Plaintiff's Motion for Summary Judgment at 21–22, U.S. Dep't of Justice v. Regenerative Sciences, 878 F.Supp.2d 248 (D.D.C. 2012)).

222. *United States v. Regenerative Sciences*, No. 1:10-CV-1327, at 7 (D.D.C., July 23, 2012) (memorandum opinion) [hereinafter *Memorandum Opinion*]; see *United States v. Regenerative Sciences, LLC*, No. 10-1327 (D.D.C. July 23, 2012) (order).

223. *Memorandum Opinion*, *supra* note 222 at 18–19.

224. *Id.* at 21.

225. *Id.* at 10–13.

226. *Id.* at 13.

more than minimal manipulation.²²⁷ Therefore, the court found that the FDA has proper authority to regulate Regenexx as a biological product and drug.²²⁸ It granted the FDA's request for a permanent injunction until Regenerative Sciences can demonstrate that it complies with the appropriate regulatory requirements and ordered Regenerative Sciences to comply with the FDA's subsequent decisions.²²⁹

VII. IMPLICATIONS FOR CELLTEX AND PHYSICIANS

A. *Celltex's Position*

Regenerative Sciences is not binding in other jurisdictions, and Regenerative Sciences will likely appeal. However, the precedent established by *Regenerative Sciences* holds that the FDA properly has authority to regulate MSCs such as those produced by Celltex, and the process of expanding the MSCs in culture during their manufacturing constitutes more than minimal manipulation, sweeping them into the regulatory category of biological products and drugs. Despite this finding, Celltex continued to advertise and provide services for MSC injections, even after the FDA's 483-page inspection report classified it as a biological drug manufacturer. Celltex asserted, contrary to FDA policy and the inspection report, that it was merely a Section 361 manufacturer and that it did not need to follow additional FDA requirements as a biological products or drug manufacturer.²³⁰ Celltex continues to argue that the FDA should regulate the MSCs under the Section 361 framework but at the time of publication has transferred the site of injections to Mexico.²³¹

B. *Texas Medical Board Rules*

In 2011, Jones, Perry, and Hardcastle initiated a lobbying effort in Texas to promote the ASC industry despite the FDA's clear position that MSCs constitute biological products and drugs.²³² After Jones performed Perry's injections, Perry contacted the Texas Medical Board

227. The court also found that Regenerative Sciences' Regenexx was adulterated and misbranded, but that discussion is outside the scope of this Article. See *id.* at 15–16.

228. *Id.*

229. See Order, *supra* note 222.

230. See *Celltex Responds to Media Reporting on FDA Visit*, CELLTEX THERAPEUTICS (June 27, 2012), <http://celltexbank.com/celltex-responds-to-fda-visit/>.

231. See David Cyranoski, *Controversial Stem Cell Company Moves Out of the US*, NATURE NEWS BLOG (Jan. 30, 2013), <http://www.nature.com/news/controversial-stem-cell-company-moves-treatment-out-of-the-united-states-1.12332>.

232. See *supra* Part II.

at Jones' behest, requesting that it promulgate rules to ensure that physicians would be permitted to perform stem cell infusions.²³³ Around the same time, Hardcastle, who also received MSC infusions from Jones, sent an email to the Board.²³⁴ Hardcastle stated that he did not intend to create "onerous and unnecessary regulations to impede the practice and research of physicians in regards to the use of investigational agents" and that Texas should work instead to protect "patients from unethical doctors using unproven treatments."²³⁵ Hardcastle's statements reflect misconceptions about the risks of the procedure, the infancy of clinical application, and the fact that ASCs are clearly defined as an unproven treatment.

Together, these efforts appeared to be leading to codification of a legal avenue for physicians to inject patients with MSCs while Celltex could challenge the FDA's method of regulating MSCs. The draft of the rules proposed to permit physicians to use investigational agents to treat their patients as long as the physician enrolled the patient into a study protocol approved by an Institutional Review Board (IRB) or submitted an investigational new drug application (IND) to the FDA.²³⁶ The FDA requires manufacturers of biological products and drugs to both submit an IND and obtain IRB approval of the research protocol. If the physician followed these rules, his actions would constitute the practice of medicine, and he could not be found guilty of unprofessional conduct or failure to practice medicine in an acceptable manner.²³⁷ Thus, if a physician found an IRB to approve a research protocol designed to study MSC injections, then he could attempt to insulate himself from professional sanction or liability arising out of injecting patients with risky, unproven "therapies."

The media in Texas took note of the Board's anticipated attempt to circumvent the FDA's requirements and questioned its authority to promulgate such a rule.²³⁸ The *San Antonio Express* highlighted Perry's high level of influence within the Board—Perry appointed eighteen of the Board's nineteen members—suggesting that Perry attempted to

233. See Letter from Rick Perry, *supra* note 12.

234. Ramshaw, *supra* note 10; Cyranoski, *supra* note 13, at 378.

235. Cyranoski, *supra* note 13, at 378.

236. Todd Ackerman, *Texas Accused of Ignoring FDA on Stem Cell Rules*, HOUS. CHRON. BLOG (Apr. 10, 2012), <http://blog.chron.com/txpotomac/2012/04/texas-accused-of-ignoring-fda-on-stem-cell-rules/>.

237. 21 C.F.R. § 1271 (2012).

238. See, e.g., Ackerman, *supra* note 236; *Conflicts Mar Decision on Stem Cells*, SAN ANTONIO EXPRESS (April 24, 2012), <http://www.mysanantonio.com/opinion/editorials/article/Conflicts-mar-decision-on-stem-cells-3506932.php>; Todd Ackerman, *Medical Board Approves Rules Regulating Adult Stem Cell Therapy*, HOUS. CHRON. (April 13, 2012), <http://www.chron.com/news/houston-texas/article/Medical-board-approves-controversial-adult-3481466.php>.

forcefully steer the outcome of the rulemaking.²³⁹ Perry previously appointed Jones to the Board, and Jones subsequently sought to influence the rulemaking session that would ultimately and substantially affect his business and his medical license.²⁴⁰ As discussed above, the relationships between key figures suggested an inappropriate level of policymaking influence with the intention to promote the ASC industry: Eller contributed to Perry's political campaign; Jones and Perry are close friends; Jones injected Perry with MSCs contrary to FDA policy; and both Eller and Jones stand to reap significant financial benefits, of which they may choose to contribute to Perry's future political career.

During the rulemaking session, a number of interested individuals submitted comments to the Board, including members of the public, Turner, and Jones.²⁴¹ Professor Turner submitted a lengthy comment to the Texas Medical Board listing seven substantive concerns regarding the rule and the potential conflict of interest relating to Jones' influence in the Board's decision-making process.²⁴² He reiterated that the FDA has asserted its authority to regulate ASCs, requiring an investigator in a clinical trial studying MSC injections to submit a protocol to both an IRB and the FDA.²⁴³ Turner also took the position that ASC injections as a subset of "investigational agents" do not constitute the practice of medicine using proven therapies but rather should be classified as experimental research subject to clinical trials to determine their safety and efficacy. Importantly, Turner connected this classification and the cost of accessing MSC injections to the potential for "therapeutic misconception."²⁴⁴ As evidenced by other public comments, patients may wrongly believe that the medical field classifies MSC injections as a safe and effective therapy if a physician performs the injections as a medical practice.

In April 2012, the Texas Medical Board passed the rule with a small but important revision.²⁴⁵ The Board revised the rule's definition of "investigational agent" to exclude PHSA Section 351 and 361 products as well as products defined as drugs and biologics under the FDCA.²⁴⁶ Overlooked by most mainstream media, this minor revision held tremen-

239. *Conflicts Mar Decision*, *supra* note 238.

240. *See* Public Comments, *supra* note 201, at 4930-31.

241. *See id.*

242. Letter from Professor Leigh Turner, Ctr. for Bioethics, Univ. of Minnesota, to Rules Development, Texas Medical Board (April 8, 2013), *available at* <http://www.scribd.com/doc/88904812/April-8-2012-Leigh-Turner-Letter-to-Texas-Medical-Board>.

243. *Id.* at 3.

244. *Id.* at 4.

245. *See* 22 TEX. ADMIN. CODE §§ 198.1-198.3 (2012).

246. *Id.*

dous impact by excluding physicians who may inject MSCs from the rule's applicability.²⁴⁷ Accordingly, the rule in effect will have no change on what steps physicians are required to take to perform MSC injections if the manufacturer classifies them as a Section 361 product or a biological product or drug.

The reason for the Board's sudden revision is unclear, but it could creatively protect physicians who are performing the injections in the interim while Celltex challenges the FDA's classification of its MSCs. Celltex may challenge the FDA's classification and the FDA's attempts to enforce its requirements for MSCs through litigation, similar to Regenerative Sciences, with the hope of an alternate outcome in a different jurisdiction. Physicians performing the injections may strategically choose to enroll patient recipients into a clinical protocol to build evidence of responsible professional conduct or as insurance against sanction. It is also foreseeable that patients in Texas may come forward alleging injuries arising from the injections and attribute them to physician wrongdoing. Physicians could counter such anticipated claims by demonstrating they acted above the necessary requirements because they enrolled patients into an IRB-approved protocol even when not required and should accordingly not be found guilty of unprofessional conduct or failure to practice medicine in an acceptable manner. Such a provision undermines the accountability, transparency, and trust that should drive physician and patient interactions relating to the use of experimental agents such as MSCs.

C. Physician Duty and Texas State Law

1. Ethical Duties and the Purpose of the State Medical Board

Using the state medical board as a creative legal strategy runs contrary to the Board's purpose, physicians' ethical duties toward their patients, and Texas state law. According to the American Medical Association, physicians must act in the best interest of their patients while upholding the duty not to harm their patients.²⁴⁸ Furthermore, respecting a patient's autonomy requires a physician to protect and foster a patient's choices that arise from appropriate disclosure and informed consent.²⁴⁹ Based on Jones' statements to the media and the Board, it is uncertain whether patients seeking Celltex's MSC injections are fully informed of the serious medical risks and the uncertain clinical

247. See Letter from David Eller, Chairman & CEO, Celltex Therapeutics, to Jennifer Kaufman, Texas Medical Board (April 6, 2012), available at <http://news.sciencemag.org/scienceinsider/Celltex%20plus%20two%20DOC001.pdf>.

248. Am. College of Physicians, *Ethics Manual*, 128 ANN. INTERN. MED. 576, 577 (1998).

249. *Id.*

benefit for which they pay thousands of dollars. Performing such injections is arguably not acting in the best interest of patients because there is no guarantee of the MSCs safety and efficacy outside of the FDA's approval process. Potentially more troubling, performing such injections prior to sufficient research into clinical applications could cause grave harm and even death, both outcomes that have already surfaced in allegations against RNL's products.

The state medical board as an entity is designed to constrain the amount of risk to which physicians may expose their patients when opting to use experimental therapies. It need not accept emerging medical viewpoints as an appropriate standard of patient care.²⁵⁰ Accordingly, if a state medical board concludes that a physician's judgment exposes a patient to risks stemming from experimental treatment that are not outweighed by potential benefit, then the board ordinarily may find that the physician failed to practice medicine in an acceptable manner.²⁵¹ In this case, however, a physician who chooses to inject an improperly regulated product into patients is not merely an emerging viewpoint in experimental therapy but is acting contrary to the FDA's regulatory requirement that MSCs must first satisfy enumerated and unambiguous requirements for biological products and drugs. These products pose such a risk of patient harm that manufacturers must adhere to specific regulatory requirements prior to wide-scale clinical use by physicians. Members of the Texas Medical Board should exercise independent discretion and eliminate potentially inappropriate influence from Jones and Perry in future decisions relating to physician conduct and standards for using ASCs in patients that have not been approved by the FDA.

2. Professional Sanction or Liability for Physicians Performing Injections

Texas law already contains several provisions that may subject physicians to professional sanction or civil liability arising from injecting patients with MSCs. The Texas Occupational Code provides that the Board may discipline a physician who commits unprofessional or dishonorable conduct that is likely to deceive, defraud, or injure the public.²⁵² Accordingly, a physician who represents to patients that the MSC injection procedure entails minimal risk or makes statements suggesting the worst that may happen is that the procedure will not

250. See Katherine Drabiak-Syed, *Reining in the Pharmacological Enhancement Train: We Should Remain Vigilant About Regulatory Standards for Prescribing Controlled Substances*, 39 J.L. MED. & ETHICS 272, 276–77 (2011) (discussing a physician's subjective opinion when exercising judgment to treat patients according to an emerging viewpoint and how the state medical board could sanction physician for such actions).

251. *Id.*; see 22 TEX. ADMIN. CODE § 198.3 (2012).

252. TEX. OCC. CODE § 164.052 (2012).

work could be subject to potential professional sanction because such conduct is both dishonest and likely to deceive the public. Notably, to subject a physician to professional sanction, a patient need not suffer actual injury.²⁵³ Thus, the Board is not required to wait until patients undergoing MSC injections develop cancer, suffer myocardial infarctions, or even die from MSC-related complications to subject the physician to professional sanction.

In Texas and other states, if a physician deviates from the standard of care and subjects patients to undue risk of harm, the physician may also be civilly liable through claims for medical malpractice.²⁵⁴ The Texas Occupational Code specifies that failure to practice medicine in an acceptable professional manner consistent with the public health and welfare includes failing to treat patients according to the generally accepted standard of care.²⁵⁵ Case law has clarified that a physician merely deviating from the standard of care or violating an accepted medical standard is sufficient to satisfy this statutory definition.²⁵⁶ Thus, if the majority of physicians would not inject their patients with MSCs from manufacturers unless those manufacturers abide by the FDA's regulatory scheme, then that is standard of care. Furthermore, if a physician fails to safeguard against additional complications, then this may serve as additional evidence of failing to practice medicine in an acceptable professional manner.²⁵⁷ Additional complications from using MSCs may arise from the intrinsic nature of using stem cell manufacturing processes for validation and quality control and corporate practices to ensure compliance with cGMPs to mitigate the occurrence of avoidable risks such as cell contamination. If a physician injects MSCs that have not been adequately studied for their effects in a clinical population and is unsure whether the manufacturing process takes steps to ensure the cells are sterile, viable, and free from contamination, then the physician may be failing to safeguard the patient against foreseeable complications. However, if a physician continues to inject MSCs even after the FDA has inspected the facility (as with Celltex) and found that the facility could not guarantee the cells' sterility, uniformity, viability, or integrity, then the physician knowingly exposes the patient to such additional foreseeable complications.

253. See *Grotti v. Texas State Bd. of Med. Exam'r*, 2005 Tex. App. LEXIS 8279 (Tex. Ct. App. 2005) at 21-22; *Chalifoux v. Texas State Bd. of Med. Exam'r*, No. 03-05-00320-CV, 2006 WL 3196461, at *16 (Tex. Ct. App. 2006).

254. TEX. OCC. CODE §§ 164.051- 164.052 (2012); Tex. Admin. Code § 190.1(c)(1) (2012).

255. TEX. OCC. CODE § 164.051 (2012).

256. *Chalifoux*, 2006 WL 3196461, at *16.

257. TEX. OCC. CODE § 164.051 (2012).

Although these state law provisions exist as disincentives for physicians to perform the injections, such provisions may be insufficient to adequately deter physicians or address injury arising from a large commercial operation.²⁵⁸ Plaintiff litigation as a retrospective strategy constitutes an imperfect method of regulation because some injuries may be irreversible, or the injections may result in patient death, as alleged against RNL Bio, for which any recovery through litigation would never be sufficient. Lastly, litigation is a costly and time-consuming process that many patients may not have the means or ability to pursue.²⁵⁹ Rather than retrospectively regulating the system according to patient harm, the FDA should enforce its regulatory power over MSC manufacturers to require compliance by injunction and court order if necessary.

D. FDA's Enforcement Action: Warning Letter to Celltex

In September 2012, the FDA sent a warning letter to Celltex maintaining that the MSCs it manufactures are not solely regulated as Section 361 products.²⁶⁰ The letter specified that Celltex's processing "alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement," which means it does not fall under the category of "minimally manipulated."²⁶¹ Thus, the product would likely not meet the regulatory requirements showing homologous use.²⁶² The letter further observed that because Celltex holds out its product to consumers as a drug, it must be regulated under the more stringent regulatory framework.²⁶³ Finally, the letter referenced the lengthy list of good manufacturing practice areas originally brought to Celltex's attention in the 483 inspection report that Celltex failed to remediate and correct to the FDA's satisfaction.²⁶⁴

Celltex responded to FDA's letter the next month with a detailed explanation of disagreement and requested a meeting to discuss the impact of the FDA's decision on precedent in this area of research.²⁶⁵

258. See von Tigerstrom, *supra* note 37, at 496–97.

259. *Id.* at 497.

260. See Letter from Mary A. Malarkey, Dir., Office of Compliance & Biologics Quality, FDA, to David G. Eller, Chief Exec. Offer & President, Celltex Therapeutics Corp. (Sept. 24, 2012), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm323853.htm>.

261. *Id.*

262. *Id.*

263. See *id.*

264. *Id.*

265. Letter from David Eller, Chairman & CEO, Celltex Therapeutics Corporation, to Robert Sausville, Office of Compliance and Biologics Quality, FDA (Oct. 16, 2012), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm329736.htm>.

First, Celltex reframed the examination of the item being manipulated during the extraction and expansion process, arguing that the FDA should not consider the adipose tissue but rather the product extracted from that tissue—the MSCs—when considering whether the final product was minimally manipulated.²⁶⁶ Second, by using MSCs as the initial material, Celltex asserted the purpose of the injected MSCs constitutes homologous use.²⁶⁷ According to Celltex's argument, because MSCs are inherently multi-potent, anti-inflammatory, immunomodulatory injections, adhering to these purposes are homologous.²⁶⁸ Celltex's arguments attempt to support that the drug and biological framework is "excessive" for MSCs and that the company wants to negotiate the ability to continue utilizing the Section 361 framework.²⁶⁹ Finally, Celltex deferred to RNL Bio to provide the appropriate materials to the FDA to demonstrate corrective efforts related to the areas of noncompliance set forth in the 483 inspection report.²⁷⁰

Despite Celltex's attempt to convince the FDA to allow it to continue manufacturing the MSCs under the Section 361 framework, the FDA has held strongly to its stance that it will regulate MSCs within the framework as a drug and biological product. As discussed above, the FDA's categorization already accounts for analyzing how expansion and processing changes the biological characteristics of MSCs. The court in *Regenerative Sciences* adopted the FDA's arguments that the process of culturing and expanding MSCs changes their relevant biological characteristics, which constitutes more than minimal manipulation and places them in the category of drugs and biological products.²⁷¹

Shortly after the FDA's enforcement action through the warning letter, Celltex announced it would cease injecting patients in the United States.²⁷² In January 2013, Celltex publicly announced it had changed its operational structure to facilitate patient travel to Mexico to receive injections while coordinating regulatory compliance for its future injections in the United States.²⁷³ Despite Celltex's geographical separation as a means to circumvent the FDA's regulation of MSC injections, the procedure still poses considerable concerns related to safety, efficacy,

266. *Id.*

267. *Id.*

268. *Id.*

269. *Id.*

270. *Id.* Celltex and RNL Bio recently sued each other over financial disagreements, and it is unclear at the time of this Article how this will affect their business agreement. See Cyranoski, *supra* note 231.

271. See von Tigerstrom, *supra* note 37, at 485; Memorandum Opinion, *supra* note 222, at 12–13.

272. Letter from David Eller, *supra* note 269.

273. See Cyranoski, *supra* note 231.

and unacceptable level of risk to patients. As the plaintiffs in *Lee v. Human Biostar* allege, relocating the injection clinic does not remove the risk of numerous harms to patients, nor should it discharge the corporation from potential liability arising from patient injuries.²⁷⁴

CONCLUSION

Governor Rick Perry and Dr. Stanley Jones lauded Celltex's MSCs to the media while downplaying the potential for clinical inefficacy and denying significant safety risks. The FDA has definitively stated that it classifies autologous MSCs that are more than minimally manipulated and intended for non-homologous use as drugs and biological products under the FDCA and PHSa—not merely Section 361 products.

MSCs by their nature are inherently risky, and scientific literature describes the barriers to safety and efficacy in their clinical use. In addition to intrinsic risks, MSCs also present challenges associated with clinical application such as mitigating the occurrence of life-threatening immune reactions, myocardial infarction, benign and cancerous tumor formation, transmission of disease, and death. Manufacturers' failure to adhere to cGMPs and control processing conditions exponentially increases these risks and the resulting cells may lack viability, stability, or even pose threats of contamination to the recipient. Despite alarming findings during the FDA's facility inspection, Celltex dismissed the FDA's serious observations relating to cGMP noncompliance and issued media claims related to its manufacturing practices, scientific advances, and product safety.

Celltex's licensing partnership with RNL Bio raises additional concerns based on RNL and its subsidiaries' corporate practices. RNL Bio and RNL Life Sciences overstated the therapeutic promise of its MSC injections and denied serious risks against the consensus found in scientific literature. Both RNL Bio and RNL Life Sciences structured operations specifically to circumvent federal regulatory requirements and adopted a consumer demand model, leading former patients of both operations to allege adverse health consequences including cancer and death. Jones and Eller have adopted a number of corporate strategies from RNL and structured Celltex to avoid regulatory approval while standing to gain sizable profits from the ill, the aging, and other vulnerable patient populations.

In July 2012, the District Court for the District of Columbia set guiding precedent for companies such as Celltex that are attempting to challenge the FDA's categories for regulating MSCs under the PHSa and the FDCA. *Regenerative Sciences* agreed with the FDA's regulatory classification, holding that the number of reagents, the extensive process, and the change in cell biology during the manufacture of MSCs indeed

274. See *supra* Part VI.

constitutes more than minimal manipulation, thus placing the product under the FDA's authority to regulate.

Despite serious patient allegations against RNL and the *Regenerative Sciences* ruling, Celltex continues to challenge the FDA's authority and regulatory classification of its product and openly markets its MSCs through its website to facilitate travel to receive injections in Mexico as a means of evading the scope of FDA's regulatory power. Although Perry and Jones may have strategically attempted to modify Texas Medical Board rules in their favor, such a strategy runs contrary to physicians' ethical and legal duties to their patients and undermines the accountability and trust that should govern physician-patient interactions. Finally, as allegations against RNL demonstrated, former patients' litigating as a method to address consumer injury is an imperfect solution, which future Celltex patients who receive injections in Mexico may also encounter. The FDA must continue to enforce its authority over Celltex's MSCs injected in the United States to prevent patients from a product that may be inefficacious, or worse, a highly unsafe product that could potentially transmit viruses or endotoxins, induce a potentially fatal immune reaction, create tumors, or cause death.