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The Tin Man Needs a Heart: A Proposed Framework for the Regulation of Bioprinted Organs

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THE TIN MAN NEEDS A HEART: A PROPOSED FRAMEWORK FOR THE REGULATION OF BIOPRINTED ORGANS

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Each day, seventeen people die in the United States while waiting for an organ transplant. At least part of this need could be met by bioprinting, a technology that allows the on-demand production of custom-sized organs from a patient's own cells.

The field of bioprinting is progressing rapidly: the first bioprinted organs have already entered the clinic. Yet, developers of bioprinted organs face significant uncertainty as to how their potentially lifesaving products will be regulated—and by which government agency. Such regulatory uncertainty has the potential to decrease investment and stifle innovation in this promising technological field.

This Note examines how the current framework for the regulation of medical products and human organs might be applied to bioprinted organs. This Note concludes that the existing regulatory schemes do not sufficiently address the specific regulatory needs created by bioprinted organs, which are uniquely interdisciplinary materials. Therefore, this Note proposes a new regulatory framework to reduce uncertainty for bioprinted organ developers and to promote patient access to these bioprinted materials that might soon serve as safe and effective replacements for donor organs.

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INTRODUCTION

Before long, tin men in search of a heart will no longer need to gather their friends and embark on an epic quest down a yellow brick road to find a

wizard[1]—they can simply visit their local (bio)printshop.[2] Bioprinting is a process in which living cells and other biological molecules are placed on a surface, layer by layer, to generate a three-dimensional structure.[3] In order to bioprint an organ, cells are first isolated from a patient.[4] Such cells may either be stem cells or cells isolated from the blood or skin that can be genetically reprogrammed to a stem cell-like state.[5] These cells are then cultivated in special growth media to induce cell multiplication and differentiation[6] into the specific cells needed for the organ to be printed (e.g., heart muscle cells for an artificial heart).[7] Based on the patient's unique anatomy, a computer model of the organ is developed.[8] Using this model as a blueprint, the differentiated cells are then layered onto a biocompatible scaffold using a printhead.[9] By employing different cell types and scaffolding materials, bioprinting can achieve complex geometric structures.[10] Finally, the bioprinted construction usually undergoes a maturation step in which the cells form a biological structure that more closely resembles a human organ.[11]

Compared to traditional organ transplantation, bioprinted transplants have significant advantages. First, artificial organs can be tailored to a patient's idiosyncratic anatomy and physiological needs.[12] Second, bioprinted organs are composed of a patient's own cells.[13] As such, the risk that a patient's immune system will reject the bioprinted organ is very low.[14] This is important because in traditional organ transplantation, patients need to take immunosuppressive drugs for the remainder of their lives to prevent their

1. *See* THE WIZARD OF OZ (Metro-Goldwyn-Mayer 1939).

2. *See* Cassie Kelly, *3D-Printed Organs Nearing Clinical Trials*, AM. SOC'Y MECH. ENG'RS (Mar. 3, 2020), https://www.asme.org/topics-resources/content/3d-printed-organs-nearing-clinical-trials [https://perma.cc/EV9Y-MEX8] (discussing timelines for clinical trials involving bioprinted organs).

3. *See* Željka P. Kačarević et al., *An Introduction to 3D Bioprinting: Possibilities, Challenges and Future Aspects*, MATERIALS, Nov. 6, 2018, at 1, 1.

4. *See* Chin S. Ong et al., *3D Bioprinting Using Stem Cells*, 83 PEDIATRIC RSCH. 223, 223 (2018).

5. *See id.* Stem cells are unspecialized cells that have the potential to develop into many different cell types with different functions (e.g., a heart muscle cell, skin cell, nerve cell, bone cell). *See id.*

6. Cellular differentiation refers to a biological process in which a cell changes from a less specialized type (e.g., a stem cell) to a more specialized type (e.g., a nerve cell). *See Cell Differentiation*, BIOLOGY DICTIONARY (June 20, 2018), https://biologydictionary.net/cell-differentiation/ [https://perma.cc/PF7L-CE4Z].

7. *See* Ong et al., *supra* note 4, at 223.

8. *See* Kačarević et al., *supra* note 3, at 2.

9. *See id.*

10. *See* Christina Kryou et al., *Bioprinting for Liver Transplantation*, BIOENGINEERING, Oct. 10, 2019, at 1, 1.

11. *See* Alana Mermin-Bunnell, *Integrating Bioprinted Organs into Our Healthcare System*, INTERSECT, Apr. 2, 2021, at 1–2, 3 fig.2; Fulden Ulucan-Karnak, *3D Bioprinting in Medicine*, GLOB. J. BIOTECHNOLOGY & BIOMATERIAL SCI., Jan. 12, 2021, at 001, 001–02.

12. *See* Kačarević et al., *supra* note 3, at 2.

13. *See* Ulucan-Karnak, *supra* note 11, at 001–02.

14. *See* Prajna Guha et al., *Lack of Immune Response to Differentiated Cells Derived from Syngeneic Induced Pluripotent Stem Cells*, 12 CELL STEM CELL 407, 407 (2013).

own immune systems from attacking the foreign object.[15] Costs for these immunosuppressive drugs range from about $10,000 to $14,000 per patient annually.[16] More importantly, long-term immunosuppressive therapy reduces an organ recipient's life expectancy, because such therapy significantly increases the risk of infections and the risk of developing certain types of cancer.[17] Third, organ demand exceeds supply: seventeen people die each day while waiting for an organ transplant.[18] In contrast, bioprinted organs can be made available to patients who would not otherwise receive an organ—either because no suitable organ is available or because the patients are not prioritized to receive a transplant as compared to other patients with more pressing medical needs or larger survival benefits.[19] Finally, bioprinted organs find various additional uses outside of the human body—for example, for use in efficacy and toxicity studies during drug development or as training tools for surgeons.[20]

While the production of a fully vascularized (i.e., equipped with blood vessels), ready-to-implant, bioprinted organ has not yet been realized, the field of bioprinting is progressing rapidly.[21] Significant advances have been made in the bioprinting of cartilage and bone, as well as muscle and liver tissues.[22] Researchers have already printed a small, functioning human heart pump, and bioprinted bladders have been successfully implanted into patients.[23] Further, significant progress has been made toward providing larger organs with the blood vessels needed for oxygen supply, one of the

15. *See* Bertam L. Kasiske et al., *Payment for Immunosuppression After Organ Transplantation*, 283 J. AM. MED. ASS'N 2445, 2445 (2000) (explaining that organ recipients need to take immunosuppressive drugs "indefinitely"); Nicholas M. Wragg et al., *A Critical Review of Current Progress in 3D Kidney Biomanufacturing: Advances, Challenges, and Recommendations*, RENAL REPLACEMENT THERAPY, May 9, 2019, at 1, 2 (explaining that immunosuppressive drugs prevent the patient's immune system from attacking the new organ).

16. *See* Kasiske et al., *supra* note 15, at 2446.

17. *See, e.g.*, Wragg et al., *supra* note 15, at 2.

18. *See Organ Donation Statistics*, HEALTH RES. & SERVS. ADMIN., https://www.organdonor.gov/learn/organ-donation-statistics [https://perma.cc/S67A-NLRV] (last visited Jan. 9, 2022).

19. *See How Organ Allocation Works*, U.S. OF DEP'T HEALTH & HUM. SERVS., https://optn.transplant.hrsa.gov/learn/about-transplantation/how-organ-allocation-works/ [https://perma.cc/K48S-7JB9] (last visited Mar. 4, 2022).

20. *See* Geraldine T. Klein et al., *3D Printing and Neurosurgery—Ready for Prime Time?*, 80 WORLD NEUROSURGERY 233, 233–34 (2013).

21. *See* Kryou et al., *supra* note 10, at 1.

22. *See generally* Bin Zhang et al., *3D Bioprinting: A Novel Avenue for Manufacturing Tissues and Organs*, 5 ENG'G 777 (2019).

23. *See* Mermin-Bunnell, *supra* note 11, at 4–5 (discussing clinical trials with bioprinted bladders); *Researchers 3D Print a Working Heart Pump with Real Human Cells*, UNIV. OF MINN. (July 15, 2020), https://twin-cities.umn.edu/news-events/researchers-3d-print-working-heart-pump-real-human-cells [https://perma.cc/58B2-G5Q5]; *Tel Aviv University Scientists Print First 3D Heart Using Patient's Biological Materials*, EUREKALERT! (Apr. 15, 2019), https://www.eurekalert.org/news-releases/498733 [https://perma.cc/JW7V-8NR4].

biggest challenges in this field.[24] Given the tremendous potential of bioprinted materials to provide lifesaving organ replacements to thousands of patients in need, the question arises as to how governments can warrant the safety of these medical products without stifling innovation in this exciting scientific field.[25]

The U.S. Food and Drug Administration (FDA) is tasked with ensuring the safety, efficacy, and security of human and veterinary medical products in the United States.[26] However, this Note argues that existing regulatory frameworks are a poor fit for bioprinted organs, which creates significant uncertainty among manufacturers of these medical products (and their investors) about how to best prepare for the regulatory approval process.[27] Further, it is not clear whether the National Organ Transplant Act[28] (NOTA), which prohibits the sale of human organs, also applies to *bioprinted* organs.[29] Accordingly, to reduce uncertainty among relevant industry stakeholders while simultaneously ensuring the safety of bioprinted organs for their recipients, more regulatory guidance for bioprinted organs is needed.

This Note proposes a framework for the regulation of bioprinted organs that allows for an efficient safety and efficacy review of these medical products while at the same time promoting innovation in the bioprinting space.[30] Part I discusses the goals of federal regulation of medical products and organs. Part I also explains how the FDA has based its organizational structure on the different categories of medical products the agency regulates.

Part II applies the existing regulatory framework for medical products to bioprinted organs. Here, Part II.A notes that significant uncertainty exists as to whether NOTA applies to bioprinted organs. Part II.B discusses how bioprinted organs will likely not be afforded the minimal oversight that applies to certain cell and tissue products regulated by the FDA. Part II.C concludes that while bioprinted organs will most likely be regulated as combination products by the FDA under existing regulatory frameworks, applying the FDA's current approach to combination products to bioprinted organs might pose significant challenges.

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24. *See* Jade Boyd, *Organ Bioprinting Gets a Breath of Fresh Air*, RICE UNIV., (May 2, 2019), https://news.rice.edu/2019/05/02/organ-bioprinting-gets-a-breath-of-fresh-air-2/ [https://perma.cc/4YQB-GQTM].

25. Over 100,000 people are on the national transplant waiting list alone. *See Organ Donation Statistics*, *supra* note 18. The three-dimensional bioprinting industry has been estimated to be valued at $1.95 billion by 2025. *See 3D Bioprinting Industry Worth $1.95 Billion by 2025—Increasing Investments in Healthcare Applications, Such as Model and Organ Prototyping & Production*, CISION PR NEWSWIRE (Mar. 19, 2020, 6:00 PM), https://www.prnewswire.com/news-releases/3d-bioprinting-industry-worth-1-95-billion-by-2025---increasing-investments-in-healthcare-applications-such-as-model-and-organ-prototyping--production-301026860.html [https://perma.cc/FT3X-REBU].

26. *See What We Do*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), https://www.fda.gov/about-fda/what-we-do [https://perma.cc/Q5PX-J6J9].

27. *See infra* Part II.

28. 42 U.S.C. §§ 201 note, 273, 274–274e.

29. *See infra* Part II.A.

30. *See infra* Part III.

Finally, Part III reasons that the existing regulatory framework creates significant uncertainty for sponsors of bioprinted organs and does not offer the interdisciplinary review needed to sufficiently warrant the safety and efficacy of bioprinted organs. Accordingly, this Note outlines a new approach for the regulation of these innovative materials. Specifically, Part III.A argues that bioprinted organs do not—and should not—fall under the jurisdiction of NOTA. Thus, this Note proposes to explicitly exclude bioprinted organs from the statutory definition of human organ.[31] Further, Part III.B recommends establishing a new FDA center with the interdisciplinary expertise required to ensure the safety and efficacy of bioprinted organs. Finally, Part III.C proposes a regulatory framework that seeks to promote both innovation and competition in the bioprinted organ space. Specifically, Part III.C proposes to award bioprinted organs with a long regulatory exclusivity,[32] paired with a requirement for the FDA to disclose manufacturing information for bioprinted organs to companies seeking to produce generic versions of the organ once the exclusivity period has expired. In sum, this Note aims to reduce regulatory uncertainty for manufacturers and developers of bioprinted organs by providing a regulatory bioprinting framework that promotes innovation and competition in the bioprinting space, thus benefiting both producers and recipients of bioprinted organs.

I. EXISTING FEDERAL REGULATION OF MEDICAL PRODUCTS AND ORGANS

Before exploring how bioprinted organs *should* be regulated, it is important to understand what federal frameworks currently exist for the regulation of medical products and human organs. Part I.A discusses the goals of federal regulation of medical products, specifically the goals behind the Federal Food, Drug, and Cosmetic Act[33] (FDCA) and the Public Health Service Act[34] (PHSA). Part I.B provides a primer on different medical product categories. Part I.C discusses why developers and manufacturers of medical products care about which regulatory category their product falls into. Part I.D explains how the FDA handles the review of combination products, which have characteristics of medical products falling into more than one regulatory category. Finally, Part I.E discusses the regulation of human organs under NOTA.

31. *See infra* Part III.A.2.

32. Generally speaking, regulatory exclusivities are awarded to an entity that first brings a specific medical product to market and refer to a time period during which the FDA does not accept and/or approve FDA applications submitted by competitors for the same active ingredient or same medical product. *See* Brandon Burch, *Types of Marketing Exclusivity in Drug Development*, NUVENTRA PHARMA SCIS. (Aug. 18, 2019), https://www.nuventra.com/resources/blog/types-of-marketing-exclusivity/ [https://perma.cc/2VJN-34YU].

33. Ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

34. Ch. 373, 58 Stat. 682 (1944) (codified as amended in scattered sections of 42 U.S.C.).

A. Goals of Federal Regulations Relating to Medical Products

Medical products are regulated by several federal statutes, most prominently the FDCA and the PHSA. In passing the FDCA and its numerous amendments over the years, Congress has endowed the FDA with immense power to control the market approval, manufacturing, advertising, and distribution of medical products to health-care providers, pharmacies, and patients.[35] In fact, the FDCA has been called "one of the most important regulatory statutes in American and perhaps global history."[36] However, since the FDA's regulatory power is based on Congress's authority to regulate interstate commerce, the agency may not unduly interfere with the practice of medicine or the practice of pharmacy, which are regulated by the states.[37]

The primary goal of the FDCA, passed in 1938, was to protect consumers from dangerous products.[38] In 1962, Congress expanded the FDA's authority to require that drugs marketed in the United States are not only safe but also effective.[39] To this day, promoting public health through ensuring the safety and efficacy of medical products has remained the FDA's top priority.[40] In the 1970s, technological advances arising from space exploration resulted in an increase of medical devices marketed in the United States.[41] Although the FDA found that many of these devices presented an actual danger to patients, the agency was not authorized to take any action on these devices until *after* the devices had been marketed under the provisions of the 1938 FDCA.[42] Accordingly, the 1976 amendments of the FDCA required that manufacturers meet new safety and efficacy requirements *before* entering the market.[43] Medical devices are now divided into three

35. *See* Anna B. Laakmann, *Customized Medicine and the Limits of Federal Regulatory Power*, 19 VAND. J. ENT. & TECH. L. 285, 286 (2017).

36. *See* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 73 (2010).

37. *See* Hipolite Egg Co. v. United States, 220 U.S. 45, 57 (1911) (stating that the Pure Food and Drug Act, the precursor to the FDCA, was based "upon the power of Congress to regulate interstate commerce").

38. *See* United States v. Sullivan, 332 U.S. 689, 696 (1948) (stating that that FDCA was "designed primarily to protect consumers from dangerous products"); David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provision*s, 6 LAW & CONTEMP. PROBS. 2, 20 (1938).

39. *See* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (stating that the FDCA was amended to "assure the safety, effectiveness, and reliability of drugs").

40. *See* 21 U.S.C. § 393(b); Janet Woodcock, *Safety, Efficacy, and Quality Remain Top Priorities as We Continue Our Work to Expand Access to Cost-Saving Generic Drugs for the American Public*, U.S. FOOD & DRUG ADMIN. (May 13, 2019), https://www.fda.gov/news-events/fda-voices/safety-efficacy-and-quality-remain-top-priorities-we-continue-our-work-expand-access-cost-saving [https://perma.cc/G92K-TKMF].

41. *See* 1 JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, FOOD AND DRUG ADMIN. § 3:8 (4th ed. 2021).

42. *See* Margaret Harris, *Legislation to Regulate Medical Devices*, 3 BIOMATERIALS, MED. DEVICES & ARTIFICIAL ORGANS 261, 261 (1975).

43. *See* Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (codified as amended in scattered sections of 15, 21, and 42 U.S.C.); Harris, *supra* note 42, at 261.

groups based on the risk they pose to patients.[44] The 1976 amendments also imposed regulatory requirements that are proportional to the degree of risk posed by each device class.[45]

The 1962 and 1976 FDCA amendments concluded the FDA's transformation from a reactive policeman to a proactive gatekeeper.[46] As a result of these amendments, the (legal) marketing of a medical product in the United States is now impossible without the FDA's preapproval.[47] This transformation was not without criticism, however.[48] Some commentators have argued that the FDA has taken its gatekeeping role too far, accusing the agency of hampering innovation and precluding patients from receiving access to novel treatments.[49] Further, lawmakers have come to appreciate that patients will only benefit from safe and effective medical technologies if companies are sufficiently motivated to actually develop them.[50] Accordingly, many of the more recent FDCA amendments were explicitly aimed at fostering technological innovation and promoting competition among manufacturers of medical products.[51] For example, Congress has passed legislation to incentivize manufacturers to develop drugs for the treatment of rare diseases, stimulate innovation, and accelerate patient access to breakthrough medical technologies.[52] Similarly, both the Drug Price Competition and Patent Term Restoration Act of 1984[53] ("Hatch-Waxman Act") and the Biologics Price Competition and Innovation Act of 2009[54] ("Biologics Act") had two primary goals: (1) promoting innovation in pharmaceutical research and development and (2) increasing patient access to cheaper follow-on drugs.[55]

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44. *See* 21 U.S.C. § 360c.

45. *See id.*

46. *See* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1776 (1996).

47. *See id.* at 1753.

48. *See id.* at 1754 n.2.

49. For a good overview of the debate, see generally *id.* *See also* Henry G. Grabowski & John M. Vernon, *Consumer Protection Regulation in Ethical Drugs*, 67 AM. ECON. REV. 359 (1977); William M. Wardell, *Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison*, 14 CLINICAL PHARMACOLOGY & THERAPEUTICS 773 (1973).

50. *See, e.g.*, 21 U.S.C. § 360aa note ("Congressional Findings").

51. *See Selected Amendments to the FD&C Act*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2018), https://www.fda.gov/regulatory-information/laws-enforced-fda/selected-amendments-fdc-act [https://perma.cc/VHU4-GPR4].

52. *See* 21 U.S.C. § 360aa note ("Congressional Findings"); *id.* §§ 356, 393 note ("Advancing Regulatory Science To Promote Public Health Innovation"); 21st Century Cures Act, Pub. L. No. 114-255, §§ 3001–3102, 130 Stat. 1033, 1083–156 (2016) (codified as amended in scattered sections of 21 and 42 U.S.C.); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 1 (2014), https://www.fda.gov/media/86377/download [https://perma.cc/8QDH-ZGTS].

53. Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28, and 35 U.S.C.).

54. Pub. L. No. 111-148, tit. VII, §§ 7001–7003, 124 Stat. 804, 804–21 (codified as amended in scattered sections of the U.S.C.).

55. *See* Teva Pharm. Indus. v. Crawford, 410 F.3d 51, 54 (D.C. Cir. 2005); H.R. REP. NO. 98-857, pt. 1, at 14–15 (1984); Henry Grabowski & Erika Lietzan, *FDA Regulation of*

The FDCA is not the only federal statute relevant to medical product regulation. Certain medical products, including antibodies, cells, and tissues are also regulated under the PHSA.[56] Similar to the FDCA, the PHSA's main goal is to ensure that biologics marketed in the United States are safe, pure, and potent.[57] Further, Congress passed the PHSA in 1944, inter alia, to provide grants to advance medical and public health science to benefit the public.[58]

In short, the primary goal of medical product legislation and regulation is protecting public health by ensuring the safety and efficacy of medical products. Additionally, Congress sought to promote innovation, increase competition among manufacturers, and expand patient access to medicines.

B. Regulatory Categories of Medical Products

To streamline the regulatory approval process, Congress has created a regulatory framework, based on medical product categories, that accounts for the specific regulatory considerations that different products will demand.[59] For this Note's purposes, the most relevant regulatory categories are (1) drugs; (2) biological products; (3) medical devices; and (4) human cells, tissues, and cellular and tissue-based products ("cell and tissue products").[60] Regulatory requirements concerning safety, effectiveness for the intended use, manufacturing methods, and labeling differ significantly among these categories.[61]

Drugs are articles (other than food) intended to be used for treating, curing, preventing, or diagnosing disease in human or other animals.[62] Drugs are specifically intended to affect the structure or function of the human or animal body.[63] Because the statutory definition of drug is fairly broad, the definition technically also encompasses biologics and medical devices.[64] For

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Biosimilars, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 414, 414 (Holly F. Lynch & I. Glenn Cohen eds., 2015). In this Note, the sponsors of the first drug or biologic approved by the FDA for a specific condition are referred to as an "innovator company." Sponsors of therapies that enter the market after the innovator product are referred to in this Note as "follow-on companies."

56. *See* 42 U.S.C. § 262; *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN. (Feb. 6, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers [https://perma.cc/VL2B-BWZX].

57. *See* 42 U.S.C. § 262(a)(2)(C).

58. *See* Alanson W. Willcox, *The Public Health Service Act, 1944*, 7 SOC. SEC. BULL. 15, 16 (1944).

59. *See generally* AGATA BODIE & AMANDA K. SARATA, CONG. RSCH. SERV., IF11083, MEDICAL PRODUCT REGULATION: DRUGS, BIOLOGICS, AND DEVICES (2019).

60. *See id*.; *Tissue & Tissue Products*, U.S. FOOD & DRUG ADMIN. (Jan. 27, 2021), https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products [https://perma.cc/U82L-L8W9]. The FDA refers to these products as "HCT/Ps." *Id.*

61. *See* BODIE & SARATA, *supra* note 59.

62. *See* 21 U.S.C. § 321; *Human Drugs*, U.S. FOOD & DRUG ADMIN. (Mar. 5, 2021), https://www.fda.gov/industry/regulated-products/human-drugs [https://perma.cc/7FDD-SS9X].

63. *See* 21 U.S.C. § 321.

64. *See* BODIE & SARATA, *supra* note 59.

this Note's purposes, a "drug" refers to a compound that falls into the statutory definition of a drug but that is *not* also a biologic[65] or a medical device.[66] Most medical products referred to in this Note as "drugs" are small molecules (i.e., relatively simple chemical compounds such as aspirin).[67]

Biological products ("biologics") include therapeutic proteins, cell therapies, viruses, vaccines, blood and blood components, and similar products used for the treatment, cure, and prevention of disease.[68] While most drugs are chemically synthesized and have a known chemical structure, biologics are customarily manufactured in living cells (or *are* living cells) and constitute complex mixtures.[69] Therefore, biologics often cannot be characterized as easily as drugs.[70]

Medical devices are instruments, apparatuses, implants, or articles used in the prevention, treatment, cure, or diagnosis of a disease.[71] These devices do not achieve their primary intended purpose through chemical action within the body and are not dependent on metabolization to achieve their therapeutic effects.[72] Common medical devices include pacemakers and toothbrushes.[73]

Finally, cell and tissue products are articles that contain or consist of human cells or tissues and are implanted, transplanted, or otherwise transferred into a human recipient.[74] Examples of cell and tissue products include bones, skin, heart valves, corneas, and stem cells derived from blood.[75] The definition of cell and tissue products explicitly excludes vascularized human organs for transplantation and blood or blood components.[76]

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65. See *infra* text accompanying notes 68–70 for a definition of "biologic."

66. See *infra* text accompanying notes 72–73 for a definition of "medical device."

67. *See Points to Consider in Drug Development of Biologics and Small Molecules*, NUVENTRA PHARMA SCIS. (May 13, 2020), https://www.nuventra.com/resources/blog/small-molecules-versus-biologics/ [https://perma.cc/MBU5-FZ7Z].

68. *See* 42 U.S.C. § 262(i). This definition does not list diagnosing disease. *See id.*; *see also Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN. (July 7, 2015), https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products [https://perma.cc/V4DA-AN62].

69. *See What Are "Biologics" Questions and Answers*, *supra* note 56.

70. *See id.*

71. *See* 21 U.S.C. § 321; *How to Determine If Your Product Is a Medical Device*, U.S. FOOD & DRUG ADMIN. (Dec. 16, 2019), https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device [https://perma.cc/J6HF-7FRK].

72. *See* 21 U.S.C. § 321; *How to Determine If Your Product Is a Medical Device*, *supra* note 71.

73. *See* Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 277, 279 (2016).

74. *See* 21 C.F.R. § 1271.3(d) (2022); *Tissue & Tissue Products*, *supra* note 60.

75. *See* 21 C.F.R. § 1271.3(d).

76. *See id.* Vascularized human organs are regulated by the Health Resources and Services Administration (HRSA). *See* Organ Procurement and Transplantation Network, 78 Fed. Reg. 40,033, 40,033 (July 3, 2013) (to be codified at 42 C.F.R. pt. 21); *infra* Part I.E.

The FDA's organizational structure largely mirrors the categories of medical products the agency regulates.[77] To streamline the regulatory review process, the FDA has assigned jurisdiction for each medical product category to an FDA agency center with specialized expertise in that category.[78] The FDA's organizational structure is not static, however. Throughout its history, the FDA has formed new centers or abolished old ones in light of technological advancement and statutory expansion of the FDA's authority.[79] Further, to provide a better match between medical product and regulatory expertise, the FDA has occasionally reassigned jurisdiction for certain medical products in response to advancements in regulatory science.[80]

Currently, drug approval is overseen by the Center for Drug Evaluation and Research ("FDA drug center").[81] Biologics licensure is generally handled by the Center for Biologics Evaluation and Research ("FDA biologics center").[82] Medical devices are regulated by the Center for Devices and Radiological Health ("FDA device center").[83] Depending on their specific type, cell and tissue products are regulated by the FDA biologics or device center.[84]

In short, the FDA is organized into centers of regulatory expertise, with each center taking primary responsibility for a medical product category.[85]

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77. *See* BODIE & SARATA, *supra* note 59.

78. *See* Howard Manresa & Arlen D. Meyers, *Combination Products and the FDA: Issues and Answers*, 2 BIOTECHNOLOGY HEALTHCARE 41, 42 (2005).

79. *See, e.g.*, Delegations of Authority and Organization, 48 Fed. Reg. 8442, 8443 (Mar. 1, 1983) (to be codified at 21 C.F.R. pt. 5); Statement of Organization, Functions, and Delegations of Authority, 47 Fed. Reg. 26,913, 26,913 (June 22, 1982); *A Brief History of the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN. (Jan. 31, 2018), https://www.fda.gov/about-fda/fda-history-exhibits/brief-history-center-drug-evaluation-and-research#display_35 [https://perma.cc/V38J-3XAZ].

80. *See Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN. (Feb. 16, 2018), https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research [https://perma.cc/7Z8S-HYLV] (noting that certain biologics, which provide similar effects in the human body as small molecule drugs, have been transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research).

81. *See* 21 C.F.R. pts. 200–499 (2022) (regulation of drugs); BODIE & SARATA, *supra* note 59.

82. *See* 21 C.F.R. pts. 600–680 (2022) (regulation of biologics); BODIE & SARATA, *supra* note 59.

83. *See* 21 C.F.R. pts. 800–898 (2022) (regulation of medical devices); BODIE & SARATA, *supra* note 59.

84. *See FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, U.S. FOOD & DRUG ADMIN. (Feb. 1, 2018), https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/fda-regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-product-list [https://perma.cc/BMY7-KW66].

85. *See* Manresa & Meyers, *supra* note 78, at 42.

C. Why FDA Regulatory Categories Matter to Sponsors

Sponsors[86] care significantly about which category their medical product falls into.[87] First, the stringency of the regulatory review process (and thus the time and costs involved in obtaining FDA approval) differs significantly among different categories of medical products.[88] Further, Congress offers certain financial incentives like regulatory exclusivities to sponsors of some, but not all, medical products.[89] As such, the choice of regulatory category is an important financial consideration for sponsors and their investors.

1. Stringency of the Scientific and Regulatory Review Process

Drugs, biologics, and medical devices all require premarket approval, meaning that manufacturers need to obtain the FDA's permission *before* marketing their product.[90] Generally, drugs and biologics face a more stringent premarket review than medical devices.[91] Although the approval pathways for biologics and drugs are similar, it is generally easier for manufacturers of follow-on drugs ("generics") compared to sponsors of follow-on biologics ("biosimilars") to take advantage of certain abbreviated FDA approval pathways.[92] Finally, certain cell and tissue products are exempt from premarket approval, while others require full premarket review.[93]

Medical devices are classified based on the degree of risk they pose to consumers.[94] Most relevant for this Note are Class III devices, which are products that sustain or support life, that are implanted, or that present a potentially unreasonable risk of illness or injury.[95] Sponsors of Class III devices need to provide "reasonable assurance" that the device is both safe and effective.[96] Effectiveness must be based on well-controlled studies, which can include clinical data or, if appropriate, bench testing or animal studies.[97] Finally, manufacturers of medical devices benefit from the "least burdensome principle," meaning that sponsors are only required to provide

86. A "sponsor" is a person initiating and taking responsibility for a clinical investigation (e.g., a pharmaceutical company, a government agency, or an academic institution). *See* 21 C.F.R. § 312.3 (2022).

87. *See infra* Parts I.C.1, I.C.2.

88. *See infra* Part I.C.1.

89. *See infra* Part I.C.2.

90. *See supra* note 46 and accompanying text.

91. *See* BODIE & SARATA, *supra* note 59.

92. *See infra* text accompanying notes 106–19. See *supra* note 55 for definitions of "innovator company" and "follow-on company."

93. *See infra* text accompanying notes 120–24.

94. *See* 21 U.S.C. § 360c(a); *How to Study and Market Your Device*, U.S. FOOD & DRUG ADMIN. (Oct. 14, 2020), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device [https://perma.cc/NN2U-6XR7].

95. *See* 21 U.S.C. § 360c(a)(1)(C).

96. *See* 21 C.F.R. § 860.7(c)(1) (2022).

97. *See* 21 C.F.R. § 860.7(d)(2) (2022); *PMA Clinical Studies*, U.S. FOOD & DRUG ADMIN. (May 22, 2020), https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies#determination [https://perma.cc/ESR4-ZXMW].

the minimum amount of information that adequately addresses any regulatory questions raised by the FDA.[98]

There are significant similarities between the drug and the biologics approval pathways.[99] For example, the overall stringency of the safety and efficacy review processes for drugs and biologics is very similar.[100] Both review processes are more burdensome and costly for sponsors than the medical device review process.[101] Additionally, when it comes to efficacy, sponsors of drugs will need to provide "substantial evidence" (as opposed to only the "reasonable assurance" that is required for medical devices) that the drug will have the intended therapeutic effect.[102] Similarly, sponsors of biologics need to show that their medical product is "safe, pure, and potent."[103] Here, the FDA construes potency to include effectiveness.[104] For both drugs and biologics, a showing of effectiveness usually requires both clinical trials and preclinical studies.[105]

One practical area in which the approval pathways for drug and biologics differ is that it is easier for generics manufacturers (compared to biologics manufacturers) to rely on the innovator's clinical data as part of the follow-on manufacturer's own FDA application.[106] Congress incentivizes innovator companies to take on the costly development of novel drugs and biologics by granting regulatory exclusivities, which are essentially periods of government-sanctioned monopolies.[107] Once the monopoly period has expired, follow-on manufacturers benefit from an accelerated approval process in which they can partially or fully rely on the safety and efficacy data generated by the innovator company.[108] Such data reuse significantly reduces the cost of obtaining regulatory approval for sponsors of follow-on products and further reduces the number of unnecessary clinical trials.[109]

98. *See* U.S. FOOD & DRUG ADMIN., THE LEAST BURDENSOME PROVISIONS: CONCEPT AND PRINCIPLES 4–5 (2019), https://www.fda.gov/media/73188/download [https://perma.cc/VM7S-KRHM].

99. *See* BODIE & SARATA, *supra* note 59.

100. *See* 21 U.S.C. § 355 note ("Special Rule") (instructing the FDA to minimize the differences between the drug and biologics review processes).

101. *See* BODIE & SARATA, *supra* note 59.

102. *See* 21 U.S.C. § 355(d); *supra* note 96.

103. *See* 42 U.S.C. § 262(k)(2).

104. *See* 21 C.F.R. § 600.3(s) (2022).

105. *See generally* INST. OF MED., COMM. ON ACCELERATING RARE DISEASES RSCH. & ORPHAN PROD. DEV., *Development of New Therapeutic Drugs and Biologics for Rare Diseases*, *in* RARE DISEASES AND ORPHAN PRODUCTS 147 (Marylin J. Field & Thomas F. Boat eds., 2010).

106. *See generally* Yaniv Heled, *Follow-On Biologics Are Set Up to Fail*, U. ILL. L. REV. ONLINE 113 (2018).

107. *See infra* Part I.C.2.

108. *See Abbreviated New Drug Application (ANDA)*, U.S. FOOD & DRUG ADMIN. (Jan. 14, 2022), https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda [https://perma.cc/A8EQ-XQFM]; *Biosimilar Development, Review, and Approval*, U.S. FOOD & DRUG ADMIN. (Oct. 20, 2017), https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval [https://perma.cc/XRT6-TRM9].

109. *See Biosimilar Development, Review, and Approval*, *supra* note 108.

Finally, patients benefit because increased competition among pharmaceutical companies usually results in lower drug prices.[110]

To take advantage of the abbreviated review process for a generic, manufacturers need to show that (1) the generic contains the same active ingredient as the innovator drug; (2) the two products have the same route of administration, dosage form, and strength; and (3) the generic drug is expected to have the same therapeutic effect as the original product when administered to a patient.[111] These requirements can often be met relatively easily without the need to run clinical trials.[112]

Biologics are much more complex than small molecule drugs, and the process for manufacturing them can significantly influence a biologic's therapeutic activity.[113] To utilize the abbreviated review process for a biosimilar (i.e., a follow-on biologic), manufacturers need to demonstrate that their product is "highly similar" to the innovator biologic and that there are no clinically meaningful differences between the biological product and the innovator product in regard to safety, purity, and potency.[114] However, without precise knowledge of the hundreds of steps involved in making the innovator biologic, it is nearly impossible for a follow-on manufacturer to produce an identical copy of the innovator product.[115] While innovator companies share their manufacturing protocols with the FDA as part of their biologics license application, the FDA cannot disclose this proprietary information to biosimilar manufacturers under the FDA's confidentiality policies.[116] Additionally, the FDA may not even compare the manufacturing processes for the innovator and the follow-on drug when internally reviewing the marketing application submitted by a follow-on manufacturer.[117] Accordingly, biosimilar manufacturers not only need to develop their own manufacturing process, they further have to conduct clinical trials to demonstrate biosimilarity.[118] As a result, the development of a biosimilar is significantly more expensive and takes more time than the development of a generic.[119]

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110. *See* RYAN CONRAD & RANDALL LUTTER, U.S. FOOD & DRUG ADMIN., GENERIC COMPETITION AND DRUG PRICES: NEW EVIDENCE LINKING GREATER GENERIC COMPETITION AND LOWER GENERIC DRUG PRICES 1 (2019), https://www.fda.gov/media/133509/download [https://perma.cc/FZ3Q-DEWU].

111. *See* 21 U.S.C. § 355(j)(2).

112. *See* Heled, *supra* note 106, at 120.

113. *See Frequently Asked Questions About Therapeutic Biological Products*, *supra* note 68.

114. 42 U.S.C. § 262(k).

115. *See* Yaniv Heled, *The Case for Disclosure of Biologics Manufacturing Information*, 47 J.L. MED. & ETHICS 54, 56 (2019).

116. *See id.* at 54.

117. *See id.* at 56.

118. *See Biosimilar Development, Review, and Approval*, *supra* note 108.

119. *See Biosimilars vs. Generics: What's the Difference?*, PFIZER, https://www.pfizer.com/sites/default/files/investors/financial_reports/annual_reports/2018/our-innovation/progressing-our-science/biosimilars-vs-generics/index.html [https://perma.cc/6QHT-PZRN] (last visited Mar. 4, 2022) (noting that the development of a biologic costs more

Finally, some—but not all—cell and tissue products are subject to the same stringent safety and efficacy review that the FDA applies to drugs and biologics under the FDCA.[120] Certain cell and tissue products that pose a lower safety risk are not subject to premarket review, and their sponsors only need to comply with certain registration, manufacturing, and reporting requirements under the PHSA.[121] Cellular products are only low-risk if they are "minimally manipulated," meaning that the cells contained in the product did not undergo a type of processing that changes the cells' original relevant characteristics.[122] Further, the cell or tissue cannot be combined with another article (except for water or certain substances such as sterilizing or storage agents).[123] Accordingly, cell and tissue products that are more than just minimally manipulated (e.g., genetically modified) and/or cell and tissue products that are combined with another article (e.g., a scaffold) undergo a stricter regulatory review and require FDA approval to market.[124]

In short, the FDA's requirement for ensuring the safety and efficacy of a medical product significantly depends on which category the product falls into. Biologics and drugs generally face a more stringent regulatory review than medical devices, and some cell and tissue products are exempt from premarket review altogether.

2. Regulatory Exclusivities

Congress uses regulatory exclusivities as financial "carrots" to reward innovator companies for developing certain new medical products and bringing them to market.[125] The most valuable exclusivity type is "market exclusivity," which refers to a time period during which an innovator company is granted an exclusive right by the FDA to commercialize the company's product.[126] During this time, the FDA will generally not accept

than $100 million and may take five to nine years, whereas the development of a generic drug "only" costs $1 million to $2 million and takes about two years).

120. *See* U.S. FOOD & DRUG ADMIN., REGULATORY CONSIDERATIONS FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: MINIMAL MANIPULATION AND HOMOLOGOUS USE 2–4 (2020), https://www.fda.gov/media/109176/download [https://perma.cc/FL6F-X8EJ].

121. These lower risk cell and tissue products are regulated solely under section 261 of the PHSA (42 U.S.C. § 264) and 21 C.F.R. § 1271 (2022). *See* U.S. FOOD & DRUG ADMIN., *supra* note 120, at 2–3. For example, if a manufacturer removes the outer layer from skin and freeze-dries the remaining connective tissue, the resulting product will likely not be subject to premarket review. *See id.* at 12–13.

122. *See* 21 C.F.R. § 1271.3(f) (2022); 21 C.F.R. § 1271.10(a) (2022).

123. *See* 21 C.F.R. § 1271.10(a).

124. *See* 21 C.F.R. § 1271.20 (2022) (explaining that cell and tissue products that do not meet the exemption criteria provided in 21 C.F.R. § 1271.10(a) will be regulated as a drug, biological, or medical device).

125. *See* JOHN R. THOMAS, CONG. RSCH. SERV., 7-5700, REGULATORY EXCLUSIVITY REFORM IN THE 115TH CONGRESS (2017); Sarah Hennebry, *When a 20 Year Patent Term Just Isn't Enough: Market and Data Exclusivity*, FPA PAT. ATT'YS (Jan. 31, 2018), https://www.fpapatents.com/resource?id=483 [https://perma.cc/9WAQ-NAYR].

126. *See* Hennebry, *supra* note 125.

any applications by follow-on companies.[127] As a practical matter, this means that the innovator company can charge significantly higher prices during this time period than the company would be able to with competitors in the market.[128] "Data exclusivity" refers to a time period in which follow-on companies are prevented from utilizing an abbreviated FDA approval pathway that would allow the follow-on company to rely on certain clinical and other safety information previously submitted by the innovator drug company for the purposes of obtaining regulatory approval.[129] Follow-on companies are, of course, free to generate their own clinical safety and efficacy data and seek approval through the regular review process.[130] However, since the latter is significantly more costly, data exclusivity can still serve as a powerful deterrent to market entry for follow-on companies.[131]

In general, medical products that take more time and money to develop, manufacture, and shepherd through the FDA review process are rewarded with a longer exclusivity period.[132] For instance, biologics are afforded twelve years of market exclusivity, the longest exclusivity period awarded by the FDA.[133] In contrast, the longest exclusivity period for drugs provides up to 7.5 years of market exclusivity.[134] Finally, medical devices, which undergo a less stringent and less costly review process than drug and biologics are not awarded any *market* exclusivity.[135] However, certain medical devices are awarded six years of *data* exclusivity.[136] Congress also uses regulatory exclusivities as incentives for companies to develop therapies for specific diseases or patient populations that might otherwise be neglected by drug manufacturers (for example, because sponsors cannot recoup their investment due to a smaller patient population).[137]

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127. *See* Bo Peng & Marta Cavero Tomas, *A Cheat Sheet to Navigate the Complex Maze of Exclusivities in the United States*, 3 PHARM. PAT. ANALYST 339, 341 (2014).

128. *See* PEW CHARITABLE TRS., POLICY PROPOSAL: REDUCING THE EXCLUSIVITY PERIOD FOR BIOLOGICAL PRODUCTS (2017), https://www.pewtrusts.org/-/media/assets/2017/09/dsri_policy_proposal_reducing_the_exclusivity_period_for_biological_products.pdf [https://perma.cc/76F2-LZL3].

129. *See* Hennebry, *supra* note 125.

130. *See* Peng & Tomas, *supra* note 127, at 341.

131. *See supra* notes 108–09 and accompanying text.

132. *See* Peng & Tomas, *supra* note 127, at 341–42.

133. *See* 42 U.S.C. § 262(k)(7) (stating that biologics are awarded twelve years of market exclusivity); Peng & Tomas, *supra* note 127, at 340 fig.1, 342 (discussing regulatory exclusivities for different medical products).

134. *See* 21 C.F.R. § 314.107(b)(3)(i)(B) (2022); Peng & Tomas, *supra* note 127, at 340 fig.1, 342.

135. *See* Erika Lietzan, *Data Exclusivity for Medical Devices*, OBJECTIVE INTENT (Oct. 10, 2017), https://objectiveintent.blog/2017/10/10/data-exclusivity-for-medical-devices/ [https://perma.cc/E9U6-TYTM].

136. *See* 21 U.S.C. § 360j(h)(4)(A).

137. *See* Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAG. (Jan.–Feb. 2006), https://www.fda.gov/files/Promoting-Safe-and-Effective-Drugs-for-100-Years-%28download%29.pdf [https://perma.cc/S47C-J4US]. For example, Orphan Drug Exclusivity (seven years of additional exclusivity) is available for drugs and biologics that treat diseases affecting fewer than 200,000 patients in the United States (or more than 200,000 and no expectation of recovering costs). *See* 21 U.S.C. § 360bb; 21 C.F.R. § 316.31 (2022). Pediatric Exclusivity (six months of additional exclusivity) is available for

Whether long exclusivity periods, such as the twelve-year exclusivity period for biologics, actually encourage or stifle innovation has been the subject of ongoing debate.[138] Proponents of a longer exclusivity period for biologics argue that the higher costs and increased difficulties of producing biologics, as compared to small molecule drugs, require stronger incentives for biologics manufacturers.[139] In turn, opponents contend that true innovation results from promoting competition, not from overextending monopoly protection.[140] However, generally speaking, regulatory exclusivities can serve as powerful motivators for companies to develop covered medical products.[141]

D. Medical Products Fitting into More than One FDA Category: Combination Products

Not every product fits neatly into a single regulatory category.[142] Medical products that contain two or more regulated components falling into different categories (for example, the biologic and device categories) are called combination products.[143] When a sponsor submits an application for the marketing of a combination product, the FDA's Office of Combination Products (OCP) designates a specific regulatory pathway for the product (for example, the biologic licensure pathway) and assigns primary responsibility for the review process of the product to a single lead FDA center (for example, the FDA biologics center).[144] Once assigned, all components of the combination product have to meet the requirements of the designated

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drugs and biologics when the sponsors conduct pediatric studies. *See* 21 U.S.C. § 355a(b). Qualified Infectious Disease Product Exclusivity (five years of additional exclusivity) is available for drugs (but not biologics) that treat certain bacterial and fungal diseases. *See* 21 U.S.C. § 355f(a).

138. *See* Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVS. DRUG DISCOVERY 479, 481–82 (2008); LAURENCE J. KOTLIKOFF, STIMULATING INNOVATION IN THE BIOLOGICS INDUSTRY: A BALANCED APPROACH TO MARKETING EXCLUSIVITY 1 (2008), https://esplanner.com/files/biologics.pdf [https://perma.cc/4S6S-ZYXV]; Andrew Pollack, *Costly Drugs Known as Biologics Prompt Exclusivity Debate*, N.Y. TIMES (July 21, 2009), https://www.nytimes.com/2009/07/22/business/22biogenerics.html [https://perma.cc/S98Z-XEXG].

139. *See* Grabowski, *supra* note 138, at 481–82.

140. *See generally* KOTLIKOFF, *supra* note 138.

141. *See* Peng & Tomas, *supra* note 127, at 339.

142. *See* 21 C.F.R. § 3.2(e) (2022).

143. *See id.* Combination products are biologic/device, biologic/drug, drug/device, and biologic/drug/device combinations. *See id.* Cell and tissue products that are combined with other components are—depending on their nature—regulated as a drug, biologic, or device. *See* U.S. FOOD & DRUG ADMIN., *supra* note 120, at 3–4. As such, there are no combination products comprising "cell and tissue products" as a component.

144. *See* 21 U.S.C. § 353(g)(1); *Frequently Asked Questions About Combination Products*, U.S. FOOD & DRUG ADMIN. (Apr. 9, 2020), https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products [https://perma.cc/QA5X-RRZR]; Nobuo Uemura et al., *New Visualization Models of Designation Pathway and Group Categorization of Device-Drug and Device-Biologic Combination Products Classification in the United States: Analysis of FDA Capsular Decisions*, 55 THERAPEUTIC INNOVATION & REGUL. SCI. 807, 808 (2021).

approval pathway.[145] A goal of this designation and assignment process is to avoid the need to seek approval for the different product components from different FDA centers.[146]

To determine which center should handle review of a given combination product, the OCP looks to the combination product's primary mode of action (PMOA).[147] The PMOA is defined as the mode of action of a combination product that provides the largest contribution to the overall intended therapeutic effect of the combination product.[148] For example, an EpiPen, which is used for the emergency treatment of life-threatening allergic reactions, is a drug/device combination product.[149] The mode of action for the *device* component (injector pen) is housing the drug and providing access to the patient's anatomy.[150] The mode of action for the *drug* component (epinephrine) is to stop allergic reactions.[151] Because the mode of action for the drug dominates, EpiPens are regulated by the FDA drug center using the drug approval pathway.[152]

In cases in which the OCP cannot determine the PMOA, the FDA uses an algorithm to assign the combination product to an FDA center.[153] Specifically, the new combination product is assigned to an FDA center that oversees the review of combination products that present similar questions of safety and efficacy.[154] If no such reference combination product exists, the new combination product is assigned to the center that has the most expertise in assessing the most significant safety and effectiveness questions that are raised by the new combination product.[155]

In short, the FDA assigns a specific regulatory pathway and a lead FDA center to a combination product based on the product's PMOA.[156] If no

145. *See* Uemura et al., *supra* note 144, at 808.

146. *See* 21 U.S.C. § 353(g)(1); Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754, 58,755 (Nov. 21, 1991) (to be codified at 21 C.F.R. pt. 3).

147. *See Frequently Asked Questions About Combination Products*, *supra* note 144. A mode of action is the way a product brings about an intended therapeutic action or result. *See* 21 C.F.R. § 3.2(k) (2022).

148. *See* 21 U.S.C. § 353(g)(1)(C); 21 C.F.R. § 3.2(m) (2022). A therapeutic effect is the effect of the combination product that is intended to diagnose, cure, treat, or prevent a specific disease or to affect the structure or any function of the human body. *See* 21 C.F.R. § 3.2(k) (2022).

149. *See* Press Release, U.S. Food & Drug Admin., FDA Approves First Generic Version of EpiPen (Aug. 20, 2018), https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-version-epipen [https://perma.cc/CY9B-HCWU] (explaining that EpiPens are drug/device combination products).

150. *See* David Amor, *How to Determine A Combination Product's Primary Mode of Action (PMOA)*, MED DEVICE ONLINE (Jan. 22, 2016), https://www.meddeviceonline.com/doc/how-to-determine-a-combination-product-s-primary-mode-of-action-pmoa-0001 [https://perma.cc/27CF-9ZBW].

151. *See id.*

152. *See* Press Release, *supra* note 149.

153. *See* Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 25,527, 25,527 (May 7, 2004) (to be codified at 21 C.F.R. pt. 3).

154. *See id.* at 25,528–29.

155. *See id.* at 25,529.

156. *See Frequently Asked Questions About Combination Products*, *supra* note 144.

PMOA can be determined, the FDA attempts to assign the product to the center with the most pertinent regulatory expertise.[157]

E. Federal Regulation of Human Organs

The ultimate purpose of bioprinted organs is to decrease the demand for donor organs, which are regulated by the Health Resources and Services Administration (HRSA) under NOTA.[158] Passed in 1984, NOTA sought to address a shortage of donor organs by providing for the establishment of a fair and efficient organ allocation system.[159] NOTA also made the sale of human organs illegal.[160] The Act defines "human organs" as including "the human (including fetal) kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin or any subpart thereof."[161] However, the secretary of the U.S. Department of Health and Human Services (HHS) is authorized by statute to expand the regulatory definition of a human organ.[162] For instance, vascularized composite allografts (i.e., human body parts that contain multiple tissues including skin, muscle, bone, nerves, and blood vessels) were added to the definition of human organ in 2013.[163] Examples of vascularized composite allografts include the face or a hand.[164]

The U.S. government has contracted the United Network for Organ Sharing (UNOS) to operate as its organ procurement and transplantation network.[165] UNOS ensures transplant safety by specifying the medical criteria that a donor and recipient have to meet before a transplantation can occur.[166] For instance, organs from donors who exceed a certain age, who

157. *See* Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. at 25,529.

158. *See generally* Robert Jacobson, Note, *3-D Bioprinting: Not Allowed or NOTA Allowed?*, 91 CHI.-KENT L. REV. 1117, 1122 (2016).

159. *See* S. REP. NO. 98-382, at 15 (1984); Jacobson, *supra* note 158, at 1122.

160. *See* 42 U.S.C. § 274e(a).

161. *See* 42 U.S.C. § 274e(c)(1).

162. *See id.* Both the FDA and the HRSA are part of the HHS. *See HHS Organizational Chart*, U.S. DEP'T HEALTH & HUM. SERVS., https://www.hhs.gov/about/agencies/orgchart/index.html [https://perma.cc/AZ3Y-WRSL] (last visited Mar. 4, 2022).

163. *See* Organ Procurement and Transplantation Network, 78 Fed. Reg. 40,033, 40,033 (July 3, 2013) (to be codified at 42 C.F.R. pt. 121). Like certain bioprinted organs, VCAs are "vascularized and require[] blood flow by surgical connection of blood vessels to function after transplantation," "contain[] multiple tissue types," and are "[t]ransplanted into a human recipient as an anatomical/structural unit." 42 C.F.R. § 121.2 (2022). However, VCAs differ from bioprinted organs in that they are "[r]ecovered from a human donor as an anatomical/structural unit" and are "[m]inimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement)." *Id.* Further, VCAs are "[s]usceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient." *Id.*

164. *See* Axel Rahmel, *Vascularized Composite Allografts: Procurement, Allocation, and Implementation*, 1 CURRENT TRANSPLANTATION REPS. 173, 173 (2014).

165. *See Fast Facts*, UNOS, https://unos.org/about/fast-facts/ [https://perma.cc/G7MX-QDGN] (last visited Mar. 4, 2022).

166. *See* ORGAN PROCUREMENT & TRANSPLANTATION NETWORK, POLICIES 1, 4–6 (2021), https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf [https://perma.cc/H65S-7MNH].

are obese, and/or who suffer from certain disqualifying, underlying medical conditions are not eligible for transplantation.[167] Finally, donated organs are also screened for infectious diseases and compatibility with the recipient's immune system.[168]

II. APPLICATION OF EXISTING REGULATORY FRAMEWORKS TO BIOPRINTED ORGANS

Although the first bioprinted organs have already advanced to the clinic, the FDA has not issued guidance that clearly delineates the regulatory requirements for these innovative medical products.[169] In fact, the agency explicitly excluded "the use or incorporation of biological, cellular, or tissue-based products in [three-dimensional printing]" in its 2017 guidance on three-dimensional printed medical products.[170] So far, FDA activities relating to bioprinting have been limited to soliciting stakeholder feedback, providing grants to study and improve bioprinting, and conducting research on additive manufacturing in-house.[171] This is problematic because regulatory uncertainty discourages investment and hampers innovation.[172] In

167. *See id.*

168. *See* Martin Hertl, *Overview of Transplantation*, MERCK MANUAL CONSUMER VERSION (June 2020), https://www.merckmanuals.com/home/immune-disorders/transplantation/overview-of-transplantation [https://perma.cc/X8VN-9ZUP].

169. *See* Tesh W. Dagne, *Governance of 3D-Printing Applications in Health: Between Regulated and Unregulated Innovation*, 21 COLUM. SCI. & TECH. L. REV. 281, 314 (2020) (discussing how the lack of regulatory guidance might hinder patient access to bioprinted organs); Mermin-Bunnell, *supra* note 11, at 4–5 (discussing clinical trials for bioprinted bladders); Kelly, *supra* note 2 (noting that bioprinted organs could be ready for testing in a few years).

170. *See* U.S. FOOD & DRUG ADMIN., TECHNICAL CONSIDERATIONS FOR ADDITIVE MANUFACTURED MEDICAL DEVICES 2 (2017), https://www.fda.gov/media/97633/download [https://perma.cc/8MDM-VTKN].

171. *See Additive Manufacturing Program: Research on Additive Manufacturing for Medical Devices*, U.S. FOOD & DRUG ADMIN. (Mar. 24, 2021), https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/additive-manufacturing-program-research-additive-manufacturing-medical-devices [https://perma.cc/T7HJ-4Y9C] (noting that the FDA device center conducts research on three-dimensional printing); *FDA In Brief: FDA Awards Grants to Foster Innovation for Advanced Manufacturing Technology as Part of the Agency's Efforts to Ensure a Robust and Reliable Supply of Biological Products*, U.S. FOOD & DRUG ADMIN. (Sept. 20, 2018), https://www.fda.gov/news-events/fda-brief/fda-brief-fda-awards-grants-foster-innovation-advanced-manufacturing-technology-part-agencys-efforts [https://perma.cc/K5ZB-65AE]; *FY 2016 Report from the Director*, U.S. FOOD & DRUG ADMIN. (Jan. 19, 2017), http://wayback.archive-it.org/7993/20171114005503/https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm535743.htm (noting that the FDA biologics center held a conference focusing on "3D Modeling and Printing of Tissues and Organs" in 2016).

172. *See* Dagne, *supra* note 169, at 314 (noting that the current lack of a regulatory framework for bioprinted organs might hamper patient access to these technologies); Amy L. Stein, *Reconsidering Regulatory Uncertainty: Making a Case for Energy Storage*, 41 FLA. ST. U. L. REV. 697, 732 (2014) (discussing that regulatory uncertainty decreases investment); *Will Bioprinted Organs Be Regulated by the FDA Like Medical Devices?*, PENROD BLOG, https://penrod.co/will-bioprinted-organs-be-regulated-by-the-fda-like-medical-devices/ [https://perma.cc/ML45-V3QC] (last visited Mar. 4, 2022) (arguing that current regulations are inadequate for bioprinting); Damini Kunwar, *The Uncertainty of Regulating 3D Organ*

turn, the publication of regulatory guidance, which outlines the criteria under which the FDA intends to regulate a medical product, has been shown to significantly reduce approval times.[173] As such, guidance from the FDA on the regulation of bioprinted organs would significantly benefit manufacturers seeking to develop these innovative products, as well as patients in need of replacement organs.[174]

In lieu of guidance specifically addressing the regulation of bioprinted organs, developers of these products are forced to rely on existing statutory and regulatory frameworks to predict the regulatory requirements and exclusivities for their bioprinted products.[175] Three different regulatory frameworks stand out as candidates for governing the regulation of bioprinted organs: (1) regulation of organs by the HRSA under NOTA, (2) regulation of cell and tissue products under the PHSA, and (3) regulation of medical products by the FDA under the FDCA.[176]

Part II.A explains that significant uncertainty exists as to whether bioprinted organs fall under NOTA. Part II.B concludes that bioprinted organs will likely not be subject to the limited regulatory oversight afforded to certain cell and tissue products. Part II.C discusses that, while most bioprinted organs will likely be considered combination products, the FDA's current approach to combination products may create significant regulatory uncertainty for the developers of bioprinted organs.

A. Regulation of Bioprinted Organs as Human Organs Under NOTA

The ultimate goal of bioprinted organs is to serve as functional replacements for donated organs.[177] However, it is currently not clear whether bioprinted organs fall under NOTA's jurisdiction.[178] Clarification on this issue is critically important for companies seeking to commercialize bioprinted organs because NOTA prohibits the sale of organs.[179] Without the ability to sell their product, developers of bioprinted organs might not be able to recoup their development costs and could opt to not develop bioprinted organs altogether.[180]

It has been reasoned that bioprinted organs should fall under NOTA's jurisdiction because bioprinted organs are biologically and functionally similar to human organs.[181] Similarly, it has been suggested that bioprinted

Printing, REGUL. REV. (Dec. 10, 2019), https://www.theregreview.org/2019/12/10/kunwar-uncertainty-regulating-3d-organ-printing/ [https://perma.cc/ER4H-JNWP] (discussing concerns that bioprinted organs do not clearly fall into any category of existing law).

173. *See* Ariel Dora Stern, *Innovation Under Regulatory Uncertainty: Evidence from Medical Technology*, 145 J. PUB. ECON. 181, 181, 194 (2017).

174. *See* Dagne, *supra* note 169, at 314.

175. *See supra* note 172.

176. *See supra* Parts I.A, I.E.

177. *See* Kryou et al., *supra* note 10, at 1–2.

178. *See supra* Part I.E.

179. *See supra* note 160 and accompanying text.

180. *See supra* note 160 and accompanying text.

181. *See* Lauren M. Lentsch, *Kinkos for Your Kidneys: A Legal Blueprint for the Regulation of Bioprinted Organs*, 46 N. KY. L. REV. 43, 54 (2019).

organs should be regulated under NOTA because they can be derived from cells that can be considered to be subparts of organs.[182]

Alternatively, it has been contended that because the statute applies to *human* organs, NOTA only applies to organs that are derived from humans as functional units.[183] Here, it is worth noting that in passing NOTA, Congress made a point to distinguish organ donations from blood donations, with the latter being minimally invasive and not causing harm to the donor.[184] Blood donations are not covered under NOTA.[185] Further, some have argued that NOTA only covers naturally occurring compositions of matter, which does not include bioprinted organs.[186] Finally, it has been suggested that bioprinted organs do not raise the ethical and human rights concerns that motivated the passage of NOTA.[187] Specifically, NOTA was passed in response to an increased need for donated organs.[188] The legislative history indicates that Congress was concerned about the moral implications of citizens auctioning off their organs to the highest bidder for financial gain, a concern that does not apply to bioprinted organs.[189]

While the courts have yet to determine whether NOTA applies to bioprinted organs, the Ninth Circuit in *Flynn v. Holder*[190] examined the question of whether bone marrow transplants were subject to NOTA.[191] Bone marrow, which is explicitly recited in NOTA's organ definition, can either be isolated directly from the donor's bone (in a process called aspiration) or from the donor's blood (in a process called apheresis).[192] The court held that bone marrow stem cells obtained through the invasive, painful, and risky process of aspiration are covered by NOTA.[193] However, bone marrow stem cells present in the blood that could be extracted by painless and relatively riskless apheresis are *not* subject to NOTA.[194]

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182. *See id.* The statutory definition of "human organ" includes "subpart thereof." 42 U.S.C. § 274e(c)(1).

183. *See* Elizabeth Kelly, Comment, *FDA Regulation of 3D-Printed Organs and Associated Ethical Challenges*, 166 U. PA. L. REV. 515, 523 (2018).

184. *See* H.R. REP. NO. 98-1127, at 16 (1984) (Conf. Rep.) (stating that "[t]he term 'human organ' is not intended to include replenishable tissues such as blood or sperm"); S. REP. NO. 98-382, at 16–17 (1984) (stating that the organ sale prohibition was not "meant to include blood and blood derivatives, which can be replenished and whose donation does not compromise the health of the donor"); *National Organ Transplant Act: Hearing on H.R. 4080 Before the Subcomm. on Energy and Com.*, 98th Cong. 129 (1983) [hereinafter *Hearing on H.R. 4080*] (statement of Rep. Al Gore).

185. *See* Flynn v. Holder, 684 F.3d 852, 864–65 (9th Cir. 2012).

186. *See* Anna M. Whitacre, Note, *Don't Go Breakin' My (3D Bioprinted) Heart: Dissecting Patentability and Regulation of 3D Bioprinted Organs*, 27 J. INTELL. PROP. L. 357, 378 (2020).

187. *See* Kelly, *supra* note 183, at 525.

188. *See* Newman v. Sathyavaglswaran, 287 F.3d 786, 794 (9th Cir. 2002).

189. *See Hearing on H.R. 4080*, *supra* note 184.

190. 684 F.3d 852 (9th Cir. 2012).

191. *See id.* at 864–65.

192. *See* 42 U.S.C. § 274e(c)(1); *Flynn*, 684 F.3d at 856–57.

193. *See Flynn*, 684 F.3d at 859.

194. *See id.* at 865.

In response to the court's ruling, the HHS proposed a new rule that would have amended the definition of "human organ" in section 301 of NOTA to clarify that the prohibition on transfers of human organs applies to bone marrow stem cells regardless of whether they were recovered by aspiration or by apheresis.[195] However, in response to stakeholder feedback, the HHS withdrew the proposal in 2018 and did not amend NOTA's organ definition.[196] Given that many bioprinted organs are also generated using relatively painless and riskless methods, it is possible that bioprinted organs—like bone marrow stem cells isolated by apheresis—are not subject to NOTA.[197] However, no court has ruled on this issue so far.

In sum, significant regulatory uncertainty exists for manufacturers of bioprinted organs as to whether their product's sale will be prohibited under NOTA.

B. Regulation of Bioprinted Organs as Cell and Tissue Products Under the PHSA

Alternatively, it might be argued that bioprinted organs are composites of cells and tissues and should therefore be regulated as cell and tissue products under the PHSA.[198]

Only a certain group of cell and tissue products is exempt from premarket approval, which is otherwise required for drugs, biologics, and medical devices, and is solely regulated under section 261 of the PHSA.[199] To qualify for this exemption from premarket approval, the cell and tissue products have to be minimally manipulated and cannot be combined with other substances other than compounds such as water or sterilizing or storage agents.[200] This Note argues that bioprinted organs are neither minimally manipulated nor free from other substances and, as such, do not qualify for the exemption.

To generate a human organ using bioprinting, stem cells are isolated from, for example, a patient's blood and reprogrammed to develop into the desired cell types (e.g., heart or skin cells).[201] After the cells have been printed into a three-dimensional structure, they are cultivated under specific conditions to mature into a functional tissue.[202] Given the amount of manipulation required to turn a patient's cells into a bioprinted organ, it is likely that bioprinted organs will not be considered to comprise "minimally

195. *See* Change to the Definition of "Human Organ" Under Section 301 of the National Organ Transplant Act of 1984, 78 Fed. Reg. 60,810, 60,811–12 (Oct. 2, 2013) (to be codified at 42 C.F.R. pt. 121).

196. *See* Change to the Definition of "Human Organ" Under Section 301 of the National Organ Transplant Act of 1984; Withdrawal, 83 Fed. Reg. 60,804, 60,804 (Nov. 27, 2018) (to be codified at 42 C.F.R. pt. 121).

197. *See Flynn*, 684 F.3d at 865; *supra* text accompanying notes 4–5.

198. *See supra* text accompanying notes 3–10, 120–24.

199. *See supra* text accompanying notes 120–24.

200. *See supra* text accompanying notes 120–24.

201. *See supra* text accompanying notes 5–11.

202. *See supra* text accompanying notes 5–11.

manipulated" cells.[203] Further, many bioprinted organs use scaffolding materials, which might still be present in the fully matured bioprinted organ.[204] As such, many bioprinted organs comprise human cells and tissues that are more than minimally manipulated and have been combined with substances other than water or storage agents.[205] Accordingly, even though bioprinted organs are technically cell- or tissue-based products, they will likely not be exempt from the stringent regulatory review that applies to drugs, biologics, and medical devices.[206]

C. Regulation of Bioprinted Organs as Medical Products Under the FDCA

Finally, because bioprinted organs are intended to treat disease and affect a function of the human body, they might reasonably be regulated as medical products under the FDCA.[207] While this Note argues that bioprinted organs will likely be regulated by the FDA as combination products, the FDA's current approach to combination products may still create significant regulatory uncertainty for the developers of bioprinted organs.

1. Bioprinted Organs Will Likely Be Considered Combination Products

Like other medical products classified as combination products, bioprinted organs can exhibit characteristics of drugs, biologics, and medical devices.[208] For example, bioprinted organs contain living cells, pointing to their classification as biologics.[209] However, depending on the type of bioprinted organ, the bioprinted material might also exhibit characteristics of a medical device or drug.[210] For instance, the function of a bioprinted cornea is very much mechanical in nature, pointing to a medical device classification.[211] Specifically, the cornea focuses light, filters UV rays, and serves as a physical barrier that prevents dirt and microorganisms from entering the eye.[212] Based on these properties, (non-cellular) artificial corneas have been classified by the FDA as medical devices.[213] Similarly, the function of a heart is mainly a mechanical one (i.e., the heart circulates blood through the

203. *See supra* note 122 and accompanying text. *See also* U.S. FOOD & DRUG ADMIN., *supra* note 120, at 15 (explaining that the production of cells that cannot differentiate into a different cell type anymore from blood stem cells is generally considered to be more than minimal manipulation).

204. *See supra* text accompanying note 9.

205. *See supra* note 122 and accompanying text.

206. *See supra* Part I.C.1.

207. *See supra* notes 62–67 and accompanying text.

208. *See* Kelly, *supra* note 183, at 527.

209. *See supra* note 69 and accompanying text.

210. *See* Kelly, *supra* note 183, at 527.

211. *See Corneal Disease*, CLEVELAND CLINIC, https://my.clevelandclinic.org/health/diseases/8586-corneal-disease [https://perma.cc/FZ3J-NQXB] (last visited Mar. 4, 2022); *supra* note 72 and accompanying text.

212. *See Corneal Disease*, *supra* note 211.

213. *See Premarket Approval (PMA): Intacs Prescription Inserts/Intacs Corneal Implants*, U.S. FOOD & DRUG ADMIN. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P980031 [https://perma.cc/SH7N-DFE6] (last visited Jan. 16, 2022).

body and maintains blood pressure).[214] Accordingly, the FDA has classified (non-cellular) artificial hearts as medical devices.[215]

Alternatively, some organs achieve their biological function by secreting what are essentially small molecule drugs, which in turn fulfill important functions in the human body.[216] For example, hormones secreted by the thyroid gland regulate the body's metabolism, as well as cellular activity and development.[217]

Because many bioprinted organs will share characteristics of medical products falling into different regulatory categories, it is likely that the FDA will classify bioprinted organs as combination products. However, without additional guidance from the FDA, there is uncertainty as to whether the existing framework relating to combination products can be effectively applied to bioprinted organs. Specifically, the assignment of a combination product to a specific FDA center and approval pathway based on its PMOA can be particularly challenging for bioprinted organs.[218] Further, due to the inherently interdisciplinary nature of bioprinted organs, it is unclear whether review by a single FDA center will be sufficient to ensure the safety and efficacy of these medical products.[219]

2. Identifying the Most Appropriate FDA Center to Lead the Regulatory Review of a Bioprinted Organ Can Be Challenging

The FDA's approach of assigning combination products to a lead center based on their primary mode of action works well for combination products in which one regulatory category clearly dominates.[220] However, not all cases are so clear-cut, and sponsors have complained about inconsistencies in the designation and assignment process.[221] For example, although combination products Dermagraft and MACI are both bioabsorbable

214. *See* James Beckerman, *How the Heart Works*, WEBMD (Aug. 24, 2020), https://www.webmd.com/heart-disease/guide/how-heart-works [https://perma.cc/9WVB-99AT].

215. *See Premarket Approval (PMA): Syncardia Temporary Cardio West Total Artificial Heart (TAH-T)*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P030011 [https://perma.cc/5UMY-DMMP] (last visited Jan. 16, 2022). TAH-T is a mechanical device consisting of two artificial heart chambers and four artificial heart valves made of semirigid plastic that can temporarily replace a failing human heart. *See How Does the Syncardia Total Artificial Heart Work?,* SYNCARDIA, https://syncardia.com/patients/patient-resources/how-does-the-total-artificial-heart-work/ [https://perma.cc/UG3Y-R92X] (last visited Mar. 4, 2022).

216. *See* Susanne Hiller-Sturmhöfel & Andrezej Bartke, *The Endocrine System: An Overview*, 22 ALCOHOL HEALTH & RSCH. WORLD 153, 153 (1998) (discussing the secretion of hormones by various organs).

217. *See id.*

218. *See infra* Part II.C.2.

219. *See infra* Part II.C.3.

220. *See supra* text accompanying notes 149–52.

221. *See* Uemura et al., *supra* note 144, at 809.

scaffolds covered with living cells, Dermagraft is regulated as a medical device, while MACI is regulated as a biologic.[222]

Because form and function are so highly intertwined in bioprinted organs, the *primary* mode of action can be challenging to ascertain for these products.[223] For instance, determining the PMOA for a bioprinted organ might become a question of how granular one defines the problem to be solved. Does a bioprinted heart primarily achieve its therapeutic effect by serving as a mechanical pump, indicating a medical device mode of action?[224] Or is the artificial heart a biologic because the contractile function of the organ critically depends on the action of the heart cells making up the organ?[225] Similarly, does a bioprinted cornea exhibit a device mode of action because the cornea functions to focus and filter light and serve as a physical barrier?[226] Or does the product have a biologics mode of action because the transparency and refractory qualities of a lens are actually the result of lens crystallins (a type of protein found in the eye), which are produced by the cells that make up the cornea?[227] Accordingly, for many bioprinted organs, it might not readily be apparent what the *primary* mode of action will be, creating uncertainty for sponsors as to which regulatory pathway will apply to their product and what FDA center will handle the application.[228]

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222. *See* Letter from Raj Puri, Director, Ctr. for Biologics Evaluation & Rsch., U.S. Food & Drug Admin., to Anastacia Bilek, Vericel Corp. (May 31, 2019), https://www.fda.gov/media/127941/download [https://perma.cc/53SQ-QMXQ] (approving supplement of Biologics License Application for MACI); Charles E. Hart et al., *Dermagraft: Use in the Treatment of Chronic Wounds*, 1 ADVANCES WOUND CARE 138, 141 (2012) (discussing that Dermagraft is a Class III medical device).

223. *See* RICCARDO LEVATO ET AL., FROM SHAPE TO FUNCTION: THE NEXT STEP IN BIOPRINTING 1 (2020) (discussing the intimate linkage between tissue architecture and function). As acknowledged by the FDA, a combination product can have two or more mode of actions that equally contribute to the medical product's overall therapeutic effect. *See* Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49,848, 49,849 (Aug. 25, 2005) (to be codified at 21 C.F.R. pt. 3). For these products, the FDA admits that assessing the PMOA is "complicated." *Id.*

224. *See supra* note 72 and accompanying text.

225. *See* Dan B. Tran et al., *Anatomy, Thorax, Heart Muscles*, STATPEARLS (Sept. 18, 2021), https://www.ncbi.nlm.nih.gov/books/NBK545195/ [https://perma.cc/ZE4J-PQGL]; *supra* note 69 and accompanying text. Current regulations on PMOA discuss a scaffold for organ replacement that has been seeded with a patient's own cells and that has the shape of the target organ. *See* Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. at 49,858. According to the regulation, such a product's PMOA would be attributable to the biological product component's action. *See id.* However, the description of this exemplary hypothetical product already requires that it is the patient's own cells that enable the product to "ultimately function like the target organ in the patient," thus foreclosing a scenario in which the combination product has any significant device mode of action. *See id.* As such, it is questionable if this example would apply to a bioprinted heart or cornea. *See id.*

226. *See supra* note 72 and accompanying text.

227. *See generally* James V. Jester, *Corneal Crystallins and the Development of Cellular Transparency*, 19 SEMINARS CELL & DEVELOPMENTAL BIOLOGY 82 (2008).

228. *See, e.g.*, BioLife4D Corp., Offering Circular (Form 1-A) (Dec. 16, 2020), https://www.sec.gov/Archives/edgar/data/0001714919/000147793220007347/biolife_253g2.htm [https://perma.cc/44HW-SR6X] (stating to investors that there is no "definitive process for review and approval of 3D bioprinted devices or tissues").

If the FDA cannot identify a PMOA, the combination product is assigned to a center that reviews other combination products presenting similar questions of safety and effectiveness.[229] However, without more explicit FDA guidance, sponsors do not know for certain what such reference combination products would be.[230] For instance, a bioprinted product currently undergoing FDA review is EpiBone-Craniomaxillofacial (EB-CMF), a bioprinted bone graft for the reconstruction of facial bones.[231] EB-CMF is regulated as a biologic-led combination product by the FDA biologics center.[232] Does this mean that all bioprinted organs will be regulated by the FDA as biologics? BioLife4D, a company that is developing a fully viable heart ready for transplantation, does not seem to think so.[233] The company has emphasized to its stockholders that it believes that its product will be regulated as a Class III device.[234]

Without a reference product, the bioprinted combination product is assigned to the center that has the most expertise to assess the "most significant safety and effectiveness questions" raised by the combination product.[235] Because the mechanical and biologic properties of a bioprinted organ are highly interdependent, more than one FDA center might have regulatory expertise pertinent to the safety and effectiveness of the bioprinted organ.[236] Further, what constitutes the *most significant* safety and effectiveness question presented by the combination product requires consideration of the main therapeutic mode of action of the bioprinted product.[237] Such an inquiry would likely be difficult for bioprinted organs. In sum, the FDA's current framework for designating and assigning combination products based on a PMOA might be challenging to apply to bioprinted organs.

3. Regulatory Approval of Bioprinted Organs Might Demand Review by More than a Single FDA Lead Center

In many cases, assigning a single lead center to conduct the regulatory review of a combination product can significantly streamline the review process and reduce costs for the sponsor by avoiding the need to submit

229. *See supra* Part I.D.
230. *See supra* text accompanying note 169.
231. *See* Evaluation of EpiBone-CMF for Mandibular Ramus Reconstruction (EB-CMF), CLINICALTRIALS.GOV (Apr. 21, 2021), https://clinicaltrials.gov/ct2/show/NCT03678467 [https://perma.cc/W9EA-B3S9]; David Butcher, *EpiBone Embodies Paperless Efficiencies in Personalized Medicine*, MASTERCONTROL (Feb. 11, 2020), https://www.mastercontrol.com/gxp-lifeline/epibone-embodies-paperless-efficiencies-in-personalized-medicine/ [https://perma.cc/WCT3-Q6TK].
232. *See* Butcher, *supra* note 231.
233. *See, e.g.*, Offering Circular, *supra* note 228.
234. *See id.*
235. *See* Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 25,527, 25,529–30 (May 7, 2004) (to be codified at 21 C.F.R. pt. 3).
236. *See supra* note 223.
237. *See supra* note 147 and accompanying text.

multiple FDA applications for the same product.[238] However, it has also been suggested that interdisciplinary products also benefit from an interdisciplinary review.[239] This might be particularly true for bioprinted organs, which are inherently more interdisciplinary than other types of medical products.[240]

Most drug development involves more than one scientific discipline, such as chemistry (for synthesizing the drug), cell biology (for testing the safety and efficacy of the drug), and medicine (for designing clinical trials).[241] In contrast, even the production of a suitable candidate for a bioprinted organ requires input from a variety of scientific disciplines.[242] Take the production of a bioprinted heart as an example. A software engineer develops a three-dimensional model of the heart with guidance from a biophysicist (to ensure mechanical functionality of the heart) and a physician (to ensure patient fit).[243] A mechanical engineer then uses the model to print suitably treated cells provided by a cell biologist onto a biocompatible scaffold delivered by a material scientist.[244] Importantly, because the manufacturing process of the organ's cellular components can influence the performance of the scaffold and vice versa, bioprinting requires not only the sequential but also the simultaneous collaborative efforts of experts from different disciplines.[245]

Because the design and manufacturing process for bioprinted organs is so interdisciplinary, FDA review of these products may require the input of

238. *See* U.S. FOOD & DRUG ADMIN., FISCAL YEAR 2020 OCP PERFORMANCE REPORT IV (2020), https://www.fda.gov/media/154949/download [https://perma.cc/TAF6-KZRN].

239. *See* Jiaxin Tian et al., *Regulatory Perspectives of Combination Products*, 10 BIOACTIVE MATERIALS 492, 495 (2021) (discussing that combination products are interdisciplinary and that regulatory review should match this interdisciplinarity).

240. *See* John H. Tibbetts, *The Future of Bioprinting: Multidisciplinary Teams Seek to Create Living Human Organs*, 71 BIOSCIENCE 564, 564 (2021) (discussing the interdisciplinarity in bioprinting); Deborah Sliver et al., *Research Is the Focus: Bioprinting, Biofabrication and 3D Bioprinting*, RUTGERS (Nov. 28, 2018), https://mbs.rutgers.edu/articles/research-focus-bioprinting-biofabrication-and-3d-bioprinting [https://perma.cc/E8FQ-WH59].

241. *See generally* Richard C. Mohs & Nigel H. Greig, *Drug Discovery and Development: Role of Basic Biological Research*, 3 ALZHEIMER'S & DEMENTIA 651 (2017).

242. *See generally* Luciano P. Silva, *Current Trends and Challenges in Biofabrication Using Biomaterials and Nanomaterials: Future Perspectives for 3D/4D Bioprinting in 3D and 4D Printing*, *in* BIOMEDICAL APPLICATIONS: PROCESS ENGINEERING AND ADDITIVE MANUFACTURING 373 (Mohammed Maniruzzaman ed., 2019).

243. *See* Emma C. Moran, The Role of Biomechanisms in Liver Tissue Engineering, at 92–93 (May 2015) (Ph.D. dissertation, Wake Forest University), https://wakespace.lib.wfu.edu/bitstream/handle/10339/57098/Moran_wfu_0248D_10676.pdf [https://perma.cc/2355-KCWY] (discussing the impact of mechanical parameters such as fluid pressure on the properties of liver cells); *supra* text accompanying notes 5–11.

244. *See supra* text accompanying notes 5–11.

245. *See* U.S. FOOD & DRUG ADMIN., EVALUATION OF DEVICES USED WITH REGENERATIVE MEDICINE ADVANCED THERAPIES 10 (2019), https://www.fda.gov/media/120266/download [https://perma.cc/WQ57-34LT] (discussing interactions between the cellular and device components of combination products); Silva, *supra* note 242, at 387; LEVATO ET AL., *supra* note 223, at 1.

experts in different FDA centers.[246] This is not per se problematic, assuming the availability of efficient channels of communication between the different FDA centers. Yet, both external and FDA-internal studies have found a lack of expedient communications between different parts of the agency.[247] Such a lack of intra-agency conversation can result in discrepancies as to how the different centers manage the regulatory review process.[248] Additionally, a lack of intercenter communication can result in inadequate scientific and regulatory justifications for regulatory decisions pertaining to combination products.[249] While the FDA has taken some steps to improve its intercenter consult request process, the procedure is still quite complicated, requiring up to ten administrative steps for a nonroutine intercenter consult.[250] Further, the process requires that either the FDA officer or the sponsor *proactively* recognize that certain issues require input from another center and reach out to the person with the appropriate regulatory expertise.[251] However, in interdisciplinary and novel technologies, regulatory issues might be difficult to anticipate.[252]

In sum, the best regulatory fit for bioprinting organs under existing legal frameworks might be review by the FDA as combination products. Although there is always some uncertainty as to which regulatory pathway and lead center a combination product will be assigned to, this might be particularly true for bioprinted organs. For instance, for bioprinted organs, one might question the appropriateness of the FDA's current approach of assigning combination products to lead centers based on their PMOA. Further, because bioprinted organs are more interdisciplinary than other combination

246. *See* Manresa & Meyers, *supra* note 78, at 42 (noting that FDA scientists with expertise in drug, biologics, or medical device development are based in different FDA centers). Regulatory expertise relating to nanotechnology, another highly interdisciplinary technology, is also scattered among different FDA centers. *See Nanotechnology Programs at FDA*, U.S. FOOD & DRUG ADMIN. (Feb. 23, 2021), https://www.fda.gov/science-research/science-and-research-special-topics/nanotechnology-programs-fda [https://perma.cc/XPD8-QVHY] (providing an overview of the FDA's nanotechnology programs); *see also infra* notes 312–19.

247. *See* U.S. FOOD & DRUG ADMIN., COMBINATION PRODUCT REVIEW INTERCENTER CONSULT PROCESS STUDY 4–5 (2015), https://fda.report/media/94416/Combination-Product-Review-Intercenter-Consult-Process-Study.pdf [https://perma.cc/8D45-5M6M]; COMBINATION PRODUCTS COALITION, IMPROVING PATIENT CARE THROUGH BETTER COMBINATION PRODUCT REGULATION 1 (2014), http://combinationproducts.com/wp-content/uploads/2014/07/May-23-2014-CPC-Paper-Improving-Patient-Care.pdf [https://perma.cc/U2M9-UD72].

248. *See* COMBINATION PRODUCTS COALITION, *supra* note 247, at 4 (arguing that the FDA's review of combination products lacks consistency and occasionally leads to scientifically questionable requests for clinical data).

249. *See id.*

250. *See* U.S. FOOD & DRUG ADMIN., FDA STAFF MANUAL GUIDES, VOLUME IV—AGENCY PROGRAM DIRECTIVES: COMBINATION PRODUCTS, INTER-CENTER CONSULT REQUEST PROCESS attach. A (2018), https://www.fda.gov/media/81927/download [https://perma.cc/VY6X-XJWM] (laying out an up to ten-step process for a consult request from a different center).

251. *See id.*

252. *See Emerging Sciences*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2018), https://www.fda.gov/science-research/about-science-research-fda/emerging-sciences [https://perma.cc/H9FH-JAQS] (asking the public to educate the FDA on scientific issues that might impact regulatory review of medical products).

products, it is even less clear whether review by a single FDA center will be sufficient to ensure the safety and efficacy of these novel medical products.

III. A PROPOSED REGULATORY FRAMEWORK FOR BIOPRINTED ORGANS

Without more explicit guidance from Congress, the courts, or regulatory agencies, significant uncertainty remains for developers of bioprinted organs as to what exact regulatory hurdles their products will face before they can be marketed.[253] Accordingly, to more efficiently promote Congress's goals of incentivizing innovation and accelerating patient access to new therapies, a new regulatory framework for bioprinted organs is needed.[254] To that end, Part III.A explains that bioprinted organs will likely not—and should not—be regulated as organs under NOTA. Part III.B recommends that the FDA should establish an interdisciplinary "Center for Bioprinted Organs" to oversee the safety and efficacy review of these bioprinted materials. Finally, Part III.C proposes a regulatory scheme that promotes both innovation and competition in the bioprinting space, thus benefitting industry stakeholders and patients alike.

A. Bioprinted Organs Should Not Be Regulated as Human Organs Under NOTA

Given that the goal of bioprinted organs is to serve as fully functional organ replacements, one might reason that bioprinted organs should fall under the purview of NOTA, the law that regulates the retrieval and allocation of human organs.[255] This Note argues that such an interpretation is inconsistent with the statutory language and the problems that NOTA sought to address.

1. Bioprinted Organs Are Not Covered by NOTA's Organ Definition

Both the statutory and regulatory definitions of "human organ" support an interpretation that organs covered by NOTA (1) are biological materials that have been isolated from a donor as vascularized, functional anatomic units and (2) do not include artificially generated organs. Likewise, this Note argues that cells that were isolated from a donor and subsequently grown into functional bioprinted organs do not fall under NOTA's purview either.

First, with the exception of bone marrow, all of the human organs explicitly listed in the statutory definition of "human organ" meet three criteria. They (1) have been removed invasively from the organ donor, (2) can be transferred to the recipient "as is" or with minimal manipulation, and (3) are transplanted either as (a) an entire organ (like the heart) or (b) a subpart of an organ capable of regrowth into a full organ (like a liver lobe).[256]

253. *See supra* Part II.
254. *See supra* Part I.A; text accompanying notes 169–74.
255. *See supra* Part I.E.
256. *See* Junko Haga et al., *Liver Regeneration in Donors and Adult Recipients After Living Donor Liver Transplantation*, 14 LIVER TRANSPLANTATION 1718 (2008) (discussing the

In contrast, cells isolated from a patient for bioprinting (1) require minimal invasion to obtain (often just a puncture of a vein), (2) are subject to significant manipulation, and (3) are not ready to provide any organ functionality to the recipient when transplanted as is.[257]

Second, federal regulations provide that the HSRA administers the transplantation of "*vascularized* human organs."[258] The term "vascularized" indicates that the regulations were intended to cover organs that are ready for implantation, as opposed to cells derived from such organs.[259] Consistent with this view, the FDA's definition of cell and tissue products intended for transfer into a human recipient explicitly excludes "vascularized human organs" for transplantation.[260]

Third, the regulatory definition of a vascularized composite allograft, which was added to expand NOTA's organ definition in 2013, underscores the notion that human organs covered by NOTA are (1) transferred from donor to recipient as an anatomical/structural unit and (2) functional after transplantation, despite the fact that they are minimally manipulated and are not combined with other articles such as a device.[261] In light of the above, bioprinted organs, which are not recovered from a donor as a functional anatomic unit, should not be considered organs for the purposes of NOTA.

Even if bioprinted organs themselves are not considered organs under NOTA, it has been argued that the cells that serve as starting material for the bioprinted organ are subparts of organs and as such covered by NOTA.[262] However, the Ninth Circuit held in *Flynn* that although bone marrow is explicitly recited in NOTA's organ definition, bone marrow cells that are isolated using relatively noninvasive techniques do not fall under NOTA's purview.[263] The ruling in *Flynn*—combined with the HHS's decision to not overrule *Flynn* by regulation—suggests that starting cells to be used for bioprinting that are obtained from a patient using relatively noninvasive techniques are not subparts of organs and, as such, are not covered by NOTA. Further, many bioprinted organs are grown by first isolating stem cells from

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regeneration potential of the liver); *supra* note 161 and accompanying text. For a discussion of bone marrow, see *infra* text accompanying note 263.

257. *See supra* text accompanying notes 5–11.

258. *See* Organ Procurement and Transplantation Network, 78 Fed. Reg. 40,033, 40,034 (July 3, 2013) (to be codified at 42 C.F.R. pt. 21).

259. *See id.*

260. *See* 21 C.F.R. § 1271.3(d)(1) (2022).

261. *See supra* note 163.

262. *See supra* note 182 and accompanying text. Congress amended the definition of "human organ" in 1988 to include fetal organs. *See* Health Omnibus Programs Extension of 1988, Pub. L. No. 100-607, § 407, 102 Stat. 3048, 3116 (codified as amended in 42 U.S.C. § 274e(c)(1)). Bioprinted organs utilize cells from humans past the fetal stage and as such do not raise the same concerns that the use of fetal organs raises. *See* John A. Robertson, *Fetal Tissue Transplants*, 66 WASH. U. L.Q. 443, 467, 472 (1988); *supra* note 5 and accompanying text.

263. *See supra* Part II.A.

blood, cells which the *Flynn* court explicitly held were not considered organs under NOTA.[264]

Finally, this Note argues that the language of the remaining statutory text and NOTA's legislative history underscore that the law was intended to address the ethical and human rights concerns that arose from the sale of human organs to *another*. Specifically, the statutory language makes clear that the organ donor and the organ recipient are not the same individual.[265] In contrast, a bioprinted organ is manufactured using the patient's own biological material for use in the donor herself, eliminating many of the ethical or human rights concerns that lead to the prohibition of the sale of human organs.[266]

Further, when passing NOTA, lawmakers stressed that blood donations were not covered by NOTA due to the minimally invasive process of obtaining them.[267] As such, the small amounts of biological material (i.e., a part of a tissue or blood cells) obtained fairly noninvasively from a donor to be used in bioprinting should not be covered by NOTA either.

In sum, the statutory and regulatory definitions of "human organ," as well as the legislative history of NOTA, support the interpretation that bioprinted organs were not intended to be covered by NOTA.

2. NOTA Is Ineffective in Ensuring a Supply of Safe and Effective Bioprinted Replacement Organs

In addition to arguing that bioprinted organs will likely not be construed to fall under NOTA's jurisdiction, this Note reasons that regulating bioprinted organs under NOTA is also undesirable, as such regulation would stifle innovation in bioprinting and fail to ensure the safety and efficacy of bioprinted organs.[268]

First, making the sale of bioprinted organs for valuable consideration illegal under NOTA would be contrary to Congress's goal of incentivizing the development of new medical technologies.[269] Given the likely very significant development and manufacturing costs for a fully functional bioprinted organ, the inability to receive valuable consideration for their medical product could serve as a powerful deterrent for any for-profit company (and even nonprofit institution) to engage in the development and production of bioprinted organs in the first place.[270]

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264. *See* Flynn v. Holder, 684 F.3d 852, 864–65 (9th Cir. 2012); Ong et al., *supra* note 4, at 223.

265. *See* 42 U.S.C. § 274e(c)(4) (discussing "donor-patient pair[s]"); *id.* § 274f(d)(3) (differentiating between "donating individuals" and the "recipient of the organ").

266. *See* Kelly, *supra* note 183, at 525.

267. *See supra* notes 184–85 and accompanying text.

268. *See supra* Part III.A.1.

269. *See* 42 U.S.C. § 274e; *supra* Part I.A.

270. *See* James Jeffery, *3D Printing Human Organs—But Where's the Money for It?*, GUARDIAN (July 17, 2013, 8:30 AM), https://www.theguardian.com/technology/2013/jul/17/3d-printing-organs-money [https://perma.cc/P7RV-BXUT] (discussing the financial struggles of companies developing bioprinted organs).

Second, regulating bioprinted organs under NOTA does not sufficiently achieve Congress's goal of protecting patient safety.[271] The organization responsible for the recovery and allocation of human organs takes certain precautionary measures to promote successful organ transplantation and to reduce the risk of disease transmission.[272] However, compared to the rigorous safety and efficacy testing that medical products undergo as part of the FDA approval process, the requirements for ensuring the safety and efficacy of donated organs are minimal.[273]

The fact that NOTA does not require extensive safety and efficacy testing should not be surprising, as such testing in the context of donated organs is neither possible nor necessary. To start, organs from diseased donors remain viable only for a short amount of time.[274] Thus, the amount of testing that can be performed on an organ and its donor in this short time frame is very limited.[275] Further, in contrast to artificial biomaterials, medical professionals can presume that organs extracted from formerly living persons are generally functional.[276] Accordingly, the fact that NOTA does not require extensive safety and efficacy testing for donated organs is no particular threat to patient safety.[277]

However, the situation would be different for bioprinted organs. While a three-dimensional structure of cells and scaffolding material might be *regulated* as an organ for the purposes of NOTA, this does not mean that this structure actually *functions* as an organ and will continue to do so for years after transplantation.[278] Given that transplanted organs can last for decades, nonfunctional or unsafe organ replacements are a significant risk for patient safety.[279]

One might argue that the organ allocation network could simply revise the donor eligibility requirements to incorporate some kind of "organ functionality test" that would ensure that a bioprinted organ is fit for transplantation. However, assessing the safety and efficacy of bioprinted

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271. *See supra* Part I.A.

272. *See supra* Part I.E.

273. *See supra* Parts I.C.1, I.E.

274. A transplant team usually only has about four to thirty-six hours to evaluate donor eligibility, obtain authorization for the organ donation, identify a suitable recipient, recover the organ, transport the organ to the recipient, and transplant the organ into the recipient. *See What Is the Time Frame for Transplanting Organs?,* DONOR ALL. (Aug. 25, 2021), https://www.donoralliance.org/newsroom/donation-essentials/what-is-the-time-frame-for-transplanting-organs/ [https://perma.cc/HC55-Q384].

275. *See id.*

276. For example, in absence of signs of heart disease, the fact that a donor lived three decades before dying in a car accident is fairly good evidence that the patient indeed possessed a functional heart.

277. *See supra* Part I.E.

278. *Cf. supra* text accompanying note 181.

279. *See* S.A. Lodhi et al., *Solid Organ Allograft Survival Improvement in the United States: The Long-Term Does Not Mirror the Dramatic Short-Term Success*, 11 AM. J. TRANSPLANTATION 1126, 1127 fig.1 (2011) (illustrating that organs can function for decades after transplantation); *supra* Part I.A. (noting patient safety as one of the main goals of the FDCA).

organs requires the expertise of a regulatory team with a wide range of scientific training.[280] The expertise of UNOS, which has been contracted by the HRSA to serve as the government's organ allocation network, lies in facilitating the logistics of obtaining and allocating fully developed human organs.[281] The HSRA, in turn, specializes in providing health-care infrastructure and services.[282] In contrast, the government's expertise in evaluating the safety and efficacy of medical products has been firmly concentrated in the FDA.[283] As such, it is likely that neither UNOS nor the HSRA have the adequate interdisciplinary regulatory expertise required to assess the safety and efficacy of bioprinted organs.

In sum, because regulation of bioprinted organs under NOTA would stifle innovation in bioprinting and fail to ensure the safety and efficacy of bioprinted organs, this Note recommends explicitly excluding bioprinted organs from NOTA's jurisdiction.[284]

B. A New Center for the Regulation of Bioprinted Organs

This Note argues that bioprinted organs should not fall under the purview of NOTA.[285] Instead, they should be regulated by the federal agency with the most experience in assessing the safety and efficacy of medical products: the FDA.[286] However, which subunit of the FDA should regulate bioprinted materials? And how can lawmakers incentivize innovation while balancing the interests of innovator and follow-on companies in the bioprinted organ space?

Bioprinting is a uniquely interdisciplinary science.[287] Yet, FDA examiners with scientific expertise relevant to the development of bioprinted materials are currently scattered across three different FDA centers.[288] Thus, this Note proposes the formation of a new "Center for Bioprinted Organs" within the Office of Combination Products.[289] This center would be staffed with regulatory scientists and experts from the FDA's drug, biologic, and device centers, forming an interdisciplinary team. Rather than being subordinate to these three existing centers, the separate nature of the new Center for Bioprinted Organs would emphasize its interdisciplinary and

280. *See supra* Part II.C.3.

281. *See supra* text accompanying notes 165–68.

282. *About HRSA*, HEALTH RES. & SERVS. ADMIN., https://www.hrsa.gov/about/index.html [https://perma.cc/V49Y-FYZH] (last visited Jan. 16, 2022).

283. *See supra* text accompanying note 35.

284. *See* Jacobson, *supra* note 158, at 1140 (proposing language to explicitly exclude bioprinted organs from NOTA).

285. *See supra* Part III.A.

286. *See supra* Part I.A (discussing regulation of medical products by the FDA).

287. *See supra* Part II.C.3.

288. *See supra* Part II.C.3.

289. As a practical matter, the new center should have jurisdiction over all bioprinted materials, including bioprinted tissues. However, the regulation of bioprinted tissues is beyond the scope of this Note.

collaborative mission and avoid turf battles between existing centers.[290] This Note argues that using an interdisciplinary team to oversee the approval process for bioprinted organs is more efficient and safer than the FDA's current lead center approach for combination products. Moreover, the approach proposed by this Note is in line with Congress's goals of ensuring the safety and efficacy of medical products while enhancing patient access to new medical technologies.[291]

First, an interdisciplinary review of bioprinted organs enhances product safety by improving the quality of the regulatory review. One of the hallmarks of bioprinted organs is that interactions between the organ's living and inanimate components can have significant impact on the physical, chemical, and biological properties of the medical product.[292] An appropriately staffed, interdisciplinary team is well suited to recognize and anticipate the potential safety issues that may arise from the interactions between the different components of the bioprinted organ.[293] Furthermore, the establishment of a single center dedicated to the regulatory review of bioprinted organs can lead to a higher-quality review that more quickly identifies key issues related to safety or efficacy.[294] Finally, having a single center review all market applications for bioprinted organs will increase consistency in the review process.[295]

Second, an interdisciplinary review of bioprinted organs is more efficient. Assigning the review of bioprinted organs to a single center eliminates the need for an intercenter consult request.[296] Despite the FDA's recent improvements to the intercenter consult process, it still—quite inefficiently—requires numerous administrative steps.[297] Furthermore, the consult request process presumes that a reviewer can anticipate issues that the reviewer might simply not know about (such as issues outside of the scope of the reviewer's scientific expertise).[298] Finally, an interdisciplinary FDA team can more efficiently communicate with the sponsor's

290. *See* Susan B. Foote & Robert J. Berlin, *Can Regulation Be as Innovative as Science and Technology?: The FDA's Regulation of Combination Products*, 6 MINN. J.L. SCI. & TECH. 619, 632–33 (2005) (describing ongoing turf battles among FDA centers).

291. *See supra* Part I.A.

292. *See supra* Part II.C.3.

293. *See supra* Part II.C.3.

294. *See* Rhonda M. Hearns-Stewart et al., *The Integrated Review: FDA Modernizes the Review of New Drug Marketing Applications*, 55 THERAPEUTIC INNOVATION & REGUL. SCI. 467, 469–71 (2021); Qiong Yuan, *Accelerating Progress in Pharmaceutical R&D: The Power of Interdisciplinary Knowledge*, CAS (Aug. 8, 2021), https://www.cas.org/resources/blog/accelerating-progress-pharmaceutical-rd-power-interdisciplinary-knowledge [https://perma.cc/D5F2-WNDS] (discussing the benefits of using an interdisciplinary approach to improve FDA regulatory review).

295. *See supra* notes 248–49 and accompanying text.

296. *See supra* notes 248–51 and accompanying text.

297. *See supra* notes 250–52 and accompanying text.

298. *See supra* notes 250–52 and accompanying text.

development team.[299] This more tailored regulatory approach is in line with Congress's goal of streamlining the approval of medical products.[300]

Third, the establishment of a Center for Bioprinted Organs is consistent with the FDA's proclaimed commitment to modernizing the FDA's organizational structure, eliminating review silos between different scientific disciplines and adapting existing regulatory approaches to ensure the efficient evaluation of innovative technologies.[301] Indeed, in the past, the FDA has formed new centers or transferred jurisdiction of certain products to an FDA team with more fitting regulatory expertise in response to advancements in medical science.[302] Accordingly, this Note's argument for the establishment of a Center for Bioprinted Organs serves the FDA's goal of matching its organizational structure to the products the agency regulates.[303]

Finally, the establishment of a new FDA center to address the lack of regulatory guidance for bioprinted organs is consistent with Congress's mandate requiring the FDA to identify gaps in the regulatory process that would delay patient access to new medical technologies.[304] Indeed, Congress has specifically endorsed the establishment of Intercenter Institutes within the FDA to coordinate and streamline the regulatory review of medical products.[305] One of these Intercenter Institutes is the Oncology Center of Excellence (OCE).[306] The OCE focuses on a specific disease area rather than a specific type of product.[307] However, just like the Center for Bioprinted Organs proposed by this Note, the OCE was designed to take advantage of the combined interdisciplinary skill set of FDA reviewers with expertise in drugs, biologics, devices, and diagnostics.[308]

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299. For instance, the FDA's software expert can directly advise the sponsor's software engineer on software-related issues, while the FDA's cell cultivation expert can discuss problems with her counterpart on the sponsor's development team.

300. *See* William D. Schwieterman, *Regulating Biopharmaceuticals Under CDER Versus CBER: An Insider's Perspective*, 11 DRUG DISCOVERY TODAY 945, 950 (2006) (arguing that a more flexible and individualized regulatory approach may avoid unnecessary development costs and delays); *supra* Part I.A.

301. *See* Scott Gottlieb, *FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation*, U.S. FOOD & DRUG ADMIN. (Aug. 29, 2018), https://www.fda.gov/news-events/fda-voices/fdas-comprehensive-effort-advance-new-innovations-initiatives-modernize-innovation [https://perma.cc/4RPY-8JTM].

302. *See supra* text accompanying notes 78–79.

303. *See supra* text accompanying notes 78–79.

304. *See* 21 U.S.C. §§ 393(g), 393 note ("Advancing Regulatory Science To Promote Public Health Innovation").

305. *See* 21 U.S.C. § 399g.

306. *See Implementing The 21st Century Cures Act: A 2018 Update From FDA and NIH*, U.S. FOOD & DRUG ADMIN. (July 24, 2018), https://www.fda.gov/news-events/congressional-testimony/implementing-21st-century-cures-act-2018-update-fda-and-nih-07242018 [https://perma.cc/9Y6Z-YLYP].

307. *See Oncology Center of Excellence*, U.S. FOOD & DRUG ADMIN. (Nov. 30, 2021), https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence [https://perma.cc/83JC-DKNV].

308. *See id.* (noting that the Oncology Center of Excellence "leverages the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, devices, and diagnostics").

Some might argue that the FDA cannot establish a new center in response to every advancement made in biomedical science. Patient advocacy groups and members of Congress are already advocating for the formation of FDA centers that would advance the interests of their respective constituents, such as a Neuroscience Center of Excellence.[309] Further, forming a new FDA center constitutes a significant administrative and financial burden for an already cash-strapped agency.[310] Finally, relocating FDA employees from their current roles into a new work environment (organizationally and potentially physically) may lead employees to leave the agency.[311]

This Note does not dispute that amending a regulatory framework in response to technological change can be expensive and laborious. However, policy makers have appreciated that certain interdisciplinary technologies have the potential to provide groundbreaking benefits to patients and are thus deserving of increased attention and funding.[312] One of these groundbreaking technologies is nanotechnology, which refers to the design of structures that exhibit new properties and functions due to their very small size.[313] Per Congress's direction, the FDA established a Nanotechnology Task Force dedicated to building regulatory expertise concerning the safety and efficacy of nanotechnology products and facilitating innovation in the field.[314] Since then, Congress has directed the FDA to further intensify and expand the agency's efforts to build scientific expertise on nanomaterials.[315] Like nanotechnology, bioprinting is an inherently interdisciplinary technology that combines aspects of chemistry, biology, and physics.[316] Further, like nanotechnology, bioprinting is used in a variety of different products that include aspects reviewed by more than one FDA product center.[317] Finally, like nanotechnology, bioprinting is a disruptive technology with the potential to revolutionize health care.[318]

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309. *See Advocate for an FDA Neuroscience Center of Excellence!*, AM. BRAIN COAL., https://www.americanbraincoalition.org/page/NCOE [https://perma.cc/KKU9-7WAZ] (last visited Mar. 4, 2022).

310. *See generally* Judith Alphonse et al., *The FDA Funding Crisis*, 30 J. PHARMACY TECH. 57 (2014) (discussing the FDA's historic underfunding).

311. *See* Bob Carlson, *FDA: Change Is Good*, BIOTECHNOLOGY HEALTHCARE, March 2004, at 27, 29 (expressing worry that after a reorganization of the FDA drug and biologics centers, employees may leave the agency).

312. *See* 15 U.S.C. § 7501 (directing the president to implement a National Nanotechnology Program).

313. *See* Sangeeta Khare et al., *Nanotechnology*, *in* 2 ENCYCLOPEDIA OF FOOD MICROBIOLOGY 893, 893 (Carl A. Batt & Mary Lou Tortorello eds., 2d ed. 2014). For reference, a sheet of paper is about 100,000 nanometers thick. *See* Anne Marie Helmenstine, *Examples of Nanoscale Objects*, THOUGHTCO (Jan. 4, 2020), https://www.thoughtco.com/examples-of-nanoscale-608575 [https://perma.cc/6KTC-XJ97].

314. *See* U.S. FOOD & DRUG ADMIN., NANOTECHNOLOGY—OVER A DECADE OF PROGRESS AND INNOVATION 1, 11 (2020), https://www.fda.gov/media/140395/download [https://perma.cc/KE9L-82LZ].

315. *See* 21 U.S.C. § 399e.

316. *See* U.S. FOOD & DRUG ADMIN., *supra* note 314, at 11; *supra* Part II.C.3.

317. *See* U.S. FOOD & DRUG ADMIN., *supra* note 314, at 11; *supra* Part II.C.3.

318. *See* THOMAS H. JOVIC ET AL., 3D BIOPRINTING AND THE FUTURE OF SURGERY 8 (2020) (arguing that 3D printing and bioprinting have the potential to be the "single biggest

Accordingly, the establishment of a new center dedicated to building regulatory expertise in bioprinting is consistent with Congress's tradition of singling out specific technologies that can significantly benefit public health.[319]

C. Balancing the Interests of Innovator and Follow-on Companies in the Bioprinting Space

Because regulatory exclusivities can be powerful tools to incentivize the development of new medical technologies, this Note proposes utilizing a relatively long regulatory exclusivity period to promote innovation in the bioprinting space.[320] However, to balance the interests of innovator and follow-on companies in the context of bioprinted organs, this Note recommends promoting competition by disclosing the innovator company's manufacturing information to manufacturers seeking to market a follow-on product.[321]

1. Bioprinted Organs Should Be Awarded a Long Regulatory Exclusivity Period

Innovation is often expensive and risky.[322] Regulatory exclusivities promote innovation by allowing innovator companies to charge significantly higher prices during the exclusivity period (far more than they would be able to with competitors in the market).[323] Importantly, Congress sought to balance the benefits afforded to innovator companies by making it easier for competitor companies to enter the market once the exclusivity period had expired.[324] In the small molecule context, offering both regulatory exclusivity as well as an abbreviated pathway to FDA approval has been shown to effectively promote drug development by innovator companies and to encourage competition among generic manufacturers at the end of the exclusivity period.[325] However, there is a debate on whether long exclusivity

technological disruptor" for the design and delivery of health care in the twenty-first century); Angelo Young & Michael B. Sauter, *3D Printing, E-cigarettes Among the Most Important Inventions of the 21st Century*, USA TODAY (Jan. 9, 2020, 8:02 AM), https://www.usatoday.com/story/money/2020/01/09/21-most-important-inventions-of-the-21st-century/40934825/ [https://perma.cc/G5WX-RQK5] (listing three-dimensional printing as one of the most important inventions for the twenty-first century); *The Global 3D Printing Market Size Is Expected to Grow USD 12.6 Billion in 2021 to USD 34.8 Billion by 2026, at a CAGR of 22.5 Percent*, REPORTLINKER (Aug. 3, 2021, 4:23 AM), https://www.globenewswire.com/news-release/2021/08/03/2273364/0/en/The-global-3D-printing-market-size-is-expected-to-grow-USD-12-6-billion-in-2021-to-USD-34-8-billion-by-2026-at-a-CAGR-of-22-5.html [https://perma.cc/YLS3-MMV4].

319. *See* U.S. FOOD & DRUG ADMIN., *supra* note 314, at 3.

320. *See supra* Part I.C.2.

321. *See generally* Heled, *supra* note 115, at 62 (advocating for making innovator manufacturing information available to follow-on developers in the context of biologics).

322. *See supra* note 119; text accompanying note 172.

323. *See supra* Part I.C.2.

324. *See supra* text accompanying notes 106–19.

325. *See* CONRAD & LUTTER, *supra* note 110, at 2–3; Heled, *supra* note 106, at 115, 117, 120–21.

periods, such as the twelve-year exclusivity period for biologics, actually promote innovation or stifle competition.[326] This Note concludes that a longer exclusivity period is necessary to promote innovation in the bioprinted organ space.

When applying the concerns of innovation and competition to bioprinted organs, one should consider that bioprinted organs and their associated manufacturing processes are significantly more complex than biologics and their manufacturing processes.[327] This is important for two reasons.

On the one hand, innovator companies producing bioprinted organs might face even higher financial and technological hurdles in bringing their technologies to market as compared to innovator companies producing biologics or drugs.[328] Accordingly, one might argue that bioprinted organs should benefit from an *even longer* regulatory exclusivity period, as compared to biologics and drugs.[329]

On the other hand, Congress sought to balance the long exclusivity period awarded for new biologics by allowing biosimilar manufacturers to rely on the innovator's safety and efficacy data once the exclusivity period had expired.[330] However, the FDA is currently not allowed to disclose the innovator's manufacturing protocol to follow-on applicants.[331] As such, manufacturers of biosimilars are forced to spend significant resources on developing their own manufacturing process.[332] Additionally, many biosimilar manufacturers incur significant costs for conducting clinical trials to establish that the product generated with their independently developed manufacturing process exhibits biosimilarity to the reference product.[333] These problems will likely be exacerbated for the manufacturers of follow-on bioprinted organs, which have to devise manufacturing protocols and demonstrate similarity for a significantly more complex medical product.[334] Additionally, given the semipermanent nature of bioprinted organs once transplanted into a recipient, biosimilarity to the reference product will need to be examined over an extended period of time.[335] This can further increase the costs of clinical trials needed to bring a follow-on bioprinted organ to market.[336]

Accordingly, follow-on manufacturers of bioprinted organs might not experience the significant cost savings that Congress had envisioned for

326. *See supra* text accompanying notes 138–40.
327. *See supra* Part II.C.1.
328. *See* Jeffery, *supra* note 270; Mermin-Bunnell, *supra* note 11, at 4–5 (noting that the company developing a bioprinted bladder, the first bioprinted organ to be transplanted into a human, filed for bankruptcy in 2014).
329. *See supra* text accompanying notes 132, 139.
330. *See supra* Part I.C.2.
331. *See supra* Part I.C.1.
332. *See supra* Part I.C.1.
333. *See supra* Part I.C.2.
334. *See supra* Parts I.C.1, II.C.1.
335. *See* Silva, *supra* note 242, at 387–88.
336. *See supra* Part I.C.1.

follow-on companies filing an abbreviated FDA application.[337] Thus, affording a long exclusivity period to bioprinted organs could result in a situation in which innovator companies benefit from an extended monopoly period, but in which follow-on manufacturers struggle to recoup the benefits of the abbreviated approval process that was supposed to promote competition among manufacturers.

One way of restoring the balance between innovator and follow-on companies in the bioprinting arena might be to grant a relatively short exclusivity period to innovator companies while largely dispensing with the accelerated pathway for follow-on manufacturers. This way, the innovator company would still be rewarded for being the first to bring a product to market while follow-on manufacturers would not be barred from entering the market for extended periods of time.[338] The latter could increase competition and result in lower prices for patients.[339] However, given the significant development costs for successfully bringing a bioprinted organ to market, a relatively short exclusivity period might be insufficient to justify a company's investment into the development of a bioprinted organ in the first place.[340] Indeed, studies show that the length of the exclusivity period is one of the largest factors in determining return on investment for pharmaceutical companies.[341]

Accordingly, to stimulate innovation in the bioprinted organ space, this Note proposes a regulatory exclusivity period for bioprinted organs that is at least as long as the regulatory exclusivity period for a biologic (i.e., at least twelve years).[342] A long period of market exclusivity will allow innovator companies to recoup the substantial costs incurred by bringing the first bioprinted organ to market. This in turn helps a large number of patients awaiting organ transplants, who will only benefit from bioprinted organs if these products are actually developed and successfully shepherded through the FDA approval process.[343]

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337. *See supra* Part I.C.2.

338. This assumes that there is no patent protection on the innovator product, a topic that is beyond the scope of this Note.

339. *See supra* text accompanying note 110.

340. *See supra* note 328 and accompanying text.

341. *See* Chris P. Miller, *Increasing Market Exclusivity for New Drugs, the Cure for What Ails Us?*, 3 ACS MED. CHEMISTRY LETTERS 437, 437 (2012); Matthew J. Higgins et al., *The Role of Assets in Place: Loss of Market Exclusivity and Investment* 25–26 (Nat'l Bureau of Econ. Rsch., Working Paper No. 27588, 2020) (discussing the relevance of market exclusivity for a company's capital expenditures and research and development spending).

342. *See supra* Part I.C.2.

343. *See* Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 170, 170 (2016) (describing the length and costs of the drug approval process); *supra* text accompanying note 18.

2. The FDA Should Disclose Manufacturing Information for the Reference Product to Follow-on Companies

The award of a long exclusivity period can be a significant incentive for innovator companies to bring the first bioprinted organs to market.[344] However, this Note argues that regulatory exclusivity alone is unlikely to increase competition among follow-on manufacturers of bioprinted organs, which is required to eventually drive down prices for these medical products.[345] Accordingly, this Note recommends pairing a long exclusivity period for bioprinted organs with permission for the FDA to use the innovator company's data in the evaluation of applications by follow-on manufacturers.[346] Similarly, the FDA should be permitted to disclose the innovator company's manufacturing information to a manufacturer applying for FDA approval for a follow-on product.[347] Disclosure of manufacturing information for the reference product has the potential to significantly reduce financial, regulatory, and scientific burdens for follow-on companies seeking to enter the market once the exclusivity period has expired.[348] This in turn can promote competition, which eventually benefits patients.[349]

Importantly, this Note's proposal is consistent with Congress's goal of increasing patient access to much-needed, innovative medical technologies.[350] First, this Note's proposal significantly lowers the entry barriers for follow-on manufacturers by providing these companies with the manufacturing information needed to create a close copy of the innovator organ.[351] For many biological products, the way of manufacture *is* the product.[352] Accordingly, the more closely a follow-on company can adapt its manufacturing process to the process used by the innovator company, the more likely it is that the follow-on company can establish clinical equivalency with the innovator product.[353] This in turn would allow the follow-on company to rely on the innovator's safety and efficacy data and to submit an abbreviated FDA application, resulting in significant cost savings for follow-on manufacturers of a bioprinted organ.[354] Increased competition

344. *See supra* Part I.C.2.

345. *See generally* Heled, *supra* note 106 (predicting that the Biologics Act will unlikely be as successful in reducing prices as compared to the Hatch-Waxman Act).

346. *See* Heled, *supra* note 115, at 62 (discussing the disclosure of manufacturing information in the context of biologics).

347. *See id.*

348. *See supra* text accompanying notes 106–10.

349. *See supra* text accompanying notes 106–10.

350. *See supra* Part I.A.

351. *See supra* Part I.C.1.

352. *See* Krista H. Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 708–09 (2010); Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-on Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 561 n.21 (2008).

353. *See supra* Part I.C.1.

354. *See* Heled, *supra* note 115, at 62 (suggesting that making innovator manufacturing information available to biosimilar developers will significantly decrease costs for follow-on developers to enter the market).

can ultimately result in lower prices for patients.[355] Accordingly, combining long exclusivity periods for innovator bioprinted organs with a requirement to disclose manufacturing data to follow-on manufacturers meets Congress's desire to balance the interests of innovator and follow-on companies.[356]

Second, there is statutory precedent for making manufacturing information available to follow-on manufacturers.[357] Under the Federal Insecticide, Fungicide, and Rodenticide Act[358] (FIFRA), manufacturers of pesticides need to receive clearance from the U.S. Environmental Protection Agency (EPA) before selling their products in interstate commerce.[359] As with medical products, marketing approval for pesticides requires the submission of data demonstrating the safety and benefits of the pesticide product.[360] Further, similar to the regulatory exclusivity period for medical products, FIFRA provides for a ten-year data exclusivity period for the information that the innovator company submitted to the EPA for the purpose of obtaining marketing approval.[361]

Importantly, after expiration of the data exclusivity period, the EPA is free to use the innovator company's data when evaluating applications by follow-on manufacturers.[362] The EPA may also disclose the innovator company's information to follow-on manufacturers (regardless of whether the data includes trade secrets) if certain criteria are met.[363] This measure sought to eliminate the expensive duplication of research and make products available to consumers more quickly.[364]

Similar to FIFRA, this Note proposes to balance the interests of innovator and follow-on companies by combining a longer data exclusivity period (i.e., longer than a decade) with a requirement to disclose the innovator product's manufacturing information to follow-on manufacturers.[365] Under FIFRA, the EPA may disclose priority data relating to the innovator product only if the EPA has determined that the disclosure is required to protect public health or the environment from an unreasonable risk of injury.[366] This Note does not suggest imposing such an additional requirement for making innovator data available to follow-on manufacturers of bioprinted organs. In fact, in the context of biosimilar regulation, it has been argued that the requirement to conduct additional clinical trials to obtain regulatory approval for a

355. *See id.*
356. *See supra* Part I.C.2.
357. *See generally* Heled, *supra* note 115.
358. 7 U.S.C. §§ 136–136y.
359. *See id.* § 136a(a).
360. *See id.* § 136(bb); *supra* Part I.C.1.
361. *See* 7 U.S.C. § 136a(c)(1)(F).
362. *See id.* §§ 136a(c)(1)(F)(iv), 136h(d)(1).
363. *See id.* §§ 136a(c)(1)(F)(iv), 136h(d)(1). Specifically, the agent may disclose priority data relating to the innovator product if the agency has determined that the disclosure is "necessary to protect against an unreasonable risk of injury to health or the environment." *Id.* § 136h(d)(1)(C).
364. *See* Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1015 (1984).
365. *See* Heled, *supra* note 115, at 59 (discussing the balance of interests that FIFRA sought to achieve).
366. *See* 7 U.S.C. § 136h(d)(1).

biosimilar (after clinical trials conducted by the innovator company have already established that the product is safe) is an unreasonable violation of established international ethical standards for conducting biomedical research.[367] As such, avoiding unnecessary clinical trials for bioprinted follow-on products arguably protects patients from an unreasonable risk of injury, thus meeting FIFRA's disclosure requirement.[368] Further, minimizing the number of clinical trials that need to be conducted for a single medical product is fully in line with Congress's and the FDA's primary goal of protecting public health.[369] As such, FIFRA's disclosure-limitation clause should not be required for manufacturing information relating to bioprinted organs.

Some might argue that the FDA's disclosure of manufacturing data to follow-on manufacturers, as proposed by this Note, constitutes an uncompensated taking of the innovator company's proprietary information and is thus unconstitutional under the Fifth Amendment Takings Clause.[370] However, in the context of pesticide regulation, the U.S. Supreme Court has upheld FIFRA's data use and disclosure provisions as constitutional.[371] In *Ruckelshaus v. Monsanto Co.*,[372] the Court acknowledged that the health, safety, and environmental data submitted to the EPA can constitute highly valuable trade secret information that might be very costly to develop.[373] Nevertheless, the *Ruckelshaus* Court held that as long as the conditions of data submission to a federal agency were clearly communicated to innovator companies and as long as these conditions were related to a legitimate governmental interest, the voluntary data submission in exchange for the economic benefit of regulatory exclusivity and market registration was not a "taking" of data.[374] Additionally, the Court held that even if the disclosure and use of the innovator's data by the EPA was considered a taking, such taking would be made for "public use" and would as such be permitted.[375] In justifying the public use of FIFRA's disclosure provision, the Court relied

367. *See* Letter from Bernard Sanders, U.S. Senator, to Margaret Hamburg, Comm'r, U.S. Food & Drug Admin. (Nov. 2, 2010), http://www.keionline.org/misc-docs/biogenerics/sandersletter.pdf [https://perma.cc/BD4E-2ZBQ] (arguing that the requirement to conduct additional clinical trials to obtain regulatory approval for a biosimilar product after the innovator product has been shown to be safe is an unreasonable violation of established international ethical standards for conducting biomedical research).

368. *See* 7 U.S.C. § 136h(d)(1).

369. *See supra* Part I.A.

370. *See* Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1000–01 (1984) (discussing whether the disclosure of the health, safety, and environmental data that the innovator company submitted to the EPA constitutes an unjustified taking under the Fifth Amendment).

371. *See* Heled, *supra* note 115, at 60 (discussing the Supreme Court's decision in *Ruckelshaus*).

372. 467 U.S. 986 (1984).

373. *See id.* at 998.

374. *See id.* at 1007.

375. *See id.* at 1014–15.

on public policy goals that would equally apply to the disclosure of manufacturing information for bioprinted organs.[376]

In sum, pairing a long exclusivity period for innovator bioprinted organs with the disclosure of manufacturing information to follow-on manufacturers might be a viable option for balancing the interests of innovator and follow-on companies and encouraging both innovation and competition in the bioprinting space.[377]

CONCLUSION

Bioprinted organs have the potential to serve as lifesaving organ replacements for thousands of patients in need. While science advances quickly in the bioprinting space, there is significant uncertainty as to how existing regulatory frameworks would be applied to these innovative medical products. It is also unclear whether these frameworks would sufficiently address the specific regulatory needs of bioprinted organs, which are unusually interdisciplinary materials. Importantly, the lack of specific regulatory guidance for bioprinted organs could stifle innovation in this promising technological field, ultimately harming patients.

This Note argues that explicitly excluding bioprinted organs from the jurisdiction of NOTA, which prohibits the sale of human organs, would reduce regulatory uncertainty for developers of bioprinted organs. Additionally, in line with the FDCA's primary goals of ensuring the safety and efficacy of medical products, this Note proposes the establishment of a new FDA center with the interdisciplinary expertise needed to provide high-quality regulatory review of bioprinted organs. Finally, to meet Congress's goal of improving patient access to cutting-edge technologies, a regulatory framework that promotes innovation while minimizing barriers to entry for follow-on manufacturers in the bioprinting space is needed. Specifically, this Note advocates for awarding a long regulatory exclusivity period to the first innovator company to bring a specific bioprinted organ to market. Such exclusivity would be paired with a requirement for the innovator company to disclose the manufacturing information for the reference product to follow-on manufacturers, thus allowing for a less costly and more streamlined production of follow-on bioprinted organs once the exclusivity period has expired.

While significant scientific hurdles in the production of fully functional, ready-to-implant bioprinted organs remain, more clinical trials are expected in the next couple of years. Thus, policy makers should act now to provide

376. *See id.* at 1015 (noting that FIFRA's disclosure requirement would reduce expensive duplication of research, streamline the regulatory approval process, accelerate consumer access to new products, lower barriers to market entry for follow-on manufacturers, and increase competition among manufacturers).

377. *See* Heled, *supra* note 115, at 62–64 (discussing what legislative change might be required on a practical level to introduce a data disclosure requirement in the context of biologics regulation).

the regulatory framework needed to realize the full potential of this exciting technology for the benefit of patients.