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# THE FUTURE OF STEM CELL THERAPY REGULATION UNDER THE FDA'S COMPREHENSIVE REGENERATIVE MEDICINE POLICY FRAMEWORK THROUGH A PUBLIC HEALTH LENS

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**ABSTRACT**

To over-correct or under-correct? That is the Food and Drug Administration's (FDA) question in its launch and enforcement of the Regenerative Medicine Policy Framework. Stem cell therapies may be the new frontier in modern medicine, with endless possibilities for therapeutic applications. Too much regulatory leeway allows harmful products onto the market, which poses risks for patient and stem cell therapy researchers. Too little regulatory leeway encourages production and treatment to occur overseas, out of the reach from the FDA, and frustrates terminally ill patients' ability to access experimental drugs. The FDA provided a 36-month grace period to allow manufacturers adequate time to comply with the intricate new regulatory framework. The original deadline was extended an additional six months due to the shifting demands of the FDA during the COVID-19 pandemic. Throughout the course of the grace period, trends have emerged as to how and when the FDA will enforce its regulations. Even still, it is critical for private tort actions and state medical boards to play a role in regulating stem cell therapies with the FDA.

## INTRODUCTION

Stem cell therapies are gaining substantial attention for their potential applications in treating chronic pain and other life-threatening or debilitating conditions.[1] Positive attention also creates an inordinate risk for abuse. The Food and Drug Administration (FDA) has responded to pressure from the Right–to–Try Movement, a movement which pushes for the right to try experimental medicines and therapies that have not yet been proven safe and effective, in its new comprehensive regulatory approach to regenerative medicine advanced therapies (RMATs).[2] The FDA strives to balance the needs of the stem cell-seeking patient population and manufacturers with those of the research industry and a vulnerable public.[3] By tracing the FDA's regulatory evolution of regenerative medicines, this analysis aims to provide a conjecture about the future of stem cell regulation in the United States.

Researchers, government regulators, people in chronic pain, and medical practitioners desire access to effective therapeutics for chronic pain and other life-threatening or debilitating conditions, such as Multiple Sclerosis, Parkinson's Disease, and cancers. However, there are some "bad actors" who have identified the lucrative potential of stem cell therapies, with suboptimal regard for patient safety or the widespread implications of tarnishing the reputation of legitimate stem cell research.[4] Public health officials are tasked with identifying the ideal balance between effectively regulating RMATs and trying to

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[1] Mike Moradi, *Why Stem Cells Could Be the Medical Innovation of the Century*, WORLD ECON. FORUM (Jan. 16, 2020), https://www.weforum.org/agenda/2020/01/how-will-stem-cells-impact-the-future-of-medicine/ ("the current market for stem cell therapies is growing at 36% per year").

[2] *FDA Fact Sheet: 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).

[3] *FDA Announces Comprehensive Regenerative Medicine Policy Framework*, U.S. FOOD & DRUG ADMIN. (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework.

[4] *Statement by FDA Commissioner Scott Gottlieb, M.D., and Biologics Center Director Peter Marks, M.D., Ph.D. on FDA's Continued Efforts to Stop Stem Cell Clinics and Manufacturers from Marketing Unapproved Products that Put Patients at Risk*, U.S. FOOD & DRUG ADMIN. (Apr. 3, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-biologics-center-director-peter-marks-md-phd-fdas [hereinafter *Statement*].

avoid the unintended consequences caused by legislative overcorrection. Notable unintended consequences include stem cell tourism, regulatory non-compliance, exacerbation of the opioid crisis, pushback from the stem cell research community, heightened distrust of the government, and resentment from people who demand the right to try stem cell therapy.

The discipline of public health law studies issues such as access to stem cell therapies, by identifying the "legal powers and duties of the state to assure the conditions for people to be healthy (to identify, prevent, and ameliorate risks to health in the population).[5] Public health practitioners, who focus on healthy conditions in the aggregate, are tasked with balancing increasing access to therapies, ensuring the public's safety, and protecting the longevity of research development. So much of the debate over stem cell therapies is deeply personal, which may challenge and frustrate the study of this issue from a public health policy perspective.

The FDA has already taken public health action in the realm of stem cell therapy policies. The agency *identifies* pertinent risks by putting out numerous press announcements and guidance documents regarding the associated risks of stem cell therapy.[6] It *prevents* these risks with its active, yet selectively targeted, injunction-seeking approach.[7] Lastly, it tries to *ameliorate* the risks by issuing warning letters and by responding to feedback from the public and market players. However, the main source of risk mitigation may be coming from outside of the federal government. Private tort litigation allows private citizens to hold accountable the doctors, clinics, and manufacturers involved in premature stem cell therapies, providing a critical tool for protecting the public from harmful stem cell therapies

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[5] *See* LAWRENCE O. GOSTIN & LINDSAY F. WILEY, PUBLIC HEALTH LAW: POWER, DUTY, RESTRAINT, at xx (Univ. of Cal. Press ed., 3rd ed. 2016).

[6] *See FDA Announces Comprehensive Regenerative Medicine Policy Framework*, *supra* note 3; NAT'L INSTS. OF HEALTH, STEM CELL BASICS 1 (2020), https://stemcells.nih.gov/sites/default/files/508-Compliant-Stem-Cell%20Basics-2020.pdf.

[7] GOSTIN & WILEY, *supra* note 5 (statement by FDA Commissioner Scott Gottlieb, M.D., and Biologics Center Director Peter Marks, M.D., Ph.D. on FDA's continued efforts to stop stem cell clinics and manufacturers from marketing unapproved products that put patients at risk).

without creating corrective over legislation.[8] Another promising source of regulation may be from state medical boards which set guidelines for permissible practices of medicine in each state.[9] Each sphere of influence must work in tandem to create a sustainable and balanced model for the regulation of regenerative medicines and therapies.

The FDA established a three-year grace period for the comprehensive regenerative medicine policy framework, originally scheduled to conclude in November 2020.[10] In a press announcement, then FDA director Scott Gottlieb, M.D., described the purpose of the grace period following the enactment of the FDA's final guidance document as such:

> Under the new policy, in order to allow manufacturers of products time to comply with the requirements, for the first 36 months following issuance of the final guidance document the FDA intends to exercise enforcement discretion for certain products that are subject to the FDA's premarket review under the existing regulations, but are not currently meeting these requirements. The FDA does not intend to exercise such enforcement discretion for those products that pose a potential significant safety concern. Going forward, the FDA will apply a risk-based approach to enforcement, taking into account how products are being administered as well as the diseases and conditions for which they are being used. This risk-based approach allows product manufacturers time to engage with the FDA, as to determine if they need to submit a marketing authorization application and, if so, submit their application to the FDA for approval.[11]

Dr. Gottlieb described the process of keeping bad actors out of the stem cell market as a "whack-a-mole game";[12] as one bad actor is taken out, two more pop up in its place. Therefore, the FDA cannot be the lone enforcer charged with protecting the public and the future of stem

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[8] Claire Horner et al., *Can Civil Lawsuits Stem the Tide of Direct-to-Consumer Marketing of Unproven Stem Cell Interventions*, 3 NPJ REGENERATIVE MED. 1 (Feb. 19, 2018), https://www.nature.com/articles/s41536-018-0043-6.

[9] FED'N OF STATE MED. BDS., REGENERATIVE AND STEM CELL THERAPY PRACTICES REPORT AND RECOMMENDATIONS OF THE WORKGROUP TO STUDY REGENERATIVE AND STEM CELL THERAPY PRACTICES ADOPTED AS POLICY BY THE FEDERATION OF STATE MEDICAL BOARDS 10-11 (2018), https://www.fsmb.org/siteassets/advocacy/policies/fsmb-stem-cell-workgroup-report.pdf.

[10] *FDA Announces Comprehensive Regenerative Medicine Policy Framework*, *supra* note 3.

[11] *Id.*

[12] Laura Biel, *Bad Batch*, WONDERY (Feb. 5, 2020), https://wondery.com/shows/bad-batch/.

cell therapy research development. Additionally, the FDA must be cautious of the high propensity for unintended consequences from regulatory overcorrection of regenerative medicine, such as stem cell tourism. Based on its cautious approach thus far (as indicated by establishing a grace period) and the possible assistance from civil litigation and state medical board oversight, the FDA is unlikely to take a dramatically aggressive stronghold on RMATs once the new regulatory framework is completely implemented. However, how the FDA chooses to enforce its new policy will impact Americans researching, manufacturing, and seeking stem cell therapies.

Americans are living longer, but not necessarily better. Chronic pain and life-threatening conditions intimately permeate American society.[13] Pain management in the context of the opioid crisis is a matter of dire public health concern.[14] Stem cell therapy, which is marketed as a permanent solution addressing the underlying issues of nerve damage,[15] as opposed to masking the source of pain, may be the key to improving quality of life.

Sections I, II, and III of this analysis will introduce RMATs, the history of the FDA's regulation of these therapies, and how the Right-to-Try Movement has encouraged broadening accessibility to experimental treatments. Sections IV, V, and VI of this analysis will detail the FDA's new regulatory framework over RMATs, the FDA's new approach to regulation, and alternative sources of regulation over these therapies. Sections VII, VIII, and IX of this analysis will include regulatory comparisons from other countries, the FDA's regulation in

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[13] James Dahlhamer et al., *Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults – United States, 2016,* 67 CDC MORBIDITY MORTALITY WEEKLY REP. 1001 (2018), https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6736a2-H.pdf (citing INTERAGENCY PAIN RES. COORDINATING COMM., NAT'L PAIN STRATEGY: A COMPREHENSIVE POPULATION HEALTH-LEVEL STRATEGY FOR PAIN (2016), https://www.hsdl.org/?view&did=792119) ("Population-based estimates of chronic pain among U.S. adults range from 11% to 40%.").

[14] Richard J. Bonnie et al., *Pain Management and Opioid Regulation: Continuing Public Health Challenges*, 109 AM. J. PUB. HEALTH 31, 31–32 (2019) (noting that the prevalence on chronic pain in the United States ranges from 11%–40%, but the policy response to prescription opioid-related overdose has been to "reduce clinically unwarranted prescribing of these drugs for chronic noncancer pain").

[15] Robert Sullivan et al., *Peripheral Nerve Injury: Stem Cell Therapy and Peripheral Nerve Transfer*, 17 INT'L J. MOLECULAR SCI. 1, 6 (2016) (noting that cell-based therapy "may lead to functional improvement as well as shortened recovery times, avoiding the hurdles of additional surgeries").

the context of the COVID-19 pandemic, and the FDA's decision to extend the regulatory grace period, followed by concluding remarks about an ideal regulatory balance for the future of RMATs in the American treatment realm.

## I. REGENERATIVE MEDICINE ADVANCED THERAPIES

According to the National Institutes of Health (NIH), regenerative medicine is "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects…[and has the potential for] regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves."[16] Based on these criteria, stem cell therapies fall into the category of RMATs. Stem cells are cell lines that differentiate into other types of cells of various functionalities and can be acquired from several sources in the body.[17] Imagine needing a kidney transplant, but not being able to find a match. Imagine suffering from myocarditis, a condition in which cardiac muscle is covered in scar tissue hindering the heart's ability to pump blood. Now imagine a stem cell laboratory that can take an individual's cells and generate a new kidney or new cardiac tissue. These examples illustrate why there is so much excitement surrounding stem cell therapy.

There are researchers working tirelessly to harness the therapeutic possibilities of stem cells. Therapeutic applications span from nerve regeneration to completely re-growing an entire organ.[18] As testified by Gerald D. Fischback, M.D. and Allen M. Spiegel, M.D., stem cells

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[16] NAT'L INSTS. OF BIOMEDICAL IMAGING AND BIOENGINEERING, NAT'L INSTS. OF HEALTH, FACT SHEET – REGENERATIVE MEDICINE 1 (2010), https://archives.nih.gov/asites/report/09-09-2019/report.nih.gov/nihfactsheets/Pdfs/RegenerativeMedicine(NIBIB).pdf.

[17] The source of the stem cells has implications for their differentiation potential. For example, whether the stem cells are embryonic or non-embryonic, has implications for their pluripotent potential. *See* NAT'L INST. OF HEALTH, STEM CELL BASICS 1 (2020), https://stemcells.nih.gov/sites/default/files/508-Compliant-Stem-Cell%20Basics-2020.pdf.

[18] *See Stem Cell Research, Part 3: Hearings Before a Subcomm. of the Comm. on Appropriations*, 106th Cong. 56 (2000) (statement of Gerald D. Fischbach, M.D., Director, National Institute of Neurological Disorders and Stroke and Allen M. Spiegel, M.D., Director, National Institute of Diabetes and Digestive and Kidney Diseases), https://www.govinfo.gov/content/pkg/CHRG-106shrg66482/pdf/CHRG-106shrg66482.pdf.

may be "ideal candidates for repairing and replacing tissues and organs ravaged by disease."[19] It is understandable why stem cell therapy is perceived as the medical miracle for which so many have been waiting.

Stem cell research was notoriously deemed controversial for its methodology requiring human embryos. For example, the pro-life movement, which strongly believes that life begins at conception, gave serious pushback to the development and support of stem cell research.[20] There is a moral dilemma, in some cases founded within religious beliefs, posed by the ethical implications of stem cell research sourced from embryos for the purpose of extracting the desired cell line, and disposing of the remaining biological material.[21] As this analysis will explore further, there are other critical moral dilemmas posed by stem cell therapies, asserted both by those who support the use and by those who are trying to cautiously limit its development and distribution to the public.

There is a plethora of scientific research and clinical trials testing the potential of stem cell therapy. For example, researchers are studying how to inhibit immune system-derived nerve cell damage in multiple sclerosis patients.[22] There are also efforts to reverse the effects of macular degeneration by replacing the retinal pigment epithelium (RPE) layer.[23] Clinical trials, such as those listed above, are available for the public to search and seek eligible matches.[24] Thinking more broadly of future research opportunities, particularly in the context of

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19 *See id*. at 55.

20 *See* NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH: VOLUME 1 REPORT AND RECOMMENDATIONS OF THE NATIONAL BIOETHICS ADVISORY COMMISSION 50 (1999), https://repository.library.georgetown.edu/bitstream/handle/10822/559364/nbac_stemcell1.pdf?sequence=1&isAllowed=y [hereinafter VOLUME 1 REPORT] ("The fundamental argument of those who oppose the destruction of human embryos is that these embryos are human beings and, as such, have a right to life.").

21 *See generally id*. at 49–50.

22 *Multiple Sclerosis*, A CLOSER LOOK AT STEM CELLS, https://www.closerlookatstemcells.org/stem-cells-medicine/multiple-sclerosis/#stem-cell-potential-multiple-sclerosis (last visited Nov. 23, 2019).

23 Maya Chaddah, *Stem Cells May Be Key to Curing Retinal Disease*, INT'L SOC'Y FOR STEM CELL RSCH. (Apr. 17, 2017), https://www.closerlookatstemcells.org/2017/04/17/stem-cells-may-be-key-to-curing-retinal-disease/.

24 A list of current clinical trials may be found at https://clinicaltrials.gov/.

the opioid epidemic, one could hypothesize how post-surgical and burn victim opioid use could be weaned off sooner with stem cell injections to address nerve and muscular damage. However, such great potential may be overshadowed by the equally great need for oversight.

## II. FDA Oversight Authority Over Regenerative Medicine Advanced Therapies

The FDA derives its statutory authority over RMATs from the Public Health Service Act (PHSA).[25] Furthermore, 21 C.F.R. § 1271 codified the FDA's regulation of human cells, tissues, or cellular or tissue-based products (HCT/Ps), which are "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[26]

RMATs could fall either under Section 351 or 361 of the PHSA. Under Section 351, RMATs are regulated under higher scrutiny as either drugs and biological products, whereas under Section 361 language, the therapies are regulated under less scrutiny.[27] Section 361 is geared toward the prevention of disease transmission through biological products, rather than the efficacy and safety testing needed for drugs and biological products.[28] The distinctions between these two regulatory classification groups for HCT/Ps are important because each one comes with different levels of regulation, approval processes, and oversight.[29]

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[25] Public Health Service Act, 42 U.S.C. Ch. 6A §§ 351, 361 (LEXIS through Pub. L. No. 116-215).

[26] *See* 21 C.F.R. § 1271.3(d) (2013).

[27] *FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, U.S. FOOD & DRUG ADMIN. (Feb. 1, 2018), https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/fda-regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-product-list.

[28] Greg Pivarnik, *Cells As Drugs?: Regulating the Future of Medicine*, 40 AM. J.L. & MED. 298, 305 (2014) (citing Mary Ann Chirba, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?*, 7 J. HEALTH & BIOMEDICAL L. 233, 250 (2011)).

[29] *FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, *supra* note 27 (explaining how Section 351 products include unrelated allogenic hematopoietic stem cells, and Section 361 products include hematopoietic stem cells derived from peripheral or umbilical cord blood).

Currently, the only FDA-approved indication for stem cell therapies is for diseases of the hematopoietic system.[30] Although there is only one FDA approved use, stem cell therapies are marketed through direct-to-consumer advertising for "pain/injury relating to the bones, joints and muscles (182), illness (diseases or maladies including autoimmune disorders, degenerative conditions, genetic disorders, infectious diseases and environmental harms, other than chronic conditions primarily affecting the bones, joints and muscles) (82), cosmetic concerns (52), non-cosmetic ageing (44) and sexual enhancement (18)."[31] A systematic website analysis from the Health Law Institute at the University of Alberta found that a majority of the clinics studied, 295 of which are located in the United States, failed to include disclosures regarding efficacy, risk, and/or their regulatory approval status.[32] For this reason, among many others, the FDA must be diligent, clear, and transparent in its approach to which therapies get a stamp of approval and the necessary proof of safety and efficacy that is required before approval.

The FDA strives to ensure that products reach the market as safely and efficiently as possible. However, meticulous attention to safety and efficacy may slow down the process for getting therapies to consumers. Manufacturers may become frustrated by the difficulty with recouping their research and delivery costs quickly, and consumers may become irritated or impatient from regulatory interference with medical therapies they wish to have the right to try. Nevertheless, the FDA must cast its regulatory net wide enough and tight enough to prevent dangerous products from getting on the market and into patients' bodies.

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[30] *FDA Warns About Stem Cell Therapies*, U.S. FOOD & DRUG ADMIN. (Sept. 3, 2019), https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies (specifically using "stem cells that come from bone marrow or blood in transplant procedures to treat patients with cancer and disorders of the blood and immune system").

[31] The numbering refers to the study results, which reflects the number of websites that advertise for the particular target of stem cell therapy. *See* Blake Murdoch et al., *Exploiting Science? A Systematic Analysis of Complementary and Alternative Medicine Clinic Websites' Marketing of Stem Cell Therapies*, 8.2 BMJ OPEN 1, 2, 5 (2018).

[32] *Id.* at 5–6. The study also suggests that these deceptive advertisements could be a violation of US Federal Trade and Commission Act regulations, which "prohibits 'deceptive and unfair acts or practices'. . .those that mislead consumers and affect their 'behavior or decisions about the product or service.'" *Id.* at 8.

## III. THE RIGHT–TO–TRY MOVEMENT AND THE 21ST CENTURY CURES ACT

In 2013, a change.com petition for a 45-year-old Texan patient with end-stage ovarian cancer generated massive support in assisting her quest for access to a drug in the early stages of clinical development.[33] The final decision of whether to grant expanded access was in the hands of the drug's manufacturer, not the FDA.[34] Despite eventually being granted access to the experimental drug, the terminal patient died of cancer soon after acquiring access.[35]

Nevertheless, this woman's death was not in vain. In 2015, the Texas Legislature, following the footsteps of 20 other states, enacted its own Right-to-Try Legislation.[36] In the four years since Colorado enacted the first Right-to-Try Legislation in the nation, 40 other states enacted similar protections for its citizens.[37] After such an incredible showing of support by individual states, the federal government codified its own Right-To-Try Legislation on May 30, 2018.[38]

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[33] Sylvia Zaich, *An Examination of the Right to Try Act of 2017 and Industry's Potential Path Moving Forward*, 92 S. CAL. L. REV. 331, 332 (2019) (citing *BioMarin Pharmaceutical: Give Andrea Sloan (@andi_sloan) Access to the Cancer Drug That Could Save Her Life*, CHANGE.ORG, [hereinafter CHANGE.ORG], https://www.change.org/p/biomarin-pharmaceutical-give-andrea-sloan-andi-sloan-access-to-the-cancer-drug-that-could-save-her-life (last visited May 25, 2020)).

[34] *Id.* at 333 (explaining that although the FDA had declared Ms. Sloan eligible for the expanded access use avenue, the manufacturer BioMarin, additionally had to grant access to the drug).

[35] *Id.* (citing Meg Tirrell, *When Unapproved Drugs Are the Only Hope*, CNBC (Aug. 5, 2014)), https://www.cnbc.com/2014/08/05/a-case-for-compassionate-use-when-unapproved-drugs-are-the-only-hope.html).

[36] *Id.* at 334 (citing TEX. HEALTH & SAFETY CODE ANN. § 489 (West 2015); Eric Janez, *Andrea Sloan Bill Signed into Law*, KXAN (June 12, 2015), http://kxan.com/2015/06/12/andrea-sloan-bill-signed-into-law).

[37] *Id.* (citing Press Release, Goldwater Inst., Alaska Becomes 41st State to Enact Right-to-Try Legislation (July 13, 2018), http://righttotry.org/alaska-becomes-41st-state-to-enact-right-to-try-legislation). The states with enacted Right-to-Try laws are: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Washington, West Virginia, Wisconsin, and Wyoming.

[38] *Id.* at 335 (citing Press Release, White House, President Donald J. Trump to Sign Right to Try Legislation Fulfilling the Promise He Made to Expand Healthcare Options for Terminal Americans (May 30, 2018), https://www.whitehouse.gov/briefings-statements/president-donald-j-trump-sign-right-try-legislation-fulfilling-promise-made-expand-healthcare-options-terminal-americans).

Surprisingly, the federal Right-to-Try Act does not explicitly preempt the state versions of the law.[39]

The origins of the FDA's arduous regulatory framework were largely reactionary responses to lethal drug threats.[40] Over time, the FDA implemented numerous consumer protections, and as an effect has created arduous obstacles for drug access to patients who cannot wait for the completion of the approval process.

One of the first cases challenging pre-approval access was *United States v. Rutherford*.[41] Terminal cancer patients seeking access to Laetrile brought suit,[42] and the Supreme Court ruled for the FDA by holding that its statutory language created no exception regarding the requirement for safety and efficacy "for drugs used to treat terminally ill patients."[43] The FDA completed additional administrative hearings to determine whether Laetrile could get the premarket exemption either under the 1938 or 1962 grandfather provisions, which were the only applicable exemptions at the time.[44]

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[39] Sylvia Zaich, *An Examination of the Right to Try Act of 2017 and Industry's Potential Path Moving Forward*, 92 S. CAL. L. REV. 331, 389 (2019) (citing U.S. CONST. art. VI, cl. 2; *see also* Kate Gallin Heffernan et al., *Federal "Right to Try": Don't Disregard Your State Laws Just Yet! How Federal Preemption (or Lack Thereof) Could Influence the Use of Federal "Right to Try"*, VERRILL DANA LLP (June 12, 2018), http://www.verrilldana.com/federal-right-to-try-dont-disregard-your-state-laws-just-yet (noting that the federal Right-to-Try Act may not conflict with state versions and "state laws could reasonably be found by a court to supplement and explicate the way in which this activity… can occur in a given jurisdiction, rather than serving to frustrate Congress' intent in making the 'right to try' pathway available.")). There may also be a preemption issue with the FDA's regulatory policy over these therapies and state Right -To-Try laws. The implications of these preemption issues will not be discussed in this paper.

[40] *Id.* at 336-37 (referencing examples of such threats, including the elixir sulfanilamide that led to 100 deaths and thalidomide that resulted in unintended birth defects).

[41] *Id.* at 341 (citing United States v. Rutherford, 442 U.S. 544 (1979)).

[42] Laetrile refers to "chemical compounds similar to, or consisting at least in part of, amygdalin, a glucoside present in the kernels or seeds of most fruits." *Rutherford*, 442 U.S. at 549 (citing 42 Fed. Reg. 39768, 39770-72 (1977)).

[43] *Id.* at 551–52 (explaining how FDCA made no exception for terminally ill cancer patients based on a strict textual reading of the statute).

[44] *Id.* at 550 ("no showing that the drug currently known as Laetrile was identical in composition or labeling to any drug distributed before 1938."). *See* 21 U.S.C. § 321(p)(1)("Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or

Although terminally ill cancer patients suffered a devastating defeat in the 1970s, the pendulum started to swing further towards the right to try experimental drugs during the AIDS crisis in the 1980s, and even further with the strengthening of the Right-to-Try Movement.[45] However, there were setbacks along the way. Approximately ten years before the passage of the 21st Century Cures Act, the D.C. Circuit Court held that terminally ill patients *do not* have a "fundamental right" to experimental drugs.[46]

Before filing suit, the Abigail Alliance for Better Access to Developmental Drugs ("Alliance") had petitioned the FDA to bypass the arduous drug approval process.[47] The FDA acknowledged concerns from the Alliance but argued that its current regulatory framework was adequate to meet the needs of their population.[48] The FDA contended that implementation of Alliance's proposal "would upset the appropriate balance…by giving almost total weight to the goal of early availability and giving little recognition to the importance of marketing drugs with reasonable knowledge for patients and physicians of their likely clinical benefit and their toxicity."[49] A suit followed after the FDA's abrupt rejection of the Alliance's proposal.[50]

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suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use"); *see also* Drug Amend. of 1962 § 107(c)(4), 76 Stat. 789 ("In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201 (p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201 (p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.").

[45] Zaich, *supra* note 33, at 343–44 ("allow[ing] widespread access to an investigational drug outside of the clinical trial setting through a 'treatment protocol'" and "creat[ing] the Accelerated Approval pathway").

[46] Abigail All. for Better Access to Dev. Drugs v. von Eschenbach, 495 F.3d 695, 697 (D.C. Cir. 2007).

[47] *Id.* at 699.

[48] *Id.* at 700.

[49] *Id.* (citing Letter from Peter J. Pitts, Assoc. Comm'r for External Relations, Dep't of Health and Hum. Servs., to Frank Burroughs, President, Abigail All. for Better Access to Dev. Drugs 3, 5 (Apr. 25, 2003)).

[50] *Id.* at 700.

The need to provide access to these treatments and to speed up the approval process must be balanced against the importance of releasing drugs that will be safe and effective for their intended populations: "[a]lthough terminally ill patients desperately need curative treatments…their deaths can certainly be hastened by the use of a potentially toxic drug with no proven therapeutic benefit."[51] The D.C. Circuit Court acknowledged that the FDA could change its position in the future but that the judicial system was not the proper venue to rule on this particular issue of science and medicine.[52]

Justice Rogers' dissent evokes powerful moral arguments, citing to *Washington v. Glucksberg* in its opposition to the majority's decision: "While the potential cures may not prove *sufficient* to save the life of a terminally ill patient, they are surely *necessary* if there is to be any possibility of preserving her life."[53] In *Glucksberg*, the Court upheld Washington State's prohibition against physician assisted suicide under the Due Process Clause.[54] The dissent argued that it is not the right to experimental drugs that is at stake, rather, the right to the preservation of one's own life, a right that is, and should be, protected under the constitution.[55]

A right may be considered fundamental if it is "deeply rooted in this Nation's history and tradition"[56] and "'implicit in the concept of ordered liberty' such that 'neither liberty nor justice would exist if they were sacrificed.'"[57] Presuming that the *Alliance* was fighting to preserve a fundamental right, the FDA would have been required to demonstrate a compelling state interest in order to deny Plaintiffs'

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51 *Id.* at 713.

52 *See id.*

53 *Id.* at 714-15.

54 *See* Washington v. Glucksberg, 521 U.S. 702, 705-06 (1997).

55 *Id.* at 714.

56 *Glucksberg*, 521 U.S. at 720–21 (quoting Moore v. City of E. Cleveland, 431 U.S. 494, 503 (1977) (plurality opinion)).

57 *Id.* at 721 (quoting Palko v. Connecticut, 302 U.S. 319, 325, 326 (1937)).

request.[58] The dissent argues that the FDA had not met this burden.[59]

If the Court had found that there was a fundamental right at stake, then they would be required to apply the strict scrutiny standard: "narrowly tailored to serve a compelling governmental interest."[60] Under this higher standard, the FDA may have had more difficulty with sustaining their protective measures through the courts. However, the court rejected the notion that there was a fundamental right to experimental drugs and applied the rational basis test: rational relationship to legitimate state interest.[61]

The *Alliance* dissent insisted that the majority opinion put too much emphasis on whether the risks associated with the experimental drugs provided an adequate justification for restricting that right to experimental drugs.[62] Alternatively, preventing access to unproven treatments with unknown risks may also be regarded as preserving a fundamental right to saving one's own life: saving oneself from potentially lethal drugs.

In opposition to the majority's emphasis on the right to assume the risk, the *Alliance* dissent cites to *Cruzan v. Director, Missouri Department of Health,* a Supreme Court decision which upheld the right to refuse life-sustaining medical treatment, as support for how the majority ignores relevant precedent.[63] Surely refusing medical treatment equates to assuming the risk of the pitfalls of discontinued medical care. Moreover, the right to preserve life, specifically the right to preserve a mother's life, was upheld in *Planned Parenthood v. Casey* by retaining the exception for where a state may not forbid abortions

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[58] *See id.* at 721; *see also* Reno v. Flores, 507 U.S. 292, 302 (1993) ("[T]he Fourteenth Amendment 'forbids the government to infringe . . . 'fundamental' liberty interests at all, no matter what process is provided, unless the infringement is narrowly tailored to serve a compelling state interest.'").

[59] Abigail All., 495 F.3d at 714 ("The court conflates the inquiry as to whether a fundamental right exists at all with whether the government has demonstrated a compelling interest, when strictly scrutinized, rendering its restrictive policy constitutional.").

[60] *See* Planned Parenthood of Se. Pa. v. Casey, 505 U.S. 833, 871, 929 (1992).

[61] Abigail All., 495 F.3d at 712 (citing *Glucksberg*, 521 U.S. at 722 (indicating that "a challenged state action [must] implicate a fundamental right" to evade applying rational basis review)).

[62] *C.f.* Abigail All., 495 F.3d at 716 ("[W]hether the risks associated with doing so justify restraining that right is properly considered only after the right is deemed fundamental.").

[63] *Id.* at 718; *see* Cruzan v. Dir., Mo. Dep't of Health, 497 U.S. 261, 269, 268 (1990).

when the mother's life is in danger as a direct result thereof.[64] A prominent theorist in the Right-to-Try Movement evokes arguments under a similar principle for the argument to use experimental drugs.

Harvard professor Eugene Volokh coined the term "medical self-defense" to characterize how people have a constitutional right to medical treatments.[65] Volokh contends that the universally accepted principle of self-defense, rooted in the "right to life" within the Due Process Clause,[66] extends to the right to utilize medicine to protect oneself against lethal health conditions.[67] Volokh analogizes to the legalization of abortion under the theory that the constitution recognizes that pregnant women can pursue an abortion, a medical treatment, in instances where their health is at risk.[68]

The *Alliance* contends that critical medical conditions are comparable to other legitimate provocations for self-defense[69] and minimizes the argument regarding stem cell therapy's efficacy because "the law has never required proof that self-defense measures are certain or even likely to succeed."[70] A limitation of the argument that people deserve access to stem cell therapies for "medical self-defense" is that in order to succeed in the defense, the threat must be *imminent*.[71]

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[64] *Id.* at 720; *von Eschenbach*, 495 F.3d at 846, 879-80; *see also* Roe v. Wade, 410 U.S. 113, 164-65 (1973) (Summarizing how the Texas criminal abortion, providing only an exception for saving the mother's life "without regard to pregnancy stage and without recognition of the other interests involved, is violative of the Due Process Clause of the Fourteenth Amendment." The Roe v. Wade decision proscribes that the state may consider regulating abortion in the final stage of the first trimester when "reasonably related to maternal health" and in the stage preceding fetal viability "for the preservation of the life or health of the mother.").

[65] Kristin M. Hicks, *Embryonic Stem Cell Research and the Theory of Medical Self Defense*, 21 HARV J. L. & TECH. 547, 553 (citing Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1813 (2007)).

[66] *Id.* (citing Nicholas J. Johnson, *Self-Defense?*, 2 J. L. ECON. & POL'Y 187, 188 (2006) (arguing that self-defense is "in the first echelon of fundamental constitutional rights")).

[67] *Id.*; Volokh, *supra* note 65, at 1818.

[68] Volokh, *supra* note 65, at 1824; *see also von Eschenbach*, 495 F.3d at 700, 714–15.

[69] Petition for Writ of Certiorari at 16, Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, No. 07-444 (U.S. Sept. 28, 2007), *available at* http:// www.wlf.org/ upload/09-28-07Abigail%20ceriorari%20petition.pdf ("There is no moral or legal difference between attack by an animal and attack by mutated cancer cells.").

[70] Hicks, *supra* note 65, at 554.

[71] *Id.*

The model penal code sets out the standard for when lethal force is justified: when "such force is immediately necessary…[to prevent] death [or] serious bodily injury."[72] In the context of stem cell therapies, the imminence requirement may be satisfied if the underlying condition for which the therapy is requested poses a threat of immediate death or disability. Therefore, under Volokh's theory of medical self-defense, the fundamental right to unproven, experimental stem cell therapies belongs exclusively to terminally ill patients.[73]

Two years after the judicial defeat of the *Alliance*, the FDA revised its pathway for private citizens to seek expanded access,[74] specifically allowing "patients with serious or immediately life-threatening diseases [to] use 'an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.'"[75] For individual patient requests, the FDA makes determinations based on patient eligibility, a risk-benefit analysis, and the impact on the clinical trial process.[76] By utilizing these factors, the FDA approved almost every request submitted between 2012 and 2015.[77]

Certain provisions of the 21st Century Cures Act ("Cures Act"), signed into law on December 13th, 2016, responded to public outcry about regulatory overcorrection for new potentially life-saving therapies.[78] Among other intentions, the Cures Act was a resolution to

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[72] *Id.* at 555; MODEL PENAL CODE § 3.04(2)(b) (AM. LAW INST. 1985)

[73] *Id.* at 556.

[74] Zaich, *supra* note 33, at 347 (citing *Expanded Access to Investigational Drugs for Treatment Use*, 74 Fed. Reg. 40,900, 40,942-45 (Aug. 13, 2009) (codified at 21 C.F.R. §312, 316), https://www.govinfo.gov/content/pkg/FR-2009-08-13/pdf/E9-19005.pdf)).

[75] *Expanded Access*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/news-events/public-health-focus/expanded-access (last updated Nov. 8, 2018).

[76] *Id.* at 353.

[77] *Id.* at 357 (citing U.S. GOV'T ACCOUNTABILITY OFF., GAO-17-564, INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT SHOULD FURTHER CLARIFY HOW ADVERSE EVENTS DATA ARE USED 16-17 (2017), https://www.gao.gov/assets/690/685729.pdf (discussing findings of an FDA survey of nine manufacturers' individual patient expanded access requests, in which 99% were allowed to proceed)).

[78] *21st Century Cures Act*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act (last visited Oct. 28, 2020); 21st Century Cures Act § 3033.

expedite RMAT approval and to address persistent lobbying efforts.[79] The Cures Act spoke to the public outcry that fruitful therapeutic research for serious, life-threatening conditions should not be squashed by overburdensome regulations and that researchers should not be discouraged from pursuing research targeted towards terminally ill patients.

Under the Cures Act, a new therapy can qualify for the RMAT designation if:

> "The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
>
> The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
>
> Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition."[80]

Under Section 3033 of the Act, the FDA must first determine whether an Investigational New Drug qualifies for accelerated approval within 60 days after the request for designation.[81] The second potential step after qualifying for accelerated approval is a study to confirm the status of the drugs. [82] Confirmatory studies are designed to "verify and describe the anticipated effects of their products on

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[79] *Id.*

[80] *Regenerative Medicine Advanced Therapy Designation*, U.S. FOOD & DRUG ADMIN. (Oct. 11, 2019), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation; 21st Century Cures Act § 3033, *supra* note 78.

[81] *See* Michelle L. Butler & James E. Valentine, *The President Signs 21st Century Cures into Law; Highlights of Drug and Biologic Related Provisions (Part One)*, FDA L. BLOG (Dec. 13, 2016), http://www.fdalawblog.net/fdalaw_blog_hyman_phelps/2016/12/the-president-signs-21st-century-cures-into-law-highlights-of-drug-and-biologic-related-provisions-p.html; 21st Century Cures Act § 3033 (Westlaw through Pub. L. No. 114-255) (2016).

[82] *See* 21st Century Cures Act § 3033, *supra* note 78.

irreversible morbidity and mortality or other clinical benefit"[83] and may be satisfied in various ways.[84]

Then director of the FDA, Mark Gottlieb, M.D., clarified that the third requirement for RMAT approval "requires preliminary clinical evidence of a substantial improvement over existing therapies."[85] Proponents of stem cell therapies may showcase preliminary studies that demonstrate promising effects or substantial improvement over existing therapies, even if only in the early stages of clinical trials. Critics may point out the propensity for adverse events from the premature therapies. The FDA could not respond to the *Alliance*'s arguments with significant deregulation of the drug approval process across the board. The selective path for RMAT designation, meeting the conditions stated above, may provide an avenue to address the concerns of the terminally ill who demand the right to try experimental treatments.

The FDA and other public health policy facilitators must carefully balance between aiding terminally ill patients in gaining access to treatments that have yet to be proven safe and effective and undoubtedly exposing a much larger group of people to such treatments. Additionally, allowing people to metaphorically *cut the line* and bypass regulation without proper testing may conflict with the intended purpose of determining efficacy and risk. "Why risk getting a placebo in a trial when you can get the actual drug under the law?"[86]

Many people who successfully gain access to the right to try an unproven therapy are not doing so through an active clinical trial, either for lack of qualification or they do not have time to wait for the

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[83] U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS: GUIDANCE FOR INDUSTRY (2019); *see* 21 C.F.R. § 601.41.

[84] *Id.* at 10 (These studies may be satisfied with any of the following:" [1] The submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence such as electronic health records; [2] The collection of larger confirmatory data sets as agreed upon during product development; or [3] Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.").

[85] Peter Marks & Scott Gottlieb, *Balancing Safety and Innovation for Cell-Based Regenerative Medicine*, 378 NEW ENG. J. MED. 954, 954–59 (2018).

[86] Todd Ackerman, *Texas Poised to Pass Right-to-Try Legislation*, HOUS. CHRON.: HEALTH (May 9, 2015), https://www.houstonchronicle.com/news/health/article/Texas-poised-to-pass-right-to-try-legislation-6253623.php.

treatments to start.[87] Since these aforementioned individuals are removed from the formal clinical trial experience, they are not monitored nor are indicators of safety and efficacy collected and relayed to the appropriate entities with the same level of rigidity as they are in a traditional clinical trial.[88] Although people, many of whom may be terminally ill and out of options, are getting access to new drugs, there may be no collective benefit beyond their individual use.

The Right-to-Try Movement embodies the concerns of desperate stem cell therapy seekers. Some life-threatening conditions are the subject of clinical stem cell trials, and for these trials, there is justification for the need to expedite the approval process.[89] However, some people may seek stem cell therapy for debilitating, yet non-life-threatening conditions, such as chronic or neuropathic pain.[90] The second requirement for RMAT designation is that the condition addresses *life-threatening or serious conditions*.[91] Chronic pain is a serious condition, and one could argue that it is life-threatening, particularly in the context of the death-rate statistics of the opioid epidemic.[92] Some people would rather cure the source of the problem, which stem cell therapy purports to be able to accomplish, rather than merely numb the problem with medication. Stem cell therapy also has a more *natural* connotation and may appeal to people who want an alternative approach.

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[87] *C.f. Learn About Clinical Trials*, NIH U.S. NAT'L LIBR. MED., https://clinicaltrials.gov/ct2/about-studies/learn (last visited Jan. 8, 2021, 9:34 AM) (describing how exclusion criteria include, but are not limited to, "age, gender, the type and stage of a disease, previous treatment history, and other medical conditions").

[88] 21 C.F.R § 312.32 (2010); *see also* EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS: GUIDANCE FOR INDUSTRY, *supra* note 83, at 11 ("To help facilitate the development of data to demonstrate the safety and effectiveness of these products, CBER will work with sponsors and encourage flexibility in clinical trial design.").

[89] For example, these patients have no other viable options, and any treatment feels better than no treatment.

[90] Krishnan Chakravarthy et al., *Stem Cell Therapy for Chronic Pain Management: Review of Uses, Advances, and Adverse Effects*, 20 PAIN PHYSICIAN 293, 294 (2017); *See generally* E Russell Vickers et al., *A Preliminary Report on Stem Cell Therapy for Neuropathic Pain in Humans*, 7 J. PAIN RES. 255 (studying the effects of adipose-derived stem cells on patients experiencing diagnosed neuropathic pain).

[91] *Regenerative Medicine Advanced Therapy Designation*, *supra* note 80.

[92] The argument for why chronic pain is life-threatening is exemplified by the chain of events that lead to individuals succumbing to opioid addiction and overdose-related deaths.

In contrast to health-oriented treatments, some companies advertise stem cell therapies for cosmetic and full body healing.[93] The general public is naive as to the outlandishness of this claim and is thus easily manipulatable.[94] The FDA can attempt to limit commercial speech by requiring warnings about how the therapy is not FDA approved,[95] but there is likely to be a First Amendment push-back from anything more forceful.[96] Nonetheless, First Amendment rights have limits. When a treatment falls under the FDA's jurisdictions, the descriptions must be objective, truthful, and have appropriate warnings.[97] Such regulations benefit consumer's ability to wade through the assortment of health advertising and information.

The Cures Act reflected just one of the significant shifts in the regulatory scheme. In the year leading up to the passage to the Cures Act, Senator Mark Kirk introduced the Reliable and Effective Growth for Regenerative Health Options that Improve Wellness (REGROW) Act, which would have allowed for conditional approval for cellular and tissue therapies.[98] The Act, although unsuccessful, proposed conditional approval "if the sponsor of such [a] product demonstrates preliminary clinical evidence of safety, and a reasonable expectation of effectiveness, without initiation of phase III investigations."[99] Moreover, the regulatory wheels of change continued to turn.

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[93] Murdoch et al., *supra* note 31, at 5 (Table 3: '"Thai Regen offers stem cell therapy and other medical and holistic healing treatments in Thailand (Bangkok and Chiang Mai) for the prevention and treatment of degenerative disease as well as for anti-aging and body rejuvenation. '(http://www.thairegen.com/)").

[94] *Cf.* Murdoch et al., *supra* note 31, at 2 ('"Scienceploitation 'occurs when popular scientific ideas, such as stem cells, are used to take advantage of the social capital associated with them and induce consumer interest in products or services. It is a potentially harmful practice that can mislead the public and damage public trust in legitimate science.").

[95] This scenario is regarding advertising for services, but practitioners may be required to mention for purposes of informed consent whether a therapy is FDA approved.

[96] *See* Cent. Hudson Gas Elec. v. Pub. Serv. Comm'n of New York, 447 U.S. 557, 561 (1980) (". . . the First Amendment protects commercial speech from unwarranted governmental regulation." (citing Va. Pharmacy Bd. v. Va. Citizens Consumer Council, 425 U.S. 748, 761-62 (1976))); U.S. CONST. amend. I.

[97] *See* 21 C.F.R. § 202.1(e)(1) (noting that "advertisements…shall present a true statement of information in brief summary relating to side effects, contraindications…and effectiveness").

[98] *See* Reliable and Effective Growth for Regenerative Health Options that Improve Wellness (REGROW) Act, S. 2689, 114th Cong. (2016) (as introduced in Senate Mar. 16, 2016).

[99] *Id.* § 351B.

The Federal Right-To-Try Act of 2017, which was enacted on May 30, 2018, is a permissive framework for manufacturers to expand access to experimental drugs.[100] Eligibility under the Act hinges on (1) having a "life-threatening disease or condition"[101], (2) exhausting "approved treatment options…[and being] unable to participate in a clinical trial involving the eligible investigational drug",[102] and (3) providing "written informed consent."[103]

For an investigational drug to qualify under the Federal Right-to-Try Act, it must meet the following requirements: (1) complete phase I of a clinical trial,[104] (2) may not already be FDA approved for another use,[105] (3) either have a pending marketing application with the FDA or be the focus of an active Investigational New Drug ,[106] and (4) must be undergoing active development.[107] Lastly, the Act requires drug manufacturers and the FDA to report their usage of these provisions annually.[108]

The FDA seeks to provide both consumer protection and access in a manner that remains fair to drug manufacturers. No matter how carefully the FDA lays out and enforces its policies, "desperate patients and willing physicians seek access that can entirely circumvent regulatory oversight"[109] and may seek treatments outside the United States where the regulatory laws are likely significantly relaxed. The

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100 Zaich, *supra* note 33, at 377 (citing Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372, 1372 (2018)).

101 *Id.* at 353 (citing 21 U.S.C. § 360bbb-0a(a)(1)(A)); *see also* 21 C.F.R. §§ 312.81(a)(1-2) (2018)) (defining "life-threatening" as "where the likelihood of death is high unless the course of the disease is interrupted" or where there is the potential for fatal outcomes). The codified standard described is a relaxed standard as compared to "immediately life threatening."

102 Zaich, *supra* note 33, at 377 (citing 21 U.S.C. § 360bbb-0a(a)(1)(B) (2018)).

103 *Id.* (citing 21 U.S.C. § 360bbb-0a(a)(1)(C)); *see also* 21 C.F.R. § 50.25 (describing the basic elements of informed consent).

104 Zaich, *supra* note 33, at 378 (citing 21 U.S.C. § 360bbb-0a(a)(2)(A)).

105 *Id.* (citing 21 U.S.C. § 360bbb-0a(a)(2)(B)).

106 *Id.* (citing 21 U.S.C. § 360bbb-0a(a)(2)(C)).

107 *Id.* (citing 21 U.S.C. § 360bbb-0a(a)(2)(D) (2018)); *see also* 21 C.F.R. § 312.42(a) (clarifying that "[a] clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation.").

108 Zaich, *supra* note 33, at 379 (citing 21 U.S.C. §§ 360bbb-0a(d)(1-2)).

109 Christine Coughlin et al., *Regenerative Medicine and the Right to Try*, 18 WAKE FOREST J. BUS. & INTELL. PROP. L. 590, 632 (2018).

more aggressively the FDA pushes, the greater the incentive for providers and patients to relocate abroad. This result not only cloaks adverse events from the public eye and from FDA oversight but also removes valuable patients from clinical studies in the United States, in which they could eventually help quantify the therapeutic benefits of stem cell therapies. Policies that incentivize stem cell tourism may have the gravest consequences for patient protection and access.

Understandably, there are compelling arguments for the right to try stem cell therapy. There is a great need for clinical trials, and patients demanding the right to try treatments offer a solution, albeit not without ethical concerns.[110] Greater attention towards stem cell clinical trials could drive more funding to clarify the Investigational New Drug applications that are worthy of FDA approval.

Another barrier to access to experimental treatments, even those abroad, is the cost. Cost makes access primarily only available for the extremely wealthy due to the high price tag.[111] This high cost creates a serious risk for fraud and predation on desperate populations. If the approval process is rushed before there is compelling and satisfactory evidence of safety, these treatments may have unanticipated and dangerous adverse effects that could expedite death and morbidity, and therefore backfire against the legitimacy and public trust in stem cell therapy.

## IV. FDA'S NEW COMPREHENSIVE REGULATORY APPROACH TOWARDS REGENERATIVE MEDICINE ADVANCED THERAPIES

In November 2017, the FDA released a statement about the new direction for its regulatory process, addressed concerns with its current model considering scientific advancements in medicine, and clarified its regulatory plan and timeline for enforcement.[112] The FDA

[110] Desperate, terminally ill patients may represent a population with a heightened ethical risk.

[111] Paul Knoepfler, *How Much Does Stem Cell Therapy Cost?*, THE NICH (Jan. 24, 2021, 7:37 PM), https://ipscell.com/how-much-does-stem-cell-therapy-cost-in-2021/.

[112] *See Statement*, *supra* note 4.

issued two draft documents[113] and two final documents,[114] which make up the new RMAT regulatory framework.

The "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" guidance document clarifies the requirements and provisions of therapies eligible for RMAT designation.[115] This designated seal will allow for fast-tracked approval, falling into one of five different categories:

> *Fast track designation*: for investigational new drugs aimed at treating a serious condition, which show support for the "potential to address an unmet medical need in patients with such condition";[116]
>
> *Breakthrough therapy designation*: for investigational new drugs aimed at treating a serious condition, "and for which preliminary clinical evidence indicates that the product may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints";[117]
>
> *RMAT designation*: therapies that satisfy the conditions for RMAT,[118]" intended to treat, modify, reverse, or cure a serious condition, and preliminary clinical evidence indicates

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113 U.S. FOOD & DRUG ADMIN., EVALUATION OF DEVICES USED WITH REGENERATIVE MEDICINE ADVANCED THERAPIES: GUIDANCE FOR INDUSTRY (2019); U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS: GUIDANCE FOR INDUSTRY (2019). Author is citing to the titles of the documents, not the substance within.

114 Same Surgical Procedure Exception: Questions and Answers Regarding the Scope of the Exception; Guidance for Industry; Availability, 82 Fed. Reg. 54289 (Nov. 17, 2017) (codified at 21 C.F.R. § 1271); Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, 82 Fed. Reg. 54290 (Nov. 17, 2017) (codified at 21 C.F.R. § 1271). Author is citing to the titles of the documents, not the substance within.

115 FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS 3 (2019), https://www.fda.gov/media/120267/download (defining "serious disease or condition" as "a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning… unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy."). *See also* 21 C.F.R. § 312.300(b).

116 *Id.* at 4.

117 *Id.* at 4–5.

118 *See* 21st Century Cures Act, *supra* note 78, at § 3033(8) (defining regenerative medicines as "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations.").

> that…[therapy] has the potential to address unmet medical needs for such condition.";[119]
>
> *Priority review designation*: therapies that treat "a serious condition, and…would provide a significant improvement in the safety or effectiveness of the treatment of the condition"[120]; and
>
> *Accelerated approval:* treatments and therapies aimed at diseases where the "course is long and an extended period of time would be required to measure the intended clinical benefit of a drug."[121]

These modifications are a direct response to Right-to-Try Movement outcry and pushback from researchers. However, these clarifications may have created loopholes which seemingly benefit stakeholders who prioritize profits over patients. In a November 2017 statement, Dr. Gottlieb, emphasized the "need to provide a clear, efficient pathway for product developers, while making sure that [we] meet our obligation to help ensure the safety and efficacy of these medical products so that patients can benefit from these novel therapies."[122]

Gottlieb mentioned that "clearly unscrupulous actors" have been taking advantage of the hyped attention directed at stem cell therapies; specifically, they are making deceptive claims, taking advantage of the "lack of consumer understanding," and threatening the legitimacy of future stem cell research and therapy.[123] Due to the large number of changes to the regulatory process, the FDA designated a 36-month grace period to allow interested stakeholders adequate time to prepare and comply with the new procedures.[124] However, the FDA has

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[119] EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS, *supra* note 83, at 5–6.

[120] *Id.* at 9.

[121] *Id.* at 9–11; *see also* 21 C.F.R. pt. 314, Subpart H; 21 C.F.R. pt. 601, Subpart E.

[122] *Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA's Comprehensive New Policy Approach to Facilitating the Development of Innovative Regenerative Medicine Products to Improve Human Health*, U.S. FOOD & DRUG ADMIN. (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-comprehensive-new-policy-approach-facilitating.

[123] *Id.*

[124] *FDA Announces Comprehensive Regenerative Medicine Policy Framework*, *supra* note 3 ("Under

warned that it will still crack down on the "clearly unscrupulous actors" who are creating safety risks.[125]

## V. ADDITIONAL SOURCES OF REGULATION FOR REGENERATIVE MEDICINE ADVANCED THERAPIES

Outside of FDA action, private parties can use the civil tort litigation system to hold unethical stem cell industry actors accountable.[126] Lawyers can represent injured consumers and groups of consumers in their own civil lawsuits to protect the public. Civil lawsuits have the potential to compensate injured plaintiffs, as well as to:

> …complement other approaches to reining in unsafe practices. . .intensify publicity and raise awareness of the harms of unproven treatments, set legal precedent, reshape the media narrative from one focused on the right to try or practice to one highlighting the need for adequate safety and efficacy standards, and encourage authorities to turn their attention to policy reform and enforcement.[127]

A study on regenerative medicine clarified how less restrictive laws that stifle regulatory power facilitate the creation of a large platform for stem cell therapies, further creating risk that may lead to civil litigation.[128] The study examined 19 different stem cell therapy civil actions under theories of "product liability, misrepresentation of fact, false advertising, lack of informed consent, and financial elder abuse."[129] For example, two suits were filed in Florida under a products liability theory, which have now been settled, arising from adipose tissue-derived stem cell injections for macular degeneration.[130]

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the new policy, in order to allow manufacturers of products time to comply with the requirements, for the first 36 months following issuance of the final guidance document the FDA intends to exercise enforcement discretion for certain products that are subject to the FDA's premarket review under the existing regulations but are not currently meeting these requirements.").

125 Horner et al., *supra* note 8.

126 *Id.* at 5.

127 *Id.* at 1.

128 *Cf. id.* at 1 ("In the absence of government oversight of private sector firms, patients and consumers may need to look elsewhere to protect their interests.").

129 Horner et al., *supra* note 8, at 1–2.

130 *Id.* at 2.

Another California case, voluntarily dismissed by the plaintiff, arose from adipose tissue-derived stem cell injections for cosmetic purposes: a "stem cell lift".[131]

It is interesting to note the relationship between the location of the suits, many of which were filed in California and Florida, and the intended purpose of the injections. Some therapies were targeted towards elderly concerns (Florida) and others were targeted towards more elective/cosmetic concerns (California).[132]

A major strength of civil litigation is that it garners public attention and encourages other injured people to come forward and seek compensation for damages.[133] The study authors contended that stem cell lawsuits may help move "the focus away from the patients' right to try and instead toward misconduct by providers, holding them accountable and highlighting the need for adequate safety and efficacy testing of experimental products."[134]

This proposed outcome, if true, could allow the FDA to limit its litigation focus on clearly unscrupulous actors, leaving private attorneys to target local actors under tort theories. This divide and conquer strategy may protect patients from harmful stem cell therapies without aggravating the Right-to-Try Movement, encouraging stem cell tourism, nor stifling legitimate stem cell research. With successful civil litigation eliminating one source of regulatory burden, the FDA could have better momentum to not only win injunction actions, but to change public perception about whether there is a right to access unproven therapies.

A major drawback of civil litigation is that most cases will never see a jury trial. With confidential settlement agreements, the general public might misunderstand case dismissals (like the one referred to above) against clinics as an indication that the claims are frivolous and without basis. Additionally, the financial upset to these clinics may result in cost shifting towards patients. Lastly, plaintiff litigation firms are incentivized to only take the cases with sizable damage amounts.

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131 *Id.*

132 *Id.* Author is drawing her own conclusions as to the associations between the states and the categories of injections in Table 1.

133 *Id.* at 4.

134 Horner et al., *supra* note 8, at 3.

An influx in civil litigation may still contribute to the unintended consequence of increased costs for unproven stem cell therapies. While this may seem to be an effective disincentive at first glance, the costs are shifted towards consumers, which would simply encourage stem cell tourism.

Another regulatory force outside of the FDA and civil litigation is from state medical boards imposing greater physician responsibility to inform patients seeking such therapies of the risks. State medical boards oversee medical licensing, and therefore may be in a unique position to enforce stem cell policies with physicians in ways that the FDA and private litigation cannot.[135] The U.S. Federation of State Medical Boards (FSMB) issued a report in 2018 with 11 recommendations regarding marketing unproven stem cell therapies.[136] Of those recommendations, the most notable are:

> 1. Where evidence is unavailable for a particular treatment in the form of clinical trials or case studies, physicians must only proceed with an appropriate rationale for the proposed treatment, and justification of its use, in relation to the patient's symptoms or condition. Novel, experimental, and unproven interventions should only be proposed when traditional or accepted proven treatment modalities have been exhausted…
>
> 4. State medical boards should review professional marketing materials and claims, including any office/clinic and/or doctor websites, and information publicly available about an office/clinic or licensee on online blogs or social media, as information sources in the investigation of complaints made against physicians…
>
> 7. Physicians must avoid any claims that may be deceptive or are intentionally or knowingly false or misleading, especially in terms of making promises about uncertain or unrealistic outcomes…[and]
>
> 9. Physicians should be prepared to support any claims made about benefits of treatments or devices with documented evidence, for example with studies published in peer-reviewed publications.[137]

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135 *See* Paul Knoepfler, *Too Much Carrot and Not Enough Stick in New Stem Cell Oversight Trends*, 23 CELL STEM CELL 18, 18–20 (2018).

136 FED'N OF STATE MED. BDS., *supra* note 9.

137 *Id.* at 10–11.

## VI. FDA'S ENFORCEMENT STRATEGY

The FDA is upholding its promise of going after clearly unscrupulous actors by issuing numerous warning letters to companies such as Stem Cell Inc.[138] and CryoStem.[139] These FDA warning letter recipients seem to be not only failing to abide by proper registration regulations but are also operating in ways that deceive the public and create serious safety risks for patients.[140]

In addition to warning letters, the FDA can send out other regulatory action letters to manufacturers of stem cell products, such as Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letters, Untitled Letters, Administrative License Action Letters, and Orders of Retention, Recall, Destruction, and Cessation of Manufacturing Related to Human Cell, Tissue, and Cellular and Tissue-Based Products (HCT/Ps).[141] NIDPOE letters serve as notice to a clinical investigator that the FDA is "initiating an administrative proceeding to determine whether the clinical investigator should be disqualified from receiving investigational products".[142] Untitled letters serve as initial correspondence for violations that do not rise to the level of severity or

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138 Letter from Karlton T. Watson, Program Div. Dir., Off. of Biological Prods. Operation - Div. II, U.S. Food and Drug Admin., to Peyman Taeidi, President/CEO, Stemcell Inc. (Aug. 28, 2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stemell-inc-579013-08282019 (complaining of their lack to properly register their product and for deviating from standard practices that would ensure the creation of a safe product).

139 Letter from Elizabeth A. Waltrip, Acting Program Div. Dir., Office of Biological Prods. Operation - Div. I, U.S. Food and Drug Admin., to John S. Arnone, Am. CryoStem Corp. (Jan. 3, 2018), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/american-cryostem-corporation-535041-01032018 (complaining that their use of the product is counter to its intent and that their delivery method poses serious risks to patients).

140 Warning letters put people and corporations on notice that the FDA has identified actions constituting violations of their policies. A warning letter does not necessarily mean that the FDA will bring forth an action against the recipient.

141 *See Enforcement Actions (CBER)*, U.S. FOOD & DRUG ADMIN. (Sept. 18, 2018), https://www.fda.gov/vaccines-blood-biologics/compliance-actions-biologics/enforcement-actions-cber#untitled.

142 *Id.*

proof as those found within warning letters.[143] Administrative License Action Letters provide notice of the revocation or suspension of a license of authority to "introduce or deliver for introduction, biological products into interstate commerce."[144] Lastly, Orders of Retention, Recall, Destruction, and Cessation of Manufacturing Related to Human Cell, Tissue, and Cellular and Tissue-Based Products (HCT/Ps) are sent when one of the following conditions are met:

> [1]There are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in this part and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against the risk of communicable disease transmission; or [2] The HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or [3] An establishment is in violation of the regulations in this part and, therefore does not provide adequate protections against the risks of communicable disease transmission.[145]

Some *clearly unscrupulous actors* are so violative as to provoke the FDA to file an injunction, while others only receive a warning letter; some are not targeted at all. The distinction as to which actors receive no attention, to a warning letter, or to an injunction is relevant for

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[143] *See id*. For examples of recent Untitled Letters sent to stem cell manufacturers, see also *FDA Sends Warning to Companies for Offering Unapproved Umbilical Cord Blood Products that May Put Patients at Risk*, U.S. FOOD & DRUG ADMIN. (Dec. 6, 2019), https://www.fda.gov/news-events/press-announcements/fda-sends-warning-companies-offering-unapproved-umbilical-cord-blood-products-may-put-patients-risk; Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Ctr. for Biologics Quality, U.S. Food & Drug Admin., to Dale Carrison, Med. Dir., Dynamic Stem Cell Therapy (Apr. 1, 2020), https://www.fda.gov/media/136668/download; Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Ctr. for Biologics Quality, U.S. Food & Drug Admin., to Duncan Ross, CEO, Kimera Labs, Inc., (Apr. 10, 2020), https://www.fda.gov/media/137129/download; Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Ctr. for Biologics Quality, U.S. Food & Drug Admin., to Henry N. Small, Hous. Stem Cell (Apr. 27, 2020), https://www.fda.gov/media/137716/download; Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Ctr. for Biologics Quality, U.S. Food & Drug Admin., to Giovanni Ramundo, Valeo M.D. (Apr. 28, 2020), https://www.fda.gov/media/138076/download; Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Ctr. for Biologics Quality, U.S. Food & Drug Admin., to Rebecca Rogers, Sparrow Health & Performance, LLC (May 11, 2020), https://www.fda.gov/media/137974/download.

[144] *See Enforcement Actions (CBER)*, *supra* note 141.

[145] *Id.*

understanding what sorts of deviations from policy will be tolerated under the new RMAT regulatory framework.

In May 2018, the FDA, on behalf of the U.S. Department of Justice, filed an action for permanent injunction against US Stem Cell Clinic LLC, US Stem Cell Inc., and its Chief Scientific Officer, Kristin Comella, Ph.D.[146] Following granting the FDA's motion for summary judgment against the clinics, the Southern District of Florida issued an injunction against the parties on June 25, 2019.[147]

The actions against Stem Cell Clinic LLC and US Stem Cell Inc. were in response to the clinics blinding three patients by injecting a fat extract into their eyes.[148] The FDA's Motion for Summary Judgment was granted on the legal theory that the Defendants adulterated and misbranded their stem cell products.[149] The FDA was required to demonstrate a "reasonable likelihood of further violations in the future" in order to win its claim for injunctive relief. [150] In deciding whether to grant an injunction, courts review "[1] whether a defendant's violation was isolated or part of a pattern, [2] whether the violation was flagrant and deliberate or merely technical in nature, and [3] whether the defendant's business will present opportunities to violate the law in the future."[151]

The federal Southern District of Florida Court was the first to grant an injunction under the initial stage of the FDA's comprehensive RMAT regulatory framework, and there are additional FDA targets for litigation.[152] The Court granted the FDA's injunctions on Summary

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146 *See* Order of Permanent Injunction, United States v. U.S. Stem Cell Clinic, LLC, 403 F. Supp. 3d 1279 (S.D. Fla. 2019) (No. 0:18-cv-61047-UU).

147 *Id.*

148 Denise Grady, *Judge Halts Treatments at Florida Stem Cell Clinic*, N.Y. TIMES (June 25, 2019), https://www.nytimes.com/2019/06/25/health/stem-cells-fda-injunction.html (explaining that the injunction was limited to the Defendants' procedures involving the fat extracts).

149 Order on Motions for Summary Judgment at 29-32, United States v. U.S. Stem Cell Clinic, LLC, 403 F. Supp. 3d 1279 (S.D. Fla. 2019) (No. 0:18-cv-61047-UU).

150 United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1325 (D.C. Cir. 2014).

151 *Id.* (quoting SEC v. First City Fin. Corp., 890 F.2d 1215, 1228, (D.C. Cir. 1989)); *see supra* note 149, at 31–32.

152 *FDA Seeks Permanent Injunctions Against Two Stem Cell Clinics*, U.S. FOOD & DRUG ADMIN. (May 10, 2018), https://www.fda.gov/news-events/press-announcements/fda-seeks-permanent-injunctions-against-two-stem-cell-clinics.

Judgement for misuse of the "same surgical procedure."[153] Perhaps the "same surgical procedure provision" was the clearest section on which to adjudicate, and was thus a reliable place to start. If the FDA swings too hard and strikes out, the agency will lose its credibility and ability to effectively protect patients and expand access. Stem cell companies would simply relocate abroad, and the FDA would have little to no ability to monitor and regulate the treatments provided.

*US v. Regenerative Sciences, LLC* was a civil enforcement case in which the D.C. Circuit Court of Appeals upheld an injunction against Regenerative Sciences and its physicians.[154] The primary question in the litigation was whether a mesenchymal stem cell product treated with an antibiotic product, which was applied solely to minimize the risk of contamination, should be classified as a medical procedure, and thus protected from FDA oversight, or a drug/biological device which would be subject to FDA oversight.[155] The procedure in question was an autologous cellular transplant, which means using a patient's own cells to treat a specified condition.[156]

The Court in *Regenerative Sciences* held that the appellants could not use the minimal manipulation exception, which is only granted for substances where the mixing process does not "alter the relevant biological characteristics."[157] There was sufficient evidence that the antibiotic substance added could alter mesenchymal stem cell differentiation.[158] The Court held that the clinic had misbranded their drug[159] because they did not meet the criteria to safely distribute the product.[160]

From here, the D.C. Circuit Court derived the rule regarding the government's evidentiary burden to enforce an injunction.[161] In addition to providing the current rule for the evidentiary burden for

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153 *Id.*

154 United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1317 (D.C. Cir. 2014).

155 *Id.* at 1318.

156 *See* Pivarnik, *supra* note 28, at 298–99 (citing 21 C.F.R. § 1271.3(a) (2013)).

157 Regenerative Scis., LLC, 741 F.3d at 1321.

158 *See id.* at 1321–22.

159 *Id.* at 1324 (A "mixture", as defined by the FDA, is considered to be a prescription drug).

160 *Id.* at 1325.

161 *Id.* at 1324.

government injunctions, the *Regenerative Sciences* case provides an excellent example of how the FDA, in 2014 prior to the new regulatory framework, was acting against violators of its rules. The District Court noted that:

> [The] FDA notified [appellants] that their Regenexx™ Procedure may be in violation of the [FDCA]. It then twice inspected [appellants'] laboratories and found a number of [current good manufacturing practice] violations. [Appellants] maintained that the FDA could not regulate their cell product and did not bring their processes into compliance with [current good manufacturing practice]. Although [appellants] agreed to stop using their Regenexx™ Procedure during the pendency of this lawsuit, there remains a "cognizable danger of recurrent violation.[162]

The Court of Appeals stressed how "these findings speak to the existence of each relevant factor.[163] The fact that the FDA found violations on two separate occasions and that appellants refused to take corrective action even after multiple FDA notices suggests a pattern of deliberate, even flagrant violations."[164] Nonetheless, the FDA took a big step in its enforcement decision because the autologous cellular transplant treatment was arguably a patient's own cells which were being classified as drugs.[165] The FDA justified its decision because the cells were "more than minimally manipulated,"[166] and the District Court agreed. With the momentum of a favorable court decision and a regenerative medicine policy in formulation, the FDA continued to send a warning to manufacturers unwilling to abide by their regulations.

The FDA's grace period originally extended to November 2020, and there is arguably a trend in the agency's approach to regulating

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162 *See* United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1325 (D.C. Cir. 2014).

163 *Id.*

164 *Id.*

165 *See* Pivarnik, *supra* note 28, at 299–300 (citing Mary Ann Chirba & Alice A. Noble, *Our Bodies, Our Cells: FDA Regulation of Autologous Adult Stem Cell Therapies*, BILL HEALTH (June 2, 2013), https://lawdigitalcommons.bc.edu/cgi/viewcontent.cgi?article=1598&context=lsfp (arguing that FDA must "get a firm handle on what kinds of techniques and treatments present tolerable levels of risk when balanced with . . . the basic right of patients to use their own cells")).

166 *See* 21 C.F.R. § 1271.10(a)(1); *cf. supra* note 150, at 1326.

RMATs.[167] The FDA took a rather cautious approach, leaving room for civil litigation and state medical boards to assist. The FDA's primary approach was to issue warning letters and sparing enforcement through injunction.[168] Based on their actions during the grace period, there is an indication of which actions are considered red flags for the FDA's categorization of *clearly unscrupulous actors*.

As of April 3rd, 2019, approximately halfway through the original three-year grace period, the FDA had issued 45 warning letters or regulatory correspondence to stem cell manufacturers or providers,[169] at least four of which were warning letters to stem cell companies.[170] At least four more warning letters were issued to stem cell companies between April 2019 and March 2020,[171] and at least six more warning letters were issued to stem cell companies between June 2020 and November 2020, all of which involved unapproved and misbranded products related to the Coronavirus Disease 2019 (COVID-19).[172] To

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[167] *See infra* section VI.

[168] Order on Motions for Summary Judgment, *supra* note 149.

[169] *Statement*, *supra* note 4.

[170] *Id.*; *see also Warning Letter StemGenex Biologic Laboratories, LLC*, U.S. FOOD & DRUG ADMIN. (Oct. 31, 2018), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stemgenex-biologic-laboratories-llc-557907-10312018; *Warning Letter Genetech, Inc.*, U.S. FOOD & DRUG ADMIN. (Nov. 29, 2018), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/genetech-inc-561808-11292018; *Warning Letter Cord for Life*, Inc., U.S. FOOD & DRUG ADMIN. (Mar. 29, 2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cord-life-inc-572770-03292019.

[171] *Supra* note 143*; see also Warning Letter Stratus BioSystems, LLC*, U.S. FOOD & DRUG ADMIN. (July 1, 2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stratus-biosystems-llc-581032-07012019; *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; *Warning Letter Invitrx Therapeutics Inc.*, U.S. FOOD & DRUG ADMIN. (Mar. 16, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/invitrx-therapeutics-inc-581182-03162020

[172] *See Warning Letter EUCYT Laboratories LLC*, U.S. FOOD & DRUG ADMIN. (June 4, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eucyt-laboratories-llc-607182-06042020; *Warning Letter 21st Century LaserMed Pain Institute d/b/a Create Wellness Clinics*, U.S. FOOD & DRUG ADMIN. (July 21, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/21st-century-lasermed-pain-institute-dba-create-wellness-

illustrate the violations that warrant issuance of a warning letter, the warning letter to Cord for Life, Inc. provided the following reasons for the scrutiny:

> Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)].
>
> Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)].
>
> Failure to establish and follow written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)].
>
> Failure to establish written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)].
>
> Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)].
>
> Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)].[173]

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clinics-607654-07212020; *Warning Letter PA Green Wellness LLC dba A Predictive Biotech Certied Facility*, U.S. FOOD & DRUG ADMIN. (Aug. 17, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/pa-green-wellness-llc-dba-predictive-biotech-certified-facility-608144-08172020; *Warning Letter Predictive Biotech*, U.S. FOOD & DRUG ADMIN. (Aug. 17, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/predictive-biotech-608322-08172020; *Warning Letter Lattice Biologics, Ltd.*, U.S. FOOD & DRUG ADMIN. (Aug. 27, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lattice-biologics-ltd-607852-08272020; *Warning Letter Vibrant Health Care, Inc.*, U.S. FOOD & DRUG ADMIN. (Nov. 18, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/vibrant-health-care-inc-608426-11182020.

[173] *Warning Letter Cord for Life, Inc.*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cord-life-inc-572770-03292019.

Warning letters alone are not going to counteract the *whack-a-mole game* of stem cell therapy regulation. Further, stem cell companies, researchers, and the public are likely to have a milder response to civil litigators taking out *bad actors* as opposed to broad sweeping regulation that hinders the entire field. A more precise approach that targets *bad actors* directly may be less likely to hurt companies who are genuinely trying to follow the rules or researchers who are acting with the interests of patients and scientific advancement over their pocketbooks. However, anybody with enough money can get stem cell therapy for any ailment, no matter how unproven. These individuals may need to go abroad,[174] but that option is always going to be available if there is disproportional regulatory scheme between the United States and other countries.

Another factor to consider in determining how stem cells should be regulated is that the therapies are expensive and not covered by insurance.[175] A potential positive consequence of insurance companies covering stem cell treatments in the future, once proven safe and effective, is that they could serve as an additional mechanism for monitoring and control. Approving coverage for stem cell therapy might limit fraud if insurance companies are watching over and ensuring that the treatments are for approved indications. This hypothetical outcome may create a scenario that would diminish some of the financial incentive if insurance companies will be negotiating pricing with providers. The United States may get to this point after stem cell research has advanced enough to prove itself to be safe and effective.

## VII. COMPARISON TO OTHER REGULATORY SYSTEMS

Stem cell therapies are available around the world. Regulatory approaches for these novel therapies vary by country. Four examples

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[174] Bryn Nelson, *Stem Cell Researchers Face Down Stem Cell Tourism*, NATURE REP. STEM CELLS (June 5, 2008), https://www.nature.com/articles/stemcells.2008.89.

[175] *What is the Average Cost of Stem Cell Therapy?*, BOS. STEM CELL CTR., https://www.bostonstemcell.com/what-is-the-average-cost-of-stem-cell-therapy/ (last visited Jan. 9, 2021) (stem cell therapy can range between $900 to $6,000 per treatment, based on factors such as the severity and duration of the patient's condition and the quantity of cells and injections needed. Further, insurance companies do not cover the costs of these treatments because of the associated risk level and its "experimental" status.).

of these various approaches are detailed below: Japan, Australia, Canada, and India.

## A. The Japanese Approach

In 2014, Japan launched its RMAT regulation framework, which created a "regenerative medicine products" designation with an expedited approval process.[176] Japan was a source of inspiration for a similar regulatory scheme in the US.[177] However, there is concern that the Japanese Health Ministry was focused on the "speed of bench-to-bedside translation and commercialization, potentially at the expense of rigorous oversight."[178] Their government is being scrutinized for its lax rules that allow for treatments with no proven efficacy to be sold to patients.[179] Japan inspired the United States' RMAT regulatory policy, and it appears that both countries are dealing with the same dilemma in regulating the stem cell industry. There are similar regulatory trends in other developed countries, such as Australia, Canada, and India.[180]

## B. The Australian Approach

The Australian equivalent to the FDA, the Therapeutic Goods Administration (TGA) issued new regulations on stem cell therapies to take effect on July 1st, 2019.[181] The new regulations will only apply to treatments offered outside of a hospital setting.[182] The TGA government website explains a major loophole with the new legislation: unproven stem cell therapies are still going to be available to patients as long as they are either provided in a hospital, as part of a clinical trial, or as "treatment in other settings where a doctor has

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176 Douglas Sipp & Hideyuki Okano, *Japan Strengthens Regenerative Medicine Oversight*, 22 CELL STEM CELL 153–56 (2018).

177 *See* Knoepfler, *supra* note 111, at 18–20.

178 *Id.*

179 Editorials, *Racing hearts,. Japan Must Show that a Promising Therapy for Damaged Hearts Works as Claimed*, 557 NATURE 611–12 (2018).

180 *See* Knoepfler, *supra* note 111, at 20.

181 AUSTRALIAN GOV. DEP'T OF HEALTH THERAPEUTIC GOODS ADMIN., *TGA Strengthens Regulation of Stem Cell Treatments*, https://www.tga.gov.au/tga-strengthens-regulation-stem-cell-treatments (last visited Jan. 8, 2021).

182 *Id.*

used a special access pathway for people who are very sick or for whom established treatment options are unsuitable."[183]

## C. The Canadian Approach

The Canadian equivalent to the FDA, the Biologics and Genetic Therapies Directorate, specifically the Center for Biologics Evaluation, oversees stem cell treatments.[184] In the Canadian system, products and therapies are eligible for less regulatory scrutiny if they either satisfy six criteria: (1) minimally manipulated, (2) allogenic, (3) homologous, (4) act locally, (5) singular therapeutic entity, and (6) are proven safe and effective[185] or "have an established safety profile and therapeutic use."[186] Unlike how the United States has eliminated some of the confusion, the Canadian system has created a regulatory loophole for stem cell products that are "autologous, minimally manipulated, …intended for homologous use, …and without a systemic or metabolic effect."[187] Products that are more than minimally manipulated or non-homologous are regulated as drugs, and the guidelines are statutorily defined.[188] This ambiguity has allowed stem cell therapy providers to offer products to the public without adequate oversight and regulation.[189]

In 1998, Canada established a "fast-track," similar to that of the RMAT designation under the FDA, for therapies "with promising clinical benefits to be available for patients with serious and life-threatening or debilitating diseases or conditions for which there are no drugs available in the Canadian market."[190] Priority review is

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183 *Id.*

184 Jolene Chisholm et al., *Current State of Health Canada Regulation for Cellular and Gene Therapy Products: Potential Cures on the Horizon*, 21 CYTOTHERAPY 686, 687–88 (2019).

185 *Id.* at 690 (Table 2).

186 *Id.* at 688.

187 *See id.* at 692.

188 *See* 21 C.F.R. § 1271.3(f) (2013) ("Minimal manipulation means (1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues").

189 *Id.*

190 Jolene Chisholm et al., *supra* note 184, at 693.

available if there is "substantial evidence of clinical effectiveness for diseases/conditions for which there is no treatment available, or, an indication of a significant improvement of the risk-benefit profile over currently available treatments."[191]

In 2012, Canada conditionally approved the stem cell therapy Prochymal (Remestemcel-L) aimed at children with acute graft-versus-host disease (aGVHD), an adverse condition that develops in bone marrow recipients.[192] This conditional approval has now been expanded beyond the scope of what has been approved for stem cell therapies in the United States: a treatment for Crohn's Disease.[193] Despite being initially progressive in its stem cell therapy developments, Canada is still burdened by the effects of stem cell tourism. Canada has implemented a relatively rigid regulatory system, which may incentivize citizens seeking unproven therapies to go abroad. These patients then return home with complex follow-up care needs and serious complications.[194]

## D. The Indian Approach

India presents an interesting example of the consequences of regulatory overcorrection. The Indian government imposed harsh restrictions on stem cell therapies and research, yet is still a popular hub for stem cell tourism.[195] The Indian equivalent to the FDA, the Central Drugs Standard Control Organization (CDSCO), most recently updated their *National Stem Cell Guidelines* in 2017.[196] The regulations became stricter by identifying the limited approved disease targets for stem cell applications.[197] The CDSCO emphasized that "stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven and any stem cell use in patients, other

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191 *Id.* at 693–94.

192 *Id.* at 694.

193 *Id.*

194 *Id.* at 695.

195 Shashank S. Tiwari & Pranav N. Desai, *Unproven Stem Cell Therapies in India: Regulatory Challenges and Proposed Paths Forward*, 23 CELL STEM CELL 649, 649 (2018).

196 *Id.* (Revised from 2007 and 2013 versions).

197 *Id.*

than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present." [198]

Unfortunately, the CDSCO does not have the same enforcement power as the FDA;[199] the CDSCO's guidelines are merely guidelines.[200] Where the United States has implemented a system for enforcement, India cannot. Players in the stem cell field are aware of the lack of consequences, and therefore can proceed with less caution or fear of ramifications. Although the FDA has power to enforce its regulations, there are limitations. Not all warning letters carry consequences and stop short at a mere warning, and the FDA has only succeeded on a couple of injunction actions. It is possible that stem cell actors in the US have a similar attitude as their Indian counterparts towards the ability of regulatory bodies to deliver on their threats.

Another complicating factor in India's regulatory structure is that there are multiple sources of authority: national guidelines, regulations for fraudulent advertisements, and regulations for clinical practices.[201] A bloated regulatory system may cause extreme confusion, redundancy, and lack of faith in the ability to manage such a promising field of medicine. Although India has remedies available in its statutory framework and criminal and civil law, Indian society is not as litigious as its American counterpart, and there is extreme deference to physicians.[202] India is still working on clarifying "minimal manipulation," just like the US, which is another source of a roadblock to effective regulation.[203]

## VIII. RMAT REGULATION DURING THE COVID-19 PANDEMIC

In the wake of the unprecedented COVID-19 global pandemic, the FDA created the Coronavirus Treatment Acceleration Program, which

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198 *Id.*

199 When the FDA can proceed with an injunction action against a company which egregiously fails to abide by its regulations, the guidelines of the CDOSCO carry no enforcement measure.

200 *C.f.* Tiwari & Desai, *supra* note 195, at 649 ("The other major problem is that the violations of these guidelines carry no legal ramifications.").

201 Tiwari & Desai, *supra* note 195, at 650–51 (details are broken down into a chart and diagram).

202 *See id.* at 651.

203 *See id.* at 652.

aims to get treatments to market as safely and quickly as possible.[204] Of the numerous COVID-19 treatments being studied, over 20 are characterized as gene or cellular therapies, the category encompassing RMATs.[205] As of July 31, 2020, over 270 trials were under review by the FDA, two drugs were approved for emergency use, and no treatments had been approved by the FDA for specific use as a COVID-19 treatment.[206] Some of the current stem cell-related COVID-19 trials published on clinicaltrials.gov as of early 2021 are:[207]

1. Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients[208]
2. Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19[209]
3. Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)[210]

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[204] *See Coronavirus Treatment Acceleration Program (CTAP)*, U.S. FOOD & DRUG ADMIN. (Aug. 7, 2020), https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap. *See also The Path Forward: Coronavirus Treatment Acceleration Program*, U.S. FOOD & DRUG ADMIN. (Apr. 20, 2020), https://www.fda.gov/news-events/fda-voices/path-forward-coronavirus-treatment-acceleration-program.

[205] *See Coronavirus Treatment Acceleration Program (CTAP)*, U.S. FOOD & DRUG ADMIN. (Aug. 7, 2020), https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.

[206] *See id*.

[207] For a complete list of stem cell therapies related to the treatment of COVID-19, see NAT'L INSTS. OF HEALTH. U.S. NAT'L LIBR. OF MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/results?cond=%22Coronavirus+Infections%22&term=stem&cntry=&state=&city=&dist=&Search=Search.

[208] *See Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients*, NAT'L INSTS. HEALTH. U.S. NAT'L LIBR. MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/show/NCT04437823?term=stem&cond=%22Coronavirus+Infections%22&draw=2&rank=1.

[209] *See Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19,* NAT'L INSTS. HEALTH. U.S. NAT'L LIBR. MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/show/NCT04299152?term=stem&cond=%22Coronavirus+Infections%22&draw=2&rank=2.

[210] *See Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19),* NAT'L INSTS. HEALTH. U.S. NAT'L LIBR. MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/show/NCT04346368?term=stem&cond=%22Coronavirus+Infections%22&draw=2&rank=3.

4. Study Evaluating the Safety and Efficacy of Autologous Non-Hematopoietic Peripheral Blood Stem Cells in COVID-19 (SENTAD-COVID)[211]
5. A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia[212]

On June 17, 2020, the FDA published a consumer alert regarding stem cell and exosome therapies.[213] In its warning, the FDA reiterated that the only FDA approved stem cell therapies are those which "consist of blood-forming stem cells (also known as hematopoietic progenitor cells) that are derived from umbilical cord blood. These products are approved for use in patients with disorders that affect the production of blood (i.e., the "hematopoietic" system) but they are not approved for other uses," reiterating that these therapies are not indicated for the treatment of COVID-19, orthopedic conditions, neurological disorders, cardiovascular or pulmonary diseases, nor "autism, macular degeneration, blindness, chronic pain, or fatigue."[214]

A peer-reviewed study published in June 2020 summarized the stem cell therapy clinical trials for COVID-19 patients to date.[215] The research acknowledged that mesenchymal stem cells, which are characterized as highly proliferative and are able to differentiate into many types of cells, may have the capacity to play a role in the immune system by the "modulation of proliferation, activation, and function of various immune cells…alter[ing] the innate and adoptive immune

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211 *See Study Evaluating the Safety and Efficacy of Autologous Non-Hematopoietic Peripheral Blood Stem Cells in COVID-19 (SENTAD-COVID),* NAT' INSTS. HEALTH. U.S. NAT'L LIBR. MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/show/NCT04473170?term=stem&cond=%22Coronavirus+Infections%22&draw=2&rank=4.

212 *See A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia,* NAT' INSTS. HEALTH. U.S. NAT'L LIBR. MED., *Clinicaltrials.gov*, https://clinicaltrials.gov/ct2/show/NCT04276987?term=stem&cond=%22Coronavirus+Infections%22&draw=2&rank=5.

213 *See Consumer Alert on Regenerative Medicine Products Including Stem Cells and Exosomes*, U.S. FOOD & DRUG ADMIN. (July 22, 2020), https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes.

214 *See id.*

215 Mahmood S. Choudhery & David T. Harris, *Stem Cell Therapy for COVID-19: Possibilities and Challenges*, 44 CELL BIOLOGY INT'L 2182, 2182 (2020).

responses."[216] It is this "immunomodularity" property that may make the mesenchymal stem cell therapies a hopeful option for COVID-19 patients, particularly those who are critically ill.[217] Another benefit proposed by the study authors is that mesenchymal stem cell treatments may be able to repair damaged lung tissue.[218] The study authors lament at the level of stringency the United States takes in its approach to regulating stem cell therapies for COVID-19. However, they acknowledge that in recent clinical trials "the treated groups were given stem cells in conjunction with conventional therapy and therefore it is questionable if the effect on patients is due to administered stem cells."[219] In a time of crisis, like that posed by the COVID-19 pandemic, it may be challenging to conduct a true randomized, controlled trial with a large enough sample size needed to gain public trust in using this novel therapeutic approach.

Peter W. Marks, M.D., Ph.D and Stephen Hahn, M.D., both with the FDA, published an article addressing the risks of unproven RMATs in the wake of the COVID-19 pandemic and acknowledged that the agency's priorities have shifted.[220] Drs. Marks and Hahn note that clinics are making unsupported claims as to stem cell therapy's safety and efficacy in response to the novel virus.[221] Just a month before its announcement to extend the regulatory deadline, the FDA made the stern claim that "[i]t is time for unproven and unapproved regenerative medicine products to be identified and recognized for what they frequently are: *uncontrolled experimental procedures at a cost to patients, both financially and physically*."[222] In the article's call to the public, Drs. Marks and Hahn plead with clinicians and patients who are taking advantage of experimental therapies available to report

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216 *Id.* at 2183.

217 *Id.*

218 *Id.* at 2187 (these initial findings appear to be supported by Chinese studies, not yet those ongoing in the United States).

219 *Id.* at 2189.

220 Peter W. Marks & Stephen Hahn, *Identifying the Risks of Unproven Regenerative Medicine Therapies*, 324 JAMA 241, 241 (2020).

221 *Id.* at E1.

222 *Id.* at E2 (emphasis added).

adverse events as a way to ensure that progress can be made in this emerging area of medicine. [223]

## IV. EXTENSION OF THE FDA'S THREE-YEAR GRACE PERIOD

On July 20, 2020, the FDA announced an extension of the its three-year grace period for compliance with its Comprehensive Regenerative Medicine Policy Framework by an additional six months, directly citing the challenges presented by the COVID-19 pandemic.[224] The last year of the grace period was overshadowed by the magnitude of the COVID-19 pandemic. Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER), stated that:

> [the FDA's] policy of enforcement discretion only pertains to certain human cell, tissue and cellular and tissue-based products that do not raise potential significant safety concerns or reported safety concerns. ..we intend to continue to take action against manufacturers and health care providers who are offering unapproved regenerative medicine products that have the potential to put patients at significant risk.[225]

With a new compliance deadline of May 31, 2021, and no definite end to the COVID-19 pandemic in sight, the FDA may choose to stay on its current path of enforcing its regulations against the bad actors providing products that pose a significant risk for the public. The FDA's regulatory framework was published under a different administration, and a dramatic shift in the political agenda may impact which approach the FDA takes after the grace period reaches completion.

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223 *Id.* at E1-E2.

224 *See FDA Extends Enforcement Discretion Policy for Certain Regenerative Medicine Products*, U.S. FOOD & DRUG ADMIN. (July 20, 2020), https://www.fda.gov/news-events/press-announcements/fda-extends-enforcement-discretion-policy-certain-regenerative-medicine-products.

225 *Id.*

## CONCLUSION: THE IDEAL BALANCE – A PREDICTION FOR THE FUTURE OF RMAT REGULATION

Public health law strives to achieve an ideal balance for protecting the public and private interests. How can the FDA manage the booming, innovative stem cell industry, while still providing enough leeway for the Right-to-Try Movement and legitimate stem cell researchers? How can the FDA uphold its credibility without exacerbating stem cell tourism nor discouraging the development of non-addictive pain management solutions? If the FDA continues its strategy of targeting *clearly unscrupulous actors* and sending warning letters to second-tier violators for the remainder of the grace period and beyond, State Medical Boards should monitor physician behavior and private tort litigation could discourage or subdue perpetrators whom the FDA is unable to effectively regulate. Additionally, patients who are able to get early access to treatments should be diligent in reporting positive and negative effects to the FDA.