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THE EMERGENCE OF "NEW" ORGANS: A PROPOSAL TO REGULATE BIOPRINTING TECHNOLOGY UNDER THE MEDICAL DEVICE FRAMEWORK

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Organ bioprinting involves using cells and biomaterials to 3D print structures that resemble and imitate the functions of natural organs. Since bioprinting is a relatively new technological advancement, there is a lack of a regulatory structure in the United States, despite regulatory structures around the globe that are more developed in this field. Because of bioprinting's potential utility, a regulatory structure to ensure the efficacy and safety of bioprinted organs is needed.

The two potentially available regulatory frameworks to cover bioprinting technology in the United States are biological product and drug regulations and medical device regulations. Bioprinting does not fit neatly in either regulatory framework because bioprinted products contain elements of both medical devices and biologicals—they are "combination products." Selecting the proper regulatory framework is vital because of the ethical considerations and potential safety risks of this technology. The Class III medical device regulatory framework is best suited to regulate bioprinting technology as its requirements will ensure bioprinting's safe usage and will not stifle the growth of bioprinting technology.

TABLE OF CONTENTS

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I. INTRODUCTION

Imagine a world where thousands of deaths, nearly seventeen per day, could be prevented because people could receive the organ transplants they desperately need.[1] This became a reality for Luke Massella in 2004. Luke is alive today because he received a bioprinted replacement bladder that was made from his own cells.[2]

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[1] *Organ Donation Statistics,* HEALTH RES. & SERVS. ADMIN., https://www.organdonor.gov/learn/organ-donation-statistics [https://perma.cc/4PYP-B2ND] (last updated Mar. 2023).

[2] Padraig Belton, *'A New Bladder Made from My Cells Gave Me My Life Back,'* BBC NEWS (Sept. 11, 2018), https://www.bbc.com/news/business-45470799 [https://perma.cc/2UU5-9TPD].

By ten years old, he had already conquered surgeries for his spina bifida and was miraculously able to walk despite the bleak prognostications of doctors.[3] Unfortunately, he then faced a malfunctioning bladder, which led to kidney failure.[4] Luke expected to have to undergo dialysis for the remainder of his life, but Dr. Anthony Atala, a surgeon at Boston Children's Hospital, decided to take a piece of Luke's bladder and grow a new one.[5] During a fourteen hour surgery, Dr. Atala replaced Luke's bladder with a bioprinted bladder, made from his own tissue so that he could avoid cell rejection.[6] Luke has gone on to live a normal life, even becoming a wrestling coach.[7]

Luke remains one of about ten individuals who has a new lease on life because he received a bioprinted bladder grown from his own tissue.[8] As researchers make huge advances in the field of bioprinting, the law must catch up to guard against any irresponsible use of the technology. Technological innovation is constantly years ahead of the law, as new developments appear globally every single day while the law remains slow to adapt.[9] As a result, many technologies can exist for years without any legal regulations. Bioprinting technology is one such industry that has existed for over a decade under no clear regulatory framework.

Bioprinting has the potential to save millions of lives, as it allows for the production of working organs, tissue, and joint

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[3] *Id.*
[4] *Id.*
[5] *Id.*
[6] *Id.*
[7] Belton, *supra* note 2.
[8] *Id.*
[9] Julia Griffith, *A Losing Game: The Law is Struggling to Keep Up with Technology*, J. HIGH TECH. L. SUFFOLK U. L. SCH.: BLOG (Apr. 12, 2019), https://sites.suffolk.edu/jhtl/2019/04/12/a-losing-game-the-law-is-struggling-to-keep-up-with-technology/ [https://perma.cc/2YTR-ZYP3] ("It has been estimated that the law is at least five years behind developing a technology . . . . There are several potential reasons for this reality, one of which is that it is difficult, and many times impossible, for lawyers and lawmakers to predict new technologies before they emerge.").

cartilage at an unprecedented rate.[10] It could end years-long organ transplant lists, the deaths associated with tissue and cell rejection, and the need for animal testing. Many biotechnology companies have recognized this opportunity and have begun utilizing bioprinting technology in tissue engineering and in their research and development processes.[11]

For example, in August 2022, CollPlant Biotechnologies, a "regenerative and aesthetics medicine company developing innovative technologies and products for tissue regeneration and organ manufacturing," commenced a study to develop and test the efficacy of bioprinted regenerative breast implants.[12] CollPlant has broken into the $2.8 billion global breast implant market through the development of its recombinant human collagen-based ("rhCollagen") bioink implants.[13] CollPlant has utilized plant-derived rhCollagen, which is identical to type I collagen that humans produce.[14] "The recombinant human protein in the form of 'procollagen' is extracted from the leaves of mature plants and further processed to achieve a highly purified rhCollagen that can be used for . . . medical products."[15] CollPlant passed the preclinical

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[10] *See* JunJie Yu et al., *Current Advances in 3D Bioprinting Technology and Its Applications for Tissue Engineering*, 12 POLYMERS (2020) ("3D bioprinting is an attractive biofabrication method because it enables the precise deposition of various cells/biomaterials onto predefined locations . . . . [T]his automated technique facilitates both mass production and high-throughput production with high-resolution.").

[11] *Tissue Engineering and Regenerative Medicine*, NAT'L INST. OF BIOMEDICAL IMAGING & BIOENGINEERING, https://www.nibib.nih.gov/science-education/science-topics/tissue-engineering-and-regenerative-medicine [https://perma.cc/QG4E-T268] (last visited Mar. 4, 2023) ("Tissue engineering . . . refers to the practice of combining scaffolds, cells, and biologically active molecules into functional tissues. The goal of tissue engineering is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs.").

[12] Edward Wakefield, *CollPlant Advances 3D Bioprinted Regenerative Breast Implants*, VOXELMATTERS (Aug. 26, 2022), https://www.3dprintingmedia.network/collplant-advances-3d-bioprinted-regenerative-breast-implants/ [https://perma.cc/G9UJ-4RFG].

[13] *Id.*

[14] *RhCollagen,* COLLPLANT BIOTECHNOLOGIES LTD., https://collplant.com/technology/technology-rhcollagen/ [https://perma.cc/BBV6-V2A2] (last visited Feb. 22, 2023).

[15] *Id.*

study stage and moved into its large animal study stage.[16] This study, using reduced-size implants in a porcine model, will serve as a foundation for CollPlant's next endeavor: a human-size implant study.[17] These implants, much like all other bioprinted products, are customizable to the individual patient and will likely enhance the success rate of breast reconstruction and augmentation surgeries.[18]

CollPlant is not the only entity sticking its toe in this profitable industry. On September 8, 2022, 3D Systems, a worldwide engineering company and leader in the bioprinting industry, announced the creation of a biotechnology firm called Systemic Bio that will use bioprinting technology in drug research and development.[19] Systemic Bio will employ the technology to create "precise vascularized organ models using biomaterials and human cells" for its organ-on-a-chip platform called h-VIOS.[20] This technology will be utilized to more accurately study drug metabolism and the effects on tissue.[21] The platform will help simulate a human response to an experimental drug, possibly reducing costs and accelerating the time from trial to market.[22] The use of this program may also ultimately lessen or potentially eliminate the need for animal testing.[23]

These companies are two of several betting on the future widespread utilization of bioprinting in the biotechnology sector. However, organ bioprinting remains a relatively unregulated field of technology around the world.[24] Accordingly, this lack of

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[16] Wakefield, *supra* note 12.

[17] *Id.*

[18] *See id.*

[19] *3D Systems Announces Formation of New Biotech Company, Systemic Bio™, to Accelerate Drug Discovery and Development*, 3D SYS. (Sept. 8, 2022), https://www.3dsystems.com/press-releases/3d-systems-announces-formation-new-biotech-company-systemic-bio-accelerate-drug [https://perma.cc/N64E-R6RR].

[20] *Id.*

[21] *Id.*

[22] *Id.*

[23] *Id.*

[24] *See generally Will Bioprinted Organs Be Regulated by the FDA Like Medical Devices?*, PENROD BLOG, https://penrod.co/will-bioprinted-organs-be-regulated-

regulation creates problems for companies like CollPlant and Systemic Bio because until regulators develop an adequate regulatory framework for bioprinting technology, there will be a reluctance to expand to the market and the technology's use will be limited. As a result, companies are hesitant to utilize bioprinting technology because of uncertainties about safety risks, liability, ethical concerns, and more.

Bioprinting technology is beneficial because it provides an alternative to organ transplantation, it may decrease costs associated with organ transplants, and it will likely reduce the need for animal testing for cosmetics and drugs. However, with these benefits come certain ethical concerns, particularly the technology's use of embryonic stem cells, which remains a controversial issue.[25] Certain regions of the world, like the European Union and Australia, have already developed a variety of regulatory frameworks to cover bioprinting technology,[26] but the United States has not. The most commonly suggested regulatory frameworks involve regulating bioprinting technology as a drug/biologic or as a medical device. Despite strong arguments for bioprinting technology to fall under either category, it should be regulated under a stricter version of the Class III medical device framework, as this regulatory regime has established requirements and it is stringent enough to ensure safety while allowing for sufficient freedom to innovate. Moreover, there are obvious parallels between bioprinted structures and existing medical devices.

This Article analyzes the variety of regulatory standards for bioprinting technology around the world and recommends a regulatory regime for the United States to adopt for this technology. Part II gives an overview of bioprinting technology, including its perceived benefits in addition to ethical concerns regarding its use.

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by-the-fda-like-medical-devices/ [https://perma.cc/9X4L-S5A8] (last visited Mar. 8, 2023).

[25] *See generally* Bernard Lo et al., *Ethical Issues in Stem Cell Research*, 30 ENDOCR REV. 204 (Apr. 2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2726839 [https://perma.cc/XR8C-F6GD].

[26] *See generally* Jane Nielsen et al., *Bespoke Regulation for Bespoke Medicine? A Comparative Analysis of Bioprinting Regulation in Europe, the USA, and Australia*, 5 J. 3D PRINTING MED. 155 (2021).

Part III discusses the regulatory frameworks adopted in other countries and considers other proposed regulatory frameworks. Finally, Part IV argues that bioprinted products should not be regulated under the National Organ Transplant Act ("NOTA"), a biological products framework, or a drug framework, but rather the Class III medical device framework.

II. BIOPRINTING TECHNOLOGY: PERCEIVED BENEFITS AND ASSOCIATED ETHICAL CONCERNS

Despite remaining in the early stages of development, researchers have pointed to several beneficial opportunities presented by bioprinting technology as well as some major ethical concerns. This Section provides an overview of bioprinting technology and discusses the various benefits and ethical concerns it presents.

A. What is "Organ Bioprinting"?

Organ bioprinting involves the use of 3D-printing technologies to combine human cells and biomaterials in a "layer-by-layer fashion to produce bioartificial organs that . . . imitate their natural counterparts."[27] Biomaterials are "natural or synthetic substances containing living stem cells, which are also called bioinks."[28] Specialized bioprinters use bioinks, such as "human embryonic or induced pluripotent stem cells," to print the structures.[29] Two

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[27] Kristen Rogers, *When We'll Be Able to 3D-Print Organs and Who Will Be Able to Afford Them*, CNN HEALTH (Mar. 10, 2023, 10:40 AM), https://www.cnn.com/2022/06/10/health/3d-printed-organs-bioprinting-life-itself-wellness-scn/index.html [https://perma.cc/4MMG-Q5LM].

[28] Nabanita Panja et al., *3D Bioprinting of Human Hollow Organs*, 23 AAPS PHARMSCITECH 1, 1 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9088731/ [https://perma.cc/6CFQ-W5JH].

[29] Niki Vermeulen et al., *3D Bioprint Me: A Socioethical View of Bioprinting Human Organs and Tissues*, 43 J. MED. ETHICS 618, 618 (2017) ("[Bioprinting] is the biological variant of the recent trend towards 3D printing; small-scale manufacturing of computer-designed forms through laying down successive layers of material until the entire object is created . . . . These new forms of printing, should they be [realized], will . . . have the same revolutionary and [democratizing] effect as book printing in their applicability to regenerative medicine and industry.").

commonly-used biomaterials are collagen and gelatin.[30] To print bioprinted organs, the bioinks are loaded into a printing chamber and then printed layer-by-layer.[31] The time it takes to print an organ can vary, but it generally takes several hours.[32] From the initial biopsy of cells to the implantation of the printed organ, the entire process can take around four to six weeks.[33]

3D-printed organs look like real organs, and can be used as organ transplants or for clinical trials of drugs.[34] This cutting-edge technology constitutes a giant leap forward in the medical field, and large pharmaceutical companies like Johnson & Johnson have started to take notice.[35] The market for bioprinting technology has grown to a "hundred-million-dollar market, with an annual forty-four percent market growth," and is estimated to exceed a billion dollars in the next five years.[36] Not only is there an economic benefit to bioprinting, but the technology also has a number of real-world scientific and social benefits.

B. Perceived Benefits of Organ Bioprinting

Bioprinting technology provides an alternate source for organ transplants, potentially no longer requiring human donation, given that organs can be printed on demand.[37] The global organ transplant market was approximated to be around $12.4 billion in 2021.[38] In

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[30] Rogers, *supra* note 27.
[31] *Id.*
[32] *Id.*
[33] *Id.*
[34] Panja et al., *supra* note 28, at 5.
[35] *Id.*
[36] *Id.*
[37] Vermeulen et al., *supra* note 29, at 618 (discussing the potential benefits and ethical consequences involved in 3D bioprinting as well as practical and regulatory issues that must be tackled).
[38] *Transplantation Market Size, Share, & Trends Analysis Report by Product (Tissue Products, Immunosuppressive Drugs, Preservation Solution), By Application (Organ, Tissue Transplant), By End Use, and Segment Forecasts, 2022–2030*, GRAND VIEW RSCH. (May 23, 2022), https://www.grandviewresearch.com/industry-analysis/transplantation-market [https://perma.cc/8MZJ-DXBL] ("Growing demand for novel tissue transplantation products and organ transplantation for the treatment of organ failure is a major factor contributing to the market growth.").

the United States, over 106,000 men, women, and children patiently wait for the opportunity to receive an organ donation,[39] but because the demand heavily outweighs the supply, the prospects for many are grim.[40]

While the demand outweighs the supply, the supply also may not be where the demand is. As organs are transported long distances, many deliveries arrive damaged, which makes them unusable.[41] For example, "[a]t the University of Alabama-Birmingham, a kidney arrived frozen solid and unusable in 2014 . . . [a]nd in one week in May of [2022] . . . four kidneys had to be tossed for avoidable errors in transportation and handling."[42] As of 2022, "[o]ne in four potential donor kidneys . . . goes to waste."[43] The consistently growing demand for organ and tissue transplantation is not wavering, so the widespread availability of bioprinted organs would be a potential solution to the global organ transplant shortage and spoilage.[44] Since the tissue components of the organ are comprised of the patient's own organic material, the risk of cell rejection will be substantially reduced, meaning the organ transplant market will be more efficient.[45] The size and shape of the tissue components are also customizable to match the patient and grow in the patient, which would eliminate any need to replace the components in the future.[46]

Since bioprinting organs would reduce the need for donated human organs on a national and international scale, medical costs

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[39] Rogers, *supra* note 27.

[40] *Id.* ("In the United States, there are 106,800 men, women, and children on the national organ transplant waiting list . . . . However, living donors provide only around 6,000 organs per year on average, and there are about 8,000 deceased donors annually who each provide 3.5 organs on average.").

[41] Blake Farmer, *Transplant Agency Is Criticized for Donor Organs Arriving Late, Damaged, or Diseased*, NPR (Aug. 17, 2022), https://www.npr.org/sections/health-shots/2022/08/17/1118009567/damaged-and-diseased-organs-the-agency-overseeing-transplants-faces-intense-scru [https://perma.cc/436R-B4VX].

[42] *Id.*

[43] *Id.*

[44] Panja et al., *supra* note 28, at 1.

[45] Vermeulen et al., *supra* note 29, at 618.

[46] *Id.*

associated with transplants would likely diminish.[47] Sustaining a single patient on dialysis costs over $250,000 each year.[48] The average kidney transplant cost in 2020 was over $442,000, while bioprinters generally cost from a few thousand dollars to $100,000.[49] Organ transplants and dialysis are prohibitively expensive for the vast majority of Americans, so a successful implantation of a customized bioprinted organ could mean the difference between life and death for many individuals who otherwise could not afford treatment.

Another potential benefit of bioprinting technology is the reduced need for animal testing. Every year, over 110 million animals, including mice, rats, frogs, and guinea pigs, are killed in laboratories for medical training, drug, food, and cosmetics testing, and other experimentation.[50] Researchers have discovered that animal testing findings rarely translate to humans, and "patients and physicians should remain cautious about extrapolating the finding[s] of prominent animal research to the care of human disease."[51] In 2015, L'Oréal announced that it was partnering with San Diego-based biotech company Organovo to bioprint human skin instead of using animals for cosmetics testing.[52] The French cosmetics company had been producing "gelatinous, dime-sized blobs called EpiSkin" to test the efficacy of products rather than using live laboratory animals.[53] L'Oréal has been utilizing EpiSkin

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[47] Rogers, *supra* note 27.

[48] *Id.*

[49] *Id.*

[50] *Facts and Statistics About Animal Testing*, PETA, https://www.peta.org/issues/animals-used-for-experimentation/animals-used-experimentation-factsheets/animal-experiments-overview/ [https://perma.cc/2TGQ-S6R7] (last visited Jan. 29, 2023) (citation omitted).

[51] *Id.*

[52] Bob Woods, *Companies Are Making Human Skin in Labs to Curb Animal Testing of Products*, YAHOO! NEWS (May 28, 2017), https://www.yahoo.com/news/companies-making-human-skin-labs-170000120.html [https://perma.cc/5ARN-8QE5]; *see also* Margaret Rhodes, *Inside L'Oréal's Plan to 3-D Print Human Skin*, WIRED (May 28, 2015, 10:00 AM), https://www.wired.com/2015/05/inside-loreals-plan-3-d-print-human-skin/ [https://perma.cc/Z884-WVA4].

[53] Woods, *supra* note 52.

technology since 1997 to test ingredients and finished products before they hit the market.[54]

The European Union has also become a major player through its efforts to reduce animal testing by utilizing bioprinting technology.[55] The BRIGHTER project[56] creates human skin "using a novel bioprinting technology based on patterned laser light sheets."[57] Biotechnology firms and centers all over the world have contributed to this project to help develop a "novel Light Sheet Bioprinting process capable of producing complex and accurate in vitro models that can be used for cosmetics and drug testing within the pharmaceutical industry and in research settings."[58] If the BRIGHTER project can help further develop this technology by successfully printing in vitro skin models, bioprinting may lead to a worldwide reduction of animal experimentation in the pharmaceutical industry.[59]

The reduction in need for human organ donations, in associated treatment costs, and in animal testing are three important perceived benefits of bioprinting technology. Through these perceived benefits, bioprinting technology may substantially change the regenerative medicine industry and streamline the drug discovery

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[54] *Id.* ("In 2011, L'Oréal opened its Predictive Evaluation Center . . . [to grow] more than 100,000 human skin tissue samples annually . . . . Last year L'Oréal invested more than $900 million in research and innovation.").

[55] Hayley Everett, *3D Bioprinting Project to Deliver Brighter Alternative to Animal Testing,* 3D PRINTING INDUS. (Feb. 18, 2022, 11:32 AM), https://3dprintingindustry.com/news/3d-bioprinting-project-to-deliver-brighter-alternative-to-animal-testing-204524/ [https://perma.cc/QQ66-DE3G]; *see also Reducing Animal Testing with 3D Bioprinting: European Project BRIGHTER Brings New Light*, BRIGHTER, https://brighterproject.eu/news/reducing-animal-testing-with-3d-bioprinting-european-project-brighter-brings-new-light/ [https://perma.cc/PPP8-GDFF] (last visited Jan. 31, 2023).

[56] Everett, *supra* note 55 ("Bioprinting by light-sheet lithography: engineering of complex tissues with high resolution and high speed.").

[57] *Id.* ("According to the BRIGHTER team, their bioprinting process is also capable of generating vascularization of the printed tissue and enabling the function of the sebaceous and sweat glands, and the hair follicles to grow hair.").

[58] *Id.* ("Hydrogels will form a key component of the bioprinting process as they form the base from which cells will grow and form new tissue, and can also be personalized to individual patients using their own cells.").

[59] *See id.*

and development process. However, with bioprinting's benefits also comes an array of potential ethical and safety concerns.

C. Primary Ethical Concerns Regarding Organ Bioprinting

Organ bioprinting presents novel ethical and economic concerns. Despite being a cheaper alternative to organ transplants and dialysis, bioprinting comes with its own set of potentially substantial economic costs. For example, maintaining cell banks, culturing cells, and handling biological materials in the safest, most sterile environment can be expensive.[60]

Because organ bioprinting has yet to widely expand to the international market, scientists and lawmakers continue to tackle the uncertainties of this new territory.[61] Early studies within the organ bioprinting industry have demonstrated that some *possible* risks of bioprinted organ implantation include "teratoma and cancer[] [and] dislodgement and migrations of implant."[62] One major risk of bioprinting technology is the uncertainty associated with stem-cell testing.[63] Bioprinting technology utilizes stem cells, a relatively controversial method, to customize the treatment to a particular individual.[64] Since stem-cell therapy cannot be tested on a large sample of individuals,[65] the effectiveness of studies using stem cell research is lessened. For scientific validity, the researchers who run these studies must develop a method that will effectively test the safety and effectiveness of stem cell use in organ bioprinting.[66]

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[60] Rogers, *supra* note 27.

[61] *See* Damini Kunwar, *The Uncertainty of Regulating 3D Organ Printing*, REGUL. REV. (Dec. 10, 2019), https://www.theregreview.org/2019/12/10/kunwar-uncertainty-regulating-3d-organ-printing/ [https://perma.cc/A2XF-R5FT].

[62] Vermeulen et al., *supra* note 29, at 621.

[63] *See* Susan Dodds, *3D Printing Raises Ethical Issues in Medicine,* ABC SCI. (Feb. 2015), https://www.abc.net.au/science/articles/2015/02/11/4161675.htm [https://perma.cc/W3S2-779V].

[64] *Id.* ("[A] stem cell therapy can't be tested on a sizeable number of healthy people prior to being tested on patients and then, finally, being made available as a standard treatment.").

[65] *Id.*

[66] *Id.*

In addition to the use of embryonic stem cells, bioprinting organs involves the use of human-induced pluripotent cells.[67] "[H]uman embryonic stem cell (hESC) research is ethically and politically controversial because it involves the destruction of human embryos."[68] Embryonic stem cell research uses fertilized embryos that "can be sourced through a stem cell bank or through fertilized eggs that would otherwise be discarded."[69] This topic is controversial because it is tied to debates about abortion.[70] Those who believe that life begins at conception see an embryo as effectively a *person*, meaning that it has "interests and rights that must be respected."[71] People who have this conviction view "removing the inner cell mass to derive an embryonic stem cell line [as] tantamount to murder."[72] On the other side of the debate are those who view an embryo as a "clump of cells that can be used for research without restriction."[73] In the middle of the debate are those who believe that embryos are *potential* humans and their use requires some restriction, but scientific research justifies their use.[74]

After the *Dobbs v. Jackson Women's Health Organization* decision was announced in June 2022, scientists have speculated about whether and how the decision will affect stem cell research.[75]

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[67] *See generally* Lo et al., *supra* note 25.

[68] *Id.* at 205.

[69] Natalia Mesa, *Scientists Consider How Overturning Roe Might Affect Research*, SCIENTIST (Sept. 7, 2022), https://www.the-scientist.com/news-opinion/scientists-consider-how-overturning-roe-might-affect-research-70461 [https://perma.cc/4Q7F-N8Q4].

[70] *See* Lo et al., *supra* note 25, at 205 ("It is not disputed that embryos have the potential to become human beings; if implanted into a woman's uterus at the appropriate hormonal phase, an embryo could implant, develop into a fetus, and become a live-born child.").

[71] *Id.*

[72] *Id.*

[73] *Id.*

[74] *Id.*

[75] *See* Mauna Dasari, *The Dobbs Decision Will Make Science Less Diverse*, AWIS (Nov. 3, 2022), https://awis.org/resource/dobbs-decision-will-make-science-less-diverse/ [https://perma.cc/A6R2-EU3J]; *see also* Mesa, *supra* note 69 ("Researchers who work with materials such as fetal tissue and human embryonic stem cells are facing new restrictions, the latest in a long line of regulations, that could impede important advances.").

Embryonic stem cell research could become non-existent in states with strict abortion laws post-*Dobbs*, as these states may grant embryos "personhood" and restrict their use for research purposes.[76] Certain areas of the country could restrict the use of stem cells, effectively eliminating the potential for bioprinted organs to be created or utilized in those states among other potentially lifesaving cures and advancements in the field of medicine.

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Despite the risks, costs, and ethical considerations associated with organ bioprinting, these considerations are ultimately outweighed by the potential to save the seventeen people who die daily from needing an organ transplant they are unable to receive.[77] Since the bioprinting industry will continue to grow over the next few years, countries around the world must determine the appropriate regulatory framework to oversee the technology.

III. CURRENT STANDARDS FOR BIOPRINTING TECHNOLOGY REGULATION AND THE LACK OF A REGULATORY REGIME IN THE UNITED STATES

The sustained lack of regulations in the United States over the bioprinting industry has sparked a debate about what existing regulatory scheme, if any, should monitor bioprinting technology.[78] To ensure that this technology flourishes and the United States's regulatory plan does not fall behind the rest of the world, it is important for regulators to determine the appropriate framework through which to create the certainty needed in this field. The Food

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[76] Dasari, *supra* note 75 ("Religious employers already restrict research to only include human-induced pluripotent stem cells, but research using embryonic stem cells is especially important for understanding how to regenerate or repair diseased tissues and organs.").

[77] Rogers, *supra* note 27 ("Every day, 17 people die waiting for an organ transplant . . . [a]nd every nine minutes, another person is added to the waitlist.").

[78] *See generally FDA's Regulatory Framework for 3D Printing of Medical Devices at the Point of Care Needs More Clarity*, PEW CHARITABLE TRS. (July 27, 2022), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2022/07/fdas-regulatory-framework-for-3d-printing-of-medical-devices-needs-more-clarity [https://perma.cc/R38F-X4H6] [hereinafter *FDA's Regulatory Framework*].

& Drug Administration ("FDA") regulates technologies subject to its jurisdiction as biologics, drugs, or medical devices.[79] Bioprinting does not fall neatly under any of these existing regulatory frameworks and none of these frameworks have provided any concrete guidance as to organ bioprinting.[80] Neither the FDA's Center for Drug Evaluation and Research ("CDER"), the body that regulates drugs, nor the FDA's Center for Biologics Evaluation and Research ("CBER"), the body that regulates biological products, has announced any formal guidance on the use of bioprinting technology.[81] The Center for Devices and Radiological Health ("CDRH"), the body that regulates medical devices, has also not announced formal guidance on the use of bioprinting technology.[82] In fact, there appears to be a relatively clear split among regulators, as some believe that bioprinted organs should be regulated as a biological product or drug, while others view bioprinted organs as fitting within the medical device framework.[83]

A. Potential Regulatory Frameworks

The most commonly argued regulatory schemes that cover bioprinted organs are the "biological product/drug" framework and the "medical device" framework. Leading countries around the world have started to classify bioprinted organs as biological products, drugs, or medical devices. A few countries have established firm regulations regarding bioprinting organs, as bioprinting technology is a relatively recent development, but many other countries, including the United States, continue to struggle with categorizing this technology under an existing regulatory framework.

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[79] Jeff Mason et al., *An Overview of Clinical Applications of 3-D Printing and Bioprinting*, 175 CADTH ISSUES IN EMERGING HEALTH TECHS. 1, 7 (Apr. 2019).

[80] *See generally* Muthu Parkkavi Sekar et al., *Current Standards and Ethical Landscape of Engineered Tissues—3D Bioprinting Perspective*, 6 J. TISSUE ENG'G 1, 13 (July 2021) ("3D bioprinted tissues fall between the categories of living materials & technology and hence do not fall directly into the existing categories of regulations.").

[81] *FDA's Regulatory Framework*, *supra* note 78, at 3.

[82] *Id.*

[83] *See generally id.*

1. Classifying Bioprinted Organs as a Biological Product/Drug

Proponents of regulating bioprinted organs as biological products focus on the material components of the bioprinted organ.[84] These proponents highlight the major differences between bioprinted organs and medical devices. Medical devices typically do not consist of biological material, but rather metal or plastic.[85] Bioprinted organs are seemingly unlike these medical devices because they "cause a chemical reaction in the body and have the purpose of wholly replacing an existing organ."[86] "Biological product" refers to a "virus, therapeutic serum, toxin[,] . . . vaccine, blood, blood component or derivative, . . . [or] protein . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[87] Bioprinted organs could fit within this definition of biological product, as they consist of proteins and cells and are applicable to the treatment of conditions of humans.

Proponents of this approach also believe that bioprinted organs should be regulated under the premarket requirements of drugs and biologics because these requirements are more stringent.[88] To market a new drug, the law requires "*substantial evidence* of [the drug's] effectiveness."[89] To obtain licensure for biologics, the sponsor must demonstrate that the processes for manufacturing the product are "safe, pure, and potent."[90] In reviewing biological products, the FDA evaluates the product's safety and effectiveness, the adequacy of manufacturing methods to ensure its identity, strength, and purity, and the accuracy of labeling.[91]

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[84] Kunwar, *supra* note 61.

[85] *Id.* (discussing policymakers' difficulty with applying existing regulations to 3D organ printing).

[86] *Id.*

[87] 42 U.S.C. § 262(i)(1).

[88] AGATA BODIE & AMANDA K. SARATA, CONG. RSCH. SERV., IF11083, MEDICAL PRODUCT REGULATION: DRUGS, BIOLOGICS, AND DEVICES 1, 1 (2021), https://sgp.fas.org/crs/misc/IF11083.pdf [https://perma.cc/3DQR-DTRG].

[89] *Id.*

[90] *Id.*

[91] *Id.*

Products that are classified as a biological product or drug and regulated by CBER or CDER have a higher standard of evidence and heightened requirement for supporting data as compared to a medical device under the CDRH's regulations, but they are also eligible for certain benefits like "data or market protection in the form of regulatory exclusivity."[92] For certain drugs and biologics that have safety risks, the FDA may require a "risk evaluation and mitigation strategy" upon submission of the new drug application, which could include restrictions on the use of the drug.[93]

If bioprinted organs are regulated under the biological product/drug framework, the more stringent regulations (as compared to the medical device framework) could ultimately have a negative effect on the distribution and accessibility of bioprinting technology. The process from application-to-market of the technology could be slowed as a result of the higher thresholds that need to be met in biological products and drug applications, preventing those who need this life-saving technology from receiving it. When it comes to technology like bioprinted organs, time is of the essence for many individuals, so the lengthy process inherent in strict regulatory schemes may do more harm than good. Accordingly, the benefits associated with the regulatory framework for drugs and biologics may not translate into benefits for bioprinted organs.[94]

2. Bioprinted Organs Should be Classified Under the Medical Device Framework

Proponents of regulating bioprinted organs under the medical device framework focus more on the function of bioprinted organs as opposed to the materials used to create them. Medical devices

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[92] *Id.* at 2.

[93] *Id.* at 1.

[94] *See* Three Big Points, *Should the U.S. Government Slow its Roll in Technology Regulation?*, MIT SLOAN MGMT. REV. (Jan. 19, 2021) https://sloanreview.mit.edu/audio/should-the-u-s-government-slow-its-roll-in-technology-regulation [https://perma.cc/WKN9-5JQL] ("Pointing to the benefits of a history of relatively unfettered innovation in the United States and a lack of government expertise in emerging technology, among other factors, [Larry] Downes argues that all stakeholders are better served by a less-is-more approach to regulation.").

under the Federal Food, Drug, and Cosmetic Act ("FDCA") have traditionally been placed in three regulatory classes.[95] These classes are based on the "degree of control necessary to assure the various types of devices are safe and effective."[96]

Class I devices are those that present minimal potential for harm and are "not intended for use in supporting or sustaining life or of substantial importance in preventing impairment to human health."[97] Examples of Class I devices are bandages, tongue depressors, and reusable surgical scalpels.[98] The vast majority of these devices are exempt from FDA requirements for premarket approval.[99] Class II devices include "devices for which general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device."[100] They pose a moderate to high risk to the user and include devices that engage with a patient's cardiovascular system or organs.[101] Examples of Class II devices are catheters, blood transfusion kits, and absorbable sutures.[102]

Most relevant to bioprinted organs, Class III medical devices are products which "usually sustain or support life, are implanted[,] or

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[95] *Learn if a Medical Device Has Been Cleared by FDA for Marketing,* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing [https://perma.cc/55QN-Y4H4] (last visited Mar. 30, 2023).

[96] *Id.*

[97] Sumatha Kondabolu, *The 3 FDA Medical Device Classes: Differences and Examples Explained*, QUALIO (Jan. 25, 2023), https://www.qualio.com/blog/fda-medical-device-classes-differences [https://perma.cc/P5DP-RMPG] (emphasis omitted).

[98] *Id.*

[99] *See id.*; *see also Premarket Approval (PMA),* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma [https://perma.cc/U5UF-RLLA] ("PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).") (last visited Mar. 30, 2023).

[100] Kondabolu, *supra* note 97 (emphasis omitted).

[101] *Id.*

[102] *Id.*

present a potential unreasonable risk of illness or injury."[103] This class is generally reserved for permanent implants, smart devices, and life support systems.[104] Examples of Class III devices are breast implants, pacemakers, defibrillators, and implanted prosthetics.[105] The premarket approval ("PMA") process for Class III devices is extensive, requiring a "rigorous study . . . to prove safety and effectiveness through the development of a data-driven benefit/risk profile."[106] However, when compared to the requirements for drugs and biologics, medical device regulations are not necessarily as stringent.[107] For example, the FDA issues approval for a device when a PMA demonstrates *reasonable assurance* that a device is safe and effective.[108] The post-market requirements for biologics and Class III devices are both strict, as the FDA has mandatory recall authority over insufficient products and will temporarily suspend premarket approval or even ban a device if it presents deceptive labeling under the FDCA.[109]

According to the FDCA, a medical device is "an instrument, apparatus, . . . implant, . . . or other similar or related article . . . which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals."[110] Most importantly, a product that has a chemical action can be a device "if it does not achieve its *primary* intended purposes through that chemical action."[111] For example, the intended purpose of an

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[103] *Id.*
[104] *Id.*
[105] Kondabolu, *supra* note 97.
[106] *Id.*
[107] *See* BODIE & SARATA, *supra* note 88, at 1.
[108] *Id.*
[109] *Id.* at 2.
[110] U.S. FOOD & DRUG ADMIN., FDA-2011-D-0429, CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES AND ADDITIONAL PRODUCT CLASSIFICATION ISSUES (2017), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/classification-products-drugs-and-devices-and-additional-product-classification-issues#drug [https://perma.cc/RT37-PYUG]; 21 U.S.C. § 321(h)(1).
[111] U.S. FOOD & DRUG ADMIN., *supra* note 110 (emphasis added) ("For example, if the primary intended purpose of a hip joint replacement implant is to restore movement, and the implant also elicits a foreign body response through

absorbable suture is to rejoin tissue, but the suture is also designed to be reabsorbed by the body through a "combination of chemical action and metabolic activities."[112] The reabsorption would not be the primary intended purpose of the product, so while the suture is absorbable through chemical action, it can still be regulated as a medical device.[113]

Regulating bioprinted organs under the medical device framework would allow for greater availability and accessibility to the technology. While the regulations are strict as to ensure safety, they are not as stringent as the biological products/drugs framework. Accordingly, the technology could sooner enter the market and be utilized to save thousands of lives all over the country. Nonetheless, because bioprinted organs bear similarities to both biological products/drugs and medical devices, neither regulatory framework is a perfect fit.

B. Recent Regulatory Successes and Challenges Concerning Bioprinted Organs

Policymakers face unique regulatory challenges because bioprinted organs are "combination products."[114] Combination products are composed of any combination of a drug, device, and biological product.[115] Bioprinted organs may be categorized as combination products, as they incorporate aspects of both medical devices and biological products. These products inherently pose a challenge for regulators because of their complexity and inability to

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chemical action, that response would not be considered a primary intended purpose of the implant.").

[112] *Id.*

[113] *Id.*

[114] *See* Paul Hourd et al., *A 3D Bioprinting Exemplar of the Consequences of the Regulatory Requirements on Customized Processes*, 10 REGENERATIVE MED. 863, 864–65 (2015), https://doi.org/10.2217/rme.15.52 [https://perma.cc/KY8T-CGU7] ("In the USA, combination products as legally defined entities under 21 CFR 3.2(e), are broadly regulated by the FDA as products comprising two or more regulated components . . . that are physically, chemically or otherwise combined or mixed and produced as a single entity.").

[115] *Id.*

neatly fit into one existing regulatory scheme,[116] which might explain why regulators have been unable to agree on the proper regulatory regime for bioprinting technology.

In *Genus Medical Technologies v. FDA,*[117] the U.S. Court of Appeals for the District of Columbia Circuit provided some semblance of clarity regarding the future of combination product regulation.[118] Decided in April 2021, the issue in this case concerned the FDA's "regulatory classification of certain barium sulfate contrast imaging agents as drugs."[119] These agents improve visualization of the gastrointestinal tract in diagnostic studies, and under the FDCA they technically fall under both the definition of "drug" and "device."[120] The Court disagreed with the FDA's view that the FDA had the discretion to regulate products meeting both definitions as they would "drugs," and instead ruled that the FDA cannot regulate any product as a "drug" that also meets the definition of "device."[121] As a result of this decision, the FDA is expecting some products to shift from drug to device status insofar as regulations are concerned.[122] The FDA has noted that it "intends to regulate products that meet both the *device* and *drug* definition as

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[116] *See* Mariana E. Reis et al., *The Regulatory Challenges of Innovative Customized Combination Products*, 9 FRONTIERS MED. (LAUSANNE) (2022), https://doi.org/10.3389/fmed.2022.821094 [https://perma.cc/R44T-QATP].

[117] Genus Med. Techs. LLC v. Food & Drug Admin., 994 F.3d 631 (D.C. Cir. 2021).

[118] *Genus v. FDA D.C. Circuit Court Decision and Transition from Drugs to Devices*, U.S. FOOD & DRUG ADMIN. (Dec. 1, 2021), https://www.fda.gov/combination-products/guidance-regulatory-information/genus-v-fda-dc-circuit-court-decision-and-transition-drugs-devices [https://perma.cc/G5TJ-ULGU]; *see also* BODIE & SARATA, *supra* note 88, at 2 ("For example, in 2019 Genus Medical Technologies sued FDA for its decision to classify barium sulfate contrast imaging agents as drugs rather than devices. In August 2021, FDA announced that following a decision in that case, the agency could be requiring some approved products to transition from drug to device status.").

[119] Genus Medical Technologies LLC Versus Food and Drug Administration; Request for Information and Comments, 86 Fed. Reg. 43553 (Aug. 9, 2021), https://www.federalregister.gov/documents/2021/08/09/2021-16944/genus-medical-technologies-llc-versus-food-and-drug-administration-request-for-information-and [https://perma.cc/6HXK-7X8A].

[120] *Id.*

[121] *Id.*

[122] *Id*.

devices, except where the statute indicates that Congress intended a different classification."[123] It is difficult to tell what the implications of this case will be on the future of drug and device classifications within the United States and what this will mean for the regulation of bioprinting.

What is clear, however, is that this case substantially limits the FDA's discretion, which, prior to this case, was used to classify all products meeting the definition of a "medical device" and a "drug" as just a "drug."[124] In its decision, the Court of Appeals explained that it was not Congress's intention to "delegate unfettered discretion to the FDA to regulate all devices as drugs."[125] If the FDA could treat any product that meets both the drug and medical device definitions as a drug, this classification would dissolve the distinction between devices and drugs, effectively "turn[ing] the statutory scheme on its head."[126] Based on the reasoning of the *Genus* decision, if it is determined that bioprinted organs meet the statutory definitions of both a drug and a medical device, then a bioprinted organ should be classified as a medical device.

Regulatory difficulties are not exclusive to the United States, as international policymakers also struggle to find the best regulatory framework for bioprinting technology. The European Union ("EU") regulatory regime for "medicinal products" (a term which the EU uses to describe drugs and biologics) with biological components applies to "gene therapy, somatic cell therapy[,] and tissue-engineered products."[127] Bioprinted products are likely to be considered analogous to regenerative medicine products and thus regulated under the Advanced Therapy Medicinal Products

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[123] *Id.*

[124] Anne K. Walsh & Sara W. Koblitz, *Genus Medical Technologies, LLC v. U.S. Food and Drug Administration*, FOOD & DRUG L. INST., https://www.fdli.org/2020/10/genus-medical-technologies-llc-v-u-s-food-and-drug-administration/ [https://perma.cc/VM9V-TFZJ] (last visited Feb. 23, 2023).

[125] *Id.*

[126] *Id.*

[127] Nielsen et al., *supra* note 26, at 157 ("Medicinal products with biological components are brought within the scope of the Medicinal Products Directive by virtue of the Advanced Therapy Medicinal Products Regulation 2007 (ATMP Regulation).").

("ATMP") Regulation.[128] Advanced therapy medicinal products are "medicines for human use that are based on genes, tissues[,] or cells."[129] However, for products to fall under the ATMP Regulation framework, they must be "engineered" or substantially manipulated to "achieve certain biological, physiological[,] or structural properties or intended to achieve a function that differs from their original function."[130] Products that contain living cells that have not been substantially manipulated are considered transplants rather than ATMP products.[131] In the EU, regulators mainly focus on whether the biological component is the principal or ancillary aspect of the product to determine whether it should be regulated as a medical device or ATMP product.[132] Products are regulated under the Medical Device ("MD") Regulation if the biological component is considered ancillary, but are regulated under the ATMP Regulation if the biological component is the principal aspect.[133]

One point that remains unclear under the EU regulations for bioprinting is the "custom-made" device exemption. The "custom-made" device exemption exists under the medical device regulations, which allows for a lower threshold of regulation for "individualized" devices.[134] Manufacturers can avoid the strict regulations of medical devices under the rationale that these devices will not be readily available on the market.[135] While there is this "custom-made" device exemption for devices made specifically for particular patients, the exemption was intended to apply to devices

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[128] *Id.*

[129] *Advanced Therapy Medicinal Products: Overview*, EUR. MEDS. AGENCY, https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview [https://perma.cc/9RXW-64KA] (last visited Mar. 3, 2023).

[130] Nielsen et al., *supra* note 26, at 157.

[131] *Id.* (describing how bioprinted products derived from autologous cells might be classified as transplants and not ATMP products).

[132] *Id.* at 157–58 ("Where the biological component is ancillary to the device, assessment takes place under Article 1(8) of the MD Regulation. But where the action of the biological substance is 'a principal and not ancillary' aspect of the device, Article 6 of the ATMP Regulation will apply.").

[133] *Id.* at 158 ("In some instances, combination products may be subject to both the ATMP Regulation and the MD Regulation.").

[134] *Id.*

[135] *Id.*

like lenses and prosthetic limbs,[136] not bioprinted organs. The regulation specifies that products that are "mass produced" or mass produced using "industrial manufacturing processes" are not to be classified as custom-made devices, so the applicability of this exemption to bioprinted organs will ultimately depend "on how the terms 'mass-produced' and 'industrial manufacturing processes' are interpreted."[137]

One nation that has successfully put in place regulations for bioprinted organs is Australia. In December 2019, the Australian Department of Health released a proposed regulatory scheme that covers bioprinting organs.[138] The Therapeutic Goods Legislation Amendment Regulations 2019 required that the regulation of device/combination products fall under Class III medical devices.[139] The proposal argued that bioprinting should be regulated as a medical device with a human-origin or biological component, rather than as "pure biologicals," and emphasized the importance of ensuring consistent regulation.[140] Prior to this change in regulation,

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[136] Nielsen et al., *supra* note 26, at 158 ("Also important . . . is the 'custom-made' device 'exemption' under the MD Regulation, which attributes a lower risk threshold to individualized devices made specifically to address the needs of a particular patient. Article 2(3) of the MD Regulation exempts manufacturers from compliance . . . on the basis that these individualized devices will not generally be placed on the market.").

[137] *Id.*

[138] *See* Austl. Gov't Dep't of Health, Therapeutic Goods Admin., *Regulation Impact Statement: Proposed Regulatory Scheme for Personalised Medical Devices, Including 3D-Printed Devices*, TGA HEALTH SAFETY REGUL. (2019), https://www
.tga.gov.au/sites/default/files/regulation-impact-statement-proposed-regulatory-scheme-personalised-medical-devices-including-3d-printed-devices.pdf [permanent link unavailable].

[139] Nielsen et al., *supra* note 26, at 158.

[140] Austl. Gov't Dep't of Health, *supra* note 138, at 37 ("Some jurisdictions, including Canada, the EU and the USA, regulate medical devices with human-origin material as medical devices. In contrast, the Act specifies that any product that comprises, contains, or that is derived from human cells or human tissues is a *biological* and is thus regulated through the biologicals framework . . . . This change would mean that a medical device incorporating materials of human origin would be regulated as a medical device, more closely aligning the Australian framework with those of other jurisdictions.").

devices that contained a biological component were regulated as pure biologicals.[141]

The proposal reasoned that "3D-printed implantable scaffolds with human materials" are "analogous, from a design, engineering, production, and assessment perspective, to current implantable scaffolds with incorporated medicine . . . both of which are regulated as medical devices . . . ."[142] The proposed change would likely apply to "both viable and non-viable human origin components because the [Therapeutics Goods Administration] has the in-house expertise to evaluate both as a component of a medical device."[143] In early 2021, Australia adopted this proposal and has since treated combination device-biological bioprinted products as medical devices with a biological component.[144]

Like Australia, the United States would benefit from regulating bioprinting technology under a medical device framework because it imparts clarity and ensures that the technology is utilized safely without imposing excessive regulation. Including a biological component element to the current Class III medical device classification is a possibility to increase the safety of bioprinted organs.

IV. THE "MEDICAL DEVICE REGULATIONS" FRAMEWORK AS THE APPROPRIATE REGIME FOR BIOPRINTING TECHNOLOGY

When dealing with technological innovations, regulators must balance risk management and incentivizing innovation. Bioprinted organs have the ability to save thousands of lives every year, so the FDA must ensure that the regulatory framework that covers bioprinting technology does not too greatly restrain the development

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[141] Nielsen et al., *supra* note 26, at 158.

[142] Austl. Gov't Dep't of Health, *supra* note 138, at 37.

[143] *Id.* at 38.

[144] Nielsen et al., *supra* note 26, at 158 ("Recent amendments to the Device Regulations through the Therapeutics Goods Legislation Amendment . . . require regulation of device/cell combinations as class III medical devices. In addition, the 'viable and nonviable human origin components' of the device requiring assessment must be assessed . . . . What this means is that. . . . combination device-biological bioprinted products are now treated under the new Australian law as medical devices with a biological component.").

of these products.[145] At the same time, the FDA must balance the market demand for this technology with the need for appropriate regulation. This Section will explain that the United States should regulate bioprinting technology under the Class III medical device framework because it will provide stringent requirements for market approval while simultaneously allowing for sufficient freedom to develop the technology further.

A. Bioprinted Organs Should Not be Regulated Under NOTA

Because bioprinted organs are inherently similar to human organs and may ultimately replace the need for donated organs, some regulators have looked to the law that governs donated organs today: the National Organ Transplant Act ("NOTA").[146] NOTA classifies the term "human organs" as "human (including fetal) kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin or any subpart thereof and any other human organ . . . specified by the Secretary of Health and Human Services by regulation."[147] NOTA was established to "promote equitable access to and effective use of multiple organs and tissues, and to address technical, ethical[,] and financial issues involved in organ transplantation."[148] Some regulators argue that bioprinted organs should be classified under the "human organs" definition of NOTA

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[145] *See* Erik P.M. Vermeulen, *Artificial Intelligence, FinTech, Big Data . . . or, What Happens When Technology is Faster than the Law?*, MEDIUM (Sept. 3, 2016), https://medium.com/emergent-future/artificial-intelligence-fintech-big-data-or-what-happens-when-technology-is-faster-than-the-6c2c1528738c#.k4ohle1im [https://perma.cc/9GK2-2TKF] ("These [obstacles that can prevent consumers and entrepreneurs from enjoying the benefits and opportunities offered by new technologies or services] are not the result of technological limitations, but human choice. The law—and other regulations—can often prohibit, or otherwise limit, commercial exploitation of, and public access to, new technology.").

[146] Shelly Simana, *Reflections on Bioprinting Law: How Should 3D-Bioprinted Organs Be Classified, and What Does It Mean to Treat Them as "Property"?*, SLS BLOGS (Sept. 12, 2022), https://law.stanford.edu/2022/09/12/reflections-on-bioprinting-law-how-should-3d-bioprinted-organs-be-classified-and-what-does-it-mean-to-treat-them-as-property/ [https://perma.cc/P8HB-CAXS].

[147] *Id.*; 42 C.F.R. § 121.13 (2013).

[148] Robert Jacobson, *3-D Bioprinting: Not Allowed or NOTA Allowed?*, 91 CHI.-KENT L. REV. 1117, 1122 (2016).

because bioprinted organs are created from living material that could be considered "subparts" of humans.[149]

Other regulators argue that NOTA does not apply to bioprinted organs because the purpose of NOTA was to increase the availability of human organs and prevent the commercialization of the sale of organs. They argue that NOTA only applies to "*naturally* existing compositions of matter;"[150] in other words, because bioprinted organs are not entirely composed of biological products, they fall outside of NOTA's reach. Moreover, bioprinted organs do not present the same risks as human organ transplants, because bioprinted organs are created using a particular individual's own tissue, whereas transplants are human organs that are transferred from one person's body to another.[151] The risks associated with transplants include safety concerns, particularly the risk of organ failure or cell rejection, that are unique to human organs.

NOTA is particularly problematic for regulating bioprinted organs because the Act makes it illegal to sell human organs on the market, and bioprinted organs differ meaningfully from human organs.[152] Congress enacted the prohibition because, in its view, "human body parts should not be viewed as commodities."[153] Congress was concerned that the sale of organs would disproportionately benefit the wealthy, as they could potentially "purchase health and longevity at the expense of the poor."[154] Thus, Congress feared that a market could be cultivated in which less wealthy individuals would view organ selling as a money-making enterprise and they would be tempted to sell their organs to wealthier individuals for financial gain.[155]

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[149] Simana, *supra* note 146.

[150] *Id.* (emphasis added).

[151] *See id.*

[152] *Id*. ("NOTA determines that '[i]t shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce.' ").

[153] Jacobson, *supra* note 148, at 1122.

[154] *Id.* at 1123–24.

[155] *See generally id.*

Legislative history demonstrates that Congress did not intend for bioprinting organs to fall under NOTA's jurisdiction because bioprinted organs evade many of the concerns that initially motivated the enactment of NOTA.[156] In fact, bioprinting organs can eliminate many concerns about the sale of organs if they are regulated in such a way where only the individual whose cells make up the organ can receive it.[157]

If bioprinted organs were to be regulated under NOTA alongside human organs, it would be fatal to the bioprinting industry. Currently, NOTA makes it illegal to sell or pay to obtain organs.[158] If manufacturers of bioprinted organs could not sell their creations on the market, they would not "recoup their development costs" and may choose to completely stop developing bioprinted organs, collapsing the bioprinting market.[159] All in all, NOTA's regulations would suppress innovation and therefore, bioprinting technology and bioprinted organs should not fall under NOTA's scheme.

B. Bioprinted Organs Should be Regulated Under the Class III Medical Device Framework

Regulating organ bioprinting under the medical device framework, particularly the Class III medical device framework, would provide clarity and is the preferable method. To make this work, the FDA should broaden the definition of Class III medical devices to include biological material from humans, following Australia's regulatory scheme. The Class III framework is appropriate because this category covers devices that are implanted and that support the recipient's life.[160] Bioprinting involves the manipulation of living cells to create a printed structure that will ultimately be implanted within a body.[161] In the EU, the ATMP

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[156] *Id.* at 1124.

[157] *Id.*

[158] Simana, *supra* note 146.

[159] Linda Foit, *The Tin Man Needs a Heart: A Proposed Framework for the Regulation of Bioprinted Organs*, 90 FORDHAM L. REV. 2347, 2367 (2022).

[160] *See* U.S. FOOD & DRUG ADMIN., *supra* note 95.

[161] *See* Xiaohong Wang, *Advanced Polymers for Three-Dimensional (3D) Organ Bioprinting*, 10 MICROMACHINES (BASEL) 1–3 (Dec. 2019),

Regulation requires that "for products to qualify under this framework, they must have been subject to '*substantial* manipulation' to achieve certain . . . properties or intended to achieve a function that differs from their original function."[162] If products contain living material that has not been *substantially* manipulated, they would be regulated under a medical device framework.[163] There is currently no clear consensus as to whether bioprinted organs should be considered "*substantially* manipulated" for the purposes of regulation. Regardless, there is a strong argument that the technology fits most appropriately under the medical device regulatory framework.

The discrepancies between the material make-up of typical medical devices and bioprinted organs should not affect the regulation of this technology. The regulation should be based on the practical purpose of these bioprinted structures, which are the same as non-organic medical devices.[164] When comparing a bioprinted product with the medical devices listed above, particularly absorbable sutures and implanted pacemakers, the functions are analogous.[165] Like the absorbable sutures, whose primary intended purpose is to rejoin tissue,[166] a bioprinted bladder, while involving a chemical action within the body, has the *primary* intended purpose of mimicking the function of the human bladder.[167]

Some examples of medical products that achieve their primary intended purpose through chemical action within the body include aspirin and beta blockers.[168] Aspirin, as used for pain relief, inactivates the cyclooxygenase enzyme and inhibits "the synthesis

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6952999/pdf/micromachines-10-00814.pdf [https://perma.cc/5LTN-A2UC].

[162] Nielsen et al., *supra* note 26, at 157 (emphasis added).

[163] *Id.*

[164] *See* U.S. FOOD & DRUG ADMIN., *supra* note 110.

[165] *See generally id.* (demonstrating that a product, like an absorbable suture, that has a chemical action can still be considered a device if it does not achieve its *primary* intended purpose through the chemical action).

[166] *Id.*

[167] *See Urinary Bladder Bioprinting for Fully Autologous Transplantation*, CORDIS (2021), https://cordis.europa.eu/project/id/964883 [https://perma.cc/QJ8X-6HYP].

[168] U.S. FOOD & DRUG ADMIN., *supra* note 110.

of prostaglandin and thromboxanes, which suppresses the body's inflammatory response for pain relief."[169] Beta blockers, which are used to reduce blood pressure, bind beta receptors and "exhibit pharmacological action by inhibiting the activation of the signaling cascade. This blockage causes cardiac cells to reduce the strength of cardiac contractions and heart rate."[170] Aspirin and beta blockers demonstrate more obvious examples of products that achieve their *primary* intended purpose through chemical action, as they interact at the cellular level to promote or inhibit a bodily response.[171] While some regulators argue that bioprinted organs interact at the molecular level with bodily components to promote a response, like aspirin or beta blockers, the differences between a bioprinted organ and a drug like aspirin overshadow any similarities. Whereas aspirin or beta blockers are metabolized and eventually dissipate in the body, bioprinted organs are implanted and remain in the recipient, notwithstanding any chemical reaction that is taking place.

Organ bioprinting should be regulated under the Class III medical device framework because of the strict regulations that these medical devices must already follow to ensure patient safety.[172] Prior to marketing, Class III devices are subject to all FDA General Controls and the PMA process.[173] The FDA has determined that because of the risks involved with Class III medical devices, "general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices."[174] The PMA application for Class III devices requires valid clinical and

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[169] *Id.*

[170] *Id.*

[171] *Id.* ("[A] product exhibits 'chemical action' if it interacts at the molecular level with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) so as to alter that entity's interaction with the body.").

[172] *See* BODIE & SARATA, *supra* note 88, at 1.

[173] *See* Kondabolu, *supra* note 97 ("The PMA is the most intensive type of device marketing application required by the FDA. Some FDA Class III devices are exempt and may qualify for a 510(k) filing, but the majority are expected to gain Premarket approval.").

[174] *Id.*

non-clinical study information to support the applicant's claims.[175] Device applicants must disclose "study protocols, safety and effectiveness data, adverse reactions, device failures . . . results of statistical analyses, and any other information from the clinical investigations."[176] They must also reveal "information on microbiology, toxicology, [and] biocompatibility."[177]

In order to efficiently move organ bioprinting from early stages of development to the global market, it should be subject to the FDA's marketing application required for Class III devices. While some Class III devices are exempt from the PMA process,[178] all bioprinted devices and products, with their unique biological components and intrinsic safety risks, should be required to gain premarket approval and undergo intensive FDA review with no exemptions to ensure their safe use.

As previously explained, medical devices and drugs/biologics have different regulatory requirements.[179] Drugs and biologics, as a general matter, have more rigorous requirements.[180] However, the Class III medical device regulations are sufficient to cover bioprinting technology because bioprinted organs are implanted in individuals who voluntarily involve themselves in the process and the material that will be implanted comes from the individual's *own* cells.[181] If bioprinted organs made of a patient's cells were being implanted in another individual, this would be more similar to an

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[175] *See* U.S. FOOD & DRUG ADMIN., *supra* note 99 ("A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the Class III device . . . . If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it could impact FDA's review and approval.").

[176] *Id.*

[177] *Id.*

[178] *See* Kondabolu*, supra* note 97.

[179] *See generally* BODIE & SARATA, *supra* note 88.

[180] *Id.* at 1–2.

[181] *See* Vermeulen et al., *supra* note 29, at 618 ("The required tissue components are created from the patient's own cells (thus reducing the risk of rejection) and the geometry (size and shape) of the components can be [customized] to match perfectly with the patient's requirements. Unlike mechanical implants, such engineered tissue components that are 3D bioprinted have the ability to grow with the patient, eliminating the need for further operations to replace components which are no longer suitable.").

organ transplant. If that were the case, the FDA would want to regulate this technology to the greatest extent, as there are safety concerns, like cell rejection and infections, still common with transplanted material.[182] Since bioprinted organs are implanted into the same patient's body, this reduces the risk of cell rejection and lessens a variety of other safety concerns inherent in organ transplantation.[183] Regulators should thus allow some degree of risk-taking because of the severity of many patients' health situations. Since many of these people are likely to die if they cannot receive a donated or bioprinted organ, the more flexible Class III medical device regulations would likely be more useful than the more rigorous biological product/drug regulations.

C. Balancing Adequate Regulation with Technological Innovation

As previously stated, regulators must effectively balance the need to create sufficient regulation to protect citizens with promoting innovation in order for emerging technologies to survive. "Market innovation" refers to innovations that benefit "products, consumers, and society at large" while "social innovation" refers to "product and process innovations that create social benefits, such as cleaner air, which firms cannot directly capture through market sales."[184] "Economic regulation" sets "market conditions" and potentially affects the fairness of the market while "social regulation" seeks to protect the "welfare of society or the environment."[185] One multi-industry review found that while the extent to which regulation affects innovation is generally case specific, one common theme was that economic regulation often stifles market innovation.[186] Another discovered theme was that

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[182] *Risks of Transplantation*, WMDA, https://wmda.info/patients/risks-of-transplantation/ [https://perma.cc/A36M-T5WV] (last visited Mar. 30, 2023).

[183] *See* Vermeulen et al., *supra* note 29, at 618.

[184] Luke A. Stewart, *Appendix D: Abstract of "The Impact of Regulation on Innovation in the United States: A Cross-Industry Literature Review,"* HEALTH IT & PATIENT SAFETY: BUILDING SAFER SYSTEMS FOR BETTER CARE (Nov. 10, 2011), https://www.ncbi.nlm.nih.gov/books/NBK189657/ [https://perma.cc/R5GF-WBB7].

[185] *Id.*

[186] *Id.*

social regulation tends to encourage social innovation, but more often than not, it ultimately limits market innovation.[187]

Society has already begun to witness the adversarial relationship between innovative emerging technologies and regulations posed to protect consumers and foresee potential negative consequences. Some of the emerging technologies adjacent to bioprinting include artificial intelligence ("AI"), machine learning, and autonomous vehicles.[188] These newer digital-age technologies differ from traditional technologies of the 19th and 20th centuries because of their unprecedently fast-paced changes and concerns relating to digital privacy and security.[189] Current regulatory frameworks are better-suited for older-age technologies that did not move at the current pace because slower innovation allows for the gap between law and technology to shrink. These regulatory approaches are not well-suited to support the recent emerging technological developments, which have widened the gap between "technological advancements and the mechanisms intended to regulate them."[190]

In the case of bioprinting, this technology can be considered a *market* innovation, rather than a purely scientific innovation, as it benefits consumers and society as a whole. Regulatory bodies seek to regulate bioprinting technology to protect the welfare of society because of the uncertainty that it generates. Applying the multi-study review to bioprinting,[191] regulatory agencies may ultimately stifle advancements in bioprinting if regulations are too stringent. Existing regulatory frameworks are "slow to adapt . . . and regulatory agencies generally are risk averse. Rapid adaptation to

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[187] *Id.*

[188] William D. Eggers et al., *The Future of Regulation: Principles for Regulating Emerging Technologies*, DELOITTE (June 19, 2018), https://www2.deloitte.com/us/en/insights/industry/public-sector/future-of-regulation/regulating-emerging-technology.html [https://perma.cc/34T2-953G] ("As new business models and services emerge, such as ridesharing services and initial coin offerings, government agencies are challenged with creating or modifying regulations, enforcing them, and communicating them to the public at a previously undreamed-of pace. And they must do this while working within legacy frameworks *and* attempting to foster innovation.").

[189] *See id.*

[190] *Id.*

[191] Stewart, *supra* note 184.

emerging technology . . . poses significant hurdles—and, in turn, to the technology industries, where change occurs at a rapid rate."[192] Because of its stricter regulations,[193] the drug and biologics regulatory framework may be more likely to stifle life-saving growth in this field than the medical device framework.

While none of the existing regulatory approaches are ideal to house organ bioprinting, the high-risk Class III medical device framework is best because it requires strict regulation while also allowing enough flexibility to facilitate advances. The United States should follow Australia's plan for regulation of medical devices with human-origin components as medical devices rather than as biologics[194] and include a stricter tier of regulation and assessment to the current Class III medical device framework.

A promising solution for bioprinted products that have human and synthetic materials would be to implement this stricter tier of Class III medical device regulations that combine some elements of medical device and biologics regulations. Manufacturers of bioprinted products should be required to demonstrate more than just a *reasonable* assurance of effectiveness under the current medical device regulations because of the unknown risks that may be involved in implanting a bioprinted organ, but the biologics regulations that require *substantial* evidence of effectiveness are too strict and do not provide enough latitude.[195] This additional level of assurance is necessary considering the sensitivity and safety risks of bioprinted products as compared to currently existing and tested plastic or metal medical devices.[196]

The post-market requirements for biologics and Class III devices are similarly restrictive, as the FDA can recall insufficient products and suspend approval or even ban a device.[197] If the product created

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[192] Eggers et al., *supra* note 188.

[193] *See generally* BODIE & SARATA, *supra* note 88.

[194] *See* Austl. Gov't Dep't of Health, *supra* note 138, at 37.

[195] *See* BODIE & SARATA, *supra* note 88, at 1.

[196] *See generally* Vermeulen et al., *supra* note 29, at 621 ("3D bioprinting remains an untested clinical paradigm and is based on the use of living cells placed into a human body; there are risks including teratoma and cancer, dislodgement and migrations of implant. This is risky and potentially irreversible.").

[197] *See* BODIE & SARATA, *supra* note 88, at 2.

by bioprinting is determined to be unsafe or ineffective, the FDA should have the authority to suspend approval or prohibit use of the product. However, the stricter requirements of FDA review for drugs and biologics would likely have the effect of slowing innovation in this field because the extensive review of every method could significantly lengthen the approval process.

Robust regulation to promote public safety and autonomy for private actors to innovate will always be at odds with one another. Drugs, biologics, and medical devices will always contain an element of risk, as they cannot be 100% safe, so policymakers need to decide where to draw the line to provide the certainty needed for the industry to flourish. Stricter regulation will undoubtedly create a market of safer products that have been extensively researched and tested, but society may be sacrificing the potential discovery of a life-saving drug or medical device. Too much autonomy and freedom to innovate will undoubtedly flood the market with products, and some may be helpful, but many unsafe drugs or instruments that would otherwise not surpass the regulatory threshold could enter the market, causing serious damage. In the case of bioprinted organs, because of the dire outcomes for so many people on organ transplant lists, regulators should sacrifice the need for very stringent regulations to allow for greater enhancements in the bioprinting field. There should be relatively high thresholds that need to be met before implanted bioprinted products can be expanded on the international market, but the societal need to grow the bioprinting industry and get bioprinted organs to market outweighs the desire for excessive testing and regulatory thresholds which try to ensure absolute safety.

V. CONCLUSION

Bioprinting technology has the capacity to save lives in a way that could not have been contemplated decades ago. Individuals who would otherwise spend their lives on the transplant waiting list or potentially develop complications from organ transplantation may soon be able to undergo implantation of printed cellular material and potentially get a second chance at life, like Luke Massella. This new technology can be customized to the individual patient, can increase access to care by lowering costs, can reduce animal testing, and can

decrease safety risks typically associated with donated human organs. There are also many safety concerns, as the process of surgically placing a bioprinted implant in a patient's body is invasive, so policymakers must do their best to catch up to the technology and enact efficient regulations as quickly and as safely as possible.

As the technology continues to be tested, a balance must be struck between sufficient regulation and the freedom to innovate so that the market can finally take advantage of organ bioprinting. Medical device regulations and biological product/drug regulations both provide possible regulatory housing for bioprinted organs and ever since bioprinting technology emerged, countries have been grappling with how to regulate it properly. Considering the unique risks of bioprinting, the FDA should regulate the technology under a Class III medical device framework with a human-origin component or biological component, as this classification requires strict guidelines to protect patients while also providing enough leeway for future growth in the industry.