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## When Miracle Cures Go Bad: Regulators' Responses to Unproven Direct-to-Consumer Stem Cell Therapies

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# When Miracle Cures Go Bad: Regulators' Responses to Unproven Direct-to-Consumer Stem Cell Therapies

*Sydney Hope\**

## I. INTRODUCTION

Dorothy O'Connell was a normal and active eighty-nine year old.<sup>1</sup> However, she suffered from arthritis and was almost always in pain.<sup>2</sup> So, when her daughter heard about the potential of stem cell treatments, she was hopeful they would eliminate her mother's pain.<sup>3</sup> After Dorothy received these treatments, her condition got worse, not better.<sup>4</sup> Instead of finding herself miraculously cured by the treatments, Dorothy found herself on the verge of a heart attack and with failing kidneys.<sup>5</sup> After spending almost two months in the hospital and rehab, Dorothy was able to learn to walk again but still has continuing damage from the stem cell injections.<sup>6</sup> Dorothy's story is just one of many that involve unproven stem cell treatments gone wrong.<sup>7</sup>

These patients are often promised a miracle cure to their condition.<sup>8</sup> However, unbeknownst to the patients, these treatments are unproven and the negative impacts are unknown.<sup>9</sup> The clinics that advertise treatments do so without testing them in well-controlled trials.<sup>10</sup> Due to the growing number

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1. Laura Beil, *How Unproven Stem Cell Therapies Are Costing Desperate Patients*, TEX. MONTHLY, <https://www.texasmonthly.com/news/how-unproven-stem-cell-therapies-costing-desperate-patients/> (last visited Apr. 12, 2021).
2. *Id.*
3. *Id.*
4. *Id.*
5. *Id.*
6. *Id.*
7. Beil, *supra* note 1 (telling the stories of several Texas patients who found themselves in the hospital following stem cell injections that were not FDA approved).
8. William Wan & Laurie McGinley, *'Miraculous' Stem Cell Therapy Has Sickened People in Five States*, WASH. POST (Feb. 27, 2019), [https://www.washingtonpost.com/national/health-science/miraculous-stem-cell-therapy-has-sickened-people-in-five-states/2019/02/26/c04b23a4-3539-11e9-854a-7a14d7fec96a\\_story.html](https://www.washingtonpost.com/national/health-science/miraculous-stem-cell-therapy-has-sickened-people-in-five-states/2019/02/26/c04b23a4-3539-11e9-854a-7a14d7fec96a_story.html).
9. Peter W. Marks et al., *Clarifying Stem-Cell Therapy's Benefits and Risks*, 376 NEW ENG. J. MED. 1007, 1008 (2017).
10. *Id.*

of patients harmed by such deceptive advertising of unproven treatments, regulators have increased their regulation of these clinics.<sup>11</sup> Even with this increased enforcement, clinics continue to circumvent such regulations until after patients have already been harmed.<sup>12</sup> This Comment will discuss the direct-to-consumer stem cell industry, current U.S. Food and Drug Administration (FDA) regulation, and alternative approaches to effectively regulate these clinics.

### A. Stem Cell Treatments

Regenerative medicine, particularly stem cell therapy, has been developing for decades.<sup>13</sup> Stem cells can divide and transform into other types of cells in order to replace or replenish tissues.<sup>14</sup> Because of these potential healing benefits, the field has attracted serious investment and attention.<sup>15</sup> However, while there are significant benefits to these therapies, regulation of them is not simple.<sup>16</sup> Stakeholders in the field have advocated for less rigorous regulations to allow for the innovation of lifesaving therapies.<sup>17</sup> Others have argued that more stringent regulations are necessary to ensure patient safety.<sup>18</sup>

Regulators must therefore find a balance between promoting innovation in this advancing industry and ensuring patients' safety and efficacy of the treatments.<sup>19</sup> Within the current framework of regulations, therapies that are not approved by the FDA are still marketed to consumers.<sup>20</sup> This direct-to-consumer industry has become a significant concern for regulators and stakeholders in the industry.<sup>21</sup> Given the significant areas of laws, regulations, and

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11. Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's New Policy Steps and Enforcement Efforts to Ensure Proper Oversight of Stem Cell Therapies and Regenerative Medicine, U.S. FOOD & DRUG ADMIN. (Aug. 28, 2017), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure> [hereinafter Statement of FDA Commissioner].

12. PEW CHARITABLE TRS., FDA'S FRAMEWORK FOR REGULATING REGENERATIVE MEDICINE WILL IMPROVE OVERSIGHT 6 (2019) (describing how stem clinics offering unproven treatments argue they are not subject to FDA regulation).

13. *Id.* at 2.

14. *Id.* at 4.

15. *Id.* at 1.

16. Sarah Duranske, *Reforming Regenerative Medicine Regulation*, 34 GA. ST. U.L. REV. 631, 633 (2018).

17. *Id.*

18. *Id.*

19. *Id.*

20. PEW CHARITABLE TRS., *supra* note 12, at 6.

21. *Id.* at 1.

treatment opportunities in the stem cell industry, this Comment will focus on the area of unregulated stem cell treatments that are marketed directly to consumers.

Part II of this Comment gives an introduction to the direct-to-consumer industry for stem cell treatments nationally and on a state level. Part III discusses the current state of regulation including statutes, rules promulgated by the FDA, guidance drafted by the FDA discussing key terms and exceptions to the regulations, and the recent case *United States v. US Stem Cell Clinic, LLC*. Parts IV and V describe the impact of unclear regulations and unregulated treatments. In these parts, the author argues that regulations need further clarification from the FDA regarding therapies which fall under regulation and conclude the FDA needs to interact with other federal agencies and state actors to increase regulation in this area.

## **B. *Bad Batch* Podcast**

The stem cell therapy industry, particularly the use of unregulated treatments (discussed in Part II below) is the focus of the recent investigative podcast *Bad Batch*.<sup>22</sup> *Bad Batch* focuses on the company Liveyon, which processes and distributes stem cells derived from umbilical cord blood.<sup>23</sup> The podcast also highlights the stories of Texas patients who had bad outcomes after being injected with stem cells distributed by Liveyon.<sup>24</sup> Several patients in Texas, including Dorothy O’Connell, received injections of stem cells from a chiropractor in Houston.<sup>25</sup> These stem cell treatments were not FDA approved and Liveyon has since been reprimanded by the FDA.<sup>26</sup> Through interviews with the CEO of Liveyon and patients who received stem cell treatments, the podcast sheds light on the growing industry of stem cell treatments and its real world implications.<sup>27</sup> The podcast is continuously referenced throughout this Comment in order to explore the topic of unregulated stem cell treatments.

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22. Will Maddox, *Laura Beil’s New Podcast Bad Batch Sheds Light on the World of Unregulated Stem Cell Treatment*, D MAG. (Nov. 5, 2019), <https://www.dmagazine.com/arts-entertainment/2019/11/laura-beils-new-podcast-bad-batch-sheds-light-on-the-world-of-unregulated-stem-cell-treatment/>.

23. Beil, *supra* note 1; Wan & McGinley, *supra* note 8.

24. Beil, *supra* note 1.

25. *Id.*

26. Laurie McGinley, *California Stem Cell Company Halts Sales After FDA Warning*, WASH. POST (Dec. 13, 2019), <https://www.washingtonpost.com/health/2019/12/13/california-stem-cell-company-halts-sales-after-fda-warning/>.

27. Maddox, *supra* note 22.

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## II. DIRECT-TO-CONSUMER STEM CELL INDUSTRY

### A. The Industry

Although there are only a few stem cell therapies currently approved for clinical application, this has not stopped private clinics from advertising treatments that are not FDA approved for a variety of medical conditions.<sup>28</sup> This industry is a “vast medical experiment, uncontrolled, unsupervised, unreported, and conducted on a for-profit basis.”<sup>29</sup> It is comprised of businesses that are able to develop plans to avoid premarket testing for efficacy and patient safety.<sup>30</sup> As the field of regenerative medicine evolved, it became unclear who was responsible for regulating these businesses, which opened the door to businesses marketing unsafe and ineffective products.<sup>31</sup> Researchers found that about half of the stem cell clinics in Texas, California, and Florida do not seem to have doctors with the necessary “formal training matching the conditions they treat.”<sup>32</sup>

Many of these companies market directly to consumers through online resources.<sup>33</sup> In marketing to consumers, the websites sometimes include hype language that exaggerates the potential benefits of the therapy.<sup>34</sup> Clinic websites advertise therapies derived from sources such as bone marrow, blood, and umbilical cords.<sup>35</sup> These therapies are advertised as treatments for common bone pain, joint pain, muscle injuries, and other illnesses (such as autoimmune disorders, degenerative conditions, and other chronic conditions).<sup>36</sup> These various therapies are targeted at vulnerable populations who are looking to this treatment as their last hope.<sup>37</sup> Many times, these claims about the treatments are not supported by reliable evidence.<sup>38</sup> Despite the fact

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28. Blake Murdoch et al., *Exploiting Science? A Systematic Analysis of Complementary and Alternative Medicine Clinic Websites’ Marketing of Stem Cells Therapies*, 8 *BMJ OPEN* 1, 1 (2018), <https://bmjopen.bmj.com/content/bmjopen/8/2/e019414.full.pdf>.
  29. Douglas Sipp, *Direct-to-Consumer Stem Cell Marketing and Regulatory Processes*, 2 *STEM CELLS TRANSLATIONAL MED.* 638, 638 (2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3754464/pdf/sct638.pdf>.
  30. *Id.*
  31. PEW CHARITABLE TRS., *supra* note 12, at 1.
  32. Sangita Menon, *Texas Ranks Third for Number of Stem Cell Clinics. But That May Not Be a Good Thing*, KUT (July 8, 2019), <https://www.kut.org/post/texas-ranks-third-number-stem-cell-clinics-may-not-be-good-thing>.
  33. Murdoch et al., *supra* note 28, at 1–2.
  34. *Id.* at 5.
  35. *Id.* at 1.
  36. *Id.* at 4.
  37. PEW CHARITABLE TRS., *supra* note 12, at 6.
  38. Murdoch et al., *supra* note 28, at 1.

that these therapies are not FDA approved, research has shown that clinics often do not disclose to patients the experimental or unproven nature of the treatments.<sup>39</sup> Further, clinics do not regularly warn patients about the limited evidence of efficacy or inefficacy.<sup>40</sup> Also, clinics often do not disclose information about the risks specific to the therapy.<sup>41</sup> Even if a business seeks to indemnify themselves by disclosing the experimental nature and risks of the treatment, the waivers benefit the providers rather than help the patient.<sup>42</sup>

In addition to these online advertisements, businesses also participate in “regulatory shopping” to provide unregulated treatments.<sup>43</sup> Through this process, businesses set up clinics in neighboring areas with less strict regulations.<sup>44</sup> This practice shifts the liability to the patients who come in for treatment.<sup>45</sup> Patients assume the risk of undergoing procedures potentially outside the standard of care and lose the legal protections available from stricter regulations.<sup>46</sup>

## **B. Unregulated Therapies in Texas**

While the use of unregulated stem cell treatments are a national issue, Austin, Texas has become a hot spot for direct-to-consumer stem cell clinics.<sup>47</sup> In 2017, out of the 716 clinics in the United States that advertised stem cell treatments, 100 of them were in Texas.<sup>48</sup> The large number of clinics in Texas can partly be explained by the business-friendly regulations in the state.<sup>49</sup> Texas has more lenient regulations at the state level, which allow investigational treatments that are not FDA approved to be administered in certain circumstances.<sup>50</sup> Some argue these laws opened the door for the expansion of clinics to further practice unproven treatments.<sup>51</sup>

A law passed in Texas in 2017 allows investigational stem cell treatments for patients with severe chronic diseases or terminal illnesses who sign

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39. *Id.* at 6.

40. *Id.*

41. *Id.*

42. Sipp, *supra* note 29, at 639.

43. *Id.* at 638–39.

44. *Id.* at 639.

45. *Id.*

46. *Id.*

47. Menon, *supra* note 32.

48. *Id.*

49. Maddox, *supra* note 22.

50. Menon, *supra* note 32.

51. *Id.*

a written informed consent.<sup>52</sup> The treatment must be administered directly by a physician who is certified by an institutional review board.<sup>53</sup> The treatment must also be overseen by an institutional review board that is affiliated with a medical school, is affiliated with a hospital, is accredited by the Association of the Accreditation of Human Research Programs, is registered by the U.S. Department of Health and Human Services, or is accredited by a national accreditation organization acceptable to the Texas Medical Board.<sup>54</sup> The government may not interfere with a patient's access to this treatment unless the product is considered adulterated or misbranded, which cannot be based solely on the fact that the FDA has not approved the product.<sup>55</sup>

Proponents of the law claim that the law opens the door to medical advancement.<sup>56</sup> The law gives those who are researching stem cells and regenerative medicine more data—both positive and negative.<sup>57</sup> This research allows for the vetting of the therapies to make sure that innovation is happening safely.<sup>58</sup> The law has been criticized, however, because it opens the door to potentially more unproven and controversial treatments that risk patient safety.<sup>59</sup>

### III. FDA REGULATORY FRAMEWORK

The FDA has released several statements and warnings about the use of unapproved stem cell treatments.<sup>60</sup> In a statement on August 28, 2017, the former FDA commissioner, Scott Gottlieb, stated the importance of regulating this area where “a select few, often motivated by greed without regard to responsible patient care, are able to promote unproven, clearly illegal, and often expensive treatments that offer little hope, and, even worse, may pose significant risks to the health and safety of vulnerable patients.”<sup>61</sup> The FDA has stated it will increase its oversight and enforcement to protect patients

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52. TEX. HEALTH & SAFETY CODE ANN. §§ 1003.053–054 (West 2017).

53. *Id.* § 1003.055 (Westlaw).

54. *Id.*

55. *Id.* § 1003.058 (Westlaw).

56. Britni R. McAshan, *New Law Opens Doors for Regenerative Medicine in Texas*, TEX. MED. CTR. (Oct. 9, 2017), <https://www.tmc.edu/news/2017/10/new-law-opens-doors-regenerative-medicine-texas/>.

57. *Id.*

58. *Id.*

59. Menon, *supra* note 32.

60. *FDA Warns About Stem Cell Therapies*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies> (last updated Aug. 3, 2019); Statement of FDA Commissioner, *supra* note 11.

61. Statement of FDA Commissioner, *supra* note 11.

from dishonest stem cell treatments.<sup>62</sup> However, even with this increased oversight, the FDA still wants to encourage medical innovation so stem cell products can be used in proper ways.<sup>63</sup> In its warning on stem cell therapies, the FDA says it will take administrative, judicial, or criminal action depending on the violation.<sup>64</sup>

Part of the FDA review for approval, described in detail below, includes showing the agency how each product is manufactured so it can ensure appropriate procedures to “assure the product’s safety, purity, and strength.”<sup>65</sup> Despite clinics falsely advertising that FDA approval of their treatment is unnecessary, the FDA has clearly taken the stance that these treatments do fall under their regulations.<sup>66</sup> If a clinical trial is not completed under an Investigational New Drug Application, then the FDA has not reviewed the therapy to ensure safety and it is not FDA approved.<sup>67</sup>

#### **A. Statutes**

There are three core statutes that give the FDA the authority to regulate stem cell treatments: the Federal Food, Drug, and Cosmetic Act (FD&C Act), Public Health Services Act (PHSA), and the 21st Century Cures Act.<sup>68</sup> The FD&C Act gives the FDA the authority to regulate drugs and devices that are “intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . . or to affect the structure or any function of the body.”<sup>69</sup> Under this Act, any new drug must be approved before it can be introduced into interstate commerce.<sup>70</sup> To achieve approval, an application must be filed which includes reports of investigations showing whether or not the drug is effective; a list of articles used as components in the drug; a description of methods, facilities, and controls used in manufacturing, processing, and packaging of the drug; samples of the drug and articles used as components; and any other assessments required under Section 355(c).<sup>71</sup> So, manufacturers must “demonstrate that the product is safe and effective on the basis of adequate and well-controlled clinical trials.”<sup>72</sup>

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62. *FDA Warns About Stem Cell Therapies*, *supra* note 69.

63. *Id.*

64. *Id.*

65. *Id.*

66. *Id.*

67. *Id.*

68. PEW CHARITABLE TRS., *supra* note 12, at 7–8.

69. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 321(g)(1), (h)(2)–(3) (2018).

70. *Id.* § 355(a).

71. *Id.* § 355(b)(1).

72. PEW CHARITABLE TRS., *supra* note 12, at 7.



Sections 351 and 361 of the PHS Act also apply to stem cell treatments. Section 351 regulates the interstate commerce of biologic products.<sup>73</sup> A biologic product is a product that is “applicable to the prevention, treatment or cure of a disease or condition of human beings.”<sup>74</sup> The biologic products under this Act are subject to the same regulations under the FD&C Act, except that they are approved under a biologics license under 42 U.S.C. § 262(a).<sup>75</sup> Section 361 authorizes regulations “necessary to prevent the introduction, transmission, or spread of communicable diseases.”<sup>76</sup> Human cell products may be subject to Section 351 or 361 regulations depending on what tier of regulation they fall under, discussed more below.<sup>77</sup>

Section 3303 of the 21st Century Cures Act created an accelerated review of Regenerative Medical Advanced Therapies (RMATs).<sup>78</sup> For a drug to be considered for RMAT designation, it must meet three criteria.<sup>79</sup> The first requirement is that it must be a regenerative medicine therapy as defined in the Act.<sup>80</sup> Regenerative medicine therapy includes “cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies and products” that are not regulated solely under PHS Act § 361 and 21 C.F.R. § 1271.<sup>81</sup> There will be further discussion of which drugs fall under these regulations below. The second requirement for RMAT designation is that the drug is “intended to treat, modify, reverse, or cure a serious or life threatening disease or condition.”<sup>82</sup> Life-threatening diseases or conditions are at a stage where there is a reasonable likelihood that death will occur within months or where premature death is likely.<sup>83</sup> A serious disease or condition is “a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.”<sup>84</sup> The final requirement for RMAT designation is that “preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition.”<sup>85</sup> For a medical need to be unmet, the treatment or diagnosis cannot be addressed adequately by available therapy

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73. Public Health Services Act, 42 U.S.C. § 262(a)(1) (2018).

74. *Id.* § 262(i).

75. *Id.* § 262(j).

76. *Id.* § 264(a).

77. PEW CHARITABLE TRS., *supra* note 12, at 7.

78. 21 U.S.C. § 356(g)(1) (2018).

79. *Id.* § 356(g)(2).

80. *Id.* § 356(g)(2)(A).

81. *Id.* § 356(g)(8).

82. *Id.* § 356(g)(2)(B).

83. 21 C.F.R. § 312.300(b) (2019).

84. *Id.*

85. 21 U.S.C. § 356(g)(2)(C).

and includes “an immediate need for a defined population . . . or a longer-term need for society.”<sup>86</sup>

## **B. Risk-Based Regulatory Tiers Under 21 C.F.R. § 1271**

Title 21 of the Code of Federal Regulations creates a tiered risk-based approach for the regulation of human cells, tissue, and cellular and tissue-based products (HCT/Ps).<sup>87</sup> HCT/Ps are defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”<sup>88</sup> In creating this risk-based approach, the FDA was concerned with several public health and regulatory concerns including the prevention of communicable diseases; preventing contamination of products and preserving its integrity and function; and ensuring safety and effectiveness of the product.<sup>89</sup> Under the lowest tier, these regulations exempt certain HCT/Ps from the premarket and review requirements under the FD&C Act and PHSA.<sup>90</sup> HCT/Ps that fall under the middle tier regulation are exempt from the premarket conditions from the FD&C Act and Section 351 of the PHSA.<sup>91</sup> Thus, they are solely regulated under PHSA § 361 and 21 C.F.R. § 1271.<sup>92</sup> The highest tier of regulation treats the HCT/P as a drug, device, or biologic product under the FD&C Act and Section 351 of the PHSA and are subject to premarket approval and review under these statutes.<sup>93</sup>

### **1. Lowest Tier Regulations**

21 C.F.R. § 1271.3(d) by its text excludes several articles from the definition of HCT/Ps.<sup>94</sup> This includes human organs for transplantation, blood vessels recovered with an organ intended for use in organ transplantation, secreted or extracted human products, minimally manipulated bone marrow for homologous use and not combined with another article, ancillary products

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86. U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS 3 (2019), <https://www.fda.gov/media/120267/download>.

87. 21 C.F.R. § 1271.1(b) (2019).

88. *Id.* § 1271.3(d).

89. U.S. FOOD & DRUG ADMIN., REGULATORY CONSIDERATIONS FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: MINIMAL MANIPULATION AND HOMOLOGOUS USE 3 (2020), <https://www.fda.gov/media/109176/download> [hereinafter MINIMAL MANIPULATION AND HOMOLOGOUS USE].

90. *Id.* at 5.

91. *Id.*

92. *Id.*

93. *Id.* at 3–4.

94. 21 C.F.R. § 1271.3(d) (2019).

used in the manufacture of the HCT/Ps, and in vitro diagnostic products.<sup>95</sup> By their exclusion under the definition of HCT/Ps, these products are not subject to the 21 C.F.R. § 1271 regulations.<sup>96</sup>

Other products that do fall under the HCT/P definition may be exempt from the requirements under the list of exceptions in 21 C.F.R. § 1271.15.<sup>97</sup> The same surgical procedure exception has received guidance and explanations over the years.<sup>98</sup> This exception applies to an “establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure.”<sup>99</sup> In its guidance on this exception, the FDA explained that for an HCT/P to remain “such HCT/P,” the only processing steps allowed are rinsing, cleansing, sizing, and shaping.<sup>100</sup> The policy behind this exception is because without processing, there are no additional risks of contamination or communicable disease than in a typical surgery.<sup>101</sup>

Further, the FDA explained that generally the same surgical procedure, is a single operation performed at the same establishment.<sup>102</sup> However, there are some circumstances where the surgery may be completed over several days so long as there were no other processing steps between the removal and implantation.<sup>103</sup> Additionally, if one establishment ships the HCT/P to another establishment, that shipping creates a manufacturing step that makes the exception inapplicable.<sup>104</sup>

Many clinics advertise adipose-derived stem cell treatments, which they claim are not subject to FDA regulations because they fall under the same surgical procedure exception.<sup>105</sup> In these treatments, “cells are removed from processed fat tissue and then returned to the body.”<sup>106</sup> While these treatments

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95. *Id.*

96. *Id.*

97. *Id.* § 1271.15.

98. U.S. FOOD & DRUG ADMIN., SAME SURGICAL PROCEDURE: EXCEPTION UNDER 21 CFR 1271.15(B): QUESTIONS AND ANSWERS REGARDING THE SCOPE OF THE EXCEPTION 2–3 (2017), <https://www.fda.gov/media/89920/download> [hereinafter SAME SURGICAL PROCEDURE EXCEPTION].

99. 21 C.F.R. § 1271.15(b).

100. SAME SURGICAL PROCEDURE EXCEPTION, *supra* note 98, at 5.

101. *Id.* at 3.

102. *Id.* at 5.

103. *Id.* at 5–6.

104. *See id.* at 6.

105. Leigh G. Turner, *Federal Regulatory Oversight of US Clinics Marketing Adipose-Derived Autologous Stem Cell Interventions: Insights From 3 New FDA Draft Guidance Documents*, 90 MAYO CLINIC PROC. 567, 568 (2015).

106. *Id.*

do not come within the language of the exception, clinics still attempt to use it to circumvent regulations.<sup>107</sup> The potential for this misuse of the exception indicates the need for stronger regulations of such clinics.<sup>108</sup> Such regulation could include stronger enforcement of regulations by the FDA or, as discussed more in Part V below, the use of other forms of regulation, such as deceptive marketing, to more directly target these businesses.

## 2. Middle Tier Regulations

The rules also create a middle tier of regulations that are regulated solely under Section 361 of PHSA and regulations in 21 C.F.R. § 1271.10(a).<sup>109</sup> For an HCT/P to fall under this regulatory tier, it must meet four criteria.<sup>110</sup> The first requirement is that the HCT/P be minimally manipulated.<sup>111</sup> The FDA considers minimal manipulation based on the impact on the original relevant characteristics as the HCT/P exists in the donor, not on the intended use in the recipient.<sup>112</sup> Minimally manipulated is defined in terms of structural tissues and cells or nonstructural tissues.<sup>113</sup> The FDA has explained the difference between the two types in their guidance on the issue.<sup>114</sup> Structural tissues cannot be processed in ways that “alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.”<sup>115</sup> Examples of these characteristics include strength, flexibility, and covering, among others.<sup>116</sup> Cells or nonstructural tissues cannot be processed in a way that “alter[s] the relevant biological characteristics of cells or tissues.”<sup>117</sup> Biological characteristics include metabolic activity, differentiation, and activation state.<sup>118</sup>

The second criteria for a HCT/P to fall under this tier is that it is “intended for homologous use only, as reflected by the labeling, advertising, or

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107. *Id.*

108. *Id.* at 570.

109. 21 C.F.R. § 1271.10(a).

110. *Id.*

111. *Id.*

112. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 7.

113. 21 C.F.R. § 1271.3(f).

114. See MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 8–9, 14 (Structural tissues “physically support or serve as a barrier, or conduit, or connect, cover or cushion,” such as bone and skin. Nonstructural tissue or cells serve a “metabolic or other biochemical role in the body such as hematopoietic, immune, and endocrine functions,” such as reproductive cells or tissues.).

115. 21 C.F.R. § 1271.3(f)(1) (2019).

116. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 10.

117. 21 C.F.R. § 1271.3(f)(2).

118. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 14.

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other indications of the manufacturer's objective intent."<sup>119</sup> Homologous use is the "repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."<sup>120</sup> It is not necessary that the cell or tissue perform all of the same functions, but any basic function it is intended to perform in the recipient needs to be a basic function performed in the donor.<sup>121</sup> Thus, if a manufacturer states an unproved treatment can be used for a "myriad of diseases or conditions, the HCT/P is likely not intended for homologous use only."<sup>122</sup>

The third condition for an HCT/P to be regulated solely under Section 361 and 21 C.F.R. § 1271 regulations is that the HCT/P cannot be combined with another article (other than "water, crystalloids, or a sterilizing, preserving, or storage agent" if they do not raise new safety concerns).<sup>123</sup> The final requirement concerns the systemic effect of the HCT/P.<sup>124</sup> The HCT/P cannot have a systemic effect and cannot depend on the "metabolic activity of living cells for its primary function."<sup>125</sup> Alternatively, if the HCT/P does have a systemic effect or depends on the metabolic activity of living cells for its primary function it must also be for autologous use,<sup>126</sup> for allogenic use in a blood relative, or for reproductive use.<sup>127</sup>

Manufacturers who manufacture an HCT/P that meets these criteria must comply with regulations contained in 21 C.F.R. § 1271.<sup>128</sup> The establishment must register with the FDA and submit a list of each HCT/P manufactured to the FDA.<sup>129</sup> Additionally, manufacturers must follow the testing and screening procedures for donor eligibility laid out in 21 C.F.R. § 1271.45–.90.<sup>130</sup> The manufacturers must also follow the Current Good Tissue Practice to prevent the "introduction, transmission, or spread of commu-

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119. 21 C.F.R. § 1271.10(a)(2).

120. *Id.* § 1271.3(c).

121. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 17 (A basic function is what an HCT/P does or can do in its "native state . . . as it exists in the donor.").

122. *Id.* at 16.

123. 21 C.F.R. § 1271.10(a)(3).

124. *Id.* § 1271.10(a)(4).

125. *Id.* § 1271.10(a)(4)(i).

126. *Id.* § 1271.3(a) ("Autologous use means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.").

127. *Id.* § 1271.10(a)(4)(ii).

128. *Id.* § 1271.10(a).

129. 21 C.F.R. § 1271.10(b).

130. *Id.* § 1271.45.

nicable diseases” under 21 C.F.R. § 1271.145–.320.<sup>131</sup> These regulations are not as stringent as those imposed on manufacturers of products regulated under the FD&C Act and Section 351 of the PHSA.<sup>132</sup> Further, these HCT/Ps are not subject to the premarket approval regulations that apply to the highest tier products.<sup>133</sup>

History has given several examples of therapeutic interventions that, while supported by expert opinion, proved to be ineffective or harmful in clinical trials.<sup>134</sup> Even patients who received autologous stem cells, which raise fewer safety concerns, have had negative outcomes such as the development of tumors and permanent blindness.<sup>135</sup> Despite the fact that clinics claim their treatments fall into the lower tiers of regulation, it has been established they are subject to more stringent regulations.<sup>136</sup> This signifies that increased regulation of these treatments, through alternative approaches addressed in Part V below, could increase patient safety overall.<sup>137</sup>

### 3. Highest Tier Regulations

HCT/Ps that do not meet the exceptions under 21 C.F.R. § 1271.15 or meet the conditions above are regulated as a drug, device, or biologic product under the FD&C Act and Section 351 of the PHSA.<sup>138</sup> Thus, they require premarket approval.<sup>139</sup> As such, manufacturers must submit a new drug application or biologics license application before the product can be introduced into interstate commerce.<sup>140</sup> The clinical investigation regulations are the same for both new drugs and biologics.<sup>141</sup>

There are generally three phases of clinical investigation on new drugs.<sup>142</sup> The first phase involves a small population of subjects and patients

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131. *Id.* § 1271.145.

132. Duranske, *supra* note 16, at 642.

133. PEW CHARITABLE TRS., *supra* note 12, at 11.

134. Marks et al., *supra* note 9, at 1008.

135. *Id.*

136. *FDA Warns About Stem Cell Therapies*, *supra* note 60.

137. Liz Richardson, *Lawsuit Highlights State Role in Regulating Regenerative Medicine*, PEW CHARITABLE TRS. (May 13, 2019), <https://www.pewtrusts.org/en/research-and-analysis/articles/2019/05/13/lawsuit-highlights-state-role-in-regulating-regenerative-medicine> (discussing the need for a broad effort among state and federal regulators in protecting consumers from deceptive marketing by these clinics).

138. 21 C.F.R. § 1271.20 (2019).

139. *Id.*

140. 21 U.S.C. § 355(b)(1) (2018); 42 U.S.C. § 262(a) (2019).

141. 21 C.F.R. § 312.2(a) (2019).

142. *Id.* § 312.21.

who are closely monitored.<sup>143</sup> This phase is designed to determine the effects on humans, to help design phase two studies, and glean early evidence on the drug's effectiveness.<sup>144</sup> Phase two studies are usually well controlled and closely monitored to evaluate the drug's effectiveness in patients with a specific disease or condition.<sup>145</sup> These studies also determine common short-term side effects and risks.<sup>146</sup> Phase three are larger uncontrolled trials with more subjects to gain additional information about the drug's effectiveness and safety.<sup>147</sup> This information helps determine the general benefit-risk relationship of the drug.<sup>148</sup> In phases two and three, the FDA is not only evaluating the safety of the subjects, but it is also assessing the quality of the investigations and the likelihood that the investigation will gather sufficient data for marketing approval.<sup>149</sup>

In addition, these products are subject to current good manufacturing requirements.<sup>150</sup> These requirements include the areas of manufacturing, personnel, equipment, standard operating procedures, quality control procedures, change and document controls, packaging and labeling, and record keeping.<sup>151</sup> Given these stringent regulations, it is easy to see why manufacturers and clinics attempt to argue they are in the unregulated lowest tier.<sup>152</sup> However, the court in *United States v. US Stem Cell Clinic, LLC* held that stem cell treatments are subject to these regulations.<sup>153</sup> Despite this, stakeholders in the industry still believe that there is significant ambiguity where they fall in this regulatory framework.<sup>154</sup>

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143. *Id.* § 312.21(a).

144. *Id.*

145. *Id.* § 312.21(b).

146. *Id.*

147. 21 C.F.R. § 312.21(c).

148. *Id.*

149. *Id.* § 312.22(a).

150. Duranske, *supra* note 16, at 644 (citing *Facts About the Current Good Manufacturing Practices*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm> (June 25, 2018)).

151. *Id.* (citing 21 C.F.R. §§ 211, 601, 820 (2017)).

152. *See Menon, supra* note 32 (discussing how clinics nationwide attempt to evade regulations by interpreting these regulations in ways so that they do not apply to the clinics).

153. *United States v. US Stem Cell Clinic*, 403 F. Supp. 3d 1279, 1295 (S.D. Fla. 2019).

154. PEW CHARITABLE TRS., *supra* note 12, at 16.

The product sold by Liveyon, the focus of *Bad Batch*, is an example of a product that would be regulated under this tier.<sup>155</sup> The company has been linked to fifteen patients who were hospitalized after being injected with the products.<sup>156</sup> These patients were negatively impacted by treatments that fell into this tier of regulation but were not tested properly.<sup>157</sup> These severe negative effects show why understanding the risks of treatments through well-controlled trials is imperative to patient safety.<sup>158</sup> It further proves that increased regulation through deceptive marketing enforcement by the U.S. Federal Trade Commission (FTC) or increased oversight by state medical boards could be necessary to further prevent bad outcomes.<sup>159</sup>

It should be mentioned that there are right-to-try laws that allow access to investigational drugs for terminally ill patients on both a state and federal level.<sup>160</sup> However, these laws are beyond the scope of this article, which will focus on the use of unproven treatments on patients who would not qualify for these laws.

## C. FTC Enforcement Actions

### 1. Injunctions

In addition to these statements, the FDA recently brought an action against U.S. Stem Cell Clinic, LLC, a clinic which provided adipose tissue based treatment.<sup>161</sup> The clinic advertised that the therapy could treat “neurological, autoimmune, orthopedic, and degenerative diseases.<sup>162</sup> In this case, the FDA claimed the clinic violated regulations through their stem cell treatments.<sup>163</sup> These violations included a failure to establish and follow appropri-

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155. The FDA sent Liveyon a warning letter that advised the company that their umbilical cord products were subject to this level of regulation. *Warning Letter Liveyon Labs Inc.*, U.S. FOOD & DRUG ADMIN. (Dec. 5, 2019), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/liveyon-labs-inc-588399-12052019>.

156. Wan & McGinley, *supra* note 8.

157. *Id.*

158. Marks et al., *supra* note 9, at 1008–09 (“Without such [clinical] studies, we will not be able [to] ascertain whether the clinical benefits of such therapies outweigh any potential harms.”).

159. *See supra* note 137 and accompanying text.

160. Christine Coughlin et al., *Regenerative Medicine and the Right to Try*, 18 WAKE FOREST J. BUS. & INTELL. PROP. L. 590, 611 (2018); *Right to Try*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try> (last updated Jan. 14, 2020).

161. *United States v. US Stem Cell Clinic*, 403 F. Supp. 3d 1279, 1282 (S.D. Fla. 2019).

162. *Id.* at 1283.

163. *Id.*



ate procedures to prevent contamination of products which put patients at risk for infections.<sup>164</sup> U.S. Stem Cell argued the procedure did not fall under the FDA's authority because of the same surgical procedure exemption and thus they did not have to comply with the FDA regulations.<sup>165</sup>

The judge found that the FDA acted within its powers and that there was a "reasonable likelihood" that the clinic would continue to violate the law.<sup>166</sup> Regarding the same surgical procedure exception, the court deferred to the FDA's narrow interpretation.<sup>167</sup> Under this interpretation, the therapy did not fall under the exception because of the processing involved.<sup>168</sup> The court further found that the therapy was not homologous use and therefore the company was subject to the highest tier of regulation.<sup>169</sup>

The judge ordered a permanent injunction to prevent the company from offering stem cell treatments until they came into compliance with the law.<sup>170</sup> This case shows how clinics attempt to circumvent regulation under the current regulatory scheme.<sup>171</sup> The FDA responded to this case by saying it reinforces its position that clinics that claim they do not fall under FDA regulations are not correct.<sup>172</sup> Following this case, they will continue "aggressive oversight" prioritizing addressing clinics, individuals, and products that put patients the most at risk.<sup>173</sup> However, this response by the FDA may not be enough to stop clinics from marketing such treatments without complying with regulations.<sup>174</sup>

## 2. Warning Letters

The FDA also utilizes warning letters as part of its enforcement strategy.<sup>175</sup> For example, a warning letter was sent to Liveyon.<sup>176</sup> The letter was

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164. *Id.*

165. *Id.* at 1283–84.

166. *Id.* at 1300.

167. *US Stem Cell Clinic*, 403 F. Supp. 3d at 1296.

168. *Id.*

169. *Id.* at 1298.

170. *Id.* at 1300.

171. *See supra* note 152 and accompanying text.

172. *Statement on Stem Cell Clinic Permanent Injunction and FDA's Ongoing Efforts to Protect Patients from Risks of Unapproved Products*, U.S. FOOD & DRUG ADMIN. (June 25, 2019) <https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks> [hereinafter *Statement on Stem Cell Clinic Permanent Injunction*].

173. *Id.*

174. *See supra* note 137 and accompanying text.

175. McGinley, *supra* note 26.

sent to Liveyon and its president and chief executive officers warning them of processing and distributing unapproved products.<sup>177</sup> The letter also warned of good manufacturing practice requirements (deficient donor eligibility, inadequate aseptic practices to prevent contamination, and deficient environmental monitoring).<sup>178</sup>

Liveyon was processing and distributing products to be used by patients unrelated to the donor, for nonhomologous use.<sup>179</sup> So, they failed to meet the criteria set forth in relevant FDA regulations and are regulated as both a drug and biological product.<sup>180</sup> Under the regulations, these products may only be used in humans if there is an investigational new drug application and can only be lawfully marketed if they have a biologic license, neither of which Liveyon had.<sup>181</sup>

In response to this letter, Liveyon has suspended sales of the product and will “‘focus its efforts’ on getting the nod from the FDA to conduct a clinical trial and eventually apply for approval of the products.”<sup>182</sup> The company argued that the FDA gave a “‘narrow interpretation’ of federal rules on stem cells” by finding that their products required agency approval.<sup>183</sup> They continue to contend that they “‘appropriately marketed’ their products.”<sup>184</sup> However, they believe “‘proving the efficacy of the product through FDA clinical trials, is in the company’s best interest for the future.’”<sup>185</sup>

#### IV. IMPLICATIONS ON PATIENT SAFETY

##### A. Balancing the Benefits and Risks of Stem Cell Therapies

These kinds of unregulated treatments have serious implications on patient’s health and safety.<sup>186</sup> Claims of effectiveness and safety of a therapy must be based on evidence to keep unsafe or ineffective therapies out of routine use.<sup>187</sup> Even in cases where therapeutic interventions are “pursued on the basis of expert opinion and patient acceptance [the interventions] ultimately proved ineffective or harmful when studied in well-controlled trials

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176. *Id.*

177. *Warning Letter Liveyon Labs Inc., supra* note 155.

178. *Id.*

179. *Id.*

180. *Id.*

181. *Id.*

182. McGinley, *supra* note 26.

183. *Id.*

184. *Id.*

185. *Id.*

186. Marks et al., *supra* note 9, at 1008–09.

187. *Id.* at 1008.

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comparing them with the standard of care.”<sup>188</sup> Adverse effects are probably more common in unregulated treatments than patients think because clinics are not required to report adverse effects when administered outside of a clinical trial.<sup>189</sup> Potential safety concerns include administration site reactions, the ability of cells to move from the placement site and change into inappropriate cell types or multiply, failure of cells to work as expected, and the growth of tumors.<sup>190</sup> Without clinical trials, the FDA cannot determine if the clinical benefits outweigh these potential harms.<sup>191</sup>

## B. Real Patient Stories

The impact on patients when treatments are offered without the determination of benefits and risks is illustrated by the patient stories in *Bad Batch*.<sup>192</sup> The podcast tells the story of Texas patients who received stem cell treatments and later found themselves in the hospital with life-threatening bacterial infections.<sup>193</sup> Three patients that received treatment, with products distributed by Liveyon from a Houston chiropractor, all wound up in intensive care during one weekend.<sup>194</sup> One patient received injections in her shoulders and a couple days later was airlifted to a hospital because she was on the verge of a heart attack and kidney failure.<sup>195</sup> Even after two weeks in the hospital and six more in rehab, she still has permanent damage from the treatments.<sup>196</sup> Another patient received treatment for severe neck pain and was later admitted to the hospital with a 106 degree fever.<sup>197</sup> The third patient received treatment for pain in her back and was also rushed to the hospital.<sup>198</sup> Both of these patients survived the infection; however, they are in more pain than before the injections.<sup>199</sup>

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188. *Id.*

189. *Id.*

190. *Id.*

191. *Id.* at 1009.

192. Beil, *supra* note 1.

193. *Id.*

194. *Id.*

195. *Id.*

196. *Id.*

197. *Id.*

198. Beil, *supra* note 1.

199. *Id.*

## V. CONTINUING ISSUES WITH REGULATION

Despite the increased regulation and guidance to clarify these regulations, stakeholders still have concerns.<sup>200</sup> Among these concerns are that there still exists confusion when the HCT/P is considered under the same surgery exception or minimally manipulated.<sup>201</sup> Additionally, stakeholders are worried about the FDA's resources in executing these regulations.<sup>202</sup> This section discusses the stakeholder's concerns and possible solutions the FDA can take to correct the concerns.<sup>203</sup>

### A. Same Surgical Procedure Exception

Stakeholders are concerned that the current definition of the same surgery exception fails to address certain uses of the stem cells.<sup>204</sup> As the exception is written, it may not address nonhomologous use of the cells.<sup>205</sup> So stem cells that are isolated and re-implanted in the patient for purposes other than their basic functions may still fall under the exception.<sup>206</sup> The potential gap in the regulations could create a pathway for businesses to circumvent regulations.<sup>207</sup> Entities can use this exception on an unproven use of the stem cells claiming that they do not fall under the higher tiers of regulations.<sup>208</sup>

The FDA's purpose of this exception is that the removal and implantation of autologous cells or tissues without processing steps into the same individual raises "no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery."<sup>209</sup> Additionally, the FDA has taken clear steps to increase their regulation of stem cell therapies.<sup>210</sup> The rationale for this regulation is to ensure patient safety when the effects of the treatment may be unknown.<sup>211</sup>

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200. PEW CHARITABLE TRS., *supra* note 12, at 16.

201. *Id.* at 16–17.

202. *Id.* at 19.

203. *Id.*

204. *Id.* at 16.

205. *Id.*

206. PEW CHARITABLE TRS., *supra* note 12, at 16. For example, bone marrow stem cells may be re-implanted to treat a neurological condition. *Id.*

207. *Id.*

208. *Id.*

209. SAME SURGICAL PROCEDURE EXCEPTION, *supra* note 98, at 3.

210. FDA Warns About Stem Cell Therapies, *supra* note 60.

211. *Id.*

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Under these rationales, it would make sense for homologous use to be required to apply in this exception.<sup>212</sup> Without that clarification, entities can use cells outside of their basic functions without any regulation for that treatment.<sup>213</sup> This is precisely why the FDA has required clinical trials under the FD&C Act or PHS Act when cells or tissues are not intended for homologous use.<sup>214</sup> Further, this is the same argument used by clinics using adipose tissue based therapies such as US Stem Cell Clinic, which the FDA has clearly stated they do not agree with.<sup>215</sup> Therefore, the FDA's stance on if homologous use is required under the same surgical exception seems clear.<sup>216</sup> However, additional clarity on the issue could ease the concerns of stakeholders.<sup>217</sup>

## B. Minimal Manipulation Definition

Even after the guidance given by the FDA, stakeholders still have difficulties determining what is considered minimal manipulation.<sup>218</sup> This confusion comes from the "controversial" distinction between structural and nonstructural tissue.<sup>219</sup> While the guidance acknowledges that a tissue could have both structural and nonstructural properties, it does not really explain why it made that distinction.<sup>220</sup> The guidance gives definitions for both kinds of tissues and cells but does not truly offer how to determine when the HCT/

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212. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 4 (explaining that non-homologous uses of cells increase safety concerns because they make how the cells will function in the recipient unpredictable).

213. PEW CHARITABLE TRS., *supra* note 12, at 16.

214. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 4 ("This criterion reflects the Agency's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior, whereas HCT/Ps for homologous use can reasonably be expected to function appropriately.").

215. *Statement on Stem Cell Clinic Permanent Injunction*, *supra* note 172.

216. *See* MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 4.

217. PEW CHARITABLE TRS., *supra* note 12, at 19.

218. *Id.* at 17.

219. *Id.* at 16.

220. The FDA recognizes that structural tissues can contain cells and that some manufacturers argue a single HCT/P has both a structural and nonstructural tissue or cell functions. Despite this recognition, the FDA states that they are considered in only one category under the regulations without explaining why. MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 7.

Ps are in each category.<sup>221</sup> Stakeholders have asked for more clarity from the agency on how they will classify tissues and cells moving forward.<sup>222</sup>

This confusion among stakeholders potentially causes misperceptions about whether the product is subject to the stringent premarket requirements, and instead of seeking approval, manufacturers will just continue development and treatments on the assumption it is not required.<sup>223</sup> This creates a system of responding after the fact when treatments are already being marketed to patients.<sup>224</sup> Offering additional guidance and clarity with less room for interpretation on behalf of the manufacturer could increase safety and efficacy of treatments.<sup>225</sup> However, this could also stall innovations in the field because manufacturers are not willing to go through the process.<sup>226</sup> While giving the manufacturers clarity may have this disadvantage, it will also give them an opportunity to be aware of and meet proper regulations before the FDA takes action against them instead of attempting to come into compliance after the fact.<sup>227</sup>

### C. Roles of Other Agencies and State Actors

Stakeholders are concerned with the ability of the FDA to regulate all of the clinics.<sup>228</sup> The FDA has been using its resources to target higher risk procedures, so lower risk manufacturers may believe they are exempt or that the FDA tolerates noncompliance.<sup>229</sup> While recent enforcement actions may signal to providers that the FDA is serious, it would be more effective if a wide population of providers are targeted.<sup>230</sup> However, broad enforcement by the agency requires additional funding, training, and staffing.<sup>231</sup> Thus, there is a need for congressional support for the full implementation of this frame-

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221. The FDA states that the distinction is based on the differing safety and efficacy concerns but does not offer further explanation in determining how the determination of structural versus nonstructural tissue or cells is made. *Id.* at 6.

222. PEW CHARITABLE TRS., *supra* note 12, at 17.

223. See MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 6 (explaining how to apply the criteria to determine whether the restrictions apply).

224. *Id.* at 3–4 (explaining that if the minimally manipulated exception is met, along with the other conditions, the product is not subject to premarket review).

225. PEW CHARITABLE TRS., *supra* note 12, at 17 (explaining that stakeholders request additional clarification in order to comply with these regulations).

226. *Id.* at 11 (explaining that higher regulatory burdens can pose obstacles to innovation and keep effective therapies out of the market).

227. See MINIMAL MANIPULATION AND HOMOLOGOUS USE, *supra* note 89, at 6; see PEW CHARITABLE TRS., *supra* note 12, at 11.

228. PEW CHARITABLE TRS., *supra* note 12, at 19.

229. *Id.*

230. *Id.*

231. *Id.*

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work.<sup>232</sup> But, there is also the potential for other agencies and actors to assist in the regulation of these clinics.<sup>233</sup>

### 1. Federal Trade Commission

Both the FDA and FTC play roles in regulating health care products.<sup>234</sup> The two agencies have previously agreed on their roles in this area.<sup>235</sup> The FDA regulates the advertising of prescription drug products and the FTC regulates nonprescription drugs, devices, and cosmetics.<sup>236</sup> However, in the past it has not been clear who is in charge of regulating the advertising of unproven stem cell treatments.<sup>237</sup> But in 2018, the FTC brought charges against a physician who advertised unapproved therapies, which potentially set the stage for the agency to take over this area of regulation.<sup>238</sup> The FTC and the FDA could use a teamwork approach to target lower risk procedures that do not have the stringent premarket and clinical trial requirements.<sup>239</sup>

The FTC brought charges against a physician and his companies because “[c]linics must have solid evidence to back up their claims before advertising that stem cell therapy can treat serious medical issues.”<sup>240</sup> A California physician claimed that his stem cell therapy was capable of treating a range of serious diseases such as Parkinson’s disease, multiple sclerosis, cerebral palsy, and chronic kidney disease.<sup>241</sup> These claims were made on the companies’ social media and websites.<sup>242</sup> However, these claims were not supported by scientific evidence.<sup>243</sup> The charges brought by the FTC were

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232. *Id.* at 20.

233. *Id.* at 21.

234. Liz Richardson, *Federal Trade Commission Acts for First Time Against Stem Cell Clinics*, PEW CHARITABLE TRS. (Dec. 21, 2018), <https://www.pewtrusts.org/en/research-and-analysis/articles/2018/12/21/federal-trade-commission-acts-for-first-time-against-stem-cell-clinics>.

235. *Id.*

236. *Id.*

237. *Id.*

238. *Id.*

239. *Id.*

240. *FTC Stops Deceptive Health Claims by a Stem Cell Therapy Clinic*, U.S. FED. TRADE COMM’N (Oct. 18, 2018), <https://www.ftc.gov/news-events/press-releases/2018/10/ftc-stops-deceptive-health-claims-stem-cell-therapy-clinic>.

241. *Id.*

242. Colleen Tressler, *FTC Takes Aim At Deceptive Stem Cell Therapy Claims*, U.S. FED. TRADE COMM’N: CONSUMER INFO. BLOG (Oct. 18, 2018), <https://www.consumer.ftc.gov/blog/2018/10/ftc-takes-aim-deceptive-stem-cell-therapy-claims>.

243. *FTC Stops Deceptive Health Claims by a Stem Cell Therapy Clinic*, *supra* note 240.

settled and the physician was prohibited from making health claims in the future without scientific evidence supporting them.<sup>244</sup> Additionally, the physician and the companies had to pay money to the FTC to be used to refund consumers that were harmed by the deceptive advertising.<sup>245</sup>

This California settlement opened the door for the FTC to take a proactive role in overseeing the marketing of unproven treatments.<sup>246</sup> Given the number of clinics in the direct-to-consumer market, it is not feasible that either agency could target every clinic.<sup>247</sup> However, if the FTC followed this precedent and took steps to regulate clinics it would send a clear message to clinics that federal regulators are taking action to protect patients against unproven treatments.<sup>248</sup> This could be particularly effective for regulating clinics that are not targeted by the FDA as high risk procedures. By ensuring that the low-risk procedures are only marketed based on what they can actually treat, patients will not be swayed by the promise of magic cures for all of their ailments.<sup>249</sup> However, even with both agencies taking actions against clinics and manufacturers, it is still unlikely that their actions will reach all the clinics.<sup>250</sup> Thus, there may be some room for state actors to have a role in regulating the clinics.

## 2. State Actors

The FDA and FTC are limited in how they regulate clinics because the power to regulate the practice of medicine lies with the states.<sup>251</sup> A physician may use drugs and devices approved by the FDA in a way that is not supported by scientific evidence and go unnoticed by the FDA.<sup>252</sup> Since each state is regulated by its own board, the regulation of physicians in this respect varies nationwide.<sup>253</sup> For example, only seventeen boards reported investigat-

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244. *Id.*

245. *Id.*

246. Richardson, *supra* note 234.

247. *Id.*

248. *Id.*

249. Murdoch et al., *supra* note 28, at 5 (discussing clinics' use of hype language and nondisclosure of inefficacy or risks of the treatment).

250. Richardson, *supra* note 234.

251. FED'N OF STATE MED. BDS., REGENERATIVE AND STEM CELL THERAPY PRACTICES 9 (2018), <https://www.fsmb.org/siteassets/advocacy/policies/fsmb-stem-cell-workgroup-report.pdf>.

252. David Gorski, *The Stem Cell Hard Sell: The Medical Board of California is Forming A Task Force to Determine How to Regulate Physicians Offering Stem Cell Therapies*, SCI-BASED MED. (Dec. 10, 2018), <https://sciencebasedmedicine.org/medical-board-of-california-is-forming-a-task-force/>.

253. See FED'N OF STATE MED. BDS., *supra* note 251, at 9.



ing complaints against physicians conducting stem cell treatments.<sup>254</sup> In addition to state medical boards, there is precedent for the involvement of state attorneys general.<sup>255</sup>

In addition to federal regulation by the FTC, state attorneys general also have a role in protecting patients from businesses selling unapproved treatments.<sup>256</sup> For example, the New York Attorney General filed a lawsuit against a clinic that deceived patients “into paying thousands of dollars for unproven and potentially harmful stem cell procedures.”<sup>257</sup> Similarly, in North Dakota, the attorney general’s office investigated a clinic that was making misleading claims.<sup>258</sup> These actions by state officials prove how states may supplement federal regulation of stem cell clinics.<sup>259</sup> Due to the large number of clinics in the United States, effective regulation requires a broad approach by bodies “charged with protecting public health or protecting consumers from fraud.”<sup>260</sup> The state attorneys general play an important role in such regulation because they may target clinics in their state that are marketing unproven treatments.<sup>261</sup>

In 2018, the Federation of State Medical Boards (FSMB) released recommendations for how state medical boards could get involved in monitoring the physicians who advertise stem cell treatments.<sup>262</sup> The recommendations focus on ensuring “patient safety, autonomy, and non-exploitation.”<sup>263</sup> First, the FSMB noted the importance of data gathered from the business’ website in the investigation of the complaints against the physicians.<sup>264</sup> Additionally, the clinic’s social media and blogs could offer additional information in these investigations.<sup>265</sup> Further, the FSMB suggests boards could proactively monitor FDA warning letters, which are public information, in order to determine if an investigation against a physician should be opened.<sup>266</sup> Medical boards could also play a role in ensuring the physicians are adequately trained to perform the treatments they are advertis-

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254. *Id.*

255. Richardson, *supra* note 137.

256. *Id.*

257. *Id.*

258. *Id.*

259. *Id.*

260. *Id.*

261. *See* Richardson, *supra* note 137.

262. FED’N OF STATE MED. BDS., *supra* note 251, at 2.

263. *Id.* at 10.

264. *Id.* at 4.

265. *Id.* at 10.

266. *Id.*

ing.<sup>267</sup> This could be particularly important given the number of physicians who offer stem cell treatments outside of their specialty.<sup>268</sup> The FSMB recommendations also include guidance on how the state medical boards can promote shared decision-making between the physician and the patient.<sup>269</sup>

While these recommendations offer guidance on best practices, it is not clear how or if they will be implemented by individual state medical boards.<sup>270</sup> Some researchers have suggested this could be an important tool in regulating physicians.<sup>271</sup> Others, however, are unsure how effective state boards would be in regulation.<sup>272</sup> One critique is the lack of resources available to state medical boards.<sup>273</sup> Another critique is that in the past medical boards have been “notoriously unwilling to evaluate the science behind medical claims and crack down on other quackery.”<sup>274</sup> Therefore, it is unlikely the boards will go after these clinics that are so profitable.<sup>275</sup> Additionally, it could lead to innovation in states with less regulation on treatments, such as Texas.<sup>276</sup> Thus, while state medical boards could potentially fill in gaps in the federal statutory structure, it does not come without its challenges. Even with these challenges, the increase in patient safety suggests that such an approach would be reasonable.<sup>277</sup> Whatever the solution may be, it is clear that both state and federal legislatures need to make this a priority in order to have effective regulation.<sup>278</sup>

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267. *Id.* at 11.

268. FED’N OF STATE MED. BDS., *supra* note 251, at 5.

269. *Id.* at 11.

270. PEW CHARITABLE TRS., *supra* note 12, at 24.

271. Wayne Fu et al., *Characteristics and Scope of Training of Clinicians Participating in the US Direct-to-Consumer Marketplace for Unproven Stem Cell Interventions*, 324 JAMA 2463, 2464 (2019), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6593626/>.

272. Gorski, *supra* note 252.

273. *Id.*

274. *Id.*

275. *Id.*

276. *See* Sipp, *supra* note 29, at 639–40 (explaining the process of “regulatory shopping” where clinics set up shop in areas with less regulation rather than complying with the strict regulations of an area).

277. Fu et al., *supra* note 271, at 5.

278. Gorski, *supra* note 252 (explaining the limited resources available to state medical boards); PEW CHARITABLE TRS., *supra* note 12, at 19 (discussing stakeholders’ concerns with the availability of resources for the FDA and FTC).

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## VI. CONCLUSION

Regenerative medicine, and stem cell treatments in particular, have caught the attention of many vulnerable patients who use these treatments as their last hope.<sup>279</sup> However, while physicians and patients are excited about the potential of these treatments, regulators must be wary of the use of unproven treatments.<sup>280</sup> The FDA has created a tiered regulatory structure that heavily regulates treatments that are highly risky but has virtually no regulation for less risky treatments.<sup>281</sup> Despite the FDA making statements that stem cell treatments fall under their regulations,<sup>282</sup> physicians continue to market these therapies directly to consumers without the proper approval.<sup>283</sup> These physicians and clinics interpret the tiers of regulation so that they fall in the lowest tier, rather than the highest.<sup>284</sup> But, without the use of clinical trials, which apply to the higher risk treatments under the regulatory framework, there is no way to determine how safe and effective these procedures are.<sup>285</sup>

As seen in the *Bad Batch*, these unproven procedures can have severe negative implications for these vulnerable patients.<sup>286</sup> These patients' stories are only a few examples of how clinics have been able to circumvent the current regulatory framework.<sup>287</sup> Liveyon was able to market its product to patients, through free seminars and online, and distribute its product around the country without regulators stepping in until patients were harmed.<sup>288</sup> These patients' stories exemplify why a proactive approach to regulation is needed to ensure patient safety.

Within the current regulatory framework set out by the FDA, there are still gaps in the regulation which may be filled in by other agencies and state medical boards.<sup>289</sup> One possibility is for the FTC to take a more proactive role in monitoring and charging clinics and physicians who falsely advertise the potential benefits of their treatments.<sup>290</sup> The FTC opened the door to this option in its settlement with a California physician who advertised that treat-

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279. See Sipp, *supra* note 29, at 639.

280. *FDA Warns About Stem Cell Therapies*, *supra* note 60.

281. PEW CHARITABLE TRS., *supra* note 12, at 10.

282. *FDA Warns About Stem Cell Therapies*, *supra* note 60.

283. Murdoch et al., *supra* note 28, at 1.

284. Menon, *supra* note 32.

285. Marks et al., *supra* note 9, at 1008–09.

286. Beil, *supra* note 1.

287. *Id.* (“Providers figured out how to operate just inside the margins or simply ignored the regulations.”).

288. *Id.*

289. PEW CHARITABLE TRS., *supra* note 12, at 21.

290. *Id.*

ment could treat a long list of serious diseases without any scientific evidence to substantiate such a claim.<sup>291</sup> Oversight from the FTC has the potential to reach clinics whose procedures, while dangerous, are not the target of FDA enforcement.<sup>292</sup>

State medical boards can also play a role in the regulation of physicians who are offering the stem cell treatments.<sup>293</sup> Federal authority is necessarily limited as they cannot regulate the practice of medicine, but the state medical boards have this authority.<sup>294</sup> The FSMB released recommendations for the best practices of state medical boards in regulating these physicians, but it has yet to be seen how they will be used by the states.<sup>295</sup> The use of state medical boards in this area of regulation could be important in ensuring that the physicians are properly trained in the treatment they are offering and are not working outside of their specialties, which is a common occurrence in the direct-to-consumer stem cell treatments.<sup>296</sup> Therefore, the use of the state actor and the FTC in partnership with the FDA could offer a more full regulatory structure that reaches all levels of the industry.<sup>297</sup> For this to work, however, these entities need the proper resources, such as funding, staffing, and training.<sup>298</sup> Thus, actors in the government on all levels need to prioritize the protection of vulnerable patients from clinics offering unproven treatments.

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291. Tressler, *supra* note 242.

292. PEW CHARITABLE TRS., *supra* note 12, at 10, 22.

293. *Id.* at 24.

294. FED'N OF STATE MED. BDS., *supra* note 251, at 9.

295. PEW CHARITABLE TRS., *supra* note 12, at 24.

296. Fu et al., *supra* note 271, at 5.

297. PEW CHARITABLE TRS., *supra* note 12, at 21.

298. Gorski, *supra* note 252; PEW CHARITABLE TRS., *supra* note 12, at 19, 22 (discussing stakeholders' concerns with the availability of resources for the FDA and FTC).