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REFORMING REGENERATIVE MEDICINE REGULATION

Sarah Duranske*

INTRODUCTION

The gods were angry. Prometheus and his brother had endowed the creatures of the earth with gifts to help them survive and prosper: speed, cunning, strength. But, in error, Prometheus had overlooked man—a naked and weak creature that would surely perish unless gifted with something truly remarkable. So, Prometheus snuck onto Mount Olympus and stole fire from the gods. This gift he provided to man. But the gods disapproved—with fire, man could challenge their superiority. As punishment, Prometheus was chained to a rock. Each day, an eagle tore apart and devoured part of his liver. Each night, the liver regrew, ensuring that his torture would be unending.¹

Thus begins the story of regenerative medicine.

When humans are wounded, our bodies heal through a mixture of scar tissue formation and tissue regeneration.² We are familiar with scar tissue formation—special cells migrate to the site of the injury and produce proteins that support the tissue.³ But we have another wound-healing ability demonstrated by Prometheus—the ability of some cells to divide to produce more of themselves.⁴ In humans, the

* Thomas C. Grey Fellow and Lecturer at Law, Stanford Law School. I wish to thank Hank T. Greely, Michelle M. Mello, Norman Spaulding, W. Nicholson Price II, Yanbai Andrea Yang, Rebecca Wolitz, Alix Rogers, Ji Seon Song, and the participants of the 2017 Grey Fellows Forum for their invaluable comments.

1. Mark Cartwright, *Prometheus*, ANCIENT HIST. ENCYCLOPEDIA (Apr. 20, 2013), <https://www.ancient.eu/Prometheus/> [<https://perma.cc/KRM7-HX58>].

2. See Nat'l Insts. of Health, *Regenerative Medicine*, RES. PORTFOLIO ONLINE REPORTING TOOLS, [https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=62&key=R|\[num\]\]R](https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=62&key=R|[num]]R) [<https://perma.cc/A7BM-7SJW>] (last updated Oct. 2010) [hereinafter *NIH Fact Sheets: Regenerative Medicine*]; Univ. of Ill. at Chi., *Mechanism that Limits Scar Formation Discovered*, SCIENCE DAILY (June 11, 2010), <https://www.sciencedaily.com/releases/2010/06/100610154459.htm> [<https://perma.cc/5LXX-AQW9>].

3. Juan Diego Naranjo et al., *Regenerative Medicine: Lessons from Mother Nature*, 11 REGENERATIVE MED. 767, 768 (2016); Univ. of Ill. at Chi., *supra* note 2.

4. SCOTT F. GILBERT, DEVELOPMENTAL BIOLOGY, ch. 18 (6th ed., 2000) (ebook),

natural ability to regenerate tissue is limited. Only a few specific tissues such as bone marrow, liver, and the outer layer of skin demonstrate this ability.⁵

The ability to regenerate tissue is even more amazing in other species. The axolotl is a Mexican salamander known for its ability to regenerate lost limbs. The axolotl regenerates tissues in a way that humans cannot: the cells near the site of the injury lose their specialization and then morph into the cells needed to regrow the missing limb.⁶

The salamander's regenerative abilities inspired scientists. Could the same mechanism work in humans? In early experiments, scientists harvested stem cells from tissues in the human body and inserted the cells into an injury site.⁷ Because stem cells retain the ability to multiply (called "proliferation") and turn into different cell types (called "differentiation"), scientists hoped that the stem cells would cause the creation of new tissues. The results, however, were "disappointing at best."⁸ The interactions between stem cells, the microenvironment, the disease state, and dosing concerns stymied early efforts to create functional tissue.⁹

But early experiments have progressed into increasingly successful applications.¹⁰ Today, some regenerative medicine therapies are commercially available, with others at various stages in the research pipeline.¹¹ And the field is broader than just stem cell therapies. Regenerative medicine is defined as the branch of medicine that develops methods to regrow, repair, or replace damaged or diseased

<https://www.ncbi.nlm.nih.gov/books/NBK9971/> [<https://perma.cc/TX9T-NRD2>]; Naranjo, *supra* note 3, at 767.

5. Ricardo Londono & Stephen F. Badylak, *Biologic Scaffolds for Regenerative Medicine: Mechanisms of In vivo Remodeling*, 43 ANNALS OF BIOMEDICAL ENGINEERING 577, 582 (2014).

6. GILBERT, *supra* note 4; Naranjo, *supra* note 3, at 769.

7. ANGELO S. MAO & DAVID J. MOONEY, *Regenerative Medicine: Current Therapies and Future Directions*, 112 PNAS 14452, 14452 (2015), <http://www.pnas.org/content/112/47/14452> [<https://perma.cc/J6RC-2EHT>].

8. Naranjo, *supra* note 3, at 770.

9. *Id.*

10. *Id.*

11. MAO & MOONEY, *supra* note 7, at 14452; *NIH Fact Sheets: Regenerative Medicine*, *supra* note 2.

cells or tissues.¹² It includes a variety of approaches, such as transplanting cells to promote healing, editing genes in cells to attack cancer, and even building organs from biological materials.¹³

Regulating regenerative medicine therapies is no easy task. Finding a balance between competing interests—enabling timely access for needy patients while simultaneously ensuring a positive benefit/risk profile and promoting the development of beneficial innovations—is hard enough at any given point in time. But add in constantly advancing scientific knowledge and increasing commercialization opportunities, and the regulatory system struggles to keep pace.

As new potential therapies have emerged and challenged the existing regulatory structure, stakeholders have prodded Congress and the Food and Drug Administration (FDA) for reforms to make the pathway to the marketplace less rigorous.¹⁴ These efforts include enacted laws, such as a regenerative medicine provision in the 21st Century Cures Act, congressional bills that have been introduced but died, and policy whitepapers. But others oppose loosening the regulatory framework and argue that the current level of premarket testing for safety and efficacy is needed both to ensure public health and to advance the field of regenerative medicine by generating important clinical data.¹⁵ Still others advocate for a middle path that advances some therapies while protecting the public from the most egregious risks.¹⁶ I evaluate these reform proposals based on the dual goals of regulating medical products based on risk: protecting the public by limiting access to therapies where the risks outweigh the benefits, and promoting innovations that improve public health.

12. See *NIH Fact Sheets: Regenerative Medicine*, *supra* note 2.

13. Naranjo, *supra* note 3, at 772.

14. See Maude L. Cuchiara, Jackie K. Olive & Kirstin Matthews, *Regulating the Therapeutic Translation of Regenerative Medicine*, 15 *EXPERT OPINION ON BIOLOGICAL THERAPY* 1387, 1388 (2015), <http://www.tandfonline.com/doi/full/10.1517/14712598.2015.1064895> [<https://perma.cc/2C2X-VM3M>]; Robin Downey & Rose Geransar, *Stem Cell Research, Publics' and Stakeholder Views*, 16 *HEALTH L. REV.* 69, 69 (2008).

15. Dina Gould Halme & David A. Kessler, *FDA Regulation of Stem-Cell–Based Therapies*, 355 *NEW ENG. J. MED.* 1730, 1730 (2006).

16. Cuchiara, Olive & Matthews, *supra* note 14, at 1388–89.

I first argue that proposals to speed FDA approval through adaptive licensing are premature. These proposals, which differ in the details but share the same core features, would have the FDA approve regenerative medicine therapies based on less robust clinical evidence of safety and efficacy, but restrict the initial patient population and impose post-marketing obligations on the sponsor to gather evidence of the product's safety and efficacy in "real world" conditions. Although adaptive licensing's goals of accelerating access to therapies and generating real world evidence are sympathetic, the proposals are premature. Applying a theoretical framework of adaptive management that identifies appropriate conditions for iterative regulation highlights the fatal problem with adaptive licensing for regenerative medicine therapies: the risk of patient harm is too high. Existing evidence from other medical products approved under expedited pathways is instructive: it demonstrates that the third and final phase of clinical trials is vital to determine the safety and efficacy of a medical product, and that products approved under expedited pathways have more safety problems than those approved under the traditional process.

Second, I consider reform proposals for low and moderate-risk regenerative medicine therapies. Based on recent scientific literature, I argue that the current laws and regulations set an appropriate framework for the regulation of regenerative medicine therapies and support incremental reforms.

This current climate of reform creates an opportunity to analyze the success of the current regime in furthering the dual goals of medical product regulation: protecting public health and encouraging beneficial innovations. It invites us to consider whether other frameworks can better resolve the tension between the short-term goals of enabling access to therapies for needy patients with the longer-term goals of advancing society's understanding of the science and medicine of regenerative therapies.

Health law scholars writing on regenerative medicine have largely ignored the broader questions raised by the current reform climate and have focused instead on the legal and normative issues raised in a

2014 case regarding the authority of the FDA to regulate a subsection of therapies that use a patient's own cells as source materials.¹⁷ In that regard, this Article makes a unique contribution to the literature by using theories of risk regulation to evaluate the current structure and proposed reforms. In doing so, I seek to offer a considered and thorough legal and normative analysis of the existing regulatory framework and reform proposals that can meaningfully inform the policy debate.

This Article has four parts. Part I describes the regenerative medicine industry and the existing federal regulatory structure that governs regenerative medicine therapies. Part II addresses the need for regulation as well as the critiques of the current framework. Part III analyzes proposals for progressive licensing of higher-risk regenerative medicine therapies regulated as biologics. Part IV evaluates reforms for regenerative medicine therapies regulated as human cell and tissue products.

I. Regulating Regenerative Medicine

Scores of regenerative medicine products using regular cells from the human body (called “somatic” cells) are commercially available, and hundreds of clinical trials are investigating stem cell therapies.¹⁸ Yet the fact that only one type of stem cell product has received FDA approval has motivated some industry representatives and patient advocates to call for reforms to speed regenerative medicine products to market. The existing multi-tiered regulatory structure, however, already allows for tailored regulation depending on a therapy's risk of harm, and such tailoring includes less burdensome pathways to

17. However, two important exceptions exist. *See generally* Barbara von Tigerstrom, *Revising the Regulation of Stem Cell Based Therapies: Critical Assessment of Potential Models*, 70 *FOOD & DRUG L.J.* 315 (2015) (examining exemptions from regulation in Australia and the European Union); *see also* Margaret Foster Riley, *Twenty-First-Century Technology with Twentieth-Century Baggage: FDA Regulation of Regenerative Medicine*, in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 455, 466 (I. Glenn Cohen & Holly F. Lynch, eds., 2015) (noting that altering the minimal manipulation and homologous use standards may speed access to regenerative medicine therapies).

18. MAO & MOONEY, *supra* note 7, at 14452; *see generally* *Clinicaltrials.gov*, U.S. NAT'L LIBRARY OF MED., <https://clinicaltrials.gov/> [<https://perma.cc/YC38-82HD>] (last visited Jan. 6, 2018) (providing “a database of privately and publicly funded clinical studies conducted around the world”).

market for lower-risk therapies. In this section, I describe the state of the regenerative medicine industry and the harms the therapies can cause. I then explain the current regulatory structure and its critiques.

A. *The State of the Industry*

Regenerative medicine therapies seek to harness the body's ability to heal itself. Stem cell therapies epitomize regenerative medicine therapies because of their potential to heal and to harm. The potential of stem cells to regrow, repair, or replace damaged or diseased cells, organs, or tissues motivated early researchers and continues to excite today.¹⁹ Thousands of stem cell trials have been completed, and many hundreds more are ongoing.²⁰ In these trials, investigators study how new combinations of stem cell products and delivery mechanisms affect a range of diseases and conditions.²¹ Yet, in spite of this progress, the FDA has approved only one type of stem cell product: hematopoietic (blood forming) stem cells from cord blood to reconstitute a patient's blood and immune system after myeloablative treatments like radiation.²²

19. Erin Allday, 'Super exciting' Results in Stem Cell Therapy Trial, SFGATE (Oct. 2, 2017, 9:09AM), <http://www.sfgate.com/health/article/Super-exciting-results-in-stem-cell-therapy-12245199.php> [<https://perma.cc/6YG3-7HA5>] (reporting on Asterias Biotherapeutics' Phase 1/2 clinical trial results which demonstrated that four out of six paralyzed patients receiving a stem-cell derived injection showed improvement in motor levels); *Asterias Announces Two Significant Developments for Spinal Cord Injury Program*, ASTERIAS BIOTHERAPEUTICS (Oct. 2, 2017), http://www.asteriasbiotherapeutics.com/inv_news_releasre_text.php?releaseid=2303887&date=October+02%2C+2017&title=Asterias+Announces+Two+Significant+Developments+for+Spinal+Cord+Injury+Program [<https://perma.cc/29N7-RT2T>].

20. See *Clinicaltrials.gov*, *supra* note 18 (searching the term "stem cell," limited to recruiting, enrolling, and active interventional (or clinical) trials returned 1,518 results, and the same search for completed trials returned 1,746 results).

21. One well-publicized trial transplanted autologous iPSC-derived retinal cells to treat age-related macular degeneration. Erin Kimbrel & Robert Lanza, *Pluripotent Stem Cells: The Last 10 Years*, 11 REGENERATIVE. MED. 831, 834–36 (2016). The transplant into the first patient went well, but the trial was suspended before transplant into the second patient because the sample was found to contain a genetic mutation that could increase the risk that the patient would develop cancer from the transplant. *Id.* Separately, a Phase 1 trial tested the safety and feasibility of human embryonic stem cell-derived cardiac progenitor cells embedded onto a patch. *Id.* The patch was then embedded into the heart during surgery. *Id.* This clinical trial was based on preclinical evidence that the cells engrafted and then differentiated into cardiac muscle cells in preclinical models. *Id.* Another trial is planned to study the safety and effectiveness of a drug delivery device implanted under the skin that releases human embryonic stem cell-derived pancreas cells to treat type I diabetes. *Id.*

22. The product Hemacord provides hematopoietic (blood-forming) stem cells from a donor's

Excitement over stem cells has also led to the exploitation of desperate patients. Stem cell clinics offer unproven and unregulated stem cell treatments to cure a variety of ailments, so long as a patient can pay the out-of-pocket costs. In a 2016 study, Professors Paul Knoepfler and Leigh Turner identified 351 businesses engaged in direct-to-consumer marketing of stem cell interventions at 570 clinics.²³ The majority of these businesses marketed autologous interventions, where the stem cells used for treatment came from the patients' own tissues.²⁴ The most common source for the autologous stem cells was adipose (fat) tissue, followed by bone marrow. Stem cell clinics promote their treatments for a variety of diseases and conditions, ranging from autism and Alzheimer's disease to sports injuries and cosmetic surgery.²⁵ The cost of treatment can range from \$5,000 to \$20,000.²⁶

Although stem cell-based therapies have garnered much attention, therapies that use other cell and tissue sources also fall under the rubric of regenerative medicine therapies.²⁷ Several products that use somatic cells or cell-derivatives are commercially available. For example, Carticel, an FDA-approved product to treat articular cartilage defects (injuries to the slick cartilage at knee joints and other joints), uses chondrocytes (the cell type in healthy cartilage) harvested from the patient's cartilage, expanded in a lab, and re-inserted at the site of injury.²⁸ The cosmetic product laViv uses

allogeneic cord blood to reconstitute the patient's blood and immune systems after myeloablative treatment (such as radiation). MAO & MOONEY, *supra* note 7, at 14452; *Approved Cellular and Gene Therapy Products*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProAppro/> [<https://perma.cc/DJ5H-FE44>] (last updated Sept. 20, 2017). Similar transplants occur using stem cells from a donor's own cord blood. See Kang-Hsi Wu et al., *Letter to the Editor: Autologous Cord Blood Transplantation in a Child with Stage 4 Neuroblastoma*, 48 BONE MARROW TRANSPLANTATION 317, 318 (2013).

23. Leigh Turner & Paul Knoepfler, *Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry*, 19 CELL STEM CELL 154, 154 (2016).

24. *Id.* at 155.

25. *Id.* at 155–56.

26. Usha Lee McFarling, *FDA Weighs Crackdown that Could Shut Hundreds of Stem Cell Clinics*, STAT (Sept. 9, 2016), <https://www.statnews.com/2016/09/09/stem-cell-fda-hearing/> [<https://perma.cc/E8GU-HHGW>].

27. MAO & MOONEY, *supra* note 7, at 14452.

28. *Id.*

autologous fibroblasts (the main cell found in connective tissue, sourced from the patient) to improve the appearance of nasolabial fold wrinkles in adults.²⁹ The product Apligraf uses human foreskin fibroblasts to create wound-healing grafts.³⁰

Rounding out the major types of regenerative medicine therapies are gene editing products and bioengineering products. The FDA approved the first gene therapy in the United States in August 2017.³¹ Kymriah, a cell-based CAR-T gene therapy from Novartis, is created from a patient's own T-cells.³² The patient's T-cells are collected and then genetically modified to include a new gene.³³ When the cells are infused back into the patient, the modified gene causes the cell to target and kill certain leukemia cells.³⁴ Other gene therapies remain in the research pipeline. A large number of gene editing trials modify the genes in T-cells to alter their susceptibility to autoimmune viruses, like HIV, or to enhance their ability to recognize and bind to diseased cells.³⁵

Researchers are also working to manufacture human tissue, even entire organs. Bioengineering, or tissue engineering, is the process of creating cell-based products for the structural repair of various tissue defects.³⁶ At the Wake Forest Institute for Regenerative Medicine, Dr. Anthony Atala has tested 3-D printing technology that has printed cartilage, bone, and muscle tissue that was then successfully implanted into rodents.³⁷ Dr. Laura Niklason has commenced a Phase

29. *Id.* at 14452–53.

30. *Id.*

31. Press Release, U.S. Food & Drug Admin., FDA Approval Brings First Gene Therapy to the United States (Aug. 30, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm> [<https://perma.cc/D6X2-CBHW>].

32. *In Historic First, FDA Approves Gene Therapy for Acute Lymphoblastic Leukemia*, MANAGED CARE (Aug. 30, 2017), <https://www.managedcaremag.com/news/historic-first-fda-approves-gene-therapy-acute-lymphoblastic-leukemia> [<https://perma.cc/68DZ-7TEH>].

33. *Id.*

34. *Id.*

35. Kuang-Yui Chen & Paul S. Knoepfler, *To CRISPR and Beyond: The Evolution of Genome Editing in Stem Cells*, 11 REGENERATIVE MED. 801, 809 (2016).

36. The Comm. for Advanced Therapies (CAT) & The CAT Sci. Secretariat, *Challenges with Advanced Therapy Medicinal Products and How to Meet Them, Perspectives*, 9 NATURE REV. 195, 196 (2010).

37. Mathew Shaer, *Need a New Organ? Surgeon Anthony Atala Sees a Future Where You Can*

3 clinical trial testing bioengineered blood vessels grown from human cells that are seeded into a biodegradable scaffold, and given nutrients and mechanical signals to coax them to grow into a new blood vessel.³⁸

B. Regulatory Framework

As the primary agency in the United States regulating medical products, the FDA is tasked with ensuring the safety and efficacy of regenerative medicine therapies. It regulates these therapies based on three goals: (1) to prevent the use of contaminated cells and tissues with the potential for transmitting infectious diseases including AIDS and hepatitis; (2) to prevent improper handling that might contaminate or damage cells and tissues; and (3) to ensure that clinical safety and effectiveness is demonstrated for cells and tissues that are highly processed, are used for atypical functions, are combined with non-tissue components, or are used for metabolic purposes.³⁹

Prior to 1997, federal regulation of cell and tissue products was fragmented. The FDA viewed organ and tissue transplants as simply part of the practice of medicine.⁴⁰ Because the FDA does not regulate the practice of medicine, but instead has jurisdiction over the tools used by doctors in the practice of medicine, it declined to assert authority over tissue transplants.⁴¹ But two trends started to blur the line between the practice of medicine and the FDA's jurisdiction: first, technological advances allowed for the storing, transporting,

Simply Print It Out, SMITHSONIAN MAG. (Dec. 2016), <http://www.smithsonianmag.com/innovation/miracle-maker-anthony-atala-winner-smithsonian-ingenuity-awards-2016-life-sciences-180961121/> [https://perma.cc/R4Y8-4EVV].

38. *37: Humacyte*, CNBC (June 7, 2016, 6:03 AM), <http://www.cnbc.com/2016/06/06/humacyte-2016-disruptor-50.html> [https://perma.cc/7GQM-2S63].

39. Martha A. Wells, *Overview of FDA Regulation of Human Cellular and Tissue-Based Products*, 52 FOOD & DRUG L.J. 401, 406 (1997).

40. Frank A. Duckworth, *Regulation of Human Tissues and Organs*, 46 FOOD DRUG COSMETIC L.J. 1, 12 (1991).

41. *Id.* But see Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 427–28 (2015) (arguing that, contrary to the conventional wisdom that states regulate medical practice while the federal government regulates medical products, the federal government does—and should—regulate medical practice when public health is affected).

and preserving of organs and tissues, which added new variables to transplant procedures; and second, the AIDS crisis heightened the consequences of communicable disease transmission.⁴²

Thus, in 1997, the FDA proposed its current approach to regulation for articles “containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”⁴³ The regulatory regime was designed to “improve the protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products.”⁴⁴ The FDA delineated three levels of regulation for human cell and tissue products based on the product’s risk-level: (1) products not subject to regulation; (2) products regulated as human cell, tissues, or cellular- or tissue-based products (“cell or tissue products”) under Section 361 of the Public Health Service Act (PHSA); and (3) products regulated as biological drugs under Section 351 of the PHSA.⁴⁵ The FDA’s current solution is therefore a three-tiered framework based on a therapy’s risks of communicable disease, safety, and effectiveness.⁴⁶ This section provides an overview of the framework from the lowest level of regulation to the highest.

1. *Same Surgical Procedure Exemption*

The lowest tier of regulation is no regulation. The FDA does not regulate cells and tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure.⁴⁷ The FDA reasoned that the communicable disease risks, as well as safety and effectiveness risks, from these procedures would be no different than those typically associated with surgery.⁴⁸

42. Duckworth, *supra* note 40.

43. 21 C.F.R. § 1271.3(d) (2017).

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

45. Wells, *supra* note 39, at 406.

46. *Id.* The current three-tiered system was introduced in 1997, with the final rule becoming effective in 2005. *Id.*

47. 21 C.F.R. § 1271.15(b) (2017).

48. 21 C.F.R. § 1271.3(d); U.S. FOOD & DRUG ADMIN., DOC. NO. 97N-0068, PROPOSED APPROACH

And, because surgery is part of the practice of medicine, and therefore generally regulated by the state and not the federal government, the FDA exempted these procedures from its rules.⁴⁹ For policy reasons, the FDA also excludes cells or tissues removed from a donor and immediately transferred to an intimate sexual partner.⁵⁰

Some articles are not covered in the FDA's human cell and tissue regulatory scheme because they are covered by other regulations.⁵¹ These include whole organs; minimally manipulated bone marrow; blood products such as whole blood, platelets, and plasma; and extracts such as human milk, collagen, and growth factors.⁵²

2. Section 361 Products

The FDA implemented an intermediate tier of regulation for cell or tissue products between 1997 and 2005. The thrust of the new rules was to address those products whose main risk to public health and safety was the transmission of communicable diseases. The rules were promulgated under the authority of section 361 of the PHSA, which provides jurisdiction for “regulations . . . necessary to prevent the introduction, transmission, or spread of communicable diseases”⁵³

Only those cell or tissue products that meet four criteria qualify as “section 361” products under this intermediate tier of regulation. First, the product can be no more than minimally manipulated.⁵⁴ This means that the product cannot be processed in a manner that alters

TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS 12 (1997) [hereinafter PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS].

49. See, e.g., Zettler, *supra* note 41, at 436–37, 482–93.

50. 21 C.F.R. § 1271.15(e); see also PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS, *supra* note 48, at 13.

51. 21 C.F.R. § 1271.3(d)(1–8).

52. *Id.*

53. 42 U.S.C. § 264(a) (2012).

54. James R. Ravitz, Naomi J. L. Halpern & Emily M. Leongini, *FDA Announces “New” Framework to Regulate Stem Cell Therapies and Regenerative Medicine*, LEXOLOGY (Sept. 8, 2017), <https://www.lexology.com/library/detail.aspx?g=bb78fe6e-1cdd-499a-907d-087ebb5fc28f> [<https://perma.cc/Q7N3-FX8Q>].

the cells' or tissues' relevant characteristics.⁵⁵ Second, the product must be intended for homologous use, which means that the cells or tissues must perform the same basic function in the recipient as in the donor.⁵⁶ Third, the product's manufacturer must not combine the cells or tissues with any other article except for "water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving or storage agent does not raise any new clinical safety concerns with respect to the [cell or tissue product]."⁵⁷ Fourth, the product must either (a) not have a systemic effect and not be dependent on the metabolic activity of living cells for its primary function, or (b) if it does have a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, it must be for autologous use, for allogeneic use in a close relative, or for reproductive use.⁵⁸

The obligations for establishments that manufacture section 361 products are relatively light compared to those for biologics manufacturers. The establishments must register with the FDA; follow procedures for testing, screening, and determining donor eligibility; and follow current Good Tissue Practices to prevent the introduction, transmission, or spread of communicable disease.⁵⁹

3. *Biologics/Drugs*

If a regenerative medicine product does not meet either the same surgical procedure exemption or the requirements of section 361, then the product is regulated as a biologic under section 351 of the Public Health Service Act.⁶⁰ Section 351 covers biological products,

55. U.S. FOOD & DRUG ADMIN., MINIMAL MANIPULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 2 (2014) [hereinafter FDA DRAFT GUIDANCE ON MINIMAL MANIPULATION].

56. U.S. FOOD & DRUG ADMIN., HOMOLOGOUS USE OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF (2015) [hereinafter FDA DRAFT GUIDANCE ON HOMOLOGOUS USE].

57. 21 C.F.R. § 1271.10(a)(3) (2004).

58. *Id.* § 1271.10.

59. *Id.* § 1271.1(a).

60. 42 U.S.C. § 262 (Supp. 2017). A limited number of cell or tissue products are regulated as medical devices, but because the majority of cell or tissue products are biologics or human cell or tissue

including blood-derived products and products containing cells or microorganisms.⁶¹ The FDA considers biological products a subset of drugs, so the FDA's drug regulations also apply to section 351 products.⁶² Thus, the term "drug" is used in this article to cover biologic products as well. If a biologic is licensed under section 351, it does not need to be separately licensed as a new drug.⁶³

Biological products must receive a license before they can be introduced into interstate commerce.⁶⁴ The biologics license application must demonstrate that the biological product is safe, pure, and potent, and that the facility in which it is manufactured meets standards designed to ensure the product's continued safety, purity, and potency.⁶⁵ Like a new drug application, a biologics license application usually requires data from preclinical or clinical trials.⁶⁶ In order to initiate a clinical trial, the biologic's sponsor must submit an Investigational New Drug application before proceeding with the clinical trial.⁶⁷

The clinical study definitions for biologics are identical to those for new drugs.⁶⁸ As such, biologics regulated under section 351 generally go through three phases of clinical trials unless they follow an expedited path. The typical path to approval starts with a small (twenty to eighty patients) phase 1 clinical trial designed to evaluate safety and the product's mechanism of action.⁶⁹ Phase 2 trials are

products, a thorough examination of the medical device scheme is outside the scope of this article.

61. *Id.*; U.S. FOOD & DRUG ADMIN., *Frequently Asked Questions About Therapeutic Biological Products*,

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm>. [<https://perma.cc/FP7B-EKLD>] (last updated July 7, 2015).

62. U.S. FOOD & DRUG ADMIN., *supra* note 61.

63. 42 U.S.C. § 262(j).

64. *Id.* § 262(a)(1).

65. *Id.* § 262(a)(2)(C)(i).

66. 21 C.F.R. § 601.2(a) (2016); U.S. FOOD & DRUG ADMIN., APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE (2017)

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf> [<https://perma.cc/J4QP-A89J>].

67. *See* U.S. FOOD & DRUG ADMIN., *supra* note 61.

68. 21 C.F.R. § 312.2(a) (2009) ("Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act [New Drugs] or to the licensing provisions of the Public Health Service Act.")

69. *Id.* § 312.21(a).

designed to evaluate the effectiveness of a drug and to determine common short-term side effects and risks.⁷⁰ Phase 2 studies usually involve no more than several hundred patients. Large-scale phase 3 studies gather sufficient data on the product's safety and efficacy to support extrapolating the results to the general population.⁷¹ In addition to the clinical data, a biologics license application also must contain a significant amount of information about the manufacturing process, operating procedures, and equipment used in the product's manufacture.⁷²

Approved biologics must adhere to current good manufacturing requirements.⁷³ These detailed and comprehensive requirements address many aspects of the manufacturing process, personnel qualifications, equipment validation, standard operating procedures, quality control processes, change and document controls, packaging and labeling, purchasing controls, acceptance activities, and record keeping.⁷⁴ The manufacturers are also required to notify the FDA of certain changes in manufacturing and of adverse events.⁷⁵

C. *A Lifecycle Approach*

The FDA approves a new drug or biologic for marketing based on the pretrial and clinical trial evidence submitted by the sponsor.⁷⁶ This traditional approval paradigm has two drastically distinct stages: pre-approval and post-approval.⁷⁷ Before a product is approved, the only patients who may access it are those in a clinical trial who have given informed consent.⁷⁸ But after the FDA approves a biologic, it

70. *Id.* § 312.21(b).

71. *Id.* § 312.21(c).

72. *Id.* § 601.2(a).

73. *Facts About the Current Good Manufacturing Practices (CGMPs)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm> [<https://perma.cc/S2LF-7YRV>] (last visited Oct. 6, 2017).

74. 21 C.F.R. §§ 211, 601, & 820 (2017).

75. *Id.* § 314.80 (2017) (reporting for drugs); *id.* § 600.80 (2010) (reporting for biologics); *id.* § 601.12 (2012) (reporting requirements).

76. Rebecca Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 366, 370 (2007).

77. Hans-Georg Eichler et al., *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 426, 426 (2012).

78. *Id.*

generally becomes widely available.⁷⁹ In the most common scenario, patients can access the biologic without any particular eligibility requirements, and may even obtain it for unapproved conditions through an off-label prescription.⁸⁰

This traditional approval paradigm has suffered extensive criticism, because relying on pre-market evidence alone fails to give an accurate picture of a medical product's risks and benefits.⁸¹ Clinical trials are designed with narrow and specific inclusion criteria, but post approval use includes patients with different risk factors such as age, medication use, and chronic conditions.⁸² Indications for use in clinical trials are specific and well-monitored, but indications for use in the marketplace can be off-label and untested in clinical trials.⁸³ And because clinical trials are relatively short, they can fail to reveal the long-term risks or effects of the product.⁸⁴

In response, Congress and the FDA have begun shifting towards a lifecycle approach to drug evaluation where risks and benefits are monitored throughout a drug's lifecycle, including after approval.⁸⁵ This approach is reflected in the FDA's programs that expedite approval of new drugs with an accompanying commitment from the sponsor to provide postmarket evidence of safety and effectiveness.

For regenerative medicine therapies, the 21st Century Cures Act created an accelerated approval pathway for "regenerative medicine advanced therapies" (RMAT).⁸⁶ To qualify as an RMAT, a therapy

79. *Id.*

80. *Id.*

81. Shannon Gibson & Trudo Lemmens, *Overcoming "Pre-market Syndrome,"* in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 269, 269 (I. Glenn Cohen & Holly F. Lynch, eds., 2015) [hereinafter *Overcoming Pre-market Syndrome*]; Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 *FOOD & DRUG L.J.* 295, 297 (2006) (discussing the shortcomings of premarket clinical trials).

82. U.S. FOOD & DRUG ADMIN., *STRUCTURED APPROACH TO BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING: DRAFT PDUFA V IMPLEMENTATION PLAN 9* (2013).

83. Margaret Foster Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine a Reality*, 70 *FOOD & DRUG L.J.* 289, 297 (2016).

84. Eisenberg, *supra* note 76, at 376.

85. *Overcoming Pre-market Syndrome*, *supra* note 81, at 269; Eisenberg, *supra* note 76, at 376; U.S. FOOD & DRUG ADMIN., *supra* note 82, at 9.

86. 21st Century Cures Act, sec. 3033, 130 Stat. 1101 (2016) (codified at 21 U.S.C. § 356).

must first meet the statutory definition of a regenerative medicine therapy, defined to include “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.”⁸⁷ Thus, foundationally, this section only addresses those products that are not regulated as section 361 products. The therapy must also be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition,⁸⁸ and be supported by “preliminary clinical evidence” that indicates that the therapy has the potential to address unmet medical needs for the disease or condition.⁸⁹ The FDA has begun implementing this provision and, as of July 2017, had approved four requests to qualify products under the section.⁹⁰

An RMAT is entitled to the same benefits for expedited development and review as drugs that receive Breakthrough Therapy designation are,⁹¹ including interactions with the FDA throughout the development process, advice to ensure that the development program for obtaining nonclinical and clinical data is efficient, and helping to ensure that clinical trial design is as efficient as practicable.⁹²

In addition, a therapy designated as an RMAT may be eligible for Priority Review and Accelerated Approval.⁹³ This means that an RMAT may receive approval based on surrogate or intermediate endpoints “reasonably likely to predict long-term clinical benefit,” or on data obtained from a “meaningful number of sites, including through expansion to additional sites.”⁹⁴

87. The Act does not cover section 361 products, but covers only those products otherwise regulated as a drug or biologic. 21 U.S.C. § 356(g)(8) (Supp. 2016).

88. 21 U.S.C. § 356(g)(2)(B).

89. *Id.* § 356(g)(2)(C).

90. Scott Gottlieb, *How FDA Plans to Help Consumers Capitalize on Advances in Science*, U.S. FOOD & DRUG ADMIN., FDA VOICE (July 7, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/> [https://perma.cc/2D6Y-X73Y].

91. 21 U.S.C. § 356(g)(1); *see id.* § 356(a)(3)(B).

92. *Id.* § 356(a)(3)(B).

93. *Id.* §§ 356(c), 356(g)(6)(B).

94. *Id.* §§ 356(c), 356(g)(6)(B).

The RMAT approval pathway is the same as the Accelerated Approval pathway for drugs in most regards, but the Accelerated Approval pathway does not contain the option of approval based on data from “a meaningful number of sites.”⁹⁵ This may reflect a liberalization of acceptable forms of scientific evidence based on the promise of research using electronic health records.⁹⁶

A second difference is that RMATs that are approved under the accelerated pathway are subject to postapproval requirements and may meet such obligations “as appropriate” by submitting clinical evidence, clinical studies, patient registries, or “other sources of real world evidence, such as electronic health records”; by collecting larger confirmatory data sets; or by monitoring patients treated with the therapy prior to its approval.⁹⁷ This is a larger category of postapproval options than is available under the Accelerated Approval pathway, where the sole postapproval requirement option is that the “sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.”⁹⁸

FDA officials have acknowledged both the benefits and limitations of using real world evidence. In a 2016 *New England Journal of Medicine* article authored by fifteen top FDA officials, the officials observed that the definition of “real world evidence” encompasses data from randomized trials conducted in a real-world setting, so viewing “real-world evidence” and “randomized trials” as mutually exclusive is incorrect.⁹⁹ But concerns about the quality of real world evidence, and the limitations of current analytical approaches, suggest limits to the value of such data.¹⁰⁰ The quality of real world

95. *Id.* § 356(g)(6)(B)(ii).

96. See Zachary Brennan, *Real World Evidence: FDA Commits to Advancing Its Use*, RAPS (Sept. 19, 2017), <http://www.raps.org/Regulatory-Focus/News/2017/09/19/28491/Real-World-Evidence-FDA-Commits-to-Advancing-its-Use/> [<https://perma.cc/K7FX-9KB9>] (describing FDA Commissioner Scott Gottlieb’s remarks to the National Academy of Sciences’ workshop on incentivizing providers to enter data into electronic medical records at the point of care).

97. 21 U.S.C. § 356(g)(7)(A–C).

98. *Id.* § 356(c)(2)(A).

99. Rachel E. Sherman et al., *Real-World Evidence—What Is It and What Can It Tell Us*, 357 *NEW ENG. J. MED.* 2293, 2293, 2295 (2016) (referencing the Salk field trial of the polio vaccine).

100. *Id.*

evidence may be less robust than that collected in randomized clinical trials because real world evidence is not subject to the same rigorous quality requirements, like the use of eligibility criteria, detailed case reporting forms, and intensive monitoring.¹⁰¹ Rather, its collection is often not for the purpose of supporting research, and is likely not optimized or organized for research purposes.¹⁰² Stakeholders are developing methods to incorporate real world evidence into research, and efforts are ongoing.¹⁰³ Current limitations, however, are particularly evident when real world evidence is intended to support the effectiveness of a product and the expected or observed effect is relatively small.¹⁰⁴

The RMAT approval pathway is only available to those products that meet the eligibility requirements by intending to treat serious or life-threatening diseases or conditions and filling an unmet medical need.¹⁰⁵ This reflects a policy judgment that patients with serious or life-threatening diseases without access to treatment should be permitted to trade certainty for earlier access.

II. *Defenses and Critiques of Existing Regulation*

Critics charge the FDA with over-regulating regenerative medicine therapies.¹⁰⁶ They point to patients with serious illnesses for whom a delay in product approval may prove fatal.¹⁰⁷ At the extreme, some stakeholders argue that regenerative medicine therapies, or at least significant subsets, should not be regulated at all. For example, in *U.S. v. Regenerative Sciences*, the defendant unsuccessfully argued to the District of Columbia Circuit Court that the regenerative medicine product at issue was not a drug, biological product, or tissue product, but rather the practice of medicine.¹⁰⁸ Because this case and its

101. *Id.* at 2293.

102. Sherman et al., *supra* note 99, at 2294.

103. *Id.*

104. *Id.* at 2295.

105. 21 U.S.C. § 356(g)(2)(B)–(C).

106. *See, e.g.*, Riley, *supra* note 17, at 465; *c.f.*, Margaret Hamburg, M.D. & Joshua M. Sharfstein, M.D., *The FDA as a Public Health Agency*, 360 NEW ENG. J. MED. 2493, 2493 (2009).

107. *See* Hamburg & Sharfstien, *supra* note 106, at 2493.

108. *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014).

implications have been thoroughly analyzed elsewhere,¹⁰⁹ I will not restate the issues, but the court was right to deny the defendant's argument, for both legal and normative reasons. Fundamentally, regulation of regenerative medicine therapies is important to protect the public health and to encourage data generation that advances scientific understanding of the field.

A. *Why Regulation is Important*

The goal of public health is to “fulfill . . . society’s interests in assuring the conditions in which people can be healthy.”¹¹⁰ As a public health agency, the FDA supports the goal of assuring healthy conditions not only by ensuring the safety, efficacy, and security of medical products like drugs, devices, and biologics, but also by “helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products.”¹¹¹

To ensure the safety, efficacy, and security of new products, the FDA seeks to reduce harms before they occur by acting as a gatekeeper to the marketplace for new biologics and drugs.¹¹² To do this, the FDA evaluates evidence of a product’s safety and efficacy submitted by the product sponsor, and balances the potential benefits that a therapy can provide with its potential harms.¹¹³ When

109. See, e.g., Mary Ann Chirba & Stephanie Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Intervention with the Practice of Medicine?*, 7 J. HEALTH & BIOMEDICAL L. 233, 253, 271 (2011); Greg Pivarnik, *Cells as Drugs? Regulating the Future of Medicine*, 40 AM. J. L. & MED. 298, 319 (2014); Barbara von Tigerstrom, *The Food and Drug Administration, Regenerative Sciences, and the Regulation of Autologous Stem Cell Therapies*, 66 FOOD & DRUG L.J. 479, 504 (2011).

110. Hamburg & Sharfstein, *supra* note 106, at 2493 (providing the Institute of Health’s definition of “public health”).

111. U.S. FOOD & DRUG ADMIN., *What We Do*, <https://www.fda.gov/aboutfda/whatwedo/> [<https://perma.cc/5C7J-5PGK>] (last updated Dec. 29, 2017).

112. See Sidney Shapiro & Robert L. Glicksman, RISK REGULATION AT RISK: RESTORING A PRAGMATIC APPROACH 6 (2003) (quoting John Applegate, *The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control*, 91 COLUM. L. REV. 261, 273 (1991)) (“Regulation based on risk permits regulatory action based on *ex ante* collective danger rather than *ex post* individual injury, and also operates preventively to avert injury to the public as a whole.”).

113. Hamburg & Sharfstein, *supra* note 106, at 2492.

determining whether to approve a product, the agency considers the severity of the targeted disease or condition, whether alternative treatments are available, and the level of knowledge about patient responses to the therapy.¹¹⁴

This gatekeeping function is vital for patient protection because a patient, by herself, has inadequate information to determine whether a drug or biologic is safe and effective even after receiving it.¹¹⁵ Although the patient can certainly identify whether she feels better or worse after receiving a drug or biologic intervention, factors other than the therapy may cause some or all of the change in her wellbeing.¹¹⁶ Because of this inability to judge the therapy even after experiencing it, the patient must rely on the expertise of her doctor both to determine her need for treatment and to choose the correct medical treatment.¹¹⁷ A dishonest doctor could exploit the patient's lack of information by recommending a product or treatment that is unnecessary, ineffective, harmful, or more expensive than other options.¹¹⁸ Regulations that reduce this information asymmetry by demanding that products demonstrate safety and effectiveness before entering the marketplace help protect patients against receiving unsafe or ineffective treatments.

The FDA's role in public health is not limited to approving or denying applications for premarket approval. It has another mission,

114. *Id.*

115. STEPHEN BREYER, REGULATION AND ITS REFORM 28 (1982); W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 MICH. L. REV. 421, 461–65 (2017); Michael R. Darby & Edi Karni, *Free Competition and the Optimal Amount of Fraud*, 16 J. L. & ECON. 67, 81 (1973) (introducing the concept of credence goods).

116. This is, of course, the reason that randomized, controlled trials remain the gold-standard in determining the safety and efficacy of new treatments. *See, e.g.*, Bonnie Sibbald & Martin Roland, *Understanding Controlled Trials: Why Are Randomised Trials Important?*, 316 BRIT. MED. J. 201, 201 (1998).

117. *See, e.g.*, Uwe Dulleck & Rudolf Kerschbamer, *On Doctors, Mechanics, and Computer Specialists: The Economics of Credence Goods*, 44 J. ECON. LIT. 5, 6 (2006).

118. Dulleck and Kerschbamer provide specific examples that demonstrate that information asymmetry matters in medical decision-making. A 1997 Swiss study reported that the average person's likelihood of receiving one of seven major surgeries was one-third greater than that of a physician or a physician's family member. *See id.* at 6 (citing Winand Emons, *Credence Goods and Fraudulent Experts*, 28 RAND J. ECON. 107 (1997)). A Federal Trade Commission study revealed the tendency of optometrists to prescribe unnecessary treatments. *See id.* at 6 (citing Asher Wolinsky, *Competition in a Market for Informed Experts' Services*, 24 RAND J. ECON. 380 (1993)).

to promote innovation that makes drugs and biologics safer, more effective, and more affordable.¹¹⁹ And it uses its gatekeeper requirements for this purpose as well. By requiring private firms to submit clinical trial evidence for premarket approval, the FDA incentivizes those firms to create valuable data on the risks and benefits of medical products.¹²⁰ This information is used not only to advise doctors and patients,¹²¹ but also to further scientific understanding of how the medical product acts within the human body.¹²² This understanding enhances biomedical knowledge, and researchers and firms can use it to increase the efficiency of research and development of new potential therapies.¹²³

Regenerative medicine therapies are appropriate subjects for pre-market regulation both to protect patients and to promote innovation. Harms from unsafe or ineffective regenerative medicine treatments can manifest as economic, physical, or opportunity cost harms. Additionally, data from clinical trials can advance the state of understanding of how regenerative medicines affect the human body.

1. *Economic Harms*

Economic harm occurs when a patient spends money on a therapy that does not provide the benefits promised by its marketing or advertising claims.¹²⁴ This was the underlying claim in a putative class action lawsuit against Stemgenex Medical Group, Inc., a stem cell clinic in southern California.¹²⁵ The five named plaintiffs

119. Eisenberg, *supra* note 76, at 370.

120. *Id.*

121. *See, e.g.*, Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 69 (D.D.C. 1998) (dismissed on appeal as moot) (upholding substantial government interest in ensuring that physicians receive accurate and unbiased information so that they make informed prescription choices); Eisenberg, *supra* note 76, at 374 (“The doctors who prescribe drugs are the principle targets of information dissemination by pharmaceutical firms, although in recent years pharmaceutical firms have increasingly advertised their products directly to patients.”).

122. Daria Kim, *Knowledge Sharing as a Social Dilemma in Pharmaceutical Innovation*, 71 FOOD & DRUG L.J. 673, 691–92 (2016).

123. *Id.*

124. *See, e.g.*, Dulleck & Kerschbamer, *supra* note 117, at 6.

125. Fourth Amended Complaint at 2, *Moorer v. Stemgenex Med. Grp., Inc.*, No. 3:16-cv-02816-AJB-NLS, 2017 WL 3992747 (S.D. Cal. May 18, 2017); *see also* Michael Hiltzik, *The Stem Cell Therapies Offered by this La Jolla Clinic Aren’t FDA Approved, May Not Work—and Cost \$15,000*,

suffered from various conditions, including lupus, diabetes, a “painful condition affecting [plaintiff’s] spine and joints,” and multiple sclerosis.¹²⁶ They alleged that, because of the stem cell clinic’s marketing claims, they spent \$14,900 per treatment on stem cell therapy that had no beneficial effect.¹²⁷ Similarly, a separate lawsuit against the Lung Institute, a Florida-based stem cell clinic, alleged that the clinic promised that its stem cell therapies would treat lung disease, charged the plaintiff \$7,500 for the initial treatment, and then blamed her for the treatment’s ineffectiveness because she could not afford monthly “reboost” shots costing an additional \$70 per month.¹²⁸ Instead of benefiting the patients’ wellbeing, these expensive treatments caused them economic harms.

2. *Physical Harms*

Even more troubling are the direct physical harms that patients may suffer from regenerative medicine therapies. Physical harms have occurred in both clinical trial settings and in unregulated stem cell clinics. Harms in some regenerative medicine trials have been well-publicized. For example, two patients’ deaths in a 2016 gene editing cancer treatment trial caused the FDA to halt the trial.¹²⁹

Unregulated treatments from stem cells clinics have also caused significant physical harms. Two separate lawsuits filed by patients against a Florida stem cell clinic alleged that the clinic directly injected a purported stem cell therapy into their eyes as treatment for macular degeneration.¹³⁰ As a result, the plaintiffs alleged that they

L.A. TIMES (Mar. 31, 2017, 1:50 PM), <http://www.latimes.com/business/hiltzik/la-fi-hiltzik-stemgenex-20170330-story.html> [<https://perma.cc/G2SU-2AB7>].

126. Fourth Amended Complaint, *supra* note 125, at 3–5.

127. *Id.* at 5. The Fourth Amended Complaint incorporates screen shots from StemGenex’s website that touts “stem cell therapy studies” for autoimmune diseases, diabetes, multiple sclerosis, and osteoarthritis and rheumatoid arthritis, among other conditions. *Id.* at 11–14.

128. Complaint at 4, *Rivero v. Lung Institute, LLC*, No. 45360019 (Fla. Cir. Ct. Aug. 14, 2016); *see also* Tony Marrero, *Unsatisfied Former Patient Files Class-Action Lawsuit Against Lung Institute*, TAMPA BAY TIMES (Aug. 26, 2016, 1:27 AM), <http://www.tampabay.com/news/courts/civil/unsatisfied-former-patient-files-class-action-lawsuit-against-lung/2290989> [<https://perma.cc/H3FM-R76S>].

129. Damian Garde & Meghana Keshavan, *Two Patient Deaths Halt Trial of Juno’s New Approach to Treating Cancer*, STAT (Nov. 23, 2016), <https://www.statnews.com/2016/11/23/juno-cancer-immunotherapy-deaths-2/> [<https://perma.cc/Y4LM-8RDW>].

130. Amended Complaint for Damages and Demand for Jury Trial at 1, *Bade v. Greenbaum*, No.:

suffered permanent damage, including blindness.¹³¹ Another patient, a sixty-six-year-old man who sought treatment for lingering effects from an ischemic stroke, received multiple stem cell injections, described as mesenchymal, embryonic, and fetal neural, at several clinics outside the United States.¹³² He developed a massive lesion growing around his spinal cord; a biopsy revealed that the cells were not from his body. He developed lower back pain, paraplegia, and urinary incontinence.¹³³ In another example, a boy who received fetal stem cell transplants at age nine developed abnormal growths in his brain and spinal cord.¹³⁴ Researchers discovered that the brain tumor contained cells from two or more donors, at least one of whom was female, suggesting that the stem cells caused the tumor.¹³⁵

3. Opportunity Cost Harms

Patients who receive regenerative medicine therapies may forego conventional treatment options that are more effective, less harmful, or less expensive. By choosing an inferior regenerative medicine therapy instead of a different, superior therapy, a patient suffers not only economic or physical harms wrought by the therapy, but also the lost value that she would have received from the superior therapy. It is hard to quantify this risk. In one sense, because many developing regenerative medicine therapies are intended to treat or mitigate the effects of diseases or conditions that have no current effective

2015-021463 CA 30 (Fla. Cir. Ct. July 19, 2016) [hereinafter *Bade Complaint*]; Complaint at 2, *Noble v. U.S. Stem Cell, Inc.*, No: CACE-15-021101 (04) (Fla. Cir. Ct. Nov. 30, 2015) [hereinafter *Noble Complaint*].

131. The *Bade* complaint specifically alleges that the plaintiffs suffered permanent blindness. *Bade Complaint*, *supra* note 130, at 1. The *Noble* complaint did not specifically allege this fact; both complaints listed identical damages. *See id.* at 11; *Noble Complaint*, *supra* note 130, at 16 (noting that alleged damages include “bodily injury; pain and suffering; disability; disfigurement; loss of the capacity for the enjoyment of life; aggravation of pre-existing conditions; medical and hospital care and expenses; loss of earnings; loss of earning capacity in the future; rehabilitation expenses; and mental distress”).

132. U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCES RELATING TO THE REGULATION OF HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS 106 (Sept. 12, 2016).

133. *Id.*

134. Ninette Amariglio et al., *Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient*, 6 PLOS MEDICINE 221, 223 (2009).

135. *Id.* at 255–26.

treatment, the potential for opportunity cost harms may be relatively small. But past experience demonstrates that opportunity cost harms are not merely theoretical, and will likely increase as additional regenerative medicine therapies become available.¹³⁶

History provides us with a compelling example of opportunity cost. Between 1985 and 1998, over 30,000 women in the United States with breast cancer received high-dose chemotherapy plus autologous bone marrow transplants instead of the standard-dose treatments for breast cancer.¹³⁷ Early observations of tumor shrinkage in the 1980s, followed by Phase 2 clinical trials reporting improved survival rates, excited researchers and patients.¹³⁸ Although the treatment was expensive at \$80,000,¹³⁹ and “very toxic,”¹⁴⁰ the combined forces of patients’ hopes, powerful lobbying efforts, oncology researchers, and media coverage drove the adoption of this novel therapy.¹⁴¹ But more critical inquiries in the early 1990s noted methodological shortcomings in the Phase 2 trials, particularly selection bias.¹⁴² As additional Phase 2 and Phase 3 trial results were published in the late 1990s that indicated high-dose chemotherapy plus autologous bone marrow transplants did not increase the patients’ survival rates, enthusiasm for the treatment plummeted.¹⁴³ But those patients who received the treatment forewent the opportunity to receive conventional breast cancer treatment that involved decidedly fewer side effects. Instead, these patients’ choice of the novel treatment exposed them to risks of acute-onset toxicities,

136. See Michelle M. Mello & Troyen A. Brennan, *The Controversy Over High-Dose Chemotherapy with Autologous Bone Marrow Transplant for Breast Cancer*, 20 HEALTH AFFAIRS 101, 101 (2001).

137. Daniel F. Hayes, *False Hope: Bone Marrow Transplantation for Breast Cancer*, 357 N. ENGL. J. MED. 1059, 1059 (2007) (book review); see also Mello & Brennan, *supra* note 136, at 110 (estimating that 42,680 autologous bone marrow transfers were performed on breast cancer patients between 1990 and 1999).

138. Mello & Brennan, *supra* note 136, at 103.

139. *Id.* at 102.

140. *Id.* (quoting Position Statement, Am. Soc’y of Clinical Oncology, High-Dose Chemotherapy with Bone Marrow Transplant for Breast Cancer Patients, (Mar. 2000) (on file with author)).

141. *Id.* at 106–07.

142. *Id.* at 103.

143. *Id.* For one significant study demonstrating no benefit, see S. Rodenhuis et al., *Randomised Trial of High-Dose Chemotherapy and Haemopoietic Progenitor-Cell Support in Operable Breast Cancer with Extensive Axillary Lymph-Node Involvement*, 352 LANCET 515 (1998).

such as sepsis and pulmonary failure, and, among others, leukemia, bone marrow insufficiency, psychosexual disorders, increased vulnerability to infection, and even death.¹⁴⁴

4. *Furthering Scientific Understanding*

Requiring clinical trials to demonstrate safety and efficacy can also further the field of regenerative medicine. Cells are extraordinarily complex, which makes predicting their behavior in a new environment challenging.¹⁴⁵ Clinical trial data can further the science of regenerative medicine. Publication of clinical trial results can “promote transparency in the clinical translation of stem cell-based therapies, . . . ensure development of clinically effective and competitive stem cell-based therapies, . . . prevent individuals in future clinical trials from being subjected to unnecessary risk, and . . . respect research subjects’ contribution.”¹⁴⁶ As former FDA officials cautioned, “[W]e must first understand [a regenerative medicine therapy’s] risks and benefits and develop therapeutic approaches based on sound science. Without a commitment to the principles of adequate evidence generation that have led to so much medical progress, we may never see stem-cell therapy reach its full potential.”¹⁴⁷

B. *Stakeholder Critiques*

At a public hearing in September 2016, the FDA solicited feedback from stakeholders on the regulation of regenerative medicine therapies.¹⁴⁸ Participants raised many specific issues, but two arose time and again: the regulation of allografts (tissue

144. Mello & Brennan, *supra* 136, at 110–11.

145. Peter W. Marks, Celia M. Witten & Robert M. Califf, *Clarifying Stem-Cell Therapy’s Benefits and Risks*, 376 NEW ENG. J. MED. 1007, 1008 (2017).

146. INT’L SOC’Y FOR STEM CELL RESEARCH, GUIDELINES FOR STEM CELL RESEARCH AND CLINICAL TRANSLATION 24 (2016).

147. Marks et al., *supra* note 145, at 1007.

148. See, e.g., Riley, *supra* note 17, at 458; *c.f.*, Hamburg & Sharfstein, *supra* note 106, at 2493 (stating that “the ultimate measures of the FDA’s success should reflect its fundamental goals and go beyond such intermediate measures as the number of facilities inspected or drugs approved”).

transplants from one person to another) and the regulation of unapproved stem cell therapies.¹⁴⁹ On both issues, some stakeholders argued for less robust regulation while others defended the existing structure and argued for stronger enforcement of the existing regulations.¹⁵⁰

Regulatory economist Bruce Yandle observed that interest groups are more powerful when two factions join together: the economically-motivated, and those providing a moral justification for the same regulatory policy.¹⁵¹ His colorful name for this theory, “Bootleggers and Baptists,” derives from two distinct groups’ support for a law that required liquor stores to close on Sundays. The Baptists supported the law for religious purposes, while the bootleggers supported the law because the absence of competition once a week increased demand for their product. The coalition of Baptists and bootleggers made it easier for politicians to favor both groups—they could present themselves as being motivated by the public interest, while benefitting from the financial support of the bootleggers.¹⁵² Scholars have observed the persuasive power of similar alliances across a number of regulatory settings.¹⁵³ The coalition of stakeholder interests in regenerative medicine provides another such example.

First, consider allografts. Some stakeholders advocated for a looser interpretation of the section 361 requirements so that their products would qualify as section 361 products and fall under the intermediate regulatory tier instead of the more stringent biologics tier.¹⁵⁴ But in

149. U.S. FOOD & DRUG ADMIN., CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, PART 15 HEARING: DRAFT GUIDANCES RELATING TO THE REGULATION OF HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS 29 (Sept. 12, 2016) [hereinafter CBER HCT/Ps Hearing, Sept. 12, 2016].

150. *Id.*

151. ADAM SMITH & BRUCE YANDLE, *BOOTLEGGERS & BAPTISTS: HOW ECONOMIC FORCES AND MORAL PERSUASION INTERACT TO SHAPE REGULATORY POLITICS* at viii (2014).

152. *Id.*

153. *Id.*; see also Jonathan H. Adler et al., *Baptists, Bootleggers & Electronic Cigarettes*, 33 *YALE J. ON REG.* 313 (2016).

154. See, e.g., CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 20–21 (statement of Pamela Vetter, director of regulatory policy at Allosource, a nonprofit cellular and tissue network, arguing for broader definitions of “original relevant characteristics” and “main function”); *id.* at 71 (statement of Dr. Justin Deurling, RTI Surgical, a manufacturer and distributor of HCT/Ps, arguing for a broader reading

response, an alliance of financial and moral interests defended the existing requirements for premarket approval. Representing financial interests were those firms that manufacture products subject to the highest tier of FDA regulation. For example, at the hearing, the company that makes Apligraf, an FDA-approved product, argued that competitive products should be required to obtain premarket approval.¹⁵⁵ Representing the moral interest were healthcare providers who warned the FDA that patients' health may be put at risk when allograft products are marketed without FDA approval because healthcare providers may unknowingly use an allograft that has not undergone the clinical trials required for FDA approval.¹⁵⁶ Dr. Scott James, a vascular surgeon at Beth Israel Deaconess Plymouth Hospital explained, "The patients that we see in our practice have devastating conditions and the consequences of using treatments that are not backed by rigorous science can be disastrous. Our patients deserve to know that the therapies we give them have been proven to be both safe and effective."¹⁵⁷

Similar alliances arose around unapproved stem cell treatments with Baptists and bootleggers on both sides. Stakeholders who claim that the FDA overregulates stem cells point to the FDA's approval of a single class of stem cell products as evidence that the FDA moves too slowly.¹⁵⁸ Industry representatives, who would benefit financially from lighter regulation, argued that autologous stem cell therapies should not be regulated, and raised concerns of federalism and patient autonomy.¹⁵⁹ Patients and their advocates lent moral credence

of "minimal manipulation" to cover certain sterilization and decellularization techniques).

155. *Id.* at 67.

156. *See, e.g.*, U.S. FOOD & DRUG ADMIN. CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, PART 15 HEARING: DRAFT GUIDANCES RELATING TO THE REGULATION OF HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS 96 (Sept. 13, 2016) [hereinafter CBER HCT/Ps Hearing, Sept. 13, 2016] (statement of Dr. Harold Brem, Surgeon and Professor of Surgery at Stony Brook University School of Medicine); *id.* at 132 (statement of Marie Louise Gehling, N.P.); *id.* at 181 (statement of Sheila Sabon DeCastro, N.P. at Mass General Hospital and a consulting director to the tissue program at Beth Israel Deaconess Hospital Plymouth).

157. *Id.* at 149.

158. Alexey Bersnenev, *Is FDA Slowing Down the Progress in Clinical Cell Therapy?*, STEM CELL ASSAYS (Nov. 27, 2011), <http://stemcellassays.com/2011/11/fda-slowing-progress-cell-therapy/> [https://perma.cc/8RFV-X774].

159. *See, e.g.*, CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 81–82 (statement of Kristin

to these claims. One patient suffering from rheumatoid arthritis obtained an unapproved adipose-derived treatment from a stem cell clinic in California and credited the treatment with her remission.¹⁶⁰ Another patient suffering from juvenile idiopathic arthritis credited an unapproved adipose-derived treatment with drastically improving her quality of life.¹⁶¹ Still another credited a similar treatment with alleviating her multiple sclerosis symptoms.¹⁶²

But other stakeholders argued for increased enforcement of existing regulations, and included health care providers and representatives of competing products regulated as biologics.¹⁶³ Not only do unapproved stem cell treatments lack scientific evidence of efficacy,¹⁶⁴ they argued, but patients also have insufficient information to understand the treatments¹⁶⁵ and may suffer physical harm.¹⁶⁶

Comella, U.S. Stem Cell); *id.* at 151 (statement of Dr. Elliott Lander, Cell Surgical Network); *id.* at 153 (statement of Michael Badowski, AdiCyte). A significant point, oft repeated, was the claim that the treatments offered by stem cells clinics are like surgery, and thus should be included in the same surgical procedure exception. *Id.* The second major argument was that of patient autonomy: “Patients have a right to provide informed consent decision about how they’re going to use these treatments themselves. They have a right to alternative therapies.” *Id.* at 85. Another similar argument was raised: “Why would the FDA regulate our own body tissue and consider this a drug?” *Id.* at 83.

160. See CBER HCT/Ps Hearing, Sept. 13, 2016, *supra* note 156, at 109–10 (statement of Georgianna Crocker).

161. See *id.* at 142–43 (statement of Sarah Hughes).

162. See *id.* at 168–70 (statement of Kristin Marr).

163. See, e.g., CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 44–45 (statement of Dr. Eric Daniels). Even these competing manufacturers couched their advocacy in publicly-interested terminology. Consider the statements of Dr. Eric Daniels, the chief medical officer of Kerastem Technologies, which sponsors a Phase 2 trial investigating the role of adipose and its derivative stromal vascular fraction for genetic alopecia. Dr. Daniels warned that after a decade and a half of cell therapies, “we still lack certainty around critical issues of identity, purity, and dose response.” *Id.* at 44–45. He continued, “Ad hoc manufacturing in an operating room, using unregulated systems and tools and/or processes, as well as negligent promotion will not help uncover and, more importantly, broadly disseminate the therapeutic potential—in this case of adipose-derived therapies. This will only come from a series of focused, well-designed, and controlled clinical trials.” *Id.*

164. See CBER HCT/Ps Hearing, Sept. 13, 2016, *supra* note 156, at 156 (Jeanne Loring, stem cell researcher at the Scripps Research Institute, stated, “Adipose cell therapy is governed by that overused axiom, if the only tool you have is a hammer, you will treat everything as if it is a nail. It isn’t logical or scientific to assume that all disorders can be treated with a single type of cell.”)

165. See CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 97 (statement of Dr. Steve Bauer, FDA, reviewing September 8, 2016, workshop of Scientific Evidence in development of HCT/P products that are subject to premarket approval). On the concern that stem cell clinics may untruthfully or confusingly allege that the therapies are part of a clinical trial subject to IRB approval, see Paul Knoepfler, *Does Stem Cell Clinic IRB Approval Mean Much? Insights from Blinding Cases*, NICHE (Mar. 23, 2017), <https://ipsell.com/2017/03/does-stem-cell-clinic-irb-approval-mean-much-insights->

The Bootleggers and Baptists theory suggests the use of financial incentives to sway a policymaker's support. And although it is nearly impossible to link financial contributions directly to policymaker action, it is worth noting that the regenerative medicine arena is subject to the same lobbying influences as many other areas. For example, MiMedx, a for-profit company that sells regenerative products created from amniotic tissue, received an untitled letter from the FDA in 2013 asserting that the company's product failed to receive the proper premarket approval. In 2016, MiMedx contributed ten thousand dollars to the campaign of the senator who introduced the REGROW Act, the reform bill discussed in the next section.¹⁶⁷

III. Reform of Section 351 Products

Building on the criticism that the FDA's regulation of regenerative medicine products is overinclusive and too slow, reform advocates have pushed for speedier FDA review in the form of adaptive licensing. Under this proposed framework the FDA would approve a product based on less-than-standard clinical evidence of efficacy and safety, and would restrict patient access to the product while the sponsor gathers postmarket evidence of the product's effect in a real world setting. Then, based on the evidence continuously gathered, the FDA could withdraw the product's initial approval, adjust marketing restrictions, or lift the restrictions altogether.¹⁶⁸

While adaptive licensing offers the benefits of early market access and the continued generation of evidence of a product's safety and effectiveness (or purity and potency), a closer analysis reveals

from-blinding-case/ [https://perma.cc/7SPV-XBUG].

166. CBER HCT/PS Hearing, Sept. 12, 2016, *supra* note 149, at 105–06.

167. Paul Knoepfler, *REGROW Act, Mark Kirk Lobbying & Contributions Yield Stem Cell Surprises*, NICHE (Nov. 3, 2016), <https://ipsell.com/2016/11/regrow-act-mark-kirk-lobbying-contributions-yield-stem-cell-surprises/> [https://perma.cc/6VNL-JLHC]; Candidate Information for Mark Kirk, FED. ELECTION COMM'N, https://classic.fec.gov/finance/disclosure/candcmte_info.shtml [https://perma.cc/RH3V-DKEM] (last visited Mar. 5, 2018) (searching “Mark Kirk” in the “partial name” field). Astellas Pharma, a Japanese pharma company involved in stem cell research, also made a contribution to Kirk's campaign. *Id.*

168. Shannon Gibson & Trudo Lemmens, *Niche Markets and Evidence Assessment in Transition: A Critical Review of Proposed Drug Reforms*, 22 MED. L. REV. 200, 208 (2014). This is called “adaptive licensing.” *Id.*

fundamental flaws. Not only would it require Congress to grant new authority to the FDA, but the risk of harm to patients and practical barriers to industry participation make such a framework unworkable and unwise. A structural overhaul of the premarket approval system would be expensive, and evidence suggests that regulatory science is not yet able to accurately predict when the potential benefits of early access outweigh the risks of harm.

This section outlines three proposals for adaptive licensing. By evaluating the proposals using a theory of adaptive regulation, I conclude that implementing an adaptive licensing scheme does not offer sufficient benefits to outweigh the risks and burdens.

A. Adaptive Licensing

Adaptive licensing reform proposals reached a zenith in the REGROW Act, which was introduced in 2015 but ultimately died without a vote.¹⁶⁹ It did, however, set the stage for the inclusion of RMAT provisions in the 21st Century Cures Act, which passed the following year.¹⁷⁰ The REGROW Act arose from the proposals that preceded it: Arnold Caplan co-authored the initial proposal, then served as an “expert panelist” with the Bipartisan Policy Center during its promulgation of the second proposal.¹⁷¹ Mark Kirk, the politician who introduced the third proposal, the REGROW Act, specifically credited the Bipartisan Policy Center report when he introduced his bill.¹⁷²

169. See S. 2689 – REGROW Act, CONGRESS.GOV, <https://www.congress.gov/bill/114th-congress/senate-bill/2689> [<https://perma.cc/FV4G-4QAE>] (last visited Jan. 14, 2018).

170. 21st Century Cures Act, sec. 3033, 130 Stat. 1101 (2016) (codified at 21 U.S.C. § 356).

171. Michael Eisenstein, *Regulation: Rewriting the Regenerative Rulebook*, 540 NATURE S65, S66 (2016) (“Caplan helped formulate the REGROW Act.”), <https://www.nature.com/articles/540S63a.pdf> [<https://perma.cc/KAD4-SR3T>].

172. Press Release, Office of Senator Mark Kirk, REGROW Act Accelerates New Therapies to Help Patients Living with Disease; Stem Cell Therapies Help Alzheimer’s, Parkinson’s, Sickle Cell Patients (Mar. 16, 2016) (on file with author); see also Cade Hildreth, Kirk, Manchin, Collins Introduce Bill to Speed Development of Regenerative Medicine, BIOINFORMANT (Mar. 16, 2016), <https://www.bioinformant.com/kirk-manchin-collins-introduce-bill-to-speed-development-of-regenerative-medicine/#more-5609> [<http://perma.cc/GVY5-4JRZ>].

1. Describing Adaptive Licensing

Adaptive licensing exemplifies a lifecycle approach to medical product evaluation where market access for drugs is progressive.¹⁷³ The model diverges from the traditional approval model where a drug transitions from experimental to approved in a single moment, and grows from the principle that there is no “magic moment” when regulators can conclusively determine that a drug is safe and effective.¹⁷⁴ Adaptive licensing frameworks envision two (or more) stages in a licensing pathway.¹⁷⁵ In the first stage, a drug receives an initial license based on less rigorous evidence than the two Phase 3 randomized controlled trials typically required for approval.¹⁷⁶ The initial patient population is restricted; the particular restrictions depend on the product’s particular issues and the level of knowledge about the product’s use.¹⁷⁷ In the second stage, after the initial license is granted, the sponsor continues to generate evidence on the drug’s use.¹⁷⁸ This evidence could “encompass the full methodology spectrum, including randomly-controlled clinical trials (RCTs), pragmatic clinical trials, clustered RCTs, observational studies based on electronic medical records, registries, and other forms of active and passive surveillance.”¹⁷⁹ Access expands, or the drug is withdrawn, as the sponsor reports additional postmarket evidence of safety and effectiveness.¹⁸⁰

173. See, e.g., Gibson & Lemmens, *supra* note 168, at 208; W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1061 (2016); Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305, 332 (2011) (discussing adaptive licensing for new drugs). W. Nicholson Price II, *supra* note 115, at 461–65 (discussing adaptive licensing for medical algorithms).

174. Eichler, *supra* note 77, at 427; see also Laakmann, *supra* note 173, at 308.

175. Eichler, *supra* note 77, at 430.

176. INST. OF MED. (US) COMM. OF ACCELERATING RARE DISEASE RESEARCH & ORPHAN PROD. DEV., RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT 155 (Marilyn J. Field & Thomas F. Boat eds., 2010).

177. Arnold I. Caplan & Michael D. West, *Progressive Approval: A Proposal for a New Regulatory Pathway for Regenerative Medicine*, 3 STEM CELLS TRANSLATIONAL MED. 560, 562 (2014); Eichler, *supra* note 77, at 430.

178. Caplan & West, *supra* note 177, at 561.

179. Eichler, *supra* note 77, at 429.

180. *Id.* at 431; Caplan & West, *supra* note 177, at 561.

Depending on the risk factors of the product, the path to approval would vary for each therapy.¹⁸¹ Just as the current system's accelerated approval pathway acknowledges that patients, practitioners, and regulators are willing to trade greater unknowns about safety and effectiveness to enable access for patients facing life-threatening or serious conditions with a lack of treatment options, an adaptive licensing framework would expect that other trade-offs between certainty and access might be acceptable in scenarios less extreme than those that already qualify for accelerated approval.¹⁸²

Three proposals suggest variations on the theme of adaptive licensing for regenerative medicines, but differ in important aspects. First, they differ as to which therapies qualify. Under the Caplan and West proposal, only those therapies that offer an advantage in treating serious diseases are eligible for adaptive licensing, whereas the other two restrict eligibility to certain lower-risk therapies. Second, they differ as to the evidence required for approval. The Caplan and West proposal demands only pretrial and Phase 1 studies, while the other two require both Phase 1 and Phase 2 trials. Third, they vary on postmarketing controls. The Caplan and West proposal suggests the use of significant controls to slow product diffusion into the marketplace, while the other two suggest no controls to slow diffusion, but do implement monitoring and reporting requirements (Bipartisan Policy Center) or informed consent requirements (REGROW Act). As I will address in the following subsection, weaknesses in each of these proposals renders them impracticable and unwise.

2. *Caplan and West*

In a 2014 article in a scientific journal, Caplan and West proposed an alternate regulatory pathway that would allow the marketing of regenerative medicine therapies without any evidence of efficacy.¹⁸³ Under their proposal, a therapy would be subject to two regulatory

181. Eichler, *supra* note 77, at 428.

182. *See id.* at 427.

183. Caplan & West, *supra* note 177, at 561.

steps. The first step would establish product safety through preclinical assessments of the therapy's proposed mechanism of action and Phase 1 clinical trials.¹⁸⁴ Based on this preliminary evidence, the therapy would be approved for marketing.¹⁸⁵ In the second step, postmarketing studies would rely on inputs from physicians and patients to “capture, in real time, the full experience of a large population.”¹⁸⁶ Effectiveness would be established through this postmarket evidence-gathering.¹⁸⁷ The sponsor would also be required to conduct a five-to-ten year follow up to establish the long-term safety of the procedures.¹⁸⁸ Only those therapies intended to provide a meaningful advancement in the treatment of a serious or life-threatening disease would be eligible.¹⁸⁹ The product's diffusion through the marketplace would be controlled through distribution restrictions, physician training, and credentialing.¹⁹⁰ Under Caplan and West's proposal, the therapies on the market would not be considered “investigational,” so they would be subject to the same coverage and reimbursement policies as therapies that are approved after demonstrating efficacy.¹⁹¹

3. *The Bipartisan Policy Center Report*

The Bipartisan Policy Center issued a report in December 2015 entitled, “Advancing Regenerative Cellular Therapies.”¹⁹² The report called for the creation of a new regulatory pathway for regenerative medicine therapies regulated as biologics.¹⁹³ To qualify, a product would have to meet a set of criteria designed to exclude the highest risk therapies.¹⁹⁴ Therapies that fall under this new pathway would be

184. *Id.*

185. *Id.*

186. *Id.*

187. *Id.*

188. *Id.*

189. Caplan & West, *supra* note 177, at 561.

190. *Id.* at 562.

191. *Id.* at 562.

192. BIPARTISAN POLICY CTR., ADVANCING REGENERATIVE MEDICINE: MEDICAL INNOVATION FOR HEALTHIER AMERICANS I (2015).

193. *Id.* at 12.

194. *Id.* at 13–15. The qualifying products either would be (1) (A) intended for homologous use and

conditionally approved based on Phase 1 and Phase 2 trials demonstrating safety and efficacy.¹⁹⁵ Patients would have access to these conditionally-approved therapies subject to monitoring and reporting requirements to the FDA.¹⁹⁶ Within three years of receiving conditional approval, the sponsor would be required to submit a biologics license application based on the accrued data of actual use.¹⁹⁷

4. *The REGROW Act*

In March 2016, Mark Kirk, a Republican senator from Illinois, introduced a bill entitled, “Reliable and Effective Growth for Regenerative Health Options that Improve Wellness” or the “REGROW” Act.¹⁹⁸ In his press release announcing the REGROW Act, Senator Kirk stated that the bill “builds on [the December 2015 Bipartisan Policy Center report].”¹⁹⁹ The bill ultimately died,²⁰⁰ but offers another example of a reform proposal.

Under the REGROW Act, the FDA would have been required to establish a program to “conditionally approve” certain regenerative medicine therapies that demonstrated safety and a “reasonable expectation of effectiveness.”²⁰¹ Importantly, Phase 3 clinical trials would not be required for those therapies before they became

(B) more-than-minimally manipulated but where processing does not alter the cells’ or tissues’ relevant biological characteristics or function; or (2) (A) intended for non-homologous use that helps perform or restore function in the recipient (“to reflect attributes of stem cells to differentiate and co-opt biological processes to restore the cells/tissue into which they are placed”) and (B) either minimally-manipulated or more-than-minimally manipulated but where processing does not alter the cells’ or tissues’ relevant biological characteristics or function. *Id.* Therapies that fall into this category include autologous culture-expanded adipose mesenchymal stem cells for subcutaneous injection, autologous adipose stromal vascular fraction to reduce arthritic inflammation in joints, and allogeneic or autologous bone marrow or cord tissue-derived mesenchymal stem cells for treatment of acute ischemic heart attack. *Id.*

195. *Id.* at 13.

196. *Id.*

197. *Id.*

198. S. 2689, 114th Cong. (2016). An identical bill, H.R. 4762, was introduced in the House by Representative Mike Coffman, R-CO. H.R. 4762, 114th Cong. (2016).

199. Press Release, *supra* note 172; *see also* Cade Hildreth, *Kirk, Manchin, Collins Introduce Bill to Speed Development of Regenerative Medicine*, BIOINFORMANT (Mar. 16, 2016), <https://www.bioinformant.com/kirk-manchin-collins-introduce-bill-to-speed-development-of-regenerative-medicine/#more-5609> [http://perma.cc/GVY5-4JRZ].

200. *See* S. 2689 – *REGROW Act*, *supra* note 169.

201. S. 2689, 114th Cong. § (2)(b) (2016).

available to patients.²⁰² To be eligible, products would also have to: (1) not provoke an unintended immune response; (2) not be genetically modified; and (3) be exclusively for a use that performs, or helps achieve or restore, the same or similar function in the recipient as in the donor.²⁰³ Within five years after conditional approval, the therapy's sponsor would be required to apply for the therapy's approval as a biologic.²⁰⁴ The only proposed limitation on patient access would require informing patients receiving the conditionally approved therapy of the therapy's conditional status.²⁰⁵

None of these proposals strikes an appropriate balance between access and risk because none require two necessary elements: (1) significant evidence of safety and effectiveness, and (2) meaningful measures to control the product's diffusion.

B. *Theorizing Adaptive Licensing*

Adaptive licensing is an example of adaptive management, a regulatory reform model that envisions administrative agencies making iterative decisions instead of a single "grand decision."²⁰⁶ Adaptive management responds to criticism that agency decision-making is overly focused on front-end analysis that must be conducted and concluded prior to finalizing a regulatory decision.²⁰⁷ Such focus, critics charge, requires agency decision-makers to falsely assume that they can predict the market and nonmarket effects of their decisions, and leads to regulatory ossification and inflexibility.²⁰⁸ Adaptive management responds by proposing an

202. *Id.*

203. *Id.* § (2)(b)(2)–(5).

204. *Id.* § (2)(b).

205. *Id.* § (2)(c).

206. Robin Kundis Craig & J.B. Ruhl, *Designing Administrative Law for Adaptive Management*, 67 VAND. L. REV. 1, 7 (2014).

207. *Id.*

208. See, e.g., Thomas O. McGarity, *Some Thoughts on "Deossifying" the Rulemaking Process*, 41 DUKE L.J. 1385, 1392 (1992); J.B. Ruhl & James Salzman, *Mozart and the Red Queen: The Problem of Regulatory Accretion in the Administrative State*, 91 GEO. L.J. 757, 841 (2003) (addressing the problem of regulatory accretion); Mark Seidenfeld, *Bending the Rules: Flexible Regulation and Constraints on Agency Discretion*, 51 ADMIN. L. REV. 429, 457 (evaluating impact of ex ante restraints on agency decision-making on predictability, accountability, and flexibility); Richard B. Steward, *Administrative Law in the Twenty-First Century*, 78 N.Y.U. L. REV. 437, 447 (2003) (identifying inflexibility and rapid

iterative process by which an administrative agency decides a regulatory outcome through a multistep process that includes defining the problem, identifying goals and options, implementing action, and monitoring and evaluating outcomes.²⁰⁹

Adaptive management was born from a concern that conventional methods for natural resource management were at odds with the dynamic nature of ecosystems.²¹⁰ But the same principles can apply in a variety of other regulatory situations. Professor Robin Kundis Craig delineates three factors that suggest when adaptive management is appropriate: high uncertainty, high controllability, and low risk.²¹¹ High uncertainty describes a decision-maker's level of understanding about how the regulatory context responds to interventions.²¹² As uncertainty rises, confidence in a front-end model of decision-making erodes, and adaptive management becomes more appropriate.²¹³ High controllability is the degree to which a decision-maker can manipulate the regulatory environment.²¹⁴ Higher controllability means that the decision-maker has a greater capacity to intervene in the problem and can engage in more experimentation and option testing.²¹⁵ Low risk describes the chance that experimentation or interventions can lead to irreversible adverse consequences. High risk makes adaptive management less appropriate.²¹⁶

Under this rubric, adaptive licensing is appropriate for regenerative medicine therapies under the first principle of high uncertainty. But the second and third principles of high controllability and low risk highlight the flaws with applying adaptive licensing to regenerative medicine therapies. Limits to the FDA's authority, challenges with implementation, and concerns with shortcutting premarket evidence

obsolescence as problems of command-and-control regulation).

209. Kundis Craig & Ruhl, *supra* note 206, at 7.

210. *Id.* at 17.

211. *Id.* at 19. An optional fourth factor, "dynamic system," is not applicable to the drug approval regime, so I have omitted it from my discussion.

212. *Id.*

213. *Id.*

214. *Id.*

215. Kundis Craig & Ruhl, *supra* note 206, at 19.

216. *Id.*

generation are sufficiently serious to limit the appeal of such an approach.

1. *High Uncertainty*

The first principle for adaptive management is that the regulatory situation involves uncertainty.²¹⁷ An approval decision for regenerative medicine therapies will often involve uncertainty, particularly if a therapy is biologically complex, is difficult to define or characterize, or requires long-term evaluation of risk or efficacy.

First, regenerative medicine therapies present approval challenges due to the presence of living cells.²¹⁸ Biologics contain thousands to millions of atoms formed into intricate designs.²¹⁹ Because the behavior of a cell depends on its microenvironment, changing the cell's micro-environment from a laboratory setting to an animal model to a human means that the cells are exposed to different factors in each setting.²²⁰ This complicates safety and efficacy studies because the conditions in the laboratory may not accurately mimic the cell's environment in a human.²²¹ Furthermore, once transplanted into a human, the cells may change over time.²²² Cells may differentiate into unwanted cell types.²²³ They might also develop unwanted functions; for example, cardiomyocyte-like cells could generate electrical activity that is not coordinated with the rest of the

217. *Id.* at 19.

218. Although most do, not all regenerative medicine therapies use living cells. For example, the bioengineered blood vessel marketed by Humacyte does not contain living cells. *See, e.g.*, Abigail Xie, *Bioengineered Blood Vessels Shown to be Effective in Patients with Kidney Failure*, CHRONICLE (May 26, 2016), <http://www.dukechronicle.com/article/2016/05/bioengineered-blood-vessels-shown-to-be-effective-in-patients-with-kidney-failure> [<http://perma.cc/RQ4S-34XE>].

219. Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J. L. & ARTS 53, 82 (2016) (citing Bryan Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGIS. 363, 369 (2007)); Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., July 19, 2009, at 2.

220. The Committee for Advanced Therapies (CAT) & the CAT Scientific Secretariat, *supra* note 36, at 196–97.

221. *Id.*; Melissa K. Carpenter et al., *Developing Safe Therapies from Human Pluripotent Stem Cells*, 27 NATURE BIOTECHNOLOGY 606, 609 (2009).

222. U.S. FOOD & DRUG ADMIN., CONSIDERATIONS FOR THE DESIGN ON EARLY-PHASE CLINICAL TRIALS OF CELLULAR AND GENE THERAPY PRODUCTS: GUIDANCE FOR INDUSTRY 4 (2015) [hereinafter EARLY-PHASE: GUIDANCE].

223. *Id.*

heart.²²⁴ Similarly, cells may migrate to an unintended location within the recipient's body.²²⁵

A second related problem is the heterogeneous nature of many regenerative medicine products; they contain a variety of cell types, with one or more being the “active agent.”²²⁶ Because defining and controlling a product is essential for assessing a product's safety and efficacy, products with multiple living cell types that respond to their environment—and are therefore in flux—challenge researchers' abilities to properly characterize and control a product.²²⁷ Autologous products that are uniquely sourced for each patient compound this issue because of challenges in controlling lot-to-lot variability.²²⁸

Third, living cells' unique characteristics may require regenerative medicine therapies to undergo prohibitively long clinical trials to demonstrate efficacy or to uncover risks.²²⁹ To be effective, a regenerative therapy must repair the damaged tissue as intended.²³⁰ But the mechanism of action for tissue repair and regeneration is often unknown and may be a result of cell secretions by the transplanted cells rather than donor cell repopulation of the targeted tissues.²³¹ Given these unknowns, testing the therapy's long-term clinical outcome to determine whether the cells differentiated as intended and then functionally repaired the damaged tissue can take a long time—even several years.²³² This length of time may make clinical trials expensive and difficult because participants may be

224. *Id.*

225. *Id.*

226. Jeffrey L. Fox, *FDA Scrutinizes Human Stem Cell Therapies*, 26 NATURE BIOTECHNOLOGY 598, 599 (2008); Robert A. Preti, *Bringing Safe and Effective Cell Therapies to the Bedside*, 23 NATURE BIOTECHNOLOGY 801, 801–02 (2005).

227. Fox, *supra* note 226, at 598.

228. EARLY-PHASE: GUIDANCE, *supra* note 222, at 5.

229. The Committee for Advanced Therapies (CAT) & the CAT Scientific Secretariat, *supra* note 36, at 197.

230. *Id.*

231. Stefanie Dimmeler et al., *Translational Strategies and Challenges in Regenerative Medicine*, 20 NATURE MED. 814, 819 (2014).

232. The Committee for Advanced Therapies (CAT) & the CAT Scientific Secretariat, *supra* note 36, at 197.

unable to attend follow-up appointments or may die from their underlying conditions or other causes.²³³

Uncovering risks may also be a long-term project. Stem cells that are undifferentiated, or not completely differentiated, risk turning into tumor cells.²³⁴ Pluripotent stem cells can produce teratomas, which are an accumulation of many different cell types into a benign tumor.²³⁵ These teratomas can fill anatomical space with potentially disastrous consequences.²³⁶ They can also dedifferentiate and develop into a malignant form.²³⁷ Although determining the tumorigenicity of stem cells will be a main focus of preclinical studies, clinical factors—such as the site of implantation and the number of cells implanted—will impact a therapy’s tumorigenicity²³⁸ and will be a continued focus of long-term clinical trials.²³⁹

Adaptive licensing can address uncertainty by enabling regulators and sponsors to design an approval pathway for a regenerative medicine therapy that addresses its particular challenges. For therapies that would take an inordinate amount of time to test in a clinical trial, perhaps because the targeted condition is rare or because the mechanism of action is slow-moving, an initial license based on an unvalidated surrogate endpoint would allow limited early patient access, followed by a subsequent lifting of restrictions based on demonstrated success in meeting defined clinical endpoints.²⁴⁰ If the concern is ensuring effectiveness in a real-world population, an initial license might be based on an explanatory trial with closely-monitored inclusion criteria, and the postmarketing study would be a pragmatic, randomly-controlled trial that evaluates effectiveness in a real-world, clinical setting.²⁴¹ If the concern is uncovering rare

233. *Id.*

234. Carpenter, *supra* note 221, at 610.

235. Fox, *supra* note 226, at 599.

236. *Id.*

237. *Id.*

238. Carpenter, *supra* note 221, at 610.

239. See Evgenios Neofytou et al., *Hurdles to Clinical Translation of Human Induced Pluripotent Stem Cells*, 125 J. CLINICAL INVESTIGATION 2551, 2553 (2015); see also Amariglio, *supra* note 134, at 226 (describing diagnosis of brain tumor in boy four years after treatment with human fetal neural cells).

240. Eichler, *supra* note 77, at 431–32.

241. *Id.* at 430.

adverse events, an initial license could be based on a randomly-controlled trial, and the postmarket study could be a long-term evaluation through observational studies or patient registries.²⁴²

2. High Controllability

The second principle for adaptive management advises high controllability.²⁴³ Unlike the first principle of high uncertainty, which is met in the regenerative medicine context, evidence of controllability is less robust. Controllability in a regenerative medicine scenario implicates four components: (1) the FDA's authority to approve biologics on the basis of less-robust evidence of safety, purity, and potency; (2) the FDA's authority to require postmarketing studies from sponsors; (3) the FDA's authority to control the diffusion of the therapies; and (4) the FDA's ability to appropriately respond to new evidence.²⁴⁴ Regarding the first component, the FDA does not have the authority to approve biologics unless they are shown to be safe, pure, and potent.²⁴⁵ This limits, but does not eliminate, the FDA's current ability to approve biologics that have not undertaken Phase 3 trials. Second, the FDA's authority to require postmarketing studies is limited to specific circumstances.²⁴⁶ A broader grant of power is required if adaptive licensing is pursued. Regarding the third component, the FDA has the authority to control the diffusion of the product through its use of

242. *See id.* at 431–32; Gibson & Lemmens, *supra* note 168, at 207–08.

243. Craig & Rhule, *supra* note 206, at 19.

244. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 20 (2014) [hereinafter GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS]; John D. Balian et al., *Roadmap to Risk Evaluation and Mitigation Strategies (REMS) Success*, 1 THERAPEUTIC ADVANCES IN DRUG SAFETY 21, 21 (2010); *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm> [https://perma.cc/CHV5-BD85] (last updated July 7, 2015); *Notice to Industry: Postmarketing Requirements—Postmarket Studies and Clinical Trials*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm292758.htm> [https://perma.cc/TYV2-CTS8] (last updated Feb. 12, 2016) [hereinafter *Notice to Industry: Postmarketing Requirements*].

245. *Frequently Asked Questions About Therapeutic Biological Products*, *supra* note 244.

246. *Notice to Industry: Postmarketing Requirements*, *supra* note 244.

Risk Mitigation and Enforcement Measures (REMS).²⁴⁷ But the fourth component, the ability to respond appropriately to new evidence, will challenge the FDA for two distinct reasons: (1) withdrawing a product from the marketplace—even if legally possible—will be politically difficult, and (2) structuring an agreement with a sponsor that is both flexible enough to respond to new evidence yet certain enough to be attractive to sponsors may not be feasible.

a. Approval Authority

As an initial matter, it is necessary to determine whether the FDA has the authority to approve biologics on less robust evidence than is traditional.²⁴⁸ Fundamentally, biologics may only be approved based on evidence that demonstrates continued safety, purity, and potency.²⁴⁹ Potency is interpreted to require effectiveness.²⁵⁰ Proof of effectiveness generally requires adequate and well-controlled clinical trials, unless either the FDA waives them as inapplicable or an alternate method is adequate to substantiate effectiveness.²⁵¹ One such alternate method to substantiate effectiveness is the use of validated surrogate endpoints. The existing RMAT and Accelerated Approval pathways codify this understanding.²⁵² But the FDA cannot approve a therapy based on a body of evidence that fails to show that the product is safe, pure, and potent.²⁵³ Such a move would simply violate the FDA's legal mandate to only approve a product where existing evidence supports a conclusion of continued safety, purity, and potency.

247. Balian et al., *supra* note 244, at 21.

248. GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS, *supra* note 244, at 10.

249. 42 U.S.C. § 262 (a)(2)(C)(i)(I) (Supp. 2017).

250. 21 C.F.R. § 600.3(5) (2012); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUGS AND BIOLOGICAL PRODUCTS 4 (1988).

251. 21 C.F.R. § 314.126 (a), (c), (e) (2002).

252. Peter Marks, *This Is Not a Test: RMAT Designation Goes Live*, U.S. FOOD & DRUG ADMIN. (Mar. 21, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/> [https://perma.cc/V84Y-9Z8B].

253. 42 U.S.C. § 262 (a)(2)(C).

b. Postmarketing Authority

An adaptive licensing scheme also requires that sponsors agree to postmarketing studies as a condition of earlier approval.²⁵⁴ This second component raises an additional concern of insufficient authority on the part of the FDA. The FDA only has clear statutory authority to mandate postmarketing studies or trials based on safety risks or accelerated approval. The Food and Drug Administration Amendments Act of 2007 authorized the FDA to require the sponsor of an approved biologic to conduct postmarketing studies or clinical trials if the FDA became aware of new information about a serious risk associated with the biologic since its approval.²⁵⁵ This authority limits the FDA to requiring additional studies based only on safety concerns, not on effectiveness concerns.²⁵⁶ The FDA also may require sponsors to agree to conduct postmarketing studies as a condition of receiving approval based on a surrogate or intermediate endpoint.²⁵⁷ The pathways that enable the use of surrogate or intermediate endpoints, Accelerated Approval and the RMAT designation, are limited to therapies that are “intended to treat, modify, reverse or cure a serious or life-threatening disease or condition; and . . . have the potential to address unmet medical needs for such a disease or condition.”²⁵⁸

But an adaptive licensing framework envisions accelerated approval conditioned on postmarketing studies for a greater scope of products than those covered by the FDA’s current statutory

254. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY POSTMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF SECTION 505(O)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 2–3 (2011) [hereinafter GUIDANCE FOR INDUSTRY POSTMARKETING STUDIES AND CLINICAL TRIALS].

255. Food and Drug Administration Amendments of 2007, Public L. No. 110-85, § 901, 121 Stat. 823 (codified as 21 U.S.C. § 355(o)(3)(C)); 42 U.S.C. § 262(a)(2)(D) (Supp. 2016) (cross-referencing the PHSA with the FDCA); GUIDANCE FOR INDUSTRY POSTMARKETING STUDIES AND CLINICAL TRIALS, *supra* note 254, at 4, 16; *see, e.g.*, Rebecca S. Eisenberg & W. Nicholson Price II, *Promoting Healthcare Innovation on the Demand Side*, 10 J. L. AND BIOSCIENCES 3, 10–13 (2017); Riley, *supra* note 17, at 458–60, (discussing postmarketing provisions of FDAAA).

256. Riley, *supra* note 17, at 465–66.

257. 21 U.S.C. § 356(g)(5) (Supp. 2016); Kenneth A. Oye et al., *Legal Foundations of Adaptive Licensing*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 309, 310 (2013).

258. 21 U.S.C. § 356(g)(2)(B–C). The limitations for accelerated approval of drugs or biologics are substantively the same. *See id.* § 356(c)(2)–(3).

authority.²⁵⁹ In such a situation, where the FDA seeks to impose postmarketing requirements outside of its statutory permissions for safety issues and accelerated pathways, the FDA's authority is murky. The FDA regularly requests that sponsors conduct postmarketing studies, and sponsors commit in writing to the FDA to conduct such postmarketing commitments.²⁶⁰ But the FDA does not have clear authority to condition approval on "voluntary" postmarketing studies.²⁶¹

The biologics context can be analogized to Charles Steenburg's analysis of the new drug context.²⁶² Significantly, the statute governing the licensing of biologics is nondiscretionary: "a biologics license *shall* be issued upon a determination . . . that the establishment(s) and the product meet the applicable requirements established in this chapter."²⁶³ And such approval "shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."²⁶⁴ Thus, any requirement on the part of the FDA to require postmarketing studies as a condition of approval would lead to an incongruous result. Namely, the FDA would either (1) implicitly admit that its approval did not constitute a determination that the product meets the requirements to ensure continued safety, purity, and potency of such product, or (2) deny the sponsor its statutory right to receive premarketing approval for a biologic which has met the applicable statutory requirements.²⁶⁵

In summary, combining the sources of FDA authority for approval and postmarketing studies reveals a gap where the FDA does not currently have the ability to approve products that have not been shown to be safe, pure, and potent, or to require postmarketing

259. See Steenburg, *supra* note 81, at 361.

260. U.S. FOOD & DRUG ADMIN., REPORT TO CONGRESS, REPORTS ON POSTMARKETING STUDIES, FDAMA 130, at 1 (2001); Steenburg, *supra* note 81, at 335–36.

261. See Steenburg, *supra* note 81, at 357.

262. *Id.* at 349 (arguing that the FDA's authority to condition approval of new drugs on "voluntary" commitments to conduct postmarketing studies conflicts with the FDA's nondiscretionary mandate to approve new drugs that meet the requirements of section 505(e)).

263. 21 C.F.R. § 601.4 (2016) (emphasis added).

264. 21 C.F.R. § 601.2(d).

265. See Steenburg, *supra* note 81, at 358.

studies for regenerative medicine products that neither are subject to approval under a fast-track pathway nor raise new safety concerns. To implement a cohesive adaptive licensing scheme, it would therefore be necessary for Congress to grant the FDA authority to require postmarketing studies as a condition of earlier approval for those products neither designated as RMATs (or otherwise reviewed under a fast-track procedure) nor for which safety evidence supports requiring postmarketing obligations.

c. Controlling Diffusion

The third component of controlling the regulatory environment involves the FDA's ability to control the diffusion of a regenerative medicine therapy in the marketplace.²⁶⁶ This would allow regulators to limit initial access to patients with the most appropriate risk/benefit characteristics.²⁶⁷ Particularly for regenerative therapies that have not been previously approved for use in humans, controls would be needed to limit access until significant uncertainties are resolved.²⁶⁸ Numerous methods exist to control diffusion, including limiting use of the therapy to certain patient populations, restricting off-label prescribing, and ensuring that prescribers and pharmacists have received advanced certification. The FDA has the authority to require such controls under its power to require sponsors to develop and implement REMS, including Elements to Assure Safe Use (ETASU).²⁶⁹ These include requiring that:

- health care providers have particular training or experience, or are specially certified;

266. Turner & Knoepfler, *supra* note 23, at 156.

267. Eichler, *supra* note 77, at 429; Caplan & West, *supra* note 177, at 562.

268. R. Alta Charo, *Speed Versus Safety in Drug Development*, in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 251, 263 (I. Glenn Cohen & Holly F. Lynch, eds., 2015); Efthimios Parasidis, *FDA's Public Health Imperative: An Increased Role for Postmarket Analysis*, in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 286, 293 (I. Glenn Cohen & Holly F. Lynch, eds., 2015).

269. The Public Health Service Act provides that license applications for biological products are subject to the REMS provisions of the FDCA. 42 U.S.C. § 262(a)(2)(D) (Supp. 2017).

- pharmacies, practitioners, or health care settings that dispense the therapy are specially certified;
- the therapy be dispensed to patients only in certain health care settings;
- the therapy be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory results;
- patients be subject to certain monitoring; or
- patients be enrolled in a registry.²⁷⁰

Use of these elements would enable the FDA and sponsors to control the diffusion of a regenerative medicine therapy while continuing postmarket studies to further evaluate safety and effectiveness.

d. Responding to Evidence

The fourth component of controlling the regulatory environment is the FDA's ability to react and respond to new evidence generated in postmarketing trials and studies.²⁷¹ Adaptive licensing frameworks envision that postmarketing studies will generate evidence to support either eliminating the risk mitigation measures or removing the therapy from the market in the event that safety or efficacy issues arise.²⁷² Just like the many drugs that look promising in Phase 2 trials but fail Phase 3 trials due to safety or efficacy problems,²⁷³ it is likely

270. *Id.* § (f)(3). Although the statute limits the FDA requiring ETASU for drugs “shown to meet the standard” of safety and efficacy, the application of ETASU on drugs approved under the accelerated approval pathway based on surrogate endpoints suggest that “effective” is liberally interpreted to apply to all drugs approved by the FDA (which are, tautologically, safe and effective). *Id.*

271. Steenburg, *supra* note 81, at 320.

272. See Gibson & Lemmens, *supra* note 168, at 214–15.

273. A recent study published in *Nature Biotechnology* surveyed the drug development success rates for over 7,000 drugs from 2003 to 2011. The authors demonstrated that only half of drug indications in Phase 3 trials ultimately received approval from the FDA. Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, 32 *NATURE BIOTECHNOLOGY* 40, 44 (2014); U.S. FOOD & DRUG ADMIN., 22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS (2017); see also *ISSCR Opposes the REGROW Act*, INT'L SOC'Y FOR STEM CELL RES. (Sept. 15, 2016), <http://www.isscr.org/professional-resources/news-publicationsss/isscr-news-articles/article-listing/2016/09/15/isscr-opposes-the-regrow-act> [https://perma.cc/H4RQ-NUJ9] (stating that as many as

that if the FDA approved therapies under an adaptive licensing scheme based on less rigorous evidence, those therapies would similarly demonstrate a lack of safety or efficacy in postmarketing studies. This suggests that an adaptive licensing framework would require the FDA to have a robust ability to respond to safety or effectiveness concerns. Current, its ability is mixed.

The FDA has authority to respond to sponsor failures to complete REMS or mandatory postmarketing commitments. Under the relevant statutes, a sponsor that fails to abide by a REMS or fails to conduct a postmarketing study may not introduce the drug into interstate commerce.²⁷⁴ Doing so would constitute a misbranding violation, which could result in product seizures.²⁷⁵ The FDA also has the authority to react to evidence that a product is not safe or effective.²⁷⁶ The biologics regulations also provide that the FDA can withdraw a license in the event the product is not safe and effective for its intended uses, or is misbranded with respect to any such use.²⁷⁷

But the FDA is subject to political pressures as well. Once a new therapy is on the market, it likely will be politically difficult to withdraw it, even if safety and efficacy concerns arise.²⁷⁸ Sponsors of drug trials have been very successful in motivating grassroots support for potential therapies, and the lobbying power of the biologics and pharmaceutical industry raises concerns that regulators will be unable to avoid industry capture.²⁷⁹

Finally, creating an agreement that both allows for the FDA to react to new evidence and is sufficiently attractive to a product sponsor will likely prove difficult. From the perspective of a drug sponsor, participating in adaptive licensing involves a trade-off

40% of drug and biotechnology products that enter Phase 3 fail).

274. 21 U.S.C. § 355(p)(1)-(2) (Supp. 2016).

275. 21 U.S.C. § 355(d); 21 U.S.C. § 334 (2011). *Compare* United States v. Sandoz Pharm. Corp., 894 F.2d 825, 826 (6th Cir. 1990) (upholding seizure where the defendant failed to file a new drug application before introducing product into interstate commerce), *with* United States v. 225 Cartons, 687 F. Supp. 946, 962 (D. N.J. 1988) (upholding seizure of drugs where new drug application had not been filed with FDA pursuant to 21 U.S.C. § 355), *aff'd*, 871 F.2d 409 (3d Cir. 1989).

276. 21 U.S.C. § 355(d).

277. 21 C.F.R. § 601.5(b)(vi) (2017).

278. Gibson & Lemmens, *supra* note 168, at 216–17.

279. See *Overcoming Pre-market Syndrome*, *supra* note 81, at 275.

between rules that are certain—even if not ideal—and rules that are flexible but uncertain.²⁸⁰ For sponsors, the benefit of adaptive licensing is earlier access to the market.²⁸¹ But market forces could dampen this benefit. If payors refuse to cover a therapy, the sponsor would lose this prospective benefit.²⁸² Similarly, even if payors agree to cover the therapy, an overly-restricted pool of patients would lessen the financial benefits to sponsors, a problem that could be compounded by FDA-enforced market exclusivities. Because the FDA grants a new biologic twelve years of marketing exclusivity, a limit on the sponsor's ability to receive payment for a product during this period would act as a significant disincentive to participate in adaptive licensing.²⁸³ Furthermore, if there is significant uncertainty about how the FDA will respond to newly created evidence, such as what type and length of studies will be needed to lift restrictions, sponsors may decline to participate.²⁸⁴

The analysis of controllability reveals flaws in the application of adaptive licensing to regenerative medicine therapies under the FDA's current authority. But even assuming that Congress granted additional authority for proper implementation of an adaptive licensing framework, a robust agreement between the therapy's sponsor, the FDA—and potentially payors—would be required to properly incentivize sponsor participation. The fatal flaw with all regenerative medicine adaptive licensing proposals, however, is the absence of low risk.

3. *Low Risk*

The third principle for adaptive management, low risk, is not met by adaptive licensing of regenerative medicine therapies. Given the diversity of regenerative medicine therapies, they array widely across a measure of risk. But for many therapies, early approval increases

280. Price & Rai, *supra* note 173, at 1060.

281. Charo, *supra* note 268, at 258.

282. *Id.* at 262.

283. *Id.* at 257.

284. *Id.* at 254.

the risk that patients will either incur opportunity costs if the therapy does not work or suffer physical harms previously undiscovered.²⁸⁵

Most biologics that are investigated in clinical trials do not work. A 2016 study of clinical development success rates over ten years, from 2006 through 2015, involved almost 10,000 phase transitions and found that only 11.5% of biologics that entered Phase 1 trials ultimately received FDA approval.²⁸⁶ Of those biologics in Phase 3 trials, only half of them received FDA approval.²⁸⁷ Another study of drug development success rates for over 7,000 drugs from 2003 to 2011 tells a similar story: only slightly more than half of biologics in Phase 3 trials ultimately received FDA approval.²⁸⁸ This data is important because it means that if regenerative medicine therapies are provided to patients before Phase 3 trials are complete, we should expect around half to fail to provide a benefit that outweighs the risk. Such a system would make the initial patient population akin to a class of clinical trial participants, but without the protections provided by clinical trials.

Physical harm represents another risk. Although a product's REMS strategy could include measures to mitigate the likelihood of harm—including communication tools such as distribution of a medication guide,²⁸⁹ or communication by the sponsor to health care providers of risks and mitigating measures—concerns remain.²⁹⁰ Current evidence about drugs and biologics approved under an accelerated pathway suggest caution. Existing accelerated pathways are similar to those suggested by adaptive licensing, and many therapies that are approved under accelerated pathways based on

285. See Gibson & Lemmens, *supra* note 168, at 207.

286. DAVID W. THOMAS ET AL., CLINICAL DEVELOPMENT SUCCESS RATES 2006–2015, at 19–20 (2016).

287. *Id.*

288. Michael Hay et al., *supra* note 273, at 44; U.S. FOOD & DRUG ADMIN., *supra* note 273; see also ISSCR Opposes the REGROW Act, *supra* note 273 (stating that as many as 40% of drug and biotechnology products that enter Phase 3 fail).

289. 21 U.S.C. § 355-1(e)(2) (Supp. 2017). A medication guide highlights a safety concern and can recommend mitigating measures such as weighing risks versus benefits, observing certain symptoms that could prevent or mitigate a serious side effect, highlighting patient populations that are contraindicated for the therapy, and stressing the importance of following the dosing regimen. 21 C.F.R. § 208.20 (2008).

290. 21 U.S.C. § 355-1(e)(2)-(3); Eichler, *supra* note 77, at 429.

surrogate or intermediate endpoints fail to demonstrate the desired ultimate clinical benefit.²⁹¹

Two studies published in 2017 demonstrate the extent of the problem. Dr. Aaron Kesselheim and his colleagues published a study that showed that the medicines approved under expedited regulatory pathways had a 38% higher rate of safety changes to product labels than those approved under a traditional pathway.²⁹² The expedited drugs also had a 48% higher rate of changes to black box warnings, which are warnings designed to disclose serious or life-threatening risks, or contraindications.²⁹³ Another study found that nearly one in three drugs approved by the FDA have safety issues after approval, and the percentage is even higher for biologics and medicines approved under an accelerated pathway.²⁹⁴

The use of surrogate endpoints is partly to blame. Although surrogate endpoints allow sponsors to reduce the size, time, and cost of clinical trials,²⁹⁵ they also pose challenges. A baseline challenge is identifying those surrogate endpoints that ultimately demonstrate the desired clinical benefit. Correlation does not equal causation, and there is a risk that a beneficial change in a surrogate endpoint will not necessarily cause a benefit in a clinical endpoint.²⁹⁶ For example, a

291. An intermediate clinical endpoint is a “clinical endpoint that can be measured earlier than irreversible morbidity or mortality.” 21 U.S.C. § 356(c)(1)(A). A “surrogate endpoint” is a biomarker that is intended to substitute for a clinical endpoint. INST. OF MED., *EVALUATION OF BIOMARKERS AND SURROGATE ENDPOINTS IN CHRONIC DISEASE 3* (Christine M. Michael & John R. Ball, eds., 2010), <https://www.nap.edu/read/12869/chapter/2#3> [<https://perma.cc/ZNG9-YXEN>] [hereinafter IOM, BIOMARKERS]. Intermediate or surrogate endpoints include measures such as imaging data or markers in the blood that predict, but do not prove, ultimate endpoints. Kelly Servick, *Under 21st Century Cures Legislation, Stem Cell Advocates Expect Regulatory Shortcuts*, SCIENCE MAG., AAAS (Dec. 12, 2016, 2:45 PM) <http://www.sciencemag.org/news/2016/12/under-21st-century-cures-legislation-stem-cell-advocates-expect-regulatory-shortcuts-0> [<https://perma.cc/Z95R-6QN6>]. An example of a surrogate endpoint is blood pressure in a trial for antihypertensive drugs. IOM, BIOMARKERS, *supra*, at 3 box S-2.

292. Aaron Kesselheim, Sana R. Mostaghim & Joshua J. Gagne, *Safety Related Label Changes for New Drugs After Approval in the US through Expedited Regulatory Pathways: Retrospective Cohort Study*, 358 *BMJ* 1 (2017); Ed Silverman, *Speedy FDA Drug Reviews Also Yield More Safety Changes to Labeling*, STAT (Sept. 14, 2017), <https://www.statnews.com/pharmalot/2017/09/14/fda-drug-reviews-safety-changes/> [<https://perma.cc/MTP8-HJDJ>].

293. Kesselheim, Mostaghim & Gagne, *supra* note 292; Silverman, *supra* note 292.

294. See generally Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 *JAMA* 1854 (2017).

295. Behnood Bikdeli et al., *Two Decades of Cardiovascular Trials with Primary Surrogate Endpoints: 1990–2011*, 116 *J. AM. HEART ASS'N* 1, 1 (2017).

296. Eugene J. Sullivan, Chief Med. Officer, United Therapeutics and Lung Rx, Presentation at the

recent study of 220 cardiovascular clinical trials using surrogate endpoints found that although over 70% of the trials demonstrated the positive surrogate endpoint, only slightly more than a quarter were followed with a clinical trial testing the clinical endpoint.²⁹⁷ And of these trials testing the clinical endpoint, nearly half failed to demonstrate the clinical endpoint predicted by the surrogate endpoint.²⁹⁸ The authors concluded that their findings “raise concern about the certainty of assuming efficacy based on surrogate endpoints. Even if used for approval of therapies in urgent situations, postmarketing outcome trials are necessary.”²⁹⁹

These studies show that determining the true risk/benefit ratio of a regenerative medicine therapy based on studies with surrogate or intermediate clinical endpoints is less certain, because both the benefit and the risk may not be as fully explored in a trial that looks only at surrogate or intermediate clinical endpoints. The benefit must be extrapolated from the observed surrogate effect; the risks may not all be revealed in shorter, smaller studies.³⁰⁰

The existing challenges facing biologics in Phase 3 trials or under current accelerated pathways should give us pause before expanding the number of products approved based on early-stage clinical evidence. The regulatory system must acknowledge the trade-offs between faster access and safety. And until the expedited clinical trial process is better able to predict harms, limiting expedited review to those treatments that seek to address life-threatening conditions or unmet medical needs reflects a more reasonable balance between the FDA’s goals of protecting public health and advancing beneficial innovation.

FDA’s 2013 Clinical Investigator Training Course: Clinical Trial Endpoints (Nov. 12, 2013), <http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM283378.pdf> [<https://perma.cc/FCS3-WJGT>].

297. Bikdeli et al., *supra* note 295, at 3.

298. *Id.*

299. *Id.* at 7.

300. Sullivan, *supra* note 296.

4. *A Question of Timing?*

The principles of adaptive regulation contain an implicit fourth requirement: that the principles align at an opportune time for reform. In this sense, adaptive licensing may simply be an idea whose time has not yet come. Many of the roadblocks discussed in the previous section are surmountable. Where the FDA lacks authority, Congress can grant it. Sponsors and the FDA can negotiate, test, and revise their agreements. Concerns with payors can be worked through with input from affected parties.

But the safety concerns remain. With time, however, these roadblocks may also be surmountable. As regulatory science advances and coincides with a deeper understanding of how regenerative medicine therapies work, it may be possible to validate new surrogate endpoints or harness electronic health records in a way that offers greater assurances of safety and efficacy. The accelerated approval pathways, including RMAT designation, provide a laboratory for experimentation with the sources and content of data to improve the predictive ability of early safety and efficacy data. And this, in itself, is a form of adaptive management: defining the problem that early-stage trial data does not sufficiently predict later health and safety concerns, setting a goal to improve the data's predictive power, implementing various regulatory tools, and evaluating each for success.

If we reach this goal, it will be worth revisiting adaptive licensing. But until that hypothetical opportune moment, implementing adaptive licensing for regenerative medicine therapies is unworkable and unwise for a variety of reasons, including:

- Insufficient or unclear FDA authority to approve biologics based on evidence that does not support the continued safety, purity, and potency of the product (except for products approved under Congressionally-authorized accelerated pathways);
- Insufficient or unclear authority of the FDA to require postmarketing obligations for regenerative

medicine products regulated as biologics (except for new safety issues or under a Congressionally-authorized accelerated pathway);

- Political difficulties in removing products from the marketplace, especially if based on a sponsor's violation of protocol as opposed to newly-discovered safety or effectiveness issues;
- Hurdles to incentivizing sponsor participation, especially involving payment; and
- Risks to patients who receive regenerative medicine therapies that have not undergone thorough Phase 3 testing.

Given these impediments and challenges, the benefits derived from adaptive licensing do not outweigh the risks to patients and the costs of reform.

IV. Incremental Changes to Existing Regulations: Reform of Section 361 Products

In the previous section, I argued against adopting adaptive licensing for those regenerative medicine products regulated as biologics. In this section, I recommend reforming regenerative medicine therapies regulated as section 361 products by expanding the same surgical procedure exception and expanding the scope of section 361. Whereas the reform proposals for biologics were dramatic and would involve congressional action, FDA rulemaking, and a fundamental change in the meaning of premarket approval, the proposed reforms to the regulation of section 361 products are more modest. The proposals simply involve updating the interpretation of key statutory terms based on evolving scientific understanding.

A. FDA's Guidance on Section 361 Products

Because the FDA's regulatory requirements are most burdensome for regenerative medicine therapies regulated as biologics,

manufacturers often seek to have their products categorized into the lowest or middle regulatory tier.³⁰¹ To this end, manufacturers recently asked the FDA to clarify certain section 361 requirements, and the FDA responded by issuing guidance documents³⁰² to explain the FDA's positions on the same surgical procedure exception;³⁰³ the meaning of homologous use;³⁰⁴ the meaning of minimal manipulation;³⁰⁵ and how the regulations apply to products derived from adipose tissues.³⁰⁶

Although guidance documents are not legally binding, the FDA issues them to communicate its expectations to the industry and to stakeholders.³⁰⁷ Guidance documents assist the industry by providing clarity and consistency.³⁰⁸ Under the Good Guidance Principles adopted in 2000, the process for issuing a guidance document requires the FDA to publish a draft guidance and notify the public of its availability in hard copy and on the internet.³⁰⁹ The public is invited to submit comments, and after a time, the FDA reviews the comments and prepares a final draft that need not, but may as appropriate, address the public's comments.³¹⁰ The draft guidances contain a number of clarifications and explanations of the section 361 requirements.

301. CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 69.

302. *Id.* at 9.

303. U.S. FOOD & DRUG ADMIN., SAME SURGICAL PROCEDURE EXCEPTION UNDER 21 C.F.R. 1271.15(B): QUESTIONS AND ANSWERS REGARDING THE SCOPE OF THE EXCEPTION: DRAFT GUIDANCE FOR INDUSTRY (2014) [hereinafter FDA DRAFT GUIDANCE ON SAME SURGICAL PROCEDURE].

304. FDA DRAFT GUIDANCE ON HOMOLOGOUS USE, *supra* note 56.

305. FDA DRAFT GUIDANCE ON MINIMAL MANIPULATION, *supra* note 55.

306. U.S. FOOD & DRUG ADMIN., HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE BASED PRODUCTS (HCT/Ps) FROM ADIPOSE TISSUE: REGULATORY CONSIDERATIONS DRAFT GUIDANCE OF INDUSTRY (2014) [hereinafter FDA DRAFT GUIDANCE ON ADIPOSE TISSUE].

307. See 21 C.F.R. § 10.115(d) (2012) ("Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA."); *id.* § 10.115(g) (setting out procedures for Level 1 guidance documents).

308. Erica Seiguer & John J. Smith, *Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances*, 60 FOOD & DRUG L.J. 17, 30 (2005).

309. *Id.* at 21.

310. See 21 C.F.R. § 10.115.

1. *Same Surgical Procedure Draft Guidance*

In this draft guidance, the FDA clarifies when a product is excepted from the requirements applicable to section 361 products. The exception is codified in section 1271.15(b): “You are not required to comply with the requirements of this part if you are an establishment that removes [cell or tissue products] from an individual and implants *such [cell or tissue products]* into the same individual during the same surgical procedure.”³¹¹ The guidance clarifies that only a very limited number of steps may be performed on the cells or tissues outside of the body to qualify for the same surgical procedure exception. Specifically, the language of “such [cell or tissue products]” means that the cell or tissue product can only be “rinsed, cleaned, sized, or shaped.”³¹² Any other processing will cause the manufacturer to lose the same surgical procedure exception.³¹³

The FDA’s rationale for limiting the scope of the exception rests on the risk of infectious disease transmission.³¹⁴ Steps taken when the cells are processed, preserved, or removed from storage raise contamination concerns beyond those typically associated with surgery.³¹⁵ Thus, any such steps require the manufacturer to follow the requirements that apply to section 361 products or biologics.

2. *Minimal Manipulation Draft Guidance*

To qualify as a section 361 cell or tissue product, a product cannot be more than minimally manipulated.³¹⁶ The regulatory definition of minimal manipulation depends on whether the therapy uses a “structural tissue” or “cells or nonstructural tissue.”³¹⁷ If the tissue is structural, minimal manipulation is “processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s

311. 21 CFR § 1271.15(b) (emphasis added).

312. FDA DRAFT GUIDANCE ON SAME SURGICAL PROCEDURE, *supra* note 303, at 3 n.4.

313. *Id.* at 3.

314. *Id.*

315. *Id.* at 5.

316. Ravitz, Halpern & Leongini, *supra* note 54.

317. 21 C.F.R. § 1271.3(f)(1)–(2) (2004).

utility for reconstruction, repair, or replacement.”³¹⁸ In nonstructural tissue, minimal manipulation is “processing that does not alter the relevant biological characteristics of cells or tissues.”³¹⁹

The minimal manipulation draft guidance provides examples of minimal manipulation and provides general principles for application to other or future products.³²⁰ First, because the regulations set different standards for minimal manipulation depending on whether the tissue is structural or non-structural,³²¹ the guidance clarifies these terms. Structural tissue supports and serves “as a barrier or conduit, or connect[s], cover[s], or cushion[s].”³²² Examples of structural tissue include bone, skin, blood vessels, adipose (fat) tissue, articular cartilage, non-articular cartilage, and tendons or ligaments.³²³ Nonstructural tissues are “those that serve predominately metabolic or other biochemical roles in the body such as hematopoietic, immune and endocrine functions,” and include reproductive cells or tissues, cord blood, and pancreatic tissue, to name a few.³²⁴

Second, the draft guidance explains the standards for minimal manipulation by explaining and illustrating the foundational concepts of (1) structural tissues’ original relevant characteristics relating to its utility for reconstruction, repair, or replacement, and (2) non-structural tissues’ relevant biological characteristics.³²⁵ For instance, stem cells isolated from adipose tissue are more than minimally manipulated.³²⁶ This is because, according to the FDA, fat is a structural tissue, and its original relevant characteristics of padding and cushioning are based on its bulk and lipid storage capacity.³²⁷ Processing for stem cell extraction breaks down and eliminates the

318. *Id.* at § 1271.3(f)(1).

319. *Id.* at § 1271.3(f)(2).

320. FDA DRAFT GUIDANCE ON MINIMAL MANIPULATION, *supra* note 55, at 3, 5, 8.

321. *Id.* at 3.

322. *Id.* at 4.

323. *Id.* at 5.

324. *Id.* at 8.

325. *Id.* at 3.

326. FDA DRAFT GUIDANCE ON MINIMAL MANIPULATION, *supra* note 55, at 6.

327. *Id.* at 5–6.

structural components that provide cushioning and support, so the product is considered more than minimally manipulated.³²⁸

If a product is more than minimally manipulated, it loses section 361 status and is subject to regulation as a drug or biologic.³²⁹ The rationale is that products that are more than minimally manipulated have the potential to, or are intended to, change the cell or tissue's biological characteristics or functions, which raises concerns about the product's ultimate safety or effectiveness.³³⁰

3. *Homologous Use Draft Guidance*

A section 361 product must be intended for homologous use.³³¹ This means that the cells or tissues in the recipient must perform the same basic function in the recipient as in the donor.³³² This requirement addresses the concern that non-homologous uses raise safety and effectiveness concerns due to the diminished basis on which to predict the product's behavior.³³³ The requirement applies to both allogenic and autologous uses.³³⁴ In other words, there is no exception to this requirement even when the tissue is taken from and re-implanted into the same patient.³³⁵

The draft guidance clarifies terms and provides several examples. When the tissue is used for the exact same purpose in the donor and the recipient, the use is homologous; for example, a heart valve transplanted to replace a recipient's dysfunctional heart valve is a homologous use.³³⁶ A use in the recipient that has the same basic function as the use in the donor also qualifies.³³⁷ For example, the use of a pericardium (the membrane around heart) as a wound covering for defects of the dura mater (the membrane enveloping brain and

328. *Id.* at 8.

329. *Id.* at 2–3.

330. PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS, *supra* note 48, at 9721.

331. 21 C.F.R. § 1271.10(a)(2) (2004).

332. *Id.* § 1271.3(c).

333. FDA DRAFT GUIDANCE ON HOMOLOGOUS USE, *supra* note 56, at 3.

334. *Id.* at 2.

335. *See id.*

336. *Id.* at 4.

337. *Id.*

spinal cord) is a homologous use because it serves as a covering in both its original form and in the recipient.³³⁸ Uses that are not the same in the donor and recipient are not considered homologous.³³⁹ For example, because the basic function of hematopoietic stem cells is to form and replenish the blood system, any use outside of this purpose—like infusion to treat cerebral palsy—is not homologous.³⁴⁰ The FDA also clarifies that if the cell or tissue product is intended for use as an unproven treatment for a myriad of diseases or conditions, the use is not homologous.³⁴¹

4. *Adipose Tissue Products Draft Guidance*

In this draft guidance, the FDA specifically explains the section 361 requirements as applied to products derived from adipose (fat) tissue.³⁴² Adipose tissue is the most common source of stem cells used in unapproved stem cell therapies.³⁴³ The FDA “recently received numerous inquiries regarding [cell or tissue products] manufactured from adipose tissues.”³⁴⁴ In this draft guidance, the FDA states that it generally considers adipose tissue to be a structural tissue because it is a “connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs.”³⁴⁵ It is composed primarily of adipocyte cells, but also contains a number of other cell types.³⁴⁶

The guidance applies the section 361 requirements to adipose tissue. The FDA states that it considers adipose tissue more than minimally manipulated when it is processed to isolate the non-fat cells from the tissue.³⁴⁷ This means that the procedures stem cell

338. *See id.*

339. *See* FDA DRAFT GUIDANCE ON HOMOLOGOUS USE, *supra* note 56, at 4.

340. *See id.* at 5.

341. *See id.* at 6.

342. FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 1.

343. Turner & Knoepfler, *supra* note 23, at 156.

344. *Id.* at 2.

345. *Id.* at 1.

346. *Id.* at 1–2.

347. *Id.* at 3.

clinics use to extract stem cells from adipose tissue are generally considered more-than-minimal manipulation.³⁴⁸ In clarifying the homologous use requirement, the draft guidance states that the FDA would likely consider the use of adipose tissue as a cosmetic filler homologous use because this use reflects a basic function of adipose tissue: to support subcutaneous tissues.³⁴⁹ But the FDA would not consider the use of the tissue to treat bone and joint disease a homologous use because the tissue does not perform this function in the donor.³⁵⁰

These examples demonstrate that the FDA does not consider the products provided by stem cell clinics to meet the section 361 requirements of minimal manipulation and homologous use. The stem cell clinics generally isolate the non-fat cells for implantation, which the FDA defines as more than minimal manipulation.³⁵¹ And the clinics advertise the stem cell-derived products for functions other than those traditionally performed by adipose tissue, which the FDA interprets as non-homologous use.³⁵²

Furthermore, the draft guidance clarifies that the stem cell clinics' products are unlikely to fall within the same surgical procedure exception.³⁵³ This is because the exception considers cells to be the same cells (as expressed in the regulation, "such [cell or tissue products]") only if they are rinsed and cleansed to remove debris.³⁵⁴ Because the stem cell clinics typically engage in additional steps such as cell isolation, cell expansion, or enzymatic digestion, the products are not covered under the same surgical procedure exception.³⁵⁵

348. *Id.* at 4.

349. FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 5.

350. *Id.*

351. *Id.* at 6.

352. *Id.*

353. *Id.* at 8.

354. *Id.*

355. *See* FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 8.

B. Reforms to Expand the Scope of Section 361 and the Same Surgical Procedure Exception

1. Treatment of Autologous Therapies

a. Existing Proposals Suggest Treating Autologous Therapies as Exceptional

Several proposals for reform address the scope of section 361. A common theme among these proposals is to treat therapies that use the patient's own cells as source material, an autologous use, differently from those that use a donor's cells. This distinction is already partly captured in existing regulations: any use of cell or tissue products that affects the body systemically or depends on cell metabolism does not qualify for section 361 unless the cells come from a donor (or a first- or second-degree relative).³⁵⁶ But reformers want to see a greater distinction in the legal treatment of these uses. Professor Mary Ann Chirba and attorney Stephanie Garfield have argued that autologous therapies that are either developed or used by practicing physicians should be exempt from regulation or, alternatively, should be regulated under a more flexible framework than therapies developed by pharmaceutical companies.³⁵⁷ Failure to do so, they argued, will harm innovation, disrespect patient autonomy, and hamper the public's health.³⁵⁸ Attorney Greg Pivarnik came to a similar conclusion but for a different reason. He argued that although the FDA has the legal authority to regulate autologous stem cell treatments, it should decline to do so.³⁵⁹ He reasoned that the information asymmetry between pharmaceutical companies and patients justified premarket approval for traditional drugs and allogenic therapies, but that the personal doctor-patient relationship assuages fears that patients will make uninformed choices.³⁶⁰

356. 21 C.F.R. § 1271.10 (2017).

357. Chirba & Garfield, *supra* note 109, at 253.

358. *Id.* at 268.

359. Greg Pivarnik, *Cells as Drugs? Regulating the Future of Medicine*, 40 AM. J. L. & MED. 298, 319 (2014).

360. *Id.*

Furthermore, to the extent that doctors breach their duties to the patient, Pivarnik argued, state regulations and tort laws effectively address these concerns.³⁶¹ Other commentators, however, have disagreed and argued that autologous therapies should remain subject to FDA oversight because of their risks of contamination and infection.³⁶² Professor Barbara von Tigerstrom noted unique challenges with regulating autologous therapies, but argued that FDA regulation is still needed to ensure that the therapies are safe and effective.³⁶³

A more nuanced approach was offered by Jay Segal, chief biotechnology officer and head of scientific strategy and policy for Johnson & Johnson, during the FDA's hearing.³⁶⁴ Segal argued that the same surgical procedure exception should be applied more broadly to include autologous cell products that were minimally manipulated.³⁶⁵ The current regulations provide that only autologous therapies that are rinsed, cleansed, sized, and shaped are covered by the same surgery exception.³⁶⁶ Siegel argued that the current distinction between these products and products that undergo other "minimal" procedures, which are currently not allowed under the same surgical procedure exception, is not sound based on the cell or tissue product's risk of contamination and transmission of infectious diseases.³⁶⁷ Furthermore, he argued that existing regulations of surgical facilities ensure that these facilities have procedures in place to prevent the spread of communicable disease—so regulation of the entities as manufacturers of section 361 products is unnecessary and duplicative.³⁶⁸

361. *Id.* at 320.

362. *See, e.g.*, Barbara von Tigerstrom, *The Food and Drug Administration, Regenerative Sciences, and the Regulation of Autologous Stem Cell Therapies*, 66 *FOOD & DRUG L.J.* 479, 488, 502 (2011).

363. *Id.* at 504.

364. CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 40.

365. *Id.* at 40–42.

366. *Id.* at 88–89.

367. *Id.* at 40–42, 88–89 (statement of Dr. Jay Siegel, chief biotechnology officer and head of scientific strategy for Johnson & Johnson).

368. *Id.*

b. Autologous Therapies Should Not All Be Exempt from FDA Regulation, but Expansion of the Same Surgical Procedure Exception Is Justified

Reform proposals that promote removing *all* autologous therapies from FDA regulation are misguided. Under the current system, some autologous therapies where the cells are only rinsed, cleansed, sized, or shaped are exempt from FDA regulation;³⁶⁹ some where the cells are not more than minimally manipulated and are for homologous use are subject to the communicable disease regulations of section 361;³⁷⁰ and some that are more than minimally manipulated or not for homologous use are subject to regulation as biologics.³⁷¹ Working backward from the most restrictive to the least restrictive levels of regulation, it would be foolish to exempt all autologous regenerative medicine therapies from regulation as biologics. When a cell-based product is intended for a different purpose than the cells originally placed in the body, or when the cells have been altered in a way that affects their relevant characteristics, we do not know how the cells will function in the recipient absent clinical evidence.³⁷² And not only might the autologous therapies not work, they might cause physical harm.³⁷³ Former FDA Commissioner Robert Califf described two instances in which autologous therapies likely caused patient harms.³⁷⁴ In one instance, autologous hematopoietic stem cells that were injected into a patient with kidney failure were associated with the formation of tumors.³⁷⁵ In a separate instance, autologous stem cells derived from adipose tissue and injected into the eyes of three patients with macular degeneration were associated with worsening vision in all three.³⁷⁶

Removing all autologous therapies from section 361 regulations is also unwise. Minimal manipulation of cells—including banking,

369. *Id.* at 88–89.

370. CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 88–89.

371. *Id.* at 41–42.

372. *See* Marks et al., *supra* note 145, at 1008.

373. *Id.*

374. *Id.*

375. *Id.*

376. *Id.*

transporting, or processing—risks the transmission of communicable disease because the products are susceptible to contamination or mix-ups.³⁷⁷ For example, an infected product could cross-contaminate other products stored in the same liquid nitrogen in a freezer. Similarly, a product could contaminate processing equipment.³⁷⁸ The current Good Tissue Practice requirements that apply to all section 361 products set forth the procedures and controls to prevent such contamination.³⁷⁹ Furthermore, it is not at all clear that the regulations that govern hospitals and ambulatory surgical centers are sufficient to guard against viral and bacterial contamination.³⁸⁰

On the other hand, the FDA may be able to expand the same surgical procedure exception in some instances. For example, if certain processing techniques involve more manipulation than rinsing, cleansing, sizing, or shaping but do not increase the risk of contamination, such processes could be captured under the same surgical procedure exemption. For example, if the FDA determined that a certain closed processing system, or storage in liquid nitrogen vapors as opposed to the liquid, did not increase the risk of contamination, such processing steps could be captured under the same surgical procedure exception without compromising the purpose of the exception.

2. *Expanding the Scope of Section 361*

A second path to speeding products to market is to allow more therapies to qualify as section 361 products. This would permit the

377. PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS, *supra* note 48, at 12; *cf.* Poliana Alves Patah et al., *Microbial Contamination of Hematopoietic Progenitor Cell Products: Clinical Outcome*, 40 BONE MARROW TRANSPLANTATION 365, 366 (2007).

378. PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS, *supra* note 48, at 12.

379. See U.S. FOOD & DRUG ADMIN., CURRENT GOOD TISSUE PRACTICE (CGTP) AND ADDITIONAL REQUIREMENTS FOR MANUFACTURERS OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS): GUIDANCE FOR INDUSTRY 12 (2011).

380. See, e.g., Laura Landro, *The Informed Patient: At the Clinic, Care . . . and Infection*, WALL STREET J. (Oct. 25, 2011), <https://www.wsj.com/articles/SB10001424052970203911804576651243331232116> [https://perma.cc/63DR-TJZE] (reporting cases of dangerous transmissions of bacteria and viruses at ambulatory surgical centers).

manufacturers of these products to meet only the lighter requirements of section 361: registering with the FDA and implementing procedures to avoid contamination and the transmission of infectious disease.³⁸¹ Section 361 cell or tissue products avoid the lengthy clinical trials required to prove safety and effectiveness, or purity and potency, required for drugs and biological products.³⁸² A liberalization of section 361's requirements could occur if the FDA more loosely interpreted the homologous use and minimal manipulation requirements. For example, the homologous use requirement, as currently interpreted, states that adipose tissue used to fill in the hollows of the cheeks is a homologous use, but the use of the same tissue in breast reconstruction is not a homologous use. This is because, as stated by the FDA, the "basic function of breast tissue is to produce milk (lactation) after childbirth."³⁸³ And, because lactation is not a basic function of adipose tissue, such use would not be covered under section 361.³⁸⁴ A more liberal interpretation might allow for multiple basic function determinations of both the donated and recipient tissues.³⁸⁵ Similarly, the FDA could soften the minimal manipulation requirement. Currently, decellularization generally renders adipose tissue more than minimally manipulated because it alters its "original relevant characteristics" relating to its "utility for reconstruction, repair, or replacement."³⁸⁶ Because decellularization removes adipose tissue's bulk, it no longer provides cushioning and support, which are its original relevant characteristics.³⁸⁷ But if the FDA accepted other original relevant characteristics of adipose tissue, such as its paracrine function, additional therapies would meet the minimal manipulation requirement.³⁸⁸

381. Chirba & Garfield, *supra* note 109, at 251.

382. FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 6.

383. *Id.* at 5.

384. *Id.*

385. *See, e.g.*, CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 112 (statement of Dr. Mary Ann Chirba-Martin, professor of health law at Boston College Law School).

386. FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 4; CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 72–73.

387. FDA DRAFT GUIDANCE ON ADIPOSE TISSUE, *supra* note 306, at 1.

388. *See* CBER HCT/Ps Hearing, Sept. 12, 2016, *supra* note 149, at 115 (statement of Dr. Arnold Caplan, professor at Case Western Reserve University) ("Fat in particular has an absolutely essential

To the extent that a tissue or cell has multiple basic functions, the FDA should expand the homologous use requirement. Similarly, to the extent scientific evidence supports multiple original relevant characteristics for cells or tissues, the FDA should expand the minimal manipulation requirement. This will allow additional products that do not raise drug-level safety and effectiveness concerns to receive the lighter regulatory touch of section 361.

CONCLUSION

Reform is in the air. Industry representatives, patients and their advocates, politicians, and regulators are analyzing and advocating for changes to the regenerative medicine regulatory framework to best address how to bring innovative therapies to patients while avoiding common or foreseeable patient harms.

Significant reforms of the product approval framework for regenerative medicine therapies regulated as biologics have been proposed; they are impracticable and unwise. Existing proposals fall short because they fail to address problems with the FDA's authority, implementation challenges, and most significantly, safety and efficacy concerns. Continued study of lifecycle approaches, however, is warranted, because advances in regulatory science and regenerative medicine may enable the FDA to implement adaptive licensing with greater assurances of safety and effectiveness.

For moderate-risk products, although proposals that drastically expand the scope of products exempted from regulation are unwise, more incremental proposals that expand the same surgical procedure exception and the scope of products regulated under section 361 can be implemented without damaging section 361's underlying goals of avoiding contamination and the transmission of infectious disease.

The current system is not broken. Harnessing the body's ability to heal itself and translating this understanding into clinical practice is complicated and time-consuming, and the current framework already

paracrine activity as a tissue; and so, therefore, if you transplant or transfer fat from one tissue to another, you're taking advantage of its paracrine activities.'").

provides regulatory flexibility depending on a therapy's risks. Implementing regulatory shortcuts that will risk harming patients is not the answer, but neither is treating the current system as set in stone. Instead, advances in scientific understanding warrant incremental changes to the existing section 361 framework. And although an overhaul of the biologics framework is premature, advances in regulatory science and increased understanding of regenerative medicine may one day justify such an undertaking.

The next few years will bring significant advances to the regenerative medicine field, and its regulation must be flexible to keep pace. Whether the reforms are incremental or more transformative, measures taken now can ensure continued patient protection while advancing access to therapies when it is safe and appropriate.

