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How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology

Myrisha S. Lewis
William & Mary Law School, mslewis01@wm.edu

HOW SUBTERRANEAN REGULATION HINDERS INNOVATION IN ASSISTED REPRODUCTIVE TECHNOLOGY

Myrisha S. Lewis†

Most scholars believe assisted reproductive technology is subject only to minimal regulation, especially by the federal government. This belief, I contend, is wrong. In this Article, I examine agency documents, statements by officials, and letters that the U.S. Food and Drug Administration (FDA) has sent to physicians and researchers over the past fifteen years to reveal an overlooked regulatory program. The FDA has been targeting new forms of assisted reproductive technology that involve small genetic modifications (advanced assisted reproductive technologies or AARTs) through regulatory actions that receive little public, media, or scholarly attention. I term this method of regulation "subterranean regulation." Subterranean regulatory actions chill research as many physicians and researchers halt their research after receiving these letters or stop providing access to AARTs in the United States.

The existence of this unconventional and largely unnoticed regulatory practice raises a series of issues including whether the FDA should be regulating advanced assisted reproductive technologies at all. Moreover, a hidden, ad hoc regulatory practice is exactly the wrong kind of process to use when it comes to scientific innovations in fraught ethical areas, which includes not only assisted reproductive technology but also other DNA-modifying technologies such as gene editing (including CRISPR-Cas9). Ultimately, I recommend a regulatory approach that is as close to "minimal regulation" as possible.

† Assistant Professor, Howard University School of Law; J.D., Columbia Law School; A.B., Harvard College. For helpful suggestions and comments, I would like to thank Lori Andrews, Bernadette Atauhene, Katharine Baker, Felice Batlan, Rabia Belt, Robert Bohrer, Alexander Boni-Saenz, Marie Boyd, Elizabeth Emens, Philip Genty, Patrick Goold, Sarah Harding, Jenny Ma, Nancy Marder, Kent McKeever, Jennifer Nou, Elizabeth Pendo, Maya Sabatello, Christopher Schmidt, Carolyn Shapiro, Stephanie Stern, and workshop participants at Howard University, Florida State University, St. Thomas University, the Chicago-Kent College of Law, the California Western School of Law, the Chicago Junior Faculty Workshop, the Tenth Annual Lutie A. Lytle Black Women Law Faculty Writing Workshop, and the American Society of Comparative Law's Younger Comparativists Global Conference, where I presented earlier versions of this Article.

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INTRODUCTION

Commentators have described the regulatory environment surrounding assisted reproductive technology as "limited," "minimally regulated," and even "the Wild Wild West."[1] This Article reveals, however, that one important subset of assisted reproductive technology, the subset that contains forms of assisted reproductive technology that combine in vitro fertilization with the modification of small amounts of DNA (referred to herein as advanced assisted reproductive technologies or AARTs), is an exception to this general rule.[2] Instead, the FDA highly regulates AARTs through an overlooked regulatory program that is mostly administered through letters as opposed to clearly applicable regulations. I term this method of regulation "subterranean regulation."

The FDA uses subterranean regulation to regulate medical techniques that are accompanied by ethical controversy including cloning, advanced assisted reproductive technologies, and unconventional methods of enhancing fertility.[3] Over the past fifteen years, the FDA has sent "Untitled Letters" to practitioners who work on advanced assisted reproductive technologies.[4] Untitled Letters are one

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1 Michele Goodwin, *Prosecuting the Womb*, 76 GEO. WASH. L. REV. 1657, 1693 (2008) ("Here, the minimally regulated [assisted reproductive technology] industry thrives with minimal state interference or attention to fetal health outcomes or risks to mothers or fetuses."); Alexander N. Hecht, *The Wild Wild West: Inadequate Regulation of Assisted Reproductive Technology*, 1 HOUS. J. HEALTH L. & POL'Y 227, 228 (2001); *see, e.g.*, NAOMI R. CAHN, TEST TUBE FAMILIES: WHY THE FERTILITY MARKET NEEDS LEGAL REGULATION (2009); Naomi R. Chan & Jennifer M. Collins, *Eight Is Enough*, 103 NW. U. L. COLLOQUY 501, 507 (2009) ("Currently, regulation over reproductive technology by the state and federal government is limited. The fertility industry mostly self regulates through nonbinding guidelines and suggested ethical practices, though there are various physician licensing requirements."); Judith F. Daar, *Regulating Reproductive Technologies: Panacea or Paper Tiger?*, 34 HOUS. L. REV. 609, 615 (1997) ("[Assisted reproductive technology] is subject to little formal regulation . . . ."); *see also* DEBORA L. SPAR, THE BABY BUSINESS: HOW MONEY, SCIENCE, AND POLITICS DRIVE THE COMMERCE OF CONCEPTION 5 (2006) ("In the United States, however, regulatory and legislative authorities have largely ignored the market for reproductive services. There are very few restrictions on fertility treatments and little regulation of providers."); Marsha Garrison, *Regulating Reproduction*, 76 GEO. WASH. L. REV. 1623 (2008); Hank Greely, *Cloning and Government Regulation*, 53 HASTINGS L.J. 1085, 1089–90 (2002); Lars Noah, *Assisted Reproductive Technologies and the Pitfalls of Unregulated Biomedical Innovation*, 55 FLA. L. REV. 603, 614–15 (2003).

2 This Article will refer to these types of assisted reproductive technologies which result in small modifications of DNA which will be inherited by future generations as "advanced assisted reproductive technologies." Examples of these advanced assisted reproductive technologies include cytoplasmic transfer and mitochondrial transfer, a technique which was recently approved in the United Kingdom.

3 *See infra* note 132 (discussing Freedom of Information Act (FOIA) request 2016-4882 which provides information on the FDA's regulation by letter of AUGMENT, a fertility treatment created by an American company that revitalizes a woman's eggs; the technique is currently unavailable in the United States).

4 *See infra* note 132; *see also Warning and Untitled Letters: FDA Transparency Initiative*, U.S. FOOD & DRUG ADMIN. (Dec. 20, 2011) [hereinafter *Warning and Untitled Letters*], https://

type of communication that the FDA uses to inform companies and individuals that they are violating federal law.[5]

However, the FDA's process of issuing these letters to AART-providers differs from the usual methods that the FDA uses to inform regulated entities of statutory violations, not only in the comprehensiveness of the letters but also in the recordkeeping related to these letters. For example, the FDA's response to a Freedom of Information Act (FOIA) request that I submitted related to the first example of the FDA's subterranean regulation of AARTs revealed that the FDA is "unable" to locate the addressees of these letters to AART-providers and that it does not maintain such letters in a centralized document management system.[6] Thus, while the content of those letters is available online, it is impossible to ascertain the scope of this type of regulation without a list of addressees. In some instances of subterranean regulation, the content of the letters is not even publicly available on the FDA's website, such as in the 2013 case of a letter and subsequent communications between the FDA and a Massachusetts-based provider of innovative assisted reproductive technology services.[7]

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www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm284105.htm ("If a person or firm violates the Federal Food, Drug and Cosmetic Act (FD&C Act), FDA may give them an opportunity to take voluntary and prompt action to correct the violation before FDA initiates an enforcement action. FDA will issue either a Warning Letter or an Untitled Letter, depending upon the nature of the violation. . . . FDA uses Untitled Letters for violations that are not as significant as those that trigger warning letters. Unlike a Warning Letter, an Untitled Letter does not include a statement warning that failure to promptly correct a violation may result in an enforcement action.").

5 *See Warning and Untitled Letters*, *supra* note 4. *Compare infra* Appendix A, *with* Appendices B–D (The letter in Appendix A does not contain any statutory citation, nor does it explain how the Addressee's actions allegedly violate the statutes that the FDA has responsibility for enforcing. By comparison, Appendix B mentions at least two specific statutes). Appendix C *infra* includes citations to specific statutory violations (e.g., 21 U.S.C. §§ 321(n), 352(a) (2012)), as does Appendix D (e.g., "This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. § 321(h), because it is . . . .").

6 FOIA Request 2016-4883 revealed that the FDA was unable to "locate an admin file for the subject . . . letter." E-mail from Ashlee Eswara, Microbiologist, U.S. Food & Drug Admin., to author (Aug. 25, 2016, 8:27 AM) (on file with author). Similarly, before the request was officially closed, a conversation with an FDA employee in the FOIA division indicated that it was unlikely that the Agency would be able to find the file related to the letter because the Agency does not have a system for recordkeeping when an application is not active. *Id.*

7 *See* Letter from Ellen Lazarus, Dir., Div. of Human Tissues, Office of Cellular, Tissue & Gene Therapies, U.S. Food & Drug Admin., to Alison Lawton, Chief Operating Officer, OvaScience, Inc. (Apr. 9, 2013) (on file with author); Letter from Celia M. Witten, Dir., Office of Cellular, Tissue and Gene Therapies, U.S. Food & Drug Admin., to Alison Lawton, Chief Operating Officer, OvaScience, Inc. (Sept. 6, 2013) (on file with author); *infra* text accompanying notes 179–83 (regarding FOIA Request 2016-4882 and Massachusetts-based OvaScience's AUGMENT technology which is now available in other countries but not the United States, and the FDA's most recent 2017 letter to Dr. John Zhang); *see also* Ariana Eunjung Cha, *FDA Cracks Down on Company Marketing "Three-Parent" Babies*, WASH. POST (Aug. 8, 2017), https://www.washingtonpost.com/news/to-your-health/wp/2017/08/07/fda-cracks-down-on-company-marketing-three-parent-babies/?utm_term=.0562ad833f54.

Nevertheless, my review of Agency FOIA responses, media coverage, and, in the case of the aforementioned Massachusetts-based company, a shareholder suit, have enabled me to identify some of the recipients of the FDA's subterranean letters, even in the absence of the Agency's "admin file."

The first of the FDA's subterranean letters to AART-providers was sent on July 6, 2001 to physicians who were providing an advanced assisted reproductive technology called "cytoplasmic transfer" to patients.[8] The letter began by stating "[w]e want to advise you that the Food and Drug Administration (FDA) has jurisdiction over human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei."[9] While two federal statutes were mentioned in the letter, there was no citation to any statutory provision that would provide the FDA's "jurisdiction."[10] Even though the Agency provided no legal citation, the FDA still stated that physicians working on advanced assisted reproductive technologies would have to submit to the extensive drug approval process that applies to pharmaceutical companies seeking to market new drugs in the United States.[11]

In subsequent communications, including guidance documents and other documents posted on the Agency's website, the FDA has ordered that all advanced assisted reproductive technologies, including mitochondrial transfer, a potentially life-saving technique that has been the subject of recent media coverage, obtain premarket approval prior to clinical use.[12] However, just as with cytoplasmic transfer in 2001, the

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8 *See infra* Appendix A; *see also, e.g.*, Transcript of Center for Biologics Evaluation and Research, Food and Drug Administration, Biological Response Modifiers Advisory Committee Open Session Meeting #32, 47 (May 9, 2002, 8:00 AM) [hereinafter Meeting #32 Transcript], https://www.fda.gov/OHRMS/DOCKETS/ac/02/transcripts/3855t1-01.pdf ("FDA had concerns about whether we understood all the ramifications of this procedure and whether we understood its safety in particular, and reacted by sending letters to practitioners who were identified by publications on ooplasm [cytoplasm] transfer or by advertisements offering the procedure. We advised practitioners that we would now require the submission of an investigational new drug application, or IND, to the agency and its subsequent review to continue to treat new patients.").

9 *See infra* Appendix A. While the content of the letter is available on the FDA's website, the list of recipients is not. *See supra* note 6.

10 *See infra* Appendix A; *see also* discussion *infra* Part II (discussing how, by not providing a specific statutory provision in its Untitled Letters, this action differs from the FDA's usual practice of clearly identifying an addressee's illegal actions and the exact statutory provision that those actions violate).

11 The letter stated that "[t]he use of such genetically manipulated cells (and/or their derivatives) in humans constitutes a clinical investigation and requires submission of an Investigational New Drug application (IND) to FDA," which was followed by a confusing sentence later in the letter that stated "[w]e can advise you whether or not your activities require submission of an IND." *Infra* Appendix A.

12 *See, e.g.*, PARLIAMENTARY OFFICE OF SCI. & TECH., PREVENTING MITOCHONDRIAL DISEASE (Mar. 2013) [hereinafter PREVENTING MITOCHONDRIAL DISEASE], http://researchbriefings.files.parliament.uk/documents/POST-PN-431/POST-PN-431.pdf (providing a brief, but detailed overview of mitochondrial disease and its advantages and disadvantages.

FDA has provided no clear explanation of the source of its jurisdiction over these techniques or why this divergence from the Agency's "hands-off" treatment of conventional assisted reproductive technology is justified.[13] After receiving the FDA's letters, physicians stopped providing access to advanced assisted reproductive technologies in the United States.[14] Recent media coverage, for example, has focused on New York–based physicians who traveled to Mexico to provide mitochondrial transfer to a couple, explaining that "[t]o save lives is the ethical thing to do."[15]

This Article is the first article to combine the analysis of cytoplasmic transfer, mitochondrial transfer, and cloning to reveal that the FDA's subterranean regulation of advanced assisted reproductive technologies is based on the FDA's successful banning of human reproductive cloning in the United States through agency-issued letters in 1998. It is also the first article to review primary sources including FOIA requests (and responses) in order to posit that the FDA's regulation of genetic modifications in reproduction is driven, at least partially, by ethical objections in addition to a lack of jurisdiction over

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This document was created before the United Kingdom (U.K.) Parliament approved regulations permitting mitochondrial transfer in the United Kingdom); Steve Connor, *Three-Parent Baby Pioneer: "The Brits Will Be Ahead of the World"; Despite the Death of Prematurely Born Twins, the Doctor Behind a Revolutionary Fertility Technique Tells Steve Connor It Is Safe*, INDEPENDENT (Jan. 17, 2015), https://advance.lexis.com/api/permalink/a59bd3b8-c233-4526-9937-48e9a66c1e07/?context=1000516; *see also FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, U.S. FOOD & DRUG ADMIN. [hereinafter *FDA Regulation of Human Cells*], https://www.fda.gov/biologicsbloodvaccines/tissuetissueproducts/regulationoftissues/ucm150485.htm (last updated Feb. 2, 2018).

13 *See* Sabrina Tavernise, *His Fertility Advance Draws Ire: Shoukhrat Mitalipov's Mitochondrial Manipulations*, N.Y. TIMES (Mar. 17, 2014), http://www.nytimes.com/2014/03/18/science/shoukhrat-mitalipovs-mitochrondrial-manipulations.html ("Dr. Dorsa said the university still has not decided whether to formally ask the F.D.A. for permission to move forward with clinical trials."). As of July 12, 2016, the university still had not submitted an investigational new drug application to the FDA. *See FDA Regulation of Human Cells*, *supra* note 12 (where the FDA lists "HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL" listing "cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector" as products that are regulated under "Section 351 of the [Public Health Service] Act and/or the [Food, Drug & Cosmetic] Act" without explaining how the communicable disease provision of the Public Health Service Act "and/or" the Food, Drug, and Cosmetic Act applies to these products); *see also* discussion *infra* Part II (explaining that the application of the FDA's Human Tissue Regulations to human reproductive tissue is counterintuitive and contradictory).

14 *See* Meeting #32 Transcript, *supra* note 8; *infra* text accompanying note 87.

15 Michelle Roberts, *First "Three Person Baby" Born Using New Method*, BBC NEWS (Sept. 27, 2016), http://www.bbc.com/news/health-37485263; *see also* Denise Grady, *Pregnancy Created Using Egg Nucleus of Infertile Woman*, N.Y. TIMES (Oct. 14, 2003), http://www.nytimes.com/2003/10/14/us/pregnancy-created-using-egg-nucleus-of-infertile-woman.html (citing Dr. James Grifo, one of the physicians targeted by FDA letters on cytoplasmic transfer: "Dr. Grifo said he and his colleagues gave their findings to doctors in China because regulations imposed by the United States Food and Drug Administration in 2001 made it too difficult to continue the research in the United States.").

these forms of technology that happen to inhabit areas fraught with ethical concerns and political opposition.[16] In addition to submitting FOIA requests related to the content and scope of subterranean letters, I analyzed other primary sources, including Federal Register issuances, responses to FOIA requests, communications with researchers, congressional testimony, and FDA Advisory Committee meeting transcripts.[17] A review of these primary sources indicates that sometimes FDA employees misunderstand the science underlying AARTs and at other times, these employees attempt to muddle ethical opposition with safety concerns in order to prevent the clinical use of technology that the FDA deems objectionable.[18]

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16 *See* Susan L. Crockin & Gary A. Debele, *Ethical Issues in Assisted Reproduction: A Primer for Family Law Attorneys*, 27 J. AM. ACAD. MATRIM. LAW. 289, 301 (2015); Judith Daar, *Multi-Party Parenting in Genetics and Law: A View from Succession*, 49 FAM. L.Q. 71, 74 (2015); John A. Robertson, *Oocyte Cytoplasmic Transfers and the Ethics of Germ-Line Intervention*, 26 J.L. MED. & ETHICS 211 (1998). Some scholars have speculated on the possible reasons for the FDA's decision to assert jurisdiction over specific technologies such as cloning or cytoplasmic transfer from a regulatory or statutory perspective. *See, e.g.*, Lori B. Andrews, *Is There a Right to Clone? Constitutional Challenges to Bans on Human Cloning*, 11 HARV. J.L. & TECH. 643, 669 (1998); Valarie K. Blake, *Ovaries, Testicles, and Uteruses, Oh My! Regulating Reproductive Tissue Transplants*, 19 WM. & MARY J. WOMEN & L. 353 (2013); Clarke D. Forsythe, *Human Cloning and the Constitution*, 32 VAL. U. L. REV. 469, 470 (1998); Kerry Lynn Macintosh, *Brave New Eugenics: Regulating Assisted Reproductive Technologies in the Name of Better Babies*, 2010 U. ILL. J.L. TECH. & POL'Y 257, 271–74; Elizabeth C. Price, *Does the FDA Have Authority to Regulate Human Cloning?*, 11 HARV. J.L. & TECH. 619, 628 (1998); *see also* Gregory J. Rokosz, *Human Cloning: Is the Reach of FDA Authority Too Far a Stretch?*, 30 SETON HALL L. REV. 464, 468 (2000).

17 *See* Telephone Conference with Rachael Anatol & Celia Witten, U.S. Food & Drug Admin., and Michelle Dipp & Allison Lawton, OvaScience, Inc. (Sept. 9, 2013) (summary of teleconference on file with author); E-mail from Michelle Dipp, CEO, OvaScience, Inc., to Celia M. Witten, Dir., Office of Cellular, Tissue & Gene Therapies, U.S. Food & Drug Admin. (Sept. 10, 2013, 5:25 PM) (on file with author); Letter from Ellen Lazarus, Dir., Office of Cellular, Tissue & Gene Therapies, U.S. Food & Drug Admin., to Alison Lawton, Chief Operating Officer, OvaScience, Inc. (Apr. 9, 2013) (on file with author); E-mail from Alison Lawton, Chief Operating Officer, OvaScience, Inc., to Patrick Riggins, Branch Chief, U.S. Food and Drug Admin. (Jan. 28, 2013, 12:37 PM) (on file with author); Telephone Conference with Richard McFarland & Lori Tull, U.S. Food & Drug Admin., and Karen Nichols, OvaScience, Inc. (Dec. 20, 2013) (record of telephone conversation on file with author); E-mail from Patrick Riggins, Branch Chief, U.S. Food & Drug Admin., to unknown recipient (Aug. 22, 2013, 12:38 PM) (on file with author); E-mail from Celeste Smith, FOIA Officer, U.S. Food & Drug Admin., to author (Sept. 9, 2016, 10:08 AM) (on file with author); Letter from Catherine Wilusz, Consumer Safety Officer, U.S. Food & Drug Admin., to author (July 8, 2016) (on file with author); E-mail from John Wright, Admin. Proceedings Specialist, U.S. Food & Drug Admin., on behalf of Dynna Bigby, Supervisory Admin. Proceedings Officer, U.S. Food & Drug Admin., to author (Aug. 14, 2016, 11:23 AM) (on file with author); E-mail from Ashlee Eswara to author, *supra* note 6; Letter from Celia M. Witten to Alison Lawton, *supra* note 7; *see also* discussion *infra* Parts III–IV.

18 *See* Meeting #32 Transcript, *supra* note 8 ("FDA had concerns about whether we understood all the ramifications of this procedure and whether we understood its safety in particular, and reacted by sending letters to practitioners who were identified by publications on ooplasm [cytoplasm] transfer or by advertisements offering the procedure. We advised practitioners that we would now require the submission of an investigational new drug application, or IND, to the agency and its subsequent review to continue to treat new

This Article makes several contributions to the literature. My descriptive claim is that the FDA is regulating by letter in the area of advanced assisted reproductive technologies. This expands the administrative law literature by identifying and describing another "informal tool" that federal agencies may use to regulate industries.[19] In this Article, I both identify the concept of subterranean regulation and offer an explanation as to why the FDA might be using it. After explaining how the FDA regulates AARTs in a subterranean fashion, I argue that the FDA should not be regulating advanced assisted reproductive technologies in a subterranean manner or in any other manner that subjects them to unique federal regulation. First, it is likely that the FDA lacks jurisdiction over AARTs under applicable statutes, namely the Food, Drug and Cosmetic Act and the Public Health Service Act.[20] Second, AARTs do not fall within the categories of products that the FDA regulates, and the FDA's regulatory scheme is not structured to objectively regulate them. Third, the result of the use of the FDA's overlooked regulatory program has been to allow the FDA to insert ethical concerns into its regulation of assisted reproductive technology, which is an inappropriate action for an administrative agency that has been tasked with addressing the safety and effectiveness of regulated products such as drugs and medical devices.[21] Ultimately, the Article is driven by an effort to render the regulation of AARTs as transparent as possible.

The Article proceeds as follows. Part I provides an overview of advanced assisted reproductive technologies. Part II analyzes the jurisdictional issues related to mitochondrial transfer and other advanced assisted reproductive technologies including the confusion over whether the agency's enabling statutes apply to these technologies. Part II also analyzes the differences between AARTs and the standard categories of products regulated by the FDA (i.e., food, drugs, medical devices, and biologics).[22] I also explain the concept of "subterranean

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patients."). For a general overview of the ethical issues that arise as a result of mitochondrial transfer, see César Palacios-González, *Ethics of Mitochondrial Replacement Techniques: A Habermasian Perspective*, 31 BIOETHICS 27 (2017).

19 Tim Wu, *Agency Threats*, 60 DUKE L.J. 1841, 1841–42 (2011); *see also* Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 WIS. L. REV. 873 (1997).

20 Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–99h (2012); Public Health Service Act, 42 U.S.C. §§ 201–300mm-61 (2012).

21 *See* FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 129 (2000) ("Under 21 U.S.C. § 360j(e), the agency may 'require that a device be restricted to sale, distribution, or use . . . upon such other conditions as [the FDA] may prescribe in such regulation, if, because of its potentiality for harmful effect or the collateral measures necessary to its use, [the FDA] determines that there cannot otherwise be reasonable assurance of its safety and effectiveness.'").

22 *See What Does FDA Regulate?*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194879.htm (last updated Jan. 23, 2018).

regulation," using the regulation of AARTs as a starting point. Part III explains how longstanding concerns about ethical issues, which are mentioned in FDA officials' public statements but not included in their written communications with physicians and researchers, help explain why the FDA regulates advanced assisted reproductive technologies in a subterranean fashion. Part IV explains why the FDA should not be regulating AARTs at all. Part IV also observes that the same ethical issues that accompany advanced assisted reproductive technologies also accompany other developing technologies that may modify the human genetic code in order to treat disease, such as genome editing through CRISPR-Cas9, a technique that has received substantial media coverage not only due to its exciting treatment possibilities but also due to surrounding patent litigation, and other technologies that allow for the editing of genes.[23] In other words, the conditions that allow for and motivate subterranean regulation in the field of assisted reproductive technology such as political pressure, ethical opposition, scientific misunderstanding, and lack of federal agency jurisdiction, will continue to arise in relation to other developing biotechnologies. Thus, transparent regulation and a clear regulatory path forward will become more pressing as the FDA's current regulatory scheme will likely be an obstacle for other medical innovations as science moves towards targeting genes as a method of curing or preventing disease.

I. ADVANCED ASSISTED REPRODUCTIVE TECHNOLOGIES: COMBINING GENETIC MODIFICATIONS WITH IN VITRO FERTILIZATION

Advanced assisted reproductive technologies, such as cytoplasmic transfer and mitochondrial transfer involve the use of in vitro fertilization and genetic material from a donor.

In vitro fertilization (IVF) is a procedure by which a female egg is

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[23] *See* Ewen Callaway, *UK Scientists Gain Licence to Edit Genes in Human Embryos*, NATURE (Feb. 1, 2016), http://www.nature.com/news/uk-scientists-gain-licence-to-edit-genes-in-human-embryos-1.19270; *see also* John Cohen, *Round One of CRISPR Patent Legal Battle Goes to the Broad Institute*, SCIENCE (Feb. 15, 2017, 2:30 PM), http://www.sciencemag.org/news/2017/02/round-one-crispr-patent-legal-battle-goes-broad-institute; Antonio Regalado, *Engineering the Perfect Baby*, MIT TECH. REV. (Mar. 5, 2015), https://www.technologyreview.com/s/535661/engineering-the-perfect-baby; *Questions and Answers About CRISPR*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr (last visited Feb. 27, 2018) (noting that "[i]n January 2013, the Zhang lab" at the Broad Institute and MIT "published the first method to engineer CRISPR to edit the genome in mouse and human cells"). The terms "gene editing" and "genome editing" are used interchangeably in the literature when describing CRISPR-Cas9. *See What Are Genome Editing and CRISPR-Cas9?*, U.S. NAT'L LIBR. MED. (Feb. 20, 2018), https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting ("Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA.").

> fertilized outside the womb by male sperm, with the intent that the resulting zygote will later be transplanted into the female reproductive system of either the intended mother or another woman who is serving as a surrogate.[24]

A cell essentially contains three parts: cytoplasm, nucleus, and mitochondria.[25] The nucleus, which is the center of the cell, is surrounded by cytoplasm.[26] Mitochondria are located in the cytoplasm of the cell.[27]

With cytoplasmic transfer, donor genetic material (from the cytoplasm of an egg cell) is used to improve fertility outcomes.[28] In contrast, with mitochondrial transfer, donor genetic material (specifically mitochondria) is used in order to prevent the maternal transmission of some genetic diseases caused by defective mitochondria such as muscular dystrophy and heart and liver conditions.[29] Pre-implantation genetic diagnosis is insufficient to prevent the maternal

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24 CHARLES P. KINDREGAN, JR. & MAUREEN MCBRIEN, ASSISTED REPRODUCTIVE TECHNOLOGY: A LAWYER'S GUIDE TO EMERGING LAW AND SCIENCE 91 (2d ed. 2012).

25 *See* Charlotte Pritchard, *The Girl with Three Biological Parents*, BBC NEWS (Sept. 1, 2014), http://www.bbc.com/news/magazine-28986843 (defining the components of a cell as: "Nucleus: Where the majority of our DNA is held - this determines how we look and our personality[;] Mitochondria: Often described as the cell's factories, these create the energy to make the cell function[;] Cytoplasm: The jelly like substance that contains the nucleus and mitochondria[.]").

26 *Id.*

27 *Id.*

28 *See* GEOFF WATTS ET AL., NUFFIELD COUNCIL ON BIOETHICS, NOVEL TECHNIQUES FOR THE PREVENTION OF MITOCHONDRIAL DNA DISORDERS: AN ETHICAL REVIEW 1, 36 (2012), http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf. In cytoplasmic transfer, eggs are obtained from both the intended mother and an egg donor, and cytoplasm from a healthy egg is injected into the intended mother's egg. *Id.* Children born as a result of cytoplasmic transfer are genetically related to their intended mother and intended father; these children also have "an additional mitochondrial genetic connection to a second woman provided by an injection of her cytoplasm." *Id.* at 70.

29 *See, e.g.*, NAT'L ACADS. OF SCIS., ENG'G & MED., MITOCHONDRIAL REPLACEMENT TECHNIQUES: ETHICAL, SOCIAL, AND POLICY CONSIDERATIONS 1, 20–23 (2016) [hereinafter MITOCHONDRIAL REPLACEMENT TECHNIQUES]. Using mitochondrial transfer, scientists replace an intended mother's defective mitochondria with mitochondria from a healthy female donor either in the intended mother's egg before in vitro fertilization occurs or in a fertilized embryo after in vitro fertilization has occurred. The healthy embryo is then implanted into the intended mother. There are three ways of acquiring diseases that affect mitochondria, one of which is inheriting a harmful mitochondrial mutation from the mother. *Id.* at 4; *see also* Gráinne S. Gorman et al., *Mitochondrial Donation—How Many Women Could Benefit?*, 372 NEW ENG. J. MED. 885 (2015); Ian Sample, *Three-Person IVF: UK Government Backs Mitochondrial Transfer*, GUARDIAN (June 28, 2013), http://www.theguardian.com/science/2013/jun/28/uk-government-ivf-dna-three-people; WATTS ET AL., *supra* note 28, at 21 (noting that mitochondria generate energy for the cell, and mitochondrial mutations tend to have "the most impact on organs of the body with a relatively high need for energy" such as the "brain, heart, kidneys and major muscle groups" and thus, defective mitochondria tend to affect major organs and a number of symptoms can result including blindness, deafness, and organ failure).

transmission of mitochondrial disease.[30] While defective mitochondria are maternally transmitted, male and female children are at equal risk of developing mitochondrial disease, so selecting only male embryos would not prevent the development of mitochondrial disease.[31]

Because both cytoplasmic transfer and mitochondrial transfer involve the transfer of a donor's genetic material, both techniques would result in an inheritable genetic modification that would be passed on to future generations.[32] Nuclear DNA contains approximately 20,000 to 30,000 genes, accounting for approximately 99.9% of all of humans' genes; the remaining percentage is made of the thirty-seven genes contained in mitochondrial DNA.[33] As a result, with mitochondrial transfer, only 0.1% of the healthy child's DNA is different from that of his or her parents.[34] The value of 0.1%, which is often cited in press accounts, is actually rounded up: "mitochondrial DNA represents less than 0.054 per cent of the total DNA . . . ."[35] This change in mitochondrial DNA, in the view of some commentators, constitutes a "modification of [the] human germline" which is a source of ethical

30 *See* WATTS ET AL., *supra* note 28, at 23 ("In reproduction, a small number of the woman's mitochondria are selected to populate all the cells of the resulting child in much greater numbers, a phenomenon known as the 'mitochondrial bottleneck.'" Thus, a woman with a small proportion of defective mitochondria can pass a larger proportion of those mutant mitochondria on to her children. "Patients with the symptoms of mitochondrial DNA disorders are therefore likely to have mutations either in a high proportion of their mitochondria (heteroplasmy) in the affected tissues or, when viable, in all of the mitochondria (homoplasmy). . . .Generally, as the proportion of mutated mitochondria becomes higher, progressively more severe symptoms will result."); *see also* Daniel Paull et al., *Nuclear Genome Transfer in Human Oocytes Eliminates Mitochondrial DNA Variants*, 493 NATURE 632, 632 (2013) ("[A]n unaffected carrier of a [mitochondrial DNA] mutation may have an affected child. Although prenatal genetic diagnosis can select embryos with a reduced mutation load, variation between blastomeres in single embryos limits the effectiveness of such screening, and considerable levels of mutant [mitochondrial DNA] can remain, resulting in a carrier." (citing L.M. Cree et al., *A Reduction of Mitochondrial DNA Molecules During Embryogenesis Explains the Rapid Segregation of Genotypes*, 40 NATURE GENETICS 249 (2008))).

31 *See* MARK S. FRANKEL & BRENT T. HAGEN, NUFFIELD COUNCIL ON BIOETHICS, GERMLINE THERAPIES 11 (2011), http://nuffieldbioethics.org/wp-content/uploads/Germline_therapies_background_paper.pdf.

32 *See* Transcript of Center for Biologics Evaluation and Research, Food and Drug Administration, Cellular, Tissue, and Gene Therapies Advisory Committee Meeting #59 (Feb. 25, 2014) [hereinafter Meeting #59 Transcript], https://wayback.archive-it.org/7993/20170113010701/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM426293.pdf; Erik Parens & Eric Juengst, *Inadvertently Crossing the Germ Line*, 292 SCIENCE 397 (Apr. 20, 2001) (characterizing the transfer of mitochondrial DNA as a "side effect" of cytoplasm transfer).

33 *See* WATTS ET AL., *supra* note 28, at 18–19.

34 *See id.* at 19.

35 Sally Davies, *Sally Davies: Why I Back "Three-Parent Babies" Law*, TELEGRAPH (Feb. 3, 2015, 6:00 AM), http://www.telegraph.co.uk/news/science/science-news/11385721/Sally-Davies-Why-I-back-three-parent-babies-law.html (Professor Dame Sally Davies is the U.K.'s Chief Medical Officer and Chief Scientific Adviser to the *Telegraph*.).

opposition to advanced assisted reproductive technologies.[36] The debatable definition of a germline modification will be discussed in Part III.

AARTs transfer mitochondrial DNA and not nuclear DNA.[37] Mitochondrial DNA "is not part of the nuclear DNA, which determines our personal characteristics and traits such as personality, hair[,] and eye colour."[38] Because nuclear DNA determines inherited appearance-related traits such as eye color, hair color, and height, and AARTs only affect mitochondrial DNA, a child born as a result of the use of an advanced assisted reproductive technology would still look like his or her parents.[39]

Cytoplasmic transfer, an advanced assisted reproductive technology, has been used in the United States, but is no longer available in the United States after researchers received "Untitled Letters" from the FDA on July 6, 2001.[40] When researchers appeared at an FDA Advisory Committee meeting after receiving the letters, a total of "at least 23 children" had been born in the United States using cytoplasmic transfer.[41]

Mitochondrial transfer has not been approved for clinical use in humans in the United States even though thousands of women (and their children) could benefit from this disease-preventing technology.[42]

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36 *See* FRANKEL & HAGEN, *supra* note 31, at 1, 5–6 (citations omitted) ("Because [nuclear DNA and mitochondrial DNA are not the same], some researchers and clinicians restrict the definition of germline modification to modification of [nuclear DNA] alone. However, many argue that [mitochondrial DNA] modification does indeed amount to germline modification." (citations omitted)); *see also* Meeting #59 Transcript, *supra* note 32, at 118 (A germline modification such as that which would occur as a result of mitochondrial transfer would not only result in a mother having a healthy child, but also that child having mutation-free eggs; thus, the transmission of defective mitochondria would end in that family.).

37 *See* Davies, *supra* note 35.

38 *Id.*

39 *See* Kenan Malik, Opinion, *The Three-Parent Baby's First Step*, N.Y. TIMES (Feb. 22, 2015), http://www.nytimes.com/2015/02/23/opinion/the-three-parent-babys-first-step.html?_r=0; *see also* Andrew Sparrow, *MPs Back Mitochondrial Donation Law By Majority of 254: Politics Live Blog*, GUARDIAN: POLITICS (Feb. 3, 2015, 12:45 PM), http://www.theguardian.com/politics/blog/live/2015/feb/03/william-hagues-speech-on-english-votes-for-english-laws-evel-politics-live-blog (citing Labour Party politician Liz McInnes, a former biochemist with the National Health Service, who voted in favor of mitochondrial transfer).

40 *See* discussion *infra* Part II (discussing these Untitled Letters); *see also* Holly Firfer, *How Far Will Couples Go to Conceive?*, CNN (June 17, 2004, 6:44 AM), http://www.cnn.com/2004/HEALTH/03/12/infertility.treatment/index.html; *supra* notes 4–5 and accompanying text (discussing the FDA's use of Warning Letters and Untitled Letters).

41 Meeting #32 Transcript, *supra* note 8, at 46.

42 *See* Gorman et al., *supra* note 29, at 886 (noting that, as per 2012 data, 12,423 women of child-bearing age in the United States could possibly pass a mitochondrial disease on to their offspring); *see also* James Gallagher, *UK Approves Three-Person Babies*, BBC NEWS (Feb. 24, 2015), http://www.bbc.com/news/health-31594856; Tavernise, *supra* note 13 ("Dr. Dorsa said the university still has not decided whether to formally ask the F.D.A. for permission to move forward with clinical trials."). As of July 12, 2016, the University still had not submitted an investigational new drug application to the FDA.

After an extensive public consultation, described in Part IV, and the approval of regulatory amendments by Parliament, human clinical trials involving mitochondrial transfer are ongoing in the United Kingdom (U.K.).[43] The science underlying advanced assisted reproductive technologies has been explained in newspaper articles, parliamentary briefings, and public meetings; in other words, the science is not that difficult to understand, but as will be explained in Part III, the ethical opposition, especially in the United States, is inevitable.[44]

II. THE REGULATION OF ASSISTED REPRODUCTIVE TECHNOLOGY IN THE UNITED STATES

Although there are laws that apply to the use of assisted reproductive technology, the industry is often characterized as "unregulated," "minimally regulated,"[45] or "self-regulated" when compared to other industries.[46] In the United States, assisted reproductive technology is generally governed by state law with the exception of one federal law, the Fertility Clinic Success Rate Act.[47] With only one federal law addressing the regulation of assisted reproductive technology, the federal government has been described as "essentially silent."[48] Under the 1992 Fertility Clinic Success Rate and Certification Act, all clinics using assisted reproductive technology techniques must report success rate data to the Centers for Disease Control and Prevention on an annual basis.[49] During the congressional

43 *See* Gorman et al., *supra* note 29, at 886 (noting that, in 2015, 2,473 women of child-bearing age in the United Kingdom could possibly pass a mitochondrial disease onto their offspring); *see also* Gallagher, *supra* note 42.

44 *See* Gallagher, *supra* note 42; *see also Mitochondrial Replacement*, HUMAN FERTILISATION & EMBRYOLOGY AUTH., http://web.archive.org/web/20150912083629/http://hfea.gov.uk/6896.html (last updated July 9, 2015); PREVENTING MITOCHONDRIAL DISEASE, *supra* note 12.

45 Goodwin, *supra* note 1.

46 *See* Martha M. Ertman, *What's Wrong with a Parenthood Market?: A New and Improved Theory of Commodification*, 82 N.C. L. REV. 1, 15–16 (2003) (discussing the lack of regulation of the "parenthood market"); Jane Gitschier, *The Ethics of Our Inquiry: An Interview with Hank Greely*, 11 PLOS GENETICS (Nov. 6, 2014) (quoting an interview with Hank Greely, who characterized assisted reproductive technology as "[a]lmost entirely" unregulated in the United States); Debora Spar & Anna M. Harrington, *Building a Better Baby Business*, 10 MINN. J.L. SCI. & TECH. 41 (2009) (discussing the lack of regulation of the "fertility market," which is the market for the sale of gametes for use in assisted reproduction); Sonia M. Suter, *Giving in to Baby Markets: Regulation Without Prohibition*, 16 MICH. J. GENDER & L. 217, 231 (2009); Chan & Collins, *supra* note 1, at 507–08.

47 *See* Michele Goodwin, *A View from the Cradle: Tort Law and the Private Regulation of Assisted Reproduction*, 59 EMORY L.J. 1039, 1071–72, 1079 (2010).

48 SPAR, *supra* note 1, at 51.

49 *See* 42 U.S.C. §§ 263a-1–7 (2012) (codifying the Fertility Clinic Success Rate Act); *see also The Fertility Clinic Success Rate and Certification Act*, CENTERS DISEASE CONTROL, http://www.cdc.gov/art/nass/policy.html (last updated Feb. 8, 2017) (citing to Pub. L. No. 102-493, 106 Stat. 3146 (1992)). Also, while the National Institutes of Health (NIH) arise in discussions

debate preceding the enactment of the Fertility Clinic Success Rate and Certification Act, "the FDA was never mentioned . . . as having jurisdiction over fertility clinic procedures."[50]

State law generally does not restrict the mechanics of assisted reproductive technology, such as how many embryos can be implanted or how many times the reproductive tissue of one donor can be used.[51] States, and not the FDA, also regulate the practice of medicine through the licensing of the medical personnel who would perform procedures involving assisted reproductive technology.[52] Other than these provisions, state regulation of assisted reproductive technology is "limited."[53] Moreover, professional organizations such as the American Society for Reproductive Medicine issue guidelines for providers of

related to embryos and research funding, the NIH, while an operating division of the U.S. Department of Health and Human Services, does not have a role in the regulation of assisted reproductive technology. Instead, the NIH's role in the development of assisted reproductive technology is very limited as the agency specifically does not fund scientific research that modifies the human germline but does not regulate its legality. *See* NAT'L INSTS. OF HEALTH, DEP'T HEALTH & HUMAN SERVS., NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES) (Apr. 2016), https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948304; Francis S. Collins, *Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos*, NAT'L INSTITUTES HEALTH (Apr. 28, 2015), https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos.

50 *See* Gregory J. Rokosz, *Human Cloning: Is the Reach of FDA Authority Too Far a Stretch?*, 30 SETON HALL L. REV. 464, 503 n.201 (2000) (citing Elizabeth C. Price, *Does the FDA Have Authority to Regulate Human Cloning*, 11 HARV. J.L. & TECH. 619, 631 (1998)).

51 *See* Lars Noah, *Assisted Reproductive Technologies and the Pitfalls of Unregulated Biomedical Innovation*, 55 FLA. L. REV. 603, 615–16 (2003); Michael Ollove, *States Aren't Eager to Regulate Fertility Industry*, USA TODAY, http://www.usatoday.com/story/news/nation/2015/03/18/pew-stateline-assisted-reproduction/24984249 (last updated Mar. 26, 2015, 3:22 PM).

52 *See* Marion Abecassis, *Artificial Wombs: "The Third Era of Human Reproduction" and the Likely Impact on French and U.S. Law*, 27 HASTINGS WOMEN'S L.J. 3, 10 (2016) (explaining that states regulate the practice of medicine "through licensing of practitioners, including suspension and revocation of licenses in instances of malpractice"); *see also LASIK: FDA's Role*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm061319.htm (last updated Jan. 18, 2018); Rokosz, *supra* note 50, at 491 n.147 (quoting University of Virginia Law School professor Richard Merrill, who stated that "the FDA is not supposed to regulate the practice of medicine").

53 *See* Hillary B. Alberta et al., *Risk Disclosure and the Recruitment of Oocyte Donors: Are Advertisers Telling the Full Story?*, 42 J.L. MED. & ETHICS 232, 235 (2014); Chan & Collins, *supra* note 1, at 507 ("Currently, regulation over reproductive technology by the state and federal government is limited. The fertility industry mostly self regulates through nonbinding guidelines and suggested ethical practices, though there are various physician licensing requirements." (citations omitted)). For more on state law applying to assisted reproductive technology, such as statutes related to fraud, medical malpractice, and consumer protection, see SPAR, *supra* note 1, at 51; Noah, *supra* note 51, at 615–16. *See also* John A. Robertson, *Commerce and Regulation in the Assisted Reproduction Industry*, *in* BABY MARKETS: MONEY AND THE NEW POLITICS OF CREATING FAMILIES 191, 203 (Michele Bratcher Goodwin ed., 2010).

assisted reproductive technology to follow.[54]

States also decide how the parentage of children who are conceived through assisted reproductive technology will be assigned.[55] Because individual states have their own laws addressing family law and estate law, the legal consequences of assisted reproductive technology such as inheritance and the legality of surrogacy and other methods of family formation are similarly addressed "on a state-by-state basis . . . ."[56] The next Section of the Article explains why the characterization of the regulatory environment surrounding assisted reproductive technology as "sparse" is inaccurate when one analyzes the regulation of advanced assisted reproductive technologies.[57]

A. *The Concept of Subterranean Regulation*

In this Article, I characterize the overlooked regulatory program that the U.S. Food and Drug Administration uses to regulate advanced assisted reproductive technologies as "subterranean regulation." This concept fits within the larger administrative law scholarship on agency "soft law."[58] Within the context of administrative law, much has been written about the concept of "regulating by guidance" and other informal methods of regulating in which an agency uses informal documents to affect the actions of regulated entities.[59] Beyond guidance

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54 *See* Chan & Collins, *supra* note 1, at 507 ("Currently, regulation over reproductive technology by the state and federal government is limited. The fertility industry mostly self regulates through nonbinding guidelines and suggested ethical practices, though there are various physician licensing requirements." (citation omitted)). *But see* CAHN, *supra* note 1, at 63, 192–93 ("As the CDC emphasizes, however, the federal government does not provide any oversight of these programs, and their standards vary.").

55 *See generally* KINDREGAN & MCBRIEN, *supra* note 24.

56 Blake, *supra* note 16, at 372. The literature related to mitochondrial transfer focuses on the legal impacts of the technology on the genetically based parentage scheme in the United States and the impacts of the technology on trusts and estate law. *See* Daar, *supra* note 16; *see, e.g.*, Padmini Cheruvu, *Three-Parent IVF and Its Effect on Parental Rights*, 6 HASTINGS SCI. & TECH. L.J. 73 (2014); Yehezkel Margalit et al., *The New Frontier of Advanced Reproductive Technology: Reevaluating Modern Legal Parenthood*, 37 HARV. J.L. & GENDER 107, 128 (2014); *see also* Steve P. Calandrillo & Chryssa V. Deliganis, *In Vitro Fertilization and the Law: How Legal and Regulatory Neglect Compromised a Medical Breakthrough*, 57 ARIZ. L. REV. 311, 330 (2015) (characterizing state regulation of assisted reproductive technology as similarly "undeveloped" in comparison to federal regulation of assisted reproductive technology).

57 *See* JUDITH DAAR, REPRODUCTIVE TECHNOLOGIES AND THE LAW 682 (2d ed. 2013) (referring to the Fertility Clinic Success Rate of 1992 as "sparse law" when observing, "[t]his sparse law in the U.S. can be contrasted with comprehensive regulatory schemes in place in other countries").

58 Wu, *supra* note 19, at 1843–44; *see* Lars Noah, *Governance by the Backdoor: Administrative Law(Lessness?) at the FDA*, 93 NEB. L. REV. 89, 92 n.9 (2014) ("Guidance documents represent a form of 'soft law.'" (quoting Jacob E. Gersen & Eric A. Posner, *Soft Law: Lessons from Congressional Practice*, 61 STAN. L. REV. 573, 576–77 (2008))); Noah, *supra* note 19, at 874.

59 *See* M. Elizabeth Magill, *Agency Choice of Policymaking Form*, 71 U. CHI. L. REV. 1383,

documents, some scholarship has focused on methods that administrative agencies use to "threaten" compliance.[60] Subterranean regulation could be classified as one of these methods of informal regulation; however, one notable difference between subterranean regulation and other forms of agency "threats" is that the scholarship on administrative agency threats often does not direct a significant amount of focus to the possibility that administrative agency threats are being issued to industries that are not at all within the agency's jurisdiction.

Subterranean regulation is characterized by a lack of jurisdiction in addition to other procedural weaknesses.[61] First, subterranean regulation occurs in a regulatory space in which the administrative agency, here, the FDA, has not shown that it has jurisdiction over these techniques in the first place.[62] Thus, while the scholarship on agency threats tends to focus on agency threats to "regulated entities" or entities that are not currently regulated but clearly fall within the agency's jurisdiction, industries targeted by subterranean regulation are threatened in the absence of a regulatory basis for that threat.[63] As discussed below, this jurisdictional defect in the subterranean regulation of AARTs stems partially from the fact that the FDA has similarly not cited to any statutory provisions that provide its jurisdiction as evidenced by the Agency's letters issued on July 6, 2001, and subsequent regulatory actions and the fact that AARTs do not fit within the larger categories of products regulated by the FDA.

Second, procedurally, subterranean regulation occurs in a manner that is different from the standard process that the Agency uses. The FDA issues Untitled Letters and Warning Letters to violators of federal

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1441 (2004) ("Finally, in an example drawn from contemporary judicial decisionmaking, courts appear to be increasingly concerned about the oft-repeated charge that agencies are 'regulating by guidance'—that is, relying on interpretive rules or policy statements instead of legislative rules to effectuate their policy judgments." (citing J.B. Ruhl & James Salzman, *Mozart and the Red Queen: The Problem of Regulatory Accretion in the Administrative State*, 91 GEO. L.J 757, 781–82 (2003))); *see also* Robert A. Anthony, *Interpretive Rules, Policy Statements, Guidances, Manuals, and the Like–Should Federal Agencies Use Them to Bind the Public?*, 41 DUKE L.J. 1311, 1312 (1992) ("To use such nonlegislative documents to bind the public violates the Administrative Procedure Act (APA) and dishonors our system of limited government.").

60 Wu, *supra* note 19, at 1848–54.

61 This Section provides an overview of subterranean regulation whereas the next Section, Section II.B, provides detailed specifics on the operation of the concept.

62 *See* discussion *infra* Section II.B.2.

63 Wu, *supra* note 19, at 1843, 1848–54 ("Regulated entities that are unhappy with a de facto regime can and do test the threats, forcing the agency to use its more formal powers and therefore invoke judicial review.") (providing examples of industries in which "threats" have been used, notably that of the Federal Communications Commission to broadband providers); *see also* Noah, *supra* note 19, at 874 ("As used in this Article, administrative 'armtwisting' refers to a threat by an agency to impose a sanction or withhold a benefit in hopes of encouraging 'voluntary' compliance with a request that the agency could not impose directly on a regulated entity.").

law regularly.[64] These letters usually have specific citations to statutory provisions when issued in the context of food, drugs, and other regulated products, along with explanations of how those provisions apply to the addressee's actions or products.[65] In other words, in these letters, the FDA usually identifies the regulated entities' actions and then explains how those actions violate a specific statutory provision. However, the Untitled Letters addressing advanced assisted reproductive technologies are not as specific as the FDA's other Untitled Letters. Instead, the letters that the Agency uses to target AARTs are characterized by not only brevity and citations to guidance documents that may or may not apply to AART providers, but also by a lack of specificity. Yet at the same time, these letters are official agency communications that are assertions of wrongdoing. The content of the FDA's July 6, 2001 letter to AART providers is located in Appendix A and examples of the FDA's standard practices when issuing Untitled and Warning Letters are in Appendices B to D for comparison.

Third, subterranean regulation is difficult to find. While the content of the July 6, 2001 letters is posted online, the addressees are not. The addressee line simply states, "Dear Sponsor/Researcher" and there is no additional identifying information. Furthermore, I submitted a FOIA request to obtain the list of addressees; however, the Agency stated that it "did not locate an admin file" for the letter, therefore, it was unable to provide me with a list of addressees.[66] As a result, it is impossible to officially determine how many of these letters were sent or to whom they were sent. By reviewing primary sources, including transcripts and media accounts, I was able to ascertain some of the addressees as they spoke about receiving "the letter," but it is still impossible to ascertain all of the recipients.[67] Subsequently in 2013, for example, the FDA carried out a similar approach to regulating the

64 For examples of these letters, see *infra* Appendices C–D. *See also Warning and Untitled Letters*, *supra* note 4 (describing the FDA's use of Untitled Letters and Warning Letters).

65 *See, e.g.*, Letter from Robert A. Sausville, Dir. Div. of Case Mgmt., U.S. Food & Drug Admin., to Samuel Simons, Regulatory Manager, Protein Scis. Corp. (Mar. 12, 2015), http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM443161.pdf ("Therefore, this material misbrands Flublok under sections 502(a) and 201(n) of the Act, 21 U.S.C. § 352(a) and § 321(n), and FDA implementing regulations, Cf. 21 CFR 202.1(e)(6)(i) and (e)(7)(viii)."); Letter from Ann Simoneau, Dir. Office of Compliance & Enf't, U.S. Food & Drug Admin., to George Katsafados (Sept. 29, 2014), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm416552.htm ("Under section 201(rr) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. § 321(rr)), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), these products are tobacco products because they are made or derived from tobacco and intended for human consumption. Certain tobacco products, including cigarette tobacco and roll-your-own tobacco, are subject to FDA jurisdiction under section 901(b) of the FD&C Act (21 U.S.C. § 387a(b)).").

66 *See* Email from Ashlee Eswara to author, *supra* note 6.

67 *See* Meeting #32 Transcript, *supra* note 8, at 77.

actions of an American company providing a new fertility method; that letter was also not posted online by the FDA, and I was only able to obtain it through a FOIA request.[68] In contrast, the example of a "secret letter [sent] to various retailers and manufacturers of new 'bamboo clothing,'" cited in Tim Wu's *Agency Threats*, was accompanied by a footnote that linked to a PDF of the list of recipients, thus implying that secret letters sent by other administrative agencies are at least traceable.[69]

Fourth, subterranean regulation has a "chilling effect" on research. Even though the FDA's subterranean letters do not provide a clear basis for the Agency's jurisdiction, as official statements of wrongdoing, these issuances have a chilling effect on research.[70]

B. *Thwarted Research and Medical Advancement: The Impacts of the FDA's Subterranean Assertions of Jurisdiction over Advanced Assisted Reproductive Technologies*

The FDA has regulated cloning and advanced assisted reproductive technologies through letters as opposed to clear, targeted regulations. Cloning does not fall within this Article's definition of advanced assisted reproductive technologies since it does not operate in the same manner as human reproduction which involves at least two individuals (i.e., an intended mother and an intended father).[71]

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68 See discussion *infra* Part IV regarding the FOIA Request 2016-4882 and the shareholder lawsuit related to OvaScience's AUGMENT technology.

69 *See* Wu, *supra* note 19, at 1845.

70 For a discussion of the "chilling effect" in the context of abortion rights, see Brandice Canes-Wrone & Michael C. Dorf, *Measuring the Chilling Effect*, 90 N.Y.U. L. REV. 1095, 1096–98 (2015). "Chilling effect" is a concept that commonly arises in First Amendment jurisprudence. *Id.*

71 For the full contents of the letter, see *infra* Appendix B. *But see Cloning*, NAT'L HUMAN GENOME RES. INST., https://www.genome.gov/25020028/cloning-fact-sheet/#al-8 (last updated Mar. 21, 2017) ("Reproductive cloning would present the potential of creating a human that is genetically identical to another person who has previously existed or who still exists. This may conflict with long-standing religious and societal values about human dignity, possibly infringing upon principles of individual freedom, identity and autonomy. However, some argue that reproductive cloning could help sterile couples fulfill their dream of parenthood. Others see human cloning as a way to avoid passing on a deleterious gene that runs in the family without having to undergo embryo screening or embryo selection. Therapeutic cloning, while offering the potential for treating humans suffering from disease or injury, would require the destruction of human embryos in the test tube. Consequently, opponents argue that using this technique to collect embryonic stem cells is wrong, regardless of whether such cells are used to benefit sick or injured people."); *see also Human Cloning: How Close Is It?*, PBS, https://www.pbs.org/wgbh/pages/frontline/shows/fertility/etc/cloning.html (last visited Feb. 22, 2018).

1. Letters as Assertions of Wrongdoing

In 1998, the FDA sent a "Dear Colleague Letter" to institutional review boards in the United States asserting its jurisdiction over human reproductive cloning in reaction to media reports indicating that scientists were "contemplating" using human cloning.[72] This letter noted that clinical research on human cloning "to create a human being" could only proceed while an investigational new drug application was in effect.[73] In 2001, the FDA shifted its focus to advanced assisted reproductive technologies, sending letters to sponsors and researchers on July 6, 2001 that informed these individuals and entities that the FDA had jurisdiction over these technologies, such as cytoplasmic transfer.[74] The FDA has added mitochondrial transfer, an advanced assisted reproductive technology, to the non-exhaustive list of assisted reproductive technologies that require FDA pre-approval.[75]

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72 *Issues Raised by Human Cloning Research: Hearing Before the H. Subcomm. on Oversight and Investigations of the Comm. on Energy and Commerce*, 107th Cong. 78–81 (2001) (statement of Kathryn C. Zoon, Dir. of Ctr. for Biologics Evaluation & Research, U.S. Food & Drug Admin.) [hereinafter Statement of Kathryn C. Zoon]; Stuart L. Nightingale, *Letter About Human Cloning*, U.S. FOOD & DRUG ADMIN. (Oct. 26, 1998), http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm150508.htm. The list of addressees is not included online for this letter either. Under the U.S. Department of Health and Human Services (HHS) regulations, "45 CFR part 46, subpart E, [HHS] require[s] all IRBs to register with HHS if they will review human subjects research conducted or supported by HHS and are to be designated under an assurance of compliance approved for federalwide use (i.e., an FWA) by OHRP." *IRB Registration Process Frequently Asked Questions (FAQs)*, HHS.GOV, http://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/irb-registration/irb-registration-faq/index.html# (last visited Mar. 2, 2018). Thus, those pursuing research not supported by the U.S. Department of Health and Human Services, as cloning would not be, would possibly not be registered with the U.S. Department of Health and Human Services and thus, not receive the letter.

73 *See* Nightingale, *supra* note 72.

74 *See* Appendix A (providing the FDA's Letter to Sponsors/Researchers, on the subject of cytoplasmic transfer); *see also* General Responsibilities of Sponsors, 21 C.F.R. § 312.50 (2016) (explaining that "sponsor" in FDA terminology signifies that an individual or entity has a pending investigational new drug application before the FDA); Meeting #32 Transcript, *supra* note 8, at 47 ("FDA had concerns about whether we understood all the ramifications of this procedure and whether we understood its safety in particular, and reacted by sending letters to practitioners who were identified by publications on ooplasm [cytoplasm] transfer or by advertisements offering the procedure. We advised practitioners that we would now require the submission of an investigational new drug application, or IND, to the agency and its subsequent review to continue to treat new patients.").

75 *See FDA Regulation of Human Cells*, *supra* note 12 (listing "HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector)" as products that are "[r]egulated under Section 351 of the [Public Health Service] Act and/or the [Food, Drug & Cosmetic] Act" without explaining how the communicable disease provision of the Public Health Service Act "and/or" the Food, Drug, and Cosmetic Act applies to these products); *see also* discussion *infra* Part II (explaining that the application of the FDA's Human Tissue Regulations to human reproductive tissue is counterintuitive and contradictory).

2. Lack of Jurisdiction

The FDA's July 6, 2001 letter to sponsors and researchers was the first letter that the Agency sent regarding advanced assisted reproductive technologies after decades of little involvement in the broader field of assisted reproductive technology.[76] As noted in the Introduction, the July 6, 2001 letter stated "[w]e want to advise you that the Food and Drug Administration (FDA) has jurisdiction over human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei."[77] The letter also listed five FDA documents that provided "notice" of this jurisdiction; those documents are analyzed in Section II.C.[78] Documents, however, do not provide notice of jurisdiction, statutes do. Yet, the FDA failed to cite any *specific* statutory provisions that would explain the basis for its jurisdiction over advanced assisted reproductive technologies. Moreover, the FDA's broad reference to the Federal Food, Drug, and Cosmetic Act, a statute of significant length, is insufficient, especially when compared to the FDA's usual practice.

The FDA's July 6, 2001 letter provided a list of examples of "the transfer of genetic material" and included cytoplasmic transfer in that list.[79] The letter then stated "[t]he use of such genetically manipulated cells (and/or their derivatives) in humans constitutes a clinical investigation and requires submission of an Investigational New Drug application (IND) to FDA," although a later sentence in the letter noted "[w]e can advise you whether or not your activities require submission of an IND."[80] Thus, not only was it counterintuitive that the FDA would be asserting jurisdiction over a form of assisted reproductive technology at all, but the letter itself contained contradictions.

Beyond the Agency's failure to identify the source of its jurisdiction, the natural counterargument to an assertion that an agency does not have jurisdiction over a specific field or action is one that addresses the issue of *Chevron* deference.[81] However, as will be

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76 *See* discussion *infra* Section II.C (discussing the evolution of the FDA's regulations from not addressing in vitro fertilization to addressing advanced assisted reproductive technology).

77 *See infra* Appendix A. While the content of the letter is available on the FDA's website, the list of recipients is not. Similarly, a FOIA request revealed that the agency was unable to find the file related to the letter; therefore, a list of sponsor/researchers who received the letter is not available.

78 *See infra* Appendix A.

79 *See infra* Appendix A (examples listed were "cell nuclei (e.g., for cloning), . . . oocyte nuclei, . . . ooplasm [cytoplasm], which contains mitochondrial genetic material, and . . . genetic material contained in a genetic vector, transferred into gametes or other cells").

80 *See infra* Appendix A.

81 While *Chevron* deference is often the first type of deference referred to in the context of judicial review of agency decision-making, it is one of many types of deference. *See* Kevin M. Stack, *Purposivism in the Executive Branch: How Agencies Interpret Statutes*, 109 NW. U. L. REV.

explained in Part III, ethical views are not an area in which agencies are entitled to *Chevron* deference.

3. Obfuscation of the Evidence of Agency Action

Furthermore, it is difficult to effectively challenge agency action when one does not know the scope of that action. Other scholars of administrative law have criticized administrative agency processes for issuing "non-substantive" rules, such as guidance documents.[82] I agree with those criticisms of the shortcomings of the Administrative Procedure Act's application to those rules, including the lack of a publicly available administrative record and the difficulty in challenging those interpretative rules.[83] While non-substantive rules tend to be guidance documents, subterranean regulation often exacerbates these concerns as one can more easily find the content of guidance documents than evidence of the agency's subterranean regulation. The case of the FDA's regulation of AARTs indicates that absent a FOIA request and a FOIA response that is wholly responsive to that request, the public does not have comprehensive evidence of the content and the scope of the Agency's subterranean regulation thus rendering subterranean regulation more problematic than other forms of agency soft law.

4. "Chilling" Effects

The FDA's letters to researchers also do not threaten enforcement action; however, researchers perceive the letters as threatening. For example, one recipient of a letter, Dr. Jamie Grifo, noted, "[w]hat was threatening was they couldn't give me a sense of what the consequences would be . . . if I continued. They made it sound as if there would be

871, 878 n.22 (2015) (citing *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837 (1984)). Under *United States v. Mead Corp.*, 533 U.S. 218, 234–35 (2001), if *Chevron* deference is not warranted, the agency's interpretation will be reviewed under *Skidmore*.

82 *See* Mark Seidenfeld, *A Civic Republican Justification for the Bureaucratic State*, 105 HARV. L. REV. 1511, 1561–62 (1992) ("The Administrative Procedure Act grants agencies virtually complete discretion over the procedures they use to conduct informal adjudication and to issue general statements of policy. . . . No requirements of an open record or public discussion operate to constrain pure political influence or an agency's pursuit of a private agenda. For statements of policy, the usual justification for the absence of any required procedures is the non-binding nature of such statements. From a civic republican perspective, however, this justification is inadequate. Subsequent agency adjudicatory proceedings are adversarial and hence probably will not cure the lack of opportunities for access and deliberation. The adversarial nature of subsequent proceedings will be aggravated by the fact that the agency has already committed itself to a position and may be reluctant to consider seriously arguments to the contrary.").

83 *Id.*

recourse without saying it. I was very threatened . . . ."[84] Dr. Grifo's work actually involved a form of mitochondrial transfer called "pronuclear transfer."[85] Other addressees' work, notably the work of Dr. Jacques Cohen at the Saint Barnabas Medical Center and the work of physicians at the Jones Institute of Eastern Virginia Medical School, involved the use of cytoplasmic transfer.[86] These researchers stopped providing cytoplasmic transfer in the United States after receiving the FDA's letter.[87]

While not mentioned by the FDA in its letters to researchers, substantial penalties may result from violations of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Penalties for violating provisions of the Federal Food, Drug, and Cosmetic Act include: imprisonment for up to one year, a $1,000 fine, or both for first-time offenders; enhancements can increase the penalties to up to three years imprisonment, a $10,000 fine, or both.[88] Similarly, individuals who violate the Public Health Service Act face up to one year in prison, up to a $100,000 fine (if no death has resulted from the violation), or up to a $250,000 fine (if death has resulted from the violation).[89] Thus, while there was no specific reference to criminal penalties in the FDA's letters to those working on advanced assisted reproductive technologies, the specter of punishment still looms.

FDA employee statements in other venues reveal that the Agency is troubled by the spread of advanced assisted reproductive technologies, and in the case of cytoplasmic transfer, targeted the technology before the results had been officially published.[90] Clinical use of cytoplasmic

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84 Connor, *supra* note 12.

85 *Id.*

86 *See* Meeting #32 Transcript, *supra* note 8, at 46.

87 *See id.*

88 *See* 21 U.S.C. §§ 331, 333(a)(1)– 333(a)(2) (2012) (providing that if an individual violates the Food, Drug, and Cosmetic Act "after a conviction of him under this [same] section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both").

89 *See* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. 29785, 29788 (May 25, 2004) (also stating that "organizational defendants [face] fines [that] range up to $200,000 [if no death has resulted from the violation] and $500,000 [if death has resulted from the violation]"); *see also* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001) (The agency's 2001 final rule stated "[a]uthority for enforcement of section 361 of the PHS Act is provided by section 368 of the PHS Act (42 U.S.C. 271). Under section 368(a) of the PHS Act, any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted (18 U.S.C. 3559 and 3571(c)).").

90 *See* Meeting #32 Transcript, *supra* note 8, at 46–47 (Deborah Hursh, a cellular product reviewer for the FDA stated at a 2002 Advisory Committee meeting that the agency "was already considering action in the area of ooplasm transfer" at the time of Dr. Cohen's publication and that the agency felt that the use of cytoplasmic transfer was "beginning to spread rapidly into clinical practice in the United States by 2001." Dr. Hursh's introduction also

transfer in the United States ended after the FDA sent its 2001 letters.[91] This not only had a negative impact on medical advancement, but it also reduced the incentive for physicians to undertake follow-up studies, which already encounter difficulty in keeping patients.[92]

Subterranean regulatory actions deter investment in the biosciences. Even though assisted reproductive technology is usually one industry that needs less investment due to the willingness of couples to spend large sums of money to have a child genetically related to them, funding is crucial.[93] For example, mitochondrial transfer, although an advanced assisted reproductive technology, was developed by Dr. Shoukhrat Mitalipov in a university laboratory.[94] As a university researcher as opposed to a physician, Dr. Mitalipov would not necessarily have patients willing to spend large sums of money to have a genetically related child.[95] Federal funding is unavailable for embryo research, which leaves private investment as a primary funding source for human clinical studies.[96] However, investors also dislike unclear regulatory frameworks: "Without a clear and rapid regulatory pathway, Mitalipov says, he is unable to get the investment that he needs to pursue clinical work [related to mitochondrial transfer]."[97]

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noted that three clinics had "published on this procedure and [the] FDA [was] able to find five additional clinics that were advertising this procedure on the internet." As a result, the agency "advised practitioners that [it] would *now* require the submission of an investigational new drug application, or IND, to the agency and its subsequent review to continue to treat new patients." (emphasis added)).

91 *See* June Carbone, *Negating the Genetic Tie: Does the Law Encourage Unnecessary Risks?*, 79 UMKC L. REV. 333, 348 (2010) ("The FDA's assertion of jurisdiction was of dubious validity, but since the clinic chose not to challenge it, the result has effectively shut down research and use of the procedure in the United States."); Meeting #32 Transcript, *supra* note 8, at 48–55 (providing the testimony of Dr. Susan Lazendorff of the Jones Institute for Reproductive Medicine at the Eastern Virginia Medical School: "We were also looking at other things when we were doing these studies and before we received our letter to stop doing them.").

92 *See* Rachel Nolan, *Behind the Cover Story: Kim Tingley on the Promise and Problems of Three-Parent I.V.F.*, N.Y. TIMES (June 30, 2014, 5:00 AM), http://6thfloor.blogs.nytimes.com/2014/06/30/kim-tingley-on-the-perplexity-and-promise-of-three-parent-i-v-f; Pritchard, *supra* note 25 ("Due to a lack of funding, Cohen says, it hasn't been possible to find out about how any of the children like Alana who were born from cytoplasmic transfer are doing. But the St[.] Barnab[a]s Institute is now starting a follow up study to check their progress."); *see also* Meeting #32 Transcript, *supra* note 8, at 123–24 ("So, we have been able to do follow-up in 13 of the 17 babies. However, more recently it is more likely that some of them will refuse further investigations by us. This is not just this particular group. That is common for all infertility follow-up, that you lose sight of these patients. Some of them will move and not even leave a return address.").

93 *See* SPAR, *supra* note 1.

94 *See* Tavernise, *supra* note 13.

95 *See* SPAR, *supra* note 1, at xiv.

96 *See* I. Glenn Cohen & Eli Y. Adashi, *Preventing Mitochondrial DNA Diseases: One Step Forward, Two Steps Back*, 316 JAMA 273 (2016).

97 *See* David Cyranoski & Boer Deng, *Stem-Cell Star Lands in Same Venture as Disgraced Cloner*, NATURE (Feb. 11, 2015), http://www.nature.com/news/stem-cell-star-lands-in-same-venture-as-disgraced-cloner-1.16907 (also noting "[t]he US-based scientist who first cloned

The FDA's unclear regulatory pathway has halted research at the expense of follow-up studies on those already born as a result of advanced assisted reproductive technologies, and it has also halted the human clinical use of advanced assisted reproductive technologies. Although more than fifteen years have passed since its assertion of jurisdiction over cytoplasmic transfer, the FDA has provided no clear explanation of the source of its jurisdiction over advanced assisted reproductive technologies (which manifests through the requirement of premarket approval) or why this divergence from the Agency's "hands-off" treatment of conventional assisted reproductive technology is justified.

C. *Drugs Versus Procedures: What the FDA Does and Does Not Regulate*

The FDA regulates food, drugs, tobacco products, pharmaceuticals, medical devices, biological products, and cosmetics.[98] The FDA does not regulate the practice of medicine, which means that while it regulates the tools that physicians use in surgery (e.g., anesthesia, surgical implants such as pacemakers, bone grafts, prosthetics, etc.) or in their general practices (e.g., vaccines and prescription drugs), the FDA does not regulate surgical techniques or diagnostic decisions.[99]

The drugs and medical devices used by treatments categorized as "assisted reproductive technology" are regulated by the FDA, but the techniques used in assisted reproductive technology themselves are not regulated by the FDA. The exception to this regulatory convention lies in the FDA's regulation of advanced assisted reproductive technologies. For example, hormones, which are commonly referred to as "fertility drugs" have been described as one of the "most basic components" of assisted reproductive technology, and they are regulated by the FDA like all pharmaceuticals.[100] Similarly, while sperm and eggs used in assisted

human embryonic stem cells is taking steps to apply his reproductive technology in China to escape burdensome regulations and get funding. The result is a joint venture that brings stem-cell star Shoukhrat Mitalipov of Oregon Health and Science University in Portland together with disgraced cloner turned dog-clone entrepreneur, Woo Suk Hwang, although Mitalipov says that the pair will not collaborate on research").

98 *See* 21 U.S.C. §§ 341–46, 387a–r (2012); *see also What Does FDA Regulate?*, *supra* note 22.

99 *See What Does FDA Regulate?*, *supra* note 22. The term "bone grafts" refers to the bone that is grafted and *not* the procedure itself.

100 *See* SPAR, *supra* note 1, at 35 (noting that the "most basic components" of the fertility trade are "sperm, eggs, and hormones" and referring to what are commonly referred to as hormonal treatments as "fertility drugs"); *see also* 21 U.S.C. §§ 201, 355; *see, e.g.*, *Infertility Medications*, AM. PREGNANCY ASS'N (May 16, 2017, 7:33 AM), http://americanpregnancy.org/infertility/infertility-medications (providing an overview of many of the hormonal treatments that are a part of fertility treatment in the United States).

reproductive technology and advanced assisted reproductive technology have, since 2001, been subject to the FDA's communicable disease requirements, analyzed below in Section II.D, the FDA does not approve how those sperm and eggs are obtained, and the FDA does not prohibit the use of all sperm and eggs in assisted reproductive technology that can transmit communicable diseases.[101]

New drugs may not be introduced into interstate commerce "unless an approval of an application . . . is effective with respect to [that] drug."[102] Drugs are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and . . . articles (other than food) intended to affect the structure or any function of the body of man or other animals . . . ."[103] Thus, surgeries, for example, are not drugs. Practitioners and researchers describe AARTs as "research protocol[s]," and not drugs, when explaining why AARTs are outside of the jurisdiction of the FDA.[104] Because the definition of drug includes the word "article" and not "research protocol," AARTs are analogous to surgeries and not drugs. Similarly, methods used in assisted reproduction such as in vitro fertilization and artificial insemination are not subject to FDA approval.[105] Thus, because AARTs are techniques that use drugs and medical devices, just like other forms of assisted reproductive technology, AARTs should not be subject to federal regulation.[106] Additionally, while other scholarly articles have noted that cytoplasmic transfer could be seen as a "cure" for the disease of infertility, women who would use mitochondrial transfer are not infertile.[107]

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101 *See* discussion *infra* Section II.D (providing information on the FDA's Human Cellular and Tissue-Based Products Rule in the context of sexually intimate partners). For more on the procurement and trade of sperm and eggs, see generally CAHN, *supra* note 1.

102 21 U.S.C. § 355; *see also* MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 64–65 (discussing the Food, Drug, and Cosmetic Act and the process through which a proposed drug eventually gains FDA approval for sale in the United States: If an investigational new drug application is authorized, then a researcher may begin clinical investigations. After successful clinical investigations, a researcher (or company) may submit "a Biologic License Application . . . or a New Drug Application . . . ." That application is then reviewed by the FDA which decides whether to approve the drug.).

103 21 U.S.C. §§ 321(g)(1)(B)–(C).

104 Meeting #32 Transcript, *supra* note 8, at 280–81.

105 *See What Is Assisted Reproductive Technology?*, CENTERS DISEASE CONTROL & PREVENTION, http://www.cdc.gov/art/whatis.html (last updated Feb. 7, 2017).

106 *See* Michael J. Malinowski, *A Law-Policy Proposal to Know Where Babies Come from During the Reproduction Revolution*, 9 J. GENDER RACE & JUST. 549, 554–55 (2006).

107 *See* Kerry L. Macintosh, *Brave New Eugenics: Regulating Assisted Reproductive Technologies in the Name of Better Babies*, 2010 U. ILL. J.L. TECH. & POL'Y 257, 259 (2010). Thus, to the extent that other forms of assisted reproductive technology could arguably be considered a "cure" for infertility, thus rendering them analogous to a drug, mitochondrial transfer does not cure a mother's infertility as she would be able to reproduce without the use of assisted reproductive technology. *See supra* text accompanying note 103 (providing the definition of a drug).

"Biological products," also referred to as "biologics" are a broad category of products regulated by the FDA.[108] A biological product is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein . . . or analogous product, . . . arsphenamine or derivative of arsphenamine, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[109] So while organ transplants are not regulated by the FDA, "[b]lood and processed blood derivatives, such as plasma and clotting factors," are regulated by the FDA under the Public Health Service Act.[110]

The FDA has stated that advanced assisted reproductive technologies would be regulated "as drugs and/or biological products," but it is unclear *why* that is the case.[111] Similarly, the FDA has used this tactic in spite of the legal argument that cytoplasmic transfer and mitochondrial transfer are not drugs, but medical techniques which do not fall under the Agency's jurisdiction.[112] The FDA should clearly explain the source of its jurisdiction (if any) over advanced assisted reproductive technologies and how that jurisdiction corresponds with the manner in which advanced assisted reproductive technologies will be regulated. In light of the blurring distinctions between medical devices, human tissues, drugs, and the practice of medicine, if the FDA does have jurisdiction over advanced assisted reproductive technologies, it should clearly explain the source of that jurisdiction, not only to regulate more clearly, but also because the Agency's jurisdiction over biotechnology will continue to be contested as scientists continue to innovate and move from using pharmaceuticals to treat conditions, to using them to prevent conditions ex ante while employing techniques that target genes.

D. *The Gradual Inclusion of Reproductive Tissue into FDA*

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108 *See* 42 U.S.C. § 262 (2012).

109 *Id.*

110 PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 1154 (4th ed. 2014) (noting that "[a] relatively small share of blood is used in the form in which it was collected, i.e., as single units transfused into individual patients. Here the risk of disease transmission is confined; only the recipient of a contaminated unit of blood is potentially vulnerable. But most blood is fractionated, pooled, and processed to yield a variety of useful products"). For statutory provisions governing organ transplantation, see 42 U.S.C. §§ 273–74.

111 *FDA Regulation of Human Cells*, *supra* note 12; *see also* HUTT ET AL., *supra* note 110, at 672. This dual designation may stem from the FDA's efforts to regulate products that fall within both categories of its regulations; however, the agency has not even issued a clarification as to which FDA regulatory center would review applications by those wishing to use advanced assisted reproductive technologies clinically. Furthermore, there has still been no clear explanation as to how an advanced assisted reproductive technology would be a drug or a biologic.

112 *See* Meeting #32 Transcript, *supra* note 8, at 280.

Regulations

Over time, the FDA has increased the number of agency-issued rules that apply to human reproductive tissue and advanced assisted reproductive technologies. The FDA's July 6, 2001 letter to sponsors/researchers referenced five documents that the FDA characterized as providing "notice of the applicability of [investigational new drug] requirements to cellular and tissue-based products . . . ."[113] These five documents were: two guidance documents, one final rule, and two proposed rules.[114] However, a close examination of these five documents reveals that notice is non-existent in some of those documents and unclear in the others.

Assisted reproductive technology, which includes not only in vitro fertilization but also artificial insemination, had been used by American physicians for over fifty years before the FDA began regulating reproductive tissue.[115] In 1993, the FDA issued a document entitled, "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products."[116] This document, while cited in the July 6, 2001 FDA letter, did not state that the FDA would be regulating advanced assisted reproductive technologies or

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113 *See infra* Appendix A.

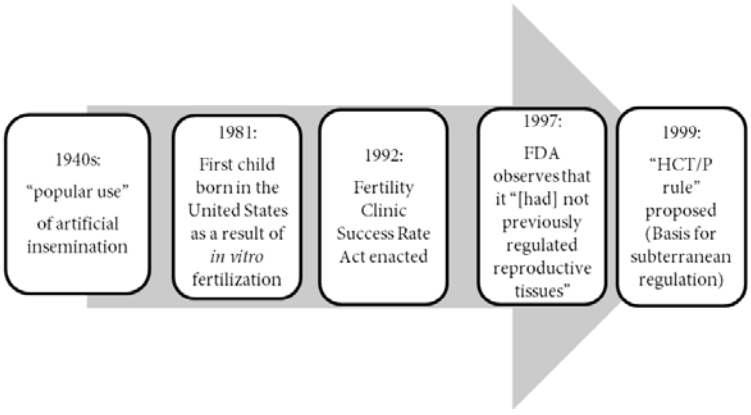
114 *Id.* The five documents were: (1) a 1993 Federal Register notice entitled, "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products," 58 Fed. Reg. 53,248 (Oct. 14, 1993); (2) the FDA's "comprehensive regulatory program for the regulation of human cellular and tissue-based products, based on a tiered, risk-based assessment," *infra* Appendix A; *see* Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting, 62 Fed. Reg. 9721 (Mar. 4, 1997); (3) "[a] final rule that establishes the criteria for regulation of human cells, tissues, and cellular and tissue based products (HCT/Ps), including reproductive cells and tissues," *infra* Appendix A; *see* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001); (4) a 1999 proposed rule entitled, "Suitability Determination for Donors of Human Cellular and Tissue-Based Products," 64 Fed. Reg. 52,696 (proposed Sept. 30, 1999); and (5) a 2001 proposed rule entitled, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement," 66 Fed. Reg. 1508 (proposed Jan. 8, 2001).

115 It is estimated that the "popular use" of artificial insemination in the United States began in the 1940s. *See* NAT'L BIOETHICS ADVISORY COMM'N, CLONING HUMAN BEINGS 5 (1997) [hereinafter CLONING HUMAN BEINGS] ("Artificial insemination by donor, for example, was considered a form of adultery when first introduced in the 1940s. It is now a widely used and accepted practice in the treatment of infertility, although some continue to have serious reservations."); Gaia Bernstein, *The Socio-Legal Acceptance of New Technologies: A Close Look at Artificial Insemination*, 77 WASH. L. REV. 1035, 1060–72 (2002); *see also The US' First Test Tube Baby*, PBS, http://ec2-184-73-243-168.compute-1.amazonaws.com/wgbh/american experience/features/general-article/babies-americas-first (last visited Mar. 1, 2018) (noting that Elizabeth Carr, the first baby born as a result of in vitro fertilization in the United States, was born in 1981).

116 *See* Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248.

mention reproductive tissue at all.[117]

Figure 1: Timeline of the Increasing Federal Regulation of AARTs[118]



In 1997, when the FDA issued a "Proposed Approach to the Regulation of Cellular and Tissue-Based Products," the FDA noted that the Agency "ha[d] not previously regulated reproductive tissues."[119] The Federal Register notice for the 1997 Proposed Approach stated that the FDA's regulatory framework would include reproductive tissues.[120] However, the actual document providing the approach stated that the FDA "would recommend, but not require, that screening and testing procedures be followed when reproductive tissues are used between sexually intimate partners . . . ."[121] Thus, the FDA's regulation of reproductive tissue began with confusion. Ultimately, the 1997 "Human

117 *Id.*

118 The dates in this timeline are a compilation of several sources cited in this Article. *See supra* note 115 and accompanying text (regarding artificial insemination); *see also* 42 U.S.C. § 264 (2012); Meeting #32 Transcript, *supra* note 8, at 280–81; *US' First Test Tube Baby*, *supra* note 115 (referring to the birth of Elizabeth Carr in 1981); *supra* note 49 (describing the 1992 Fertility Clinic Success Rate and Certification Act). For more on the gradual increase of federal regulations applicable to assisted reproductive technology and AARTs, see *infra* text accompanying notes 119–23 (regarding the 1997 document, a "Proposed Approach to Regulation of Cellular and Tissue-Based Products" and the 1999 document "Suitability Determination for Donors of Human Cellular and Tissue-Based Products").

119 FOOD & DRUG ADMIN., PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS 9 (1997) [hereinafter FDA PROPOSED APPROACH].

120 *See* Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting, 62 Fed. Reg. 9721 (Mar. 4, 1997).

121 FDA PROPOSED APPROACH, *supra* note 119.

Tissue Intended for Transplantation" rule specifically excluded "semen or other reproductive tissue."[122]

In 1999, the FDA flipped from not regulating reproductive tissue to proposing a rule that would require the application of communicable disease testing requirements to facilities that work with reproductive tissue. The proposed "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" rule would mandate communicable disease testing for many types of human tissue including semen.[123] The FDA explained that because human cell, tissue, and cellular and tissue-based products (which the agency refers to as "HCT/Ps") are derived from the human body, there is a risk that these "products" could transmit communicable diseases.[124] As the basis for its HCT/P regulations, the FDA cited to Section 361 of the Public Health Service Act which allows the FDA, by delegation, to make regulations to prohibit the transmission or spread of communicable diseases.[125] As a result, under the final rule, facilities that perform work on reproductive tissues must continue to adhere to requirements related to the testing of communicable diseases with exceptions for those facilities that are using the reproductive tissue of sexually intimate partners.[126]

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122 *See* Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429, 40,444 (July 29, 1997).

123 *See* Statement of Kathryn C. Zoon, *supra* note 72. The 1999 Suitability Determination for Donors of Human Cellular and Tissue-Based Products proposed rule cited in the July 6, 2001 letter became a final rule in 2004. However, in response to a public comment, the name of the final rule was changed to "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products," 69 Fed. Reg. 29,786 (May 25, 2005). The final rule covers many types of human tissue: reproductive tissue including embryos, semen, and eggs; cord blood; ocular tissue such as cornea donations through eye banks; and human "heart valves." *Id.* at 29,817, 29,787 ("We are issuing these new regulations under the authority of section 361 of the [Public Health Service] Act (42 U.S.C. 264).").

124 *See* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. at 29,787; *Donor Eligibility Final Rule and Guidance Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBlood Vaccines/TissueTissueProducts/QuestionsaboutTissues/ucm102842.htm (last updated Apr. 20, 2009) (citing to Section 351 of the Public Health Service Act in reference to a biological product application).

125 *See* 42 U.S.C. § 264 (2012); *Donor Eligibility Final Rule and Guidance Questions and Answers*, *supra* note 124; *see also* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. at 29,788.

126 *See* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. at 29,793 ("We have also clarified the definition by noting that directed reproductive donors do not include sexually intimate donors, who are excepted from screening and testing requirements under § 1271.90.") Anonymous semen donations remain subject to the testing requirement and six-month retesting requirement. The FDA attributes the distinction in the regulatory treatment of anonymous semen donors and sexually intimate partners to the Agency's "respect [of] the existence of relationships between people who know each other and have made a joint decision for the recipient to conceive a child." *Id.* at 29,790, 29,793 (noting that facilities working with the reproductive tissue of sexually intimate partners are not excepted from administrative requirements such as labeling and registration when semen from a directed donor is frozen before insemination due to "concerns about

The FDA's 2001 HCT/P regulations are the basis for the FDA's theory that the results of advanced assisted reproductive technologies are "drugs."[127] The FDA's tissue regulation framework conceptually distinguishes between "minimally manipulated" tissue and "more than minimally manipulated" tissue.[128] "Minimal manipulation" is: "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement . . . [or] the relevant biological characteristics of cells or tissues."[129]

The regulations do not define what the term "original relevant characteristics" means and despite public comments that the term "minimal manipulation" is vague and should be eliminated, the FDA kept the term.[130] Tissues that are minimally manipulated are "lightly regulated" and subject to communicable disease testing requirements, whereas "more than minimally" manipulated human cells and tissue products are regulated as drugs and/or biologics.[131] Not only is it

possible cross-contamination during storage"). The fifth document referenced in the July 6, 2001 letter *infra* Appendix A, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement," also provides requirements to minimize the transmission of communicable diseases within facilities. 66 Fed. Reg. 1508 (Jan. 8, 2001). The final rule, "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement" was published on November 24, 2004 with an effective date of May 25, 2005. 69 Fed. Reg. 68,611 (Nov. 24, 2004).

127 *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001); *Tissue and Tissue Product Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/QuestionsaboutTissues/ucm101559.htm (last updated Feb. 2, 2018); MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 22; *see also* 21 C.F.R. § 1271.3(d) (2016). Blood, blood products, and blood vessels are excluded from the agency's HCT/P regulations. The 2001 Human Tissue Regulations do not apply to human organs such as kidneys, livers, hearts, and lungs as they are regulated by the Health Resources Services Administration, another operating division of the U.S. Department of Health and Human Services. *Id.*

128 *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. at 5457.

129 *Id.* at 5467.

130 *Id.* at 5457 ("Eight comments asserted that 'minimal manipulation' is vague and open to subjective interpretation, and should be eliminated. Two comments asserted that it is difficult to draw a meaningful distinction between tissues that are minimally manipulated and those that are more than minimally manipulated. One of these comments suggested that instead of the minimal manipulation criterion, FDA should propose that tissue products labeled or promoted for tissue replacement, reconstruction, or restoration of function be regulated as tissue. Another comment requested the development of guidance and noted that, in light of future technological advances, a broader definition of minimal manipulation may be more appropriate.").

131 *See* Collins, *supra* note 49 (showing the impact of the FDA's regulatory scheme on federal funding and the acceptance of the FDA's view by other agencies within the U.S. Department of Health and Human Services: "The Public Health Service Act and the Federal Food, Drug, and Cosmetic Act give the FDA the authority to regulate cell and gene therapy products as biological products and/or drugs, which would include oversight of human germline

unclear what more than minimal manipulation is, it is also unclear how the FDA's ability to require communicable disease screening under the Public Health Service Act mandates that a "modified embryo" or more than minimally manipulated reproductive tissue be treated as a "drug and/or biologic."[132]

The FDA's HCT/P regulations are based on the Agency's delegated communicable disease testing authority under the Public Health Service Act; however, it is unclear how communicable disease testing requirements can prohibit the clinical use of AARTs.[133] While communicable disease testing for public health purposes is an undisputed part of the U.S. Department of Health and Human Services'

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modification. During development, biological products may be used in humans only if an investigational new drug application is in effect (21 CFR Part 312)."); *see also* U.S. DEP'T. HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., MINIMAL MANIPULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: DRAFT GUIDANCE (2014), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/Guidances/CellularandGeneTherapy/UCM427746.pdf; MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 2–27.

132 *See* MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 65. In 2013, the FDA sent a letter to OvaScience, a Massachusetts-based company, stating that the company needed to submit an investigational new drug application to continue its work on "Augment," a technology that uses a woman's own mitochondria to revitalize her eggs which are then used in in vitro fertilization. This letter, obtained through FOIA Request 2016-4882, stated, on the subject of "more than minimal manipulation":

> [O]ur understanding is that your autologous mitochondrial transfer product, AUGMENT, consists of cells isolated from a biopsy of ovarian tissue, which are processed to extract mitochondria that are then introduced into other reproductive tissues during the IVF process. The removal of mitochondria and introduction into other reproductive tissue appears to be more than minimal manipulation. This is based on the limited information available; please note that the addition of mitochondrial DNA to other reproductive tissue may raise additional regulatory concerns.

Letter from Celia M. Witten to Alison Lawton, *supra* note 7; *see* Complaint at 2, Ratner v. OvaScience, No. 13-cv-12286 (D. Mass. Sept. 16, 2013) ("Throughout the Class Period, Ova[S]cience represented to the FDA and investors that it believed that Augment qualified for designation as a 361 HCT/P, which allows human cellular and tissue based products to be tested and marketed without FDA licensure. Under FDA guidelines, organisms can only achieve this designation if they are 'only minimally manipulated', i.e., the process does not alter 'the relevant biological characteristics of the cells or tissue.' . . . Ultimately, the FDA rejected Ova[S]cience's faulty designation. On September 10, 2013, the Company disclosed that it was suspending enrollment of AUGMENT in the U.S. after receiving an 'untitled' letter from the FDA 'questioning the status of AUGMENT as a 361 HCT/P and advising the Company to file an Investigational New Drug (IND) application.'"); *see also* Bioentrepreneur, *CRISPR Germline Editing Reverberates Through Biotech Community*, NATURE.COM: TRADESECRETS (Apr. 30, 2015, 12:34 AM), http://blogs.nature.com/tradesecrets/2015/04/30/crispr-germline-editing-reverberates-through-biotech-community (noting that Augment is available in the United Kingdom, Canada, Dubai, and Turkey, but not in the United States); HUTT ET AL., *supra* note 110, at 672.

133 *See* 42 U.S.C. § 264 (2012); Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule and Notice, 69 Fed. Reg. 29,786, 29,787 (May 25, 2004); *Donor Eligibility Final Rule and Guidance Questions and Answers*, *supra* note 124.

jurisdiction (and by delegation, the FDA's), the FDA's regulation of reproductive tissues has expanded beyond communicable disease testing requirements.[134] Regulating manipulated cells and tissues utilized in advanced assisted reproductive technology as drugs exceeds the power to regulate communicable diseases. Neither interstate commerce nor international commerce would affect the transmission or spread of defective mitochondria or defective genes. If genetic diseases did somehow fall within the Agency's authority to prevent the spread of communicable diseases under the Public Health Service Act, the Agency's letters have thwarted efforts to prevent the transmission of disease-causing genetic mutations to offspring.

In none of the five documents cited by the FDA in its July 6, 2001 letter did the FDA clearly explain *how* these documents connected to the Agency's enabling statutes and how the Agency's statutory authority enabled it to prevent the use of technology that modified DNA in reproduction. Some of the cited documents stated that the FDA did not regulate reproductive tissue, whereas others provided regulations related to reproductive tissue. Others were "guidance documents," which do not provide legal requirements.[135] In those documents that did provide legal requirements, the Agency broadly cited to Section 361 of the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act generally. Yet, the authority to inhibit the spread of communicable disease is not the same as the authority to regulate genetic modifications. Moreover, the applicability of the Federal Food, Drug, and Cosmetic Act, if any, was not explained.

Not only is the regulatory framework surrounding advanced assisted reproductive technologies unclear, but the manner of regulating these technologies is unique as compared to other more traditional forms of assisted reproductive technology. To the FDA, advanced assisted reproductive technologies differ from "more traditional" methods of assisted reproductive technology because they involve the use of more than minimally manipulated tissue.[136] But why does a

134 *See* 42 U.S.C. § 264; FDA PROPOSED APPROACH, *supra* note 119, at 8–9; *see also* HUTT ET AL., *supra* note 110, at 77 (explaining that the FDA shares the power to prevent the spread of communicable diseases with the Centers for Disease Control and Prevention).

135 *See* Todd D. Rakoff, *The Choice Between Formal and Informal Modes of Administrative Regulation*, 52 ADMIN. L. REV. 159, 168 (2000) ("At the same time, the FDA takes pains to state that guidance documents 'are not legally binding on the public or the agency. Rather, they explain how the agency believes the statutes and regulations apply to certain regulated activities.' Indeed, the FDA remains open to discussing '[a]lternative methods that comply with the [applicable] statute or regulations . . . .' In short, guidance documents are meant to be statements of no legal consequence but immense practical consequence about virtually everything the agency regulates." (quoting The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8961, 8967 (Feb. 27, 1997))).

136 "Traditional" assisted reproductive technology, meaning assisted reproductive technology such as in vitro fertilization not involving genetic modifications or artificial insemination, remain "minimally regulated" by the FDA, whereas AARTs are heavily regulated.

change of 0.054% of total DNA, such as occurs in mitochondrial transfer, result in a classification of more than minimal manipulation? The FDA has not answered this question and declined requests to use a term that was not "vague" and "misleading" such as "more than minimal manipulation."[137] In light of the fact that only 0.054% of an embryo's DNA is modified as a result of mitochondrial transfer, it appears that at the very least, the term "minimal manipulation" should be replaced with "manipulation."

There are additional questions related to the regulatory treatment of human reproductive tissue as a "drug" or "biologic." If a "modified embryo" is a drug, does that mean that a child born as a result of an advanced assisted reproductive technology is a "drug"? How long are future humans "drugs" or at what point do modified embryos become humans and not drugs?[138] At some point, in theory, a child born as a result of advanced assisted reproductive technology must pass from being a "drug" into being a nonregulated entity, but it is unclear when that occurs.

III. THE ETHICAL CONCERNS THAT SILENTLY IMPACT THE FDA'S REGULATORY ACTIONS RELATED TO ADVANCED ASSISTED REPRODUCTIVE TECHNOLOGIES

When the FDA regulates advanced assisted reproductive technologies in a subterranean manner, ethical concerns can fuse with safety concerns.[139] In written communications, the FDA has not

See supra note 1 and accompanying text (regarding the regulation of traditional assisted reproductive technology); *supra* text accompanying note 129 (providing the definition of "minimal manipulation").

137 *See supra* note 130 and accompanying text (providing public comments on the FDA's HCT/P regulations).

138 *See* 21 U.S.C. § 321(g)(1) (2012) (defining "drugs" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and . . . articles (other than food) intended to affect the structure or any function of the body of man or other animals"). *But see* LA. STAT. ANN. § 9:129 (2017) ("A viable in vitro fertilized human ovum is a juridical person which shall not be intentionally destroyed by any natural or other juridical person or through the actions of any other such person. An in vitro fertilized human ovum that fails to develop further over a thirty-six hour period except when the embryo is in a state of cryopreservation, is considered non-viable and is not considered a juridical person."). *See* Letter from Mary A. Malarkey, Dir., Office of Compliance & Biologics Quality, U.S. Food & Drug Admin., to John Zhang, Chief Exec. Officer, Darwin Life, Inc. & New Hope Fertility Ctr. (Aug. 4, 2017), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM570225.pdf (referring to "genetically modified embryo[s]").

139 *See* Connor, *supra* note 12 (Dr. Grifo stated with "it"—in the subsequent statement—referring to pronuclear transfer, a type of mitochondrial transfer: "I stopped it because the FDA stopped me for safety concerns. Initially they said it was because it was cloning, which they

indicated that the science surrounding advanced assisted reproductive technologies is misunderstood.[140] Yet some statements by FDA officials in public settings indicate that safety or scientific comprehension are not driving the FDA's decisions related to AARTs; if that is indeed the case, then other considerations must be driving the FDA's subterranean actions. I argue that these "other considerations" that drive the FDA's subterranean regulation of AARTs include ethical concerns and political opposition to advanced assisted reproductive technologies.

While FDA employees acknowledge that ethical concerns can affect regulatory actions, the Agency generally avoids discussing or identifying those ethical concerns. At the 2014 FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting, an FDA employee stated that "[t]he FDA recognizes [that there are] moral, ethical, and social policy issues related to genetic modification of eggs and embryos, *and that these issues have the potential to affect regulatory decisions*."[141] But in spite of their ability to affect regulatory decisions, the Agency continually refuses to discuss these issues. In 2014—at the same Advisory Committee meeting on mitochondrial transfer where an agency employee admitted that ethical concerns can influence agency actions—the Agency purposefully limited the scope of the meeting to animal trials and general safety concerns, but not the legal and ethical issues surrounding the technique.[142] One FDA employee announced at the 2014 Advisory Committee meeting that the "FDA is [cognizant] that there are ethical, legal, and social policy issues raised by such heritable

didn't understand that it wasn't. Then they said they had to regulate it on the basis that it was genetic engineering"); *Human Cloning: How Close Is It?*, *supra* note 71; *see also* Meeting #32 Transcript, *supra* note 8, at 46 ("In March of 2001, a laboratory of Dr. Jacques Cohen reported that two children born after the ooplasm transfer protocol were heteroplasmic, which means the genotypes of both the ooplasm donor and the mother could be detected in their tissues. These children were approximately one year old at the time of this analysis, so this was a persistent heteroplasmy that had been maintained. At the time of Dr. Cohen's publication the FDA was already considering action in the area of ooplasm transfer. The report of heteroplasmy raised . . . concerns, as did information [that] two pregnancies occurring after ooplasm transfer resulted in fetuses with Turner's syndrome, a condition where there is only one X chromosome."); PREVENTING MITOCHONDRIAL DISEASE, *supra* note 12.

140 *See* Meeting #59 Transcript, *supra* note 32. In the FDA-prepared briefing document, the Agency explained the science underlying both mitochondrial transfer and cytoplasmic transfer. The Agency's briefing document also described "some of the key safety issues that have been identified" in the study of mitochondrial transfer. None of these identified "safety" issues overlapped with ethical issues. *Id.* Also, the term "safety" has various definitions as many of the agency's regulated products, namely pharmaceuticals, result in serious side effects. *See* Meeting #32 Transcript, *supra* note 8, at 47 ("FDA had concerns about whether we understood all the ramifications of this procedure and whether we understood its safety in particular, and reacted by sending letters to practitioners who were identified by publications on ooplasm [cytoplasm] transfer or by advertisements offering the procedure. We advised practitioners that we would now require the submission of an investigational new drug application, or IND, to the agency and its subsequent review to continue to treat new patients.").

141 Meeting #59 Transcript, *supra* note 32, at 13 (emphasis added).

142 *See id.* at 11–13, 25.

genetic modification of gametes, but these [a]re outside of FDA's delegated authority, and will not be discussed at this meeting."[143] The Agency did not hold a subsequent meeting to address the remaining legal and ethical issues.

Legal issues were similarly avoided during a 2002 Advisory Committee meeting after the issuance of Untitled Letters to researchers on cytoplasmic transfer.[144] There, an FDA employee informed attendees of the meeting that it would "limit . . . discussion to the science behind [cytoplasmic] transfer and not extend that discussion to FDA's jurisdiction in general, FDA's proposed rules for the regulation of human cells and tissues and other assisted reproductive technologies."[145] Thus, in spite of the importance of legal interpretation in the regulation of advanced assisted reproductive technologies, the Agency has avoided discussions of its jurisdiction and its position on ethical issues.

The public statements of FDA officials, as evidenced by the testimony of agency officials before Congress from 1997 to 2016 and FDA employees' statements in other venues between 2000 and 2016 allude to the ethical concerns that may underlie the FDA's regulatory decision-making process.[146] When subterranean regulatory actions occur, it is possible, for example, that Agency officials are not acting based on the political beliefs of the President or sound legal interpretation, but instead institutional or individual views on ethics. Transparent regulation would help to prevent this by clarifying what (or whose) ethical perspectives are being incorporated into regulatory decisions and the source of those ethical perspectives.

In spite of the unidentified basis for its assertion of jurisdiction, Dr. Kathryn Zoon, an FDA official, still asserted in congressional testimony that an investigational new drug application had to be submitted by a researcher before the commencement of "[c]linical research using cloning technology to clone a human being," although the agency would

143 *Id.* at 17–18.

144 *See* Meeting #32 Transcript, *supra* note 8, at 47.

145 *Id.* at 48.

146 *See Congressional Testimony 2017*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/NewsEvents/Testimony/ucm383860.htm (last updated June 22, 2016) (containing FDA testimony from 1997 to 2016); *Speeches by FDA Officials*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/NewsEvents/Speeches/default.htm (last updated Oct. 18, 2016). Note, while the FDA posts the speeches of "agency officials" on the websites, this does not mean that the speeches of all agency *employees* are posted online. For example, the speech by FDA Commissioner Robert M. Califf to the 2016 Food Drug and Law Institute Annual Meeting is available online; however, the subsequent speech by the Agency's Chief Counsel, Elizabeth Dickinson, is not maintained in the speeches repository. *See* Robert M. Califf, Comm'r, Speech at 2016 FDLI Annual Meeting (May 5, 2016), https://wayback.archive-it.org/7993/20170111003315/http://www.fda.gov/NewsEvents/Speeches/ucm499475.htm ("The good news is that after I'm done you'll hear from FDA's top lawyer, Liz Dickinson."). The speeches archived on the FDA website span from 1988 until 2016; however, there are very few from 1988 to 2005.

not permit any such clinical investigation to proceed due to "major unresolved safety questions . . . ."[147] These unresolved safety questions were not identified. Yet, a statement later in Dr. Zoon's testimony explained that safety issues were not the only reason for the Agency's opposition to cloning: "Because of the profound moral, ethical, and scientific issues, the Administration is unequivocally opposed to the cloning of human beings."[148] Dr. Zoon's reference to "the Administration" was likely her referring to the Food and Drug Administration; however, the Food and Drug Administration is a part of the executive branch and not an independent regulatory agency, so it is possible that political concerns affected her testimony.[149] These same concerns have surfaced in relation to other advanced assisted reproductive technologies and assisted reproductive technology in general, which forces politicians to consider their positions on reproductive rights. Much has been written in the administrative literature about the political pressures that administrative agencies face; here, ethical issues such as those related to the destruction of embryos, eugenics, and concerns about modifications of genetic material for future generations, have possibly commingled with political concerns and pressures.[150] Thus, while *Chevron* deference and issues of "reasonable" agency interpretation of a statute arise within this discussion of the FDA's regulation of AARTs, it needs to be clear what aspect of the FDA's decision is based on statutory interpretation (and of course, what statute is being interpreted), and what aspect of that interpretation is based on ethics—which would be entitled to less deference.[151]

A. *Embryo Destruction and Research: Current Iterations of a Decades-Long Debate*

The destruction of embryos and controversy related to research on embryonic tissue are likely additional "moral, ethical, and social policy

147 Statement of Kathryn C. Zoon, *supra* note 72.

148 *Id.*

149 *See FDA Laws, Regulations, and Guidance Documents*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273183.pdf (last visited June 13, 2016). For more on the differences between independent regulatory agencies and federal agencies that are a part of the Executive Branch, see Kirti Datla & Richard L. Revesz, *Deconstructing Independent Agencies (and Executive Agencies)*, 98 CORNELL L. REV. 769, 776 n.24 (2013).

150 For a general overview of pressures faced by administrative agencies, see Seidenfeld, *supra* note 82.

151 For more on *Chevron* deference, see Peter L. Strauss, *"Deference" Is Too Confusing—Let's Call Them* "Chevron *Space" and* "Skidmore *Weight"*, 112 COLUM. L. REV. 1143 (2012).

issues related to genetic modification of eggs and embryos . . . [with the] potential to affect regulatory decisions."[152] In addition to research on embryos, another issue that arises in discussions of the ethics of mitochondrial transfer is the destruction of embryos.[153] The Institute of Medicine, in a report commissioned by the FDA, also recognized the "moral status of the embryo" as an ethical issue related to mitochondrial transfer.[154] This report identified this issue, but did not analyze it nor explain how the FDA had incorporated that "moral issue" into its regulatory decision-making before.[155]

Ethical concerns have impacted federal funding decisions related to embryonic research for years.[156] However, the idea that ethical concerns could manifest as legal prohibitions on access to reproductive technology regardless of funding sources, has not received as much attention outside of discussions about access to abortion and contraception.[157]

There are many ethical issues that are ripe for a public discussion. Questions about where one "draws the line" between ethical and unethical medical practices have accompanied assisted reproductive technology since its inception.[158] Mitochondrial transfer, beyond issues

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152 Meeting #59 Transcript, *supra* note 32, at 13; *see also* James Gallagher, *Three-Person Babies - Not Three-Parent Babies*, BBC (Feb. 1, 2015), http://www.bbc.com/news/health-31044255; MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 7–9.

153 *See* Gallagher, *supra* note 152; MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 5–11.

154 MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 102–06. The Institute of Medicine recommended that non-viable human embryos be used "when possible" in preclinical research related to mitochondrial transfer. *Id.* at 12.

155 *Id.* at 1–2. After the 2014 Advisory Committee meetings on February 25-26, 2014, the FDA's Center for Biologics Evaluation and Research, Office of Cellular, Tissue, and Gene Therapies requested that a committee of the Institute of Medicine "develop a report that [would] inform the [FDA] in consideration of review of applications in the area of genetic modification of eggs and zygotes for the prevention of mitochondrial disease specific to mitochondrial DNA . . . including maternal spindle transfer, pronuclear transfer, . . . polar body transfer . . . and [possibly] other technologies not currently proposed." *Id.* at 2.

156 *See* Carbone, *supra* note 91, at 348 ("The ban on use of federal funds for embryo experimentation makes it difficult to undertake the expensive testing that might persuade the FDA to authorize use of the technique; that testing today is taking place in Britain, not the U.S." (citations omitted)). For more on funding policies affecting embryo research, see O. Carter Snead, *Science, Public Bioethics, and the Problem of Integration*, 43 U.C. DAVIS L. REV. 1529, 1552–53 (2010).

157 *See* HUTT ET AL., *supra* note 110, at 18 ("Recently, however, both the George W. Bush Administration and the Obama administration have generated controversy by interfering in the FDA decision making process regarding petitions to institute and expand over-the-counter availability of Plan B emergency contraceptives."). "No Rx/OTC switch in history has attracted more attention than the switch of the emergency contraceptive, Plan B, from prescription to nonprescription status." *Id.* at 966.

158 *See* CLONING HUMAN BEINGS, *supra* note 115, at 5 ("Artificial insemination by donor, for example, was considered a form of adultery when first introduced in the 1940s. . . . When prenatal diagnosis was introduced in the late 1960s, the public simultaneously welcomed the opportunity to prevent lethal disease in newborns but worried about the use of such techniques

of embryo storage and disposition, inevitably involves the destruction of reproductive tissue.[159] Yet, part of the difference between these long-standing issues resultant from the use of conventional assisted reproductive technology and the ethical issues resultant from the use of advanced assisted reproductive technologies is that the implicit resolution of the ethical issues related to the use of AARTs differs from the regulatory treatment of the ethical issues presented by the use of conventional assisted reproductive technology: by not asserting any interest in regulating conventional forms of assisted reproduction or diagnostic techniques such as pre-implantation genetic diagnosis or in vitro fertilization, which are other techniques that can also contribute to the destruction of embryos, the FDA essentially left these ethical questions to individual states. Now, by comparison, however, the FDA is at least partially making a decision on ethics as it relates to advanced assisted reproductive technologies and targeting them for oversight, which is a change from the Agency's previous regulatory position.

B. *Germline Modification: Changing the "Shared" Human Identity*

Germline modification is an ethical issue not only for advanced assisted reproductive technologies, but also for genome editing through CRISPR-Cas9 and other technologies that permit genome editing.[160] Part of the discussion of this ethical issue centers on what even constitutes the "germline" or a "germline modification."[161] There is no uniform definition of the human germline.[162] "In place of [the term] germline, some prefer the term 'inheritable genetic modification.'"[163] Nonetheless, some of the ethical objection to modifying the germline comes from arguments related to kinship and the belief that a shared human germline unites humankind.[164]

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to select 'vanity' characteristics or nonmedical traits in offspring. The birth of Louise Brown, conceived via in vitro fertilization, in 1978 was another dramatic event, providing a new and controversial means to parenthood.").

159 *See* Ian Sample, *"Three-Parent" Babies Explained: What Are the Concerns and Are They Justified?*, GUARDIAN (Feb. 2, 2015, 10:56 AM), https://www.theguardian.com/science/2015/feb/02/three-parent-babies-explained; *see also* Paula Amato et al., *Three-Parent In Vitro Fertilization: Gene Replacement for the Prevention of Inherited Mitochondrial Diseases*, 101 FERTILITY & STERILITY 31 (2014).

160 *See* Callaway, *supra* note 23; *see also* Regalado, *supra* note 23.

161 *See* FRANKEL & HAGEN, *supra* note 31, at 4–6; discussion *supra* Part I.

162 *See* FRANKEL & HAGEN, *supra* note 31, at 1.

163 *Id.* at 5.

164 *See* MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at xiv (The Institute of Medicine noted that mitochondrial DNA "plays a central role in genetic ancestry, [although] traits that are carried in [nuclear] DNA are those that in the public understanding constitute

To the Institute of Medicine, which issued an FDA-commissioned report on mitochondrial transfer in 2016, there is a "clear line" in American policy addressing genetic modifications of humans and that clear line is between modifications that are heritable, such as those involving germline modification, and those that are not heritable.[165] In 2015, a posting on the White House blog by the White House Director of the Office of Science and Technology Policy, entitled *A Note on Genome Editing*, stated "[t]he Administration believes that altering the human germline for clinical purposes is a line that should not be crossed at this time."[166] However, some legal analyses differentiate between germline modifications to create "designer babies" and modifications to cure medical defects.[167] Other ethicists group all germline modifications together due to a fear that once one germline modification occurs, in order to treat disease, scientists will undertake subsequent modifications for nontherapeutic reasons.[168]

A more detailed inquiry may reveal that there is a difference to the American public between using assisted reproductive technology to have a child with blue eyes instead of brown eyes, for instance, and using assisted reproductive technology to prevent the passage of muscular dystrophy to future generations.[169] Currently, it is unclear

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the core of genetic relatedness . . . ."); *see also* WATTS ET AL., *supra* note 28, at 53, 83–84.

165 *See* MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 88.

166 John P. Holdren, *A Note on Genome Editing*, WHITE HOUSE BLOG (May 26, 2015, 10:40 AM), https://obamawhitehouse.archives.gov/blog/2015/05/26/note-genome-editing; *see also* FRANKEL & HAGEN, *supra* note 31, at 1 (Although there is no uniform definition of the germ line, Frankel and Hagen explain that "[t]he term 'germline' refers to genetic material that is hereditable from parent to child.").

167 *See* Robertson, *supra* note 16, at 216 ("The prospect of oocyte cytoplasm transfers thus requires rethinking the per se ban on germ-line alterations. The question posed is whether germ-line alterations are always unacceptable. Oocyte transfers suggest that this is not always the case. Such transfers appear to serve important family and procreative interests, and present little harm to offspring or others, once the safety and efficacy of the procedure is established. The fact that the needed therapeutic intervention affects mtDNA in the germ-line has no independent ethical significance (beyond the concerns that arise with egg donation). It will prevent mitochondrial disease in offspring, and female offspring will avoid the need to undergo similar procedures if they reproduce. Indeed, a blanket ban on germ-line effects strictly applied would condemn somatic cell therapies and many other disease treatments. Many of them affect the germ-line, albeit indirectly, by enabling persons who would not have survived or been able to reproduce to do so, thus assuring that genes of that particular germ-line will be passed on.").

168 *See id.* at 216–17; *see also* David Cyranoski, *Scientists Sound Alarm over DNA Editing of Human Embryos*, NATURE (Mar. 12, 2015), http://www.nature.com/news/scientists-sound-alarm-over-dna-editing-of-human-embryos-1.17110 ("Such research could be exploited for non-therapeutic modifications. . . . Many groups, including Urnov's company, are already using gene-editing tools to develop therapies that correct genetic defects in people (such as by editing white blood cells). They fear that attempts to produce 'designer babies' by applying the methods to embryos will create a backlash against all use of the technology. . . . But other scientists disagree with that stance. Although there needs to be a wide discussion of the safety and ethics of editing embryos and reproductive cells, they say, the potential to eliminate inherited diseases means that scientists should pursue research.").

169 While designer babies based on appearance are not a possibility with mitochondrial

whether the FDA has considered this viewpoint when analyzing the regulatory treatment of technologies that result in germline modifications or advanced assisted reproductive technologies. There is no way to know how clear the line between different types of modifications actually is without an accurate explanation of the science, public input, and transparent regulation.

In addition to defining the germline, related questions about inheritable modifications will surface in discussions of all medical techniques that modify the germline such as: "Why should it be ethical to pass on faulty DNA, but unethical to impart healthy DNA?"[170] If at some point we have the ability to prevent future generations from inheriting diseases, why shouldn't we do so? Would individuals who have defective mitochondria or genes feel a pressure to use scientific techniques to prevent the transmission of those genes to future children? What are the implications, from a disability perspective, of stating that certain traits are undesirable in future generations?[171] An open public discussion would allow for an informed discussion of our present scientific capabilities, imminent and likely future capabilities, and whether there is indeed a line that should not be crossed.

C. *Organ Transplantation as Opposed to Genetic Modification: An Alternative Perspective on Replacing Defective Cell Components*

It is possible that using mitochondrial transfer is more like an organ transplant than a genetic modification or a drug. For example, mitochondria have also been analogized to the "batteries in a cell," a metaphor that resurfaces in discussions of the scientific and ethical issues related to mitochondrial transfer.[172] Many view mitochondrial transfer as similar to "changing the batteries in a laptop . . . ."[173] Similarly, the U.K.'s Chief Medical Officer has compared mitochondrial

transfer, it is not a foregone conclusion that one day, mitochondria cannot be engineered to be "better" such that these energy processing aspects of the cell could be improved. *See* FRANKEL & HAGEN, *supra* note 31, at 7 ("'[g]ood mitochondrial DNA could facilitate athleticism, and reduce risk for obesity or diabetes,' . . . [therefore,] refinement of mitochondrial donation presents the possibility of a slippery slope from treatment of [mitochondrial]DNA disease to enhancement of normal energy production capabilities." (quoting Rob Waters, *Gene Mix in Monkeys Fixes Defect, Opens New Ethics Debate*, BLOOMBERG (Aug. 26, 2009), http://www.bloomberg.com/apps/news?ppid=2107001&sid=aMTU6ucOhbnw))).

170 Malik, *supra* note 39.

171 *See* Elizabeth F. Emens, *Framing Disability*, 2012 U. ILL. L. REV. 1383 (2012).

172 *See* OFFICE FOR PUB. MGMT., MEDICAL FRONTIERS: DEBATING MITOCHONDRIA REPLACEMENT: ANNEX 1: SUMMARY OF EVIDENCE 9 (2013) (reporting members of the public referring to mitochondria as laptop batteries); WATTS ET AL., *supra* note 28, at 18.

173 WATTS ET AL., *supra* note 28, at 78.

transfer to "changing a car battery . . . ."[174] Thus, in the United Kingdom where the government executed a five-strand "project" of public engagement in spite of media coverage sensationalizing mitochondrial transfer as "three-parent in vitro fertilization," many members of the U.K.'s public indicated that they viewed mitochondrial transfer as more similar to conventional organ or tissue donation (e.g., blood donation, liver transplant, etc.), than to a eugenics practice.[175]

A *New York Times* article provides a similar American perspective: "The best analogy for mitochondrial transfer is that of an organ transplant."[176] Doctors and scientists "play God . . . every day . . . [w]hether transplanting naturally faulty hearts, or delivering a baby by cesarean section when natural birth may be impossible or dangerous, the very essence of medicine is to right the wrongs of nature."[177] If the analogy to organ transplant were indeed apt, then perhaps the technique should be regulated as an organ transplant which would move it out of the jurisdiction of the U.S. Food and Drug Administration (assuming this agency was the proper regulator in the first place), and into the jurisdiction of another agency within the U.S. Department of Health and Human Services: the Health Resources and Services Administration.[178] To have information on how many American scientists and members of the public share this view would be helpful to policymakers, lawmakers, and regulated entities.

IV. A RANGE OF REGULATORY OPTIONS

There are a number of ways to regulate advanced assisted reproductive technologies, and ultimately this Article argues that advanced assisted reproductive technologies should be subject to the same minimal regulation as other forms of assisted reproductive technology. The range of regulatory options includes: (1) maintaining

174 Sarah Knapton, *Three Parent Babies: Britain Has Breached EU Law, MEPs Warn*, TELEGRAPH (Feb. 21, 2015, 6:00 AM), http://www.telegraph.co.uk/news/11425602/Three-parent-babies-Britain-has-breached-EU-law-MEPs-warn.html.

175 *See* WATTS ET AL., *supra* note 28, at 72, 78; discussion *infra* Part IV; *see also* Hannah Darby, *Mitochondrial Replacement Consultation: Advice to Government* 24 (Human Fertilisation & Embryology Authority, Paper No. HFEA (20/03/13) 665, 2013) (providing the recommendation of the U.K.'s HFEA that "mitochondria donors should have a similar status to that of tissue donors," which means that "[c]hildren born of mitochondria replacement should not have a right to access identifying information about the donor when they reach the age of 18").

176 Malik, *supra* note 39.

177 *Id.*

178 *About Us*, ORGANDONOR.GOV, http://www.organdonor.gov/about-dot.html (last visited Mar. 3, 2018). For statutory provisions governing organ transplantation, see 42 U.S.C. §§ 273–74g (2012).

the status quo, which means the continuance of subterranean regulation; (2) modifying the status quo so as to ameliorate one or more of the features that render the FDA's regulation of advanced assisted reproductive technology subterranean; and (3) returning the state of regulation to that which existed before July 6, 2001. This Article advocates for option three, returning the state of regulation to that which existed before the FDA issued its letters on July 6, 2001. Option three would be a state-based approach to the regulation of advanced assisted reproductive technologies without the additional federal regulation that has been unique to advanced assisted reproductive technologies.

Under option one, maintaining the status quo, the FDA would continue to regulate advanced assisted reproductive technologies in a subterranean manner and nothing would change. Under this approach, advanced assisted reproductive technologies (and cloning) would continue to be illegal in the United States as a result of subterranean regulation. New technologies would continue to be hindered by such a regime. For example, in 2013 the FDA sent a letter to OvaScience, a Massachusetts-based company, stating that the company needed to submit an investigational new drug application in order to continue its work on "Augment," a technology that uses a woman's own mitochondria to revitalize her eggs which are then used in in vitro fertilization.[179] This FDA letter, obtained through FOIA Request 2016-4882 stated, on the subject of "more than minimal manipulation":

> Our understanding is that your autologous mitochondrial transfer product, AUGMENT, consists of cells isolated from a biopsy of ovarian tissue, which are processed to extract mitochondria that are then introduced into other reproductive tissues during the IVF process. The removal of mitochondria and introduction into other reproductive tissue appears to be more than minimal manipulation. This is based on the limited information available; please note that the addition of mitochondrial DNA to other reproductive tissue may raise additional regulatory concerns.[180]

I learned of this letter based on media accounts and court documents related to a shareholder lawsuit which cited to the FDA's letter. I was only able to confirm the content of this letter through a FOIA request that resulted in the transmission of a copy of the letter along with accompanying additional documents.[181] In one of those accompanying documents, representatives of the company inquired as

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179 *See* Letter from Celia M. Witten to Alison Lawton, *supra* note 7; *see also* Press Release, OvaScience, First Baby Born with OvaScience's AUGMENT Fertility Treatment (May 7, 2015), http://ir.ovascience.com/phoenix.zhtml?c=251343&p=irol-newsArticle&ID=2045382.

180 Letter from Celia M. Witten to Alison Lawton, *supra* note 7.

181 *See id.*

to whether the letter would be

> made publicly available and whether FDA intends to issue other letters. Dr. Witten stated that there are no plans to post the September 6, 2013 letter; however, she noted that should FDA receive a FOIA request, FDA would be required to comply with the disclosure rules and she does not know what the outcome of such a request would be. In response to the latter question, Dr. Witten stated that she cannot comment on what might happen in the future.[182]

Thus, as recently as 2013, the FDA was continuing to regulate nonconventional forms of assisted reproductive technology in a subterranean manner.[183] If the FDA continues to regulate advanced assisted reproductive technologies in this manner, then other scientists may be prevented from providing access to various assisted reproductive technology techniques in the United States. Furthermore, if the FDA's regulation is driven by opposition to genetic modification, then other developing technologies that use genetic modification as a method of medical treatment, such as CRISPR-Cas9 or germline editing, may also be hindered by subterranean regulation.

Option two, would involve the FDA continuing to regulate advanced assisted reproductive technologies but with increased transparency and clarity. In other words, the Agency would regulate in a less subterranean fashion. After years of regulating via letter without a legal challenge, the Agency might continue regulating advanced assisted reproductive technologies in a subterranean manner unless stakeholders successfully petition Congress for clearer legislation; Congress mandates that the Agency stop regulating AARTs; or researchers ignore the FDA's letters and successfully litigate against the Agency in an enforcement action.[184] Thus, the FDA could wait for mandatory external direction

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182 *Id.*; Telephone Conference with Rachael Anatol & Celia Witten, U.S. Food & Drug Admin., and Michelle Dipp & Allison Lawton, OvaScience Inc., *supra* note 17.

183 *Id.*; *see* Letter from Mary A. Malarkey to John Zhang, *supra* note 138. The most recent 2017 letter to a provider of three-parent in vitro fertilization was cited to in the *Washington Post* and by numerous news outlets. *See* Cha, *supra* note 7.

184 *See* Wu, *supra* note 19, at 1850 (noting that "by the 1990s, the Commodity Futures Trading Commission had begun to think that oversight of certain derivatives products might be necessary[, b]ut Congress barred regulation based on industry arguments that, among other reasons, the rapidly changing nature of the industry made regulation ill-advised" (citing Gary Gensler, *History of Derivatives Regulation, Culprit OTCs*, COMMODITYONLINE (2010))). "But it is also critical to remember that… [i]n most circumstances a party unhappy . . . can challenge the [agency] threat by ignoring it . . . . *Id.* at 1853; *see also* K.M. Lewis, *Informal Guidance and the FDA*, 66 FOOD & DRUG L.J. 507, 542 (2011) ("Likewise, unlike regulations promulgated through notice-and-comment rulemaking, obtaining judicial review of guidance documents is quite difficult due to the finality and ripeness doctrines."). Another solution, which would apply not only to the FDA but administrative agencies in general, would be "immediate review of nonlegislative rules under the Administrative Procedure Act (APA) . . . ." Mark Seidenfeld, *Substituting Substantive for Procedural Review of Guidance Documents*, 90 TEX. L. REV. 331, 333

from Congress or the judiciary that would result in the Agency regulating more transparently and with a clearer legal foundation, or the FDA could develop and implement its own transparent best practices sua sponte or in response to a citizen petition.[185] Thus, one way to improve transparency and clarity would be for the FDA to clearly explain the regulatory foundation of the letters sent to AART-providers.

The National Academy of Science's Institute of Medicine noted that foreign data could aid the FDA's assessment of the advantages and disadvantages of mitochondrial replacement therapy.[186] The FDA should not only examine the scientific data provided by foreign sources, such as scientists in the United Kingdom, but it should also consider the United Kingdom's process for approving mitochondrial transfer which included parliamentary briefings and clear explanations of the science underlying the technology as a part of the country's extensive public consultation.[187] In the United Kingdom, where human trials related to mitochondrial transfer have begun, public consultations revealed that "[t]hose in favour of the [mitochondrial transfer] techniques felt either that the only implication of changing the germ line is the removal of terrible disease from a family, that the germ line would be changed for the better, or that any negative implications would be outweighed by the positive ones."[188] While it is helpful to have the views of another advanced Western nation's view on the subject, it is critical that there be a method to obtain the views of the American public on the many issues that arise as a result of advanced assisted reproductive technologies and scientific innovations that may affect the human germline such as CRISPR-Cas9, especially if perspectives on these ethical issues will continue to impact federal regulatory decisions.

The FDA, while referred to as an "agency" is, like all organizations, composed of individuals. If the FDA continues to incorporate ethical views into regulatory decisions, then it should at least be aware of a broad spectrum of ethical views and not just the views of its employees. In the United Kingdom, the agency that wrote the draft regulations on mitochondrial transfer that were approved by Parliament recommended

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(2011).

185 *See Warning and Untitled Letters*, *supra* note 4 ("As a result of the Agency's Transparency Initiative, the Centers are working to disclose more Untitled Letters on FDA's website. The Agency believes that posting additional Untitled Letters may increase public accountability of firms, which may deter future violations and increase compliance with the law. However, due to limited resources, the Agency is not able to post all Untitled Letters at this time."). For more on citizens' petitions, see 21 C.F.R. § 10.30 (2017). *See generally* Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249 (2012).

186 *See* MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 4–12, 15.

187 *See* Darby, *supra* note 175; *see also* PREVENTING MITOCHONDRIAL DISEASE, *supra* note 12.

188 Darby, *supra* note 175, at 16.

and executed a five-strand "project" of public engagement which included deliberative public workshops, a public representative survey, an open consultation questionnaire, open consultation meetings, and a patient focus group.[189] Following the lead of the United Kingdom, which approved the clinical use of mitochondrial transfer after public discussion, the FDA should solicit public input on the ethical issues resultant from mitochondrial transfer and other advanced assisted reproductive technologies. The FDA should also aim to not only gain insights from the public about advanced assisted reproductive technologies, but also to clearly inform the public of the scientific, legal, and ethical issues that accompany the clinical use of advanced assisted reproductive technologies. The example of the United Kingdom also raises the possibility that a more appropriate governmental structure could be to have one designated federal agency that addresses all issues related to human reproduction. However, politics in the United Kingdom and the United States vary significantly, and such an agency that concentrates on health-related decision-making would likely be unwanted in the United States which also does not have a National Health Service like the United Kingdom does.[190]

The National Academy of Science's Institute of Medicine solicited public comments on ethical issues related to mitochondrial transfer to aid in the preparation of its 2016 report.[191] These comments addressed issues such as "the ethics of heritable genetic modification . . . , patient perspectives, the role of religion, and how to conduct an ethically acceptable investigation of [mitochondrial transfer]."[192] "Notice and comment" is a well-known and crucial part of federal agency rulemaking.[193] While the FDA did solicit comments on its human tissue regulations, after years of not regulating reproductive medicine, it could have been unclear to many observers that these regulations would apply to human reproductive tissue. Similarly, at the time that the human tissue regulations were promulgated, mitochondrial transfer had not received the news coverage that it has today. In other words, there was no mitochondrial transfer technology available to save human lives in 2001.

At a minimum, if the FDA is going to continue regulating advanced assisted reproductive technologies based not only on science but also certain ethical views, then it should use the Federal Register and media contacts to clearly solicit public comments with a specific focus

189 *See* PREVENTING MITOCHONDRIAL DISEASE, *supra* note 12; Darby, *supra* note 175.

190 *See About the National Health Service (NHS)*, NHS, http://www.nhs.uk/NHSEngland/thenhs/about/Pages/overview.aspx (last updated Apr. 13, 2016).

191 MITOCHONDRIAL REPLACEMENT TECHNIQUES, *supra* note 29, at 1–3.

192 *Id.* at 3.

193 *See* 5 U.S.C. § 553 (2012).

on the ethical issues related to the use of advanced assisted reproductive technologies. Public comment often involves the use of an online website, such as regulations.gov, so that members of the public can provide their comments to the agency in addition to public meetings. If the FDA continues to regulate AARTs, then unlike the promulgation of its human tissue regulations where the FDA had one public meeting related to human bone grafts, the FDA should schedule many public meetings related to the regulation of AARTs where FDA employees and technical experts would not only solicit public comments but also clearly explain the science underlying advanced assisted reproductive technologies. The FDA should not only hold these meetings in person, but it should also use web-based technology to allow more members of the public to not only gain more information about advanced assisted reproductive technologies, but also to provide their comments.[194] Furthermore, those public comments should focus on the appropriateness of continuing to regulate AARTs based on the concept of "minimal manipulation" or "more than minimal manipulation."

Once an application has been submitted to the FDA, it is too late to discuss ethical issues due not only to the Agency's decision-making process, but also to the way the Agency has structured its regulations on data and application confidentiality.[195] The FDA's regulations are so restrictive that the Agency will not confirm or deny whether an entity has submitted an investigational new drug application (unless that company has publicly acknowledged its application).[196] Thus, there is no public announcement that the FDA is even considering an application that could be impacted by ethical concerns or a bias against genetic modifications. Similarly, as noted above in the Introduction, the FDA does not maintain a complete publicly available database of the Untitled Letters and their addressees.

It is not impossible for the FDA to regulate clearly and transparently. Other agencies that contend with not only proprietary information, but also national security concerns, are able to conduct public meetings around the country where members of the public

194 *See* OFFICE OF THE FED. REGISTER, A GUIDE TO THE RULEMAKING PROCESS, https://www.federalregister.gov/uploads/2011/01/the_rulemaking_process.pdf ("During the comment period, an agency may also hold public hearings where people can make statements and submit data. Some agencies operate under laws that require rulemaking hearings. Others may hold public meetings to collect more information or to help affected groups get a better understanding of the proposed rule. Many agencies are beginning to use webcasts and interactive Internet sessions to broaden the audience attending public meetings.").

195 *See* 21 C.F.R. §§ 601.50–.51 (2018).

196 *Id.*; *see also* 21 C.F.R. § 312.50 (2016) (explaining that a "sponsor" has a specific meaning to the Agency that signifies that an individual or entity has a pending investigational new drug application before the FDA). Due to the operation of the Agency's confidentiality regulations and record-keeping practices, it is not possible for the public to obtain an accurate count of how many letters like the July 6, 2001 letter have been issued.

express their views on licensing actions and maintain comprehensive databases of the agency's public documents. For example, the U.S. Nuclear Regulatory Commission (NRC) has managed to provide online public access to the "730,000 full-text documents that the NRC has released since November 1, 1999, and several hundred new documents are added each day."[197] These available documents include documents that are not part of licensing dockets and public documents that are part of licensing dockets (even those license applications that are pending). The U.S. NRC's recordkeeping process enables it to provide public access to any array of documents in addition to screening those dockets for national security information and proprietary information.[198] The FDA's system for responding to FOIA requests reveals that the FDA is similarly capable of redacting proprietary information before providing it to the public.

Option three, which I ultimately argue for, is one in which the FDA does not regulate advanced assisted reproductive technologies at all. Instead, individual states, if they wish, should enact legislation related to the legality of AARTs, as states already do with other issues related to scientific research and family law such as cloning and the legality of surrogacy contracts.[199] States may face the same difficulty in examining ethical issues or be similarly constrained by political concerns or misinformation as the federal government; however, the benefit of a state-based approach is that there are multiple opportunities (e.g., fifty) to examine the ethical and scientific concerns underlying advanced assisted reproductive technologies, even though such an approach may lead to a domestic form of "reproductive tourism" or forum shopping.[200]

Another possible modus operandi for the third option would be that doctors simply regulate themselves; in spite of this possibility, and

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197 *ADAMS Public Documents*, U.S. NUCLEAR REG. COMM'N, http://www.nrc.gov/reading-rm/adams.html (last updated Aug. 9, 2017). The FDA has an "Electronic Reading Room"; however, that reading room is a website, which provides links to the various centers of the FDA, which is not easily searchable. *See Electronic Reading Room*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/foi/ElectronicReadingRoom/default.htm (last updated Mar. 6, 2017). The Electronic Reading Room is also a part of the Agency's FOIA requirements and not an attempt to provide public access to all publicly accessible documents. *See Freedom of Information*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/FOI (last updated Sept. 27, 2016) ("The 1996 amendments to the Freedom of Information Act (FOIA) mandate publicly accessible 'electronic reading rooms' with agency FOIA response materials and other information routinely available to the public, with electronic search and indexing features.").

198 *See Information Security*, U.S. NUCLEAR REG. COMM'N, http://www.nrc.gov/security/info-security.html (last updated Aug. 11, 2017).

199 *See* Gaia Bernstein, *Unintended Consequences: Prohibitions on Gamete Donor Anonymity and the Fragile Practice of Surrogacy*, 10 IND. HEALTH L. REV. 291, 296 (2013); Symposium, *Cloning Californians? Report of the California Advisory Committee on Human Cloning*, 53 HASTINGS L.J. 1143 (2002).

200 For more on reproductive tourism or the broader concept of "medical tourism," see I. Glenn Cohen, *Circumvention Tourism*, 97 CORNELL L. REV. 1309 (2012).

in light of past well-known instances of physicians and researchers failing to adhere to ethical guidelines for human subjects research or general medical norms, I still advocate for some state oversight, however minimal.[201] It is possible that this framework already exists through state statutes addressing research and informed consent; thus, the state-based regulation of AARTs does not necessarily require the enactment of additional regulations specific to AARTs. While there are some disadvantages to a state-based regulatory approach, those disadvantages do not outweigh the advantages of a state-based approach, which would still provide for informed consent and other patient protections.[202]

There are several reasons why the FDA should not regulate AARTs. First, it is likely that the FDA does not have jurisdiction over advanced assisted reproductive technologies at all. This characterization stems not only from confusion over whether federal statutory provisions apply to advanced assisted reproductive technologies, but also from the fact that advanced assisted reproductive technologies do not fall within the usual categories regulated by the FDA: food, drugs, medical devices, and biologics.[203] Second, even if the Agency does have jurisdiction over advanced assisted reproductive technologies, the process of asserting jurisdiction has been marked by uncertainty, opacity, and counterintuitive regulations.[204] Thus, even if the FDA has jurisdiction over AARTs, the Agency's current regulatory approach of treating AARTs like drugs or biologics does not adequately consider their accompanying legal and ethical issues and the impact of the FDA's

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201 *See, e.g.*, *The Tuskegee Timeline*, CENTERS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/tuskegee/timeline.htm (last updated Aug. 30, 2017) ("In July 1972, an Associated Press story about the Tuskegee Study caused a public outcry that led the Assistant Secretary for Health and Scientific Affairs to appoint an Ad Hoc Advisory Panel to review the study. The panel had nine members from the fields of medicine, law, religion, labor, education, health administration, and public affairs. The panel found that the men had agreed freely to be examined and treated. However, there was no evidence that researchers had informed them of the study or its real purpose. In fact, the men had been misled and had not been given all the facts required to provide informed consent. The men were never given adequate treatment for their disease. Even when penicillin became the drug of choice for syphilis in 1947, researchers did not offer it to the subjects. The advisory panel found nothing to show that subjects were ever given the choice of quitting the study, even when this new, highly effective treatment became widely used."); *see also* Dale Keiger, *Immortal Cells, Enduring Issues*, JOHNS HOPKINS MAGAZINE (June 2, 2010), http://archive.magazine.jhu.edu/2010/06/immortal-cells-enduring-issues (reviewing Rebecca Skloot's *The Immortal Life of Henrietta Lacks*: "Text on the front cover of Skloot's book reads, 'Doctors took her cells without asking.' The inside flap continues, 'Henrietta's family did not learn of her "immortality" until more than 20 years after her death, when scientists investigating HeLa began using her husband and children in research without informed consent. And though the cells had launched a multimillion-dollar industry that sells human biological materials, her family never saw any of the profits.' A significant segment of the public harbors a deeply rooted mistrust of medical research.").

202 *See* Jessica De Bord, *Informed Consent*, UNIV. WASH. SCH. MED., https://ashin.washington.edu/bioethx/topics/consent.html (last updated Mar. 7, 2014).

203 *See What Does FDA Regulate?*, *supra* note 22.

204 *See supra* Part II; *infra* Appendix A.

extant regulatory structure on scientific innovation, reproductive rights, and medical ethics. Under the current regulatory structure, the FDA is able to inject ethical concerns into a regulatory procedure that should focus on safety and efficacy and not the ethical views of a select number of federal employees.

By not subjecting advanced assisted reproductive technologies to additional regulations, advanced assisted reproductive technologies would be subject to the same regulatory regime that they were subject to before July 6, 2001 (the date on which the FDA sent letters to physicians providing cytoplasmic transfer to patients in the United States). Under this regime, advanced assisted reproductive technologies would be regulated in the same manner as conventional assisted reproductive technologies. Thus, advanced assisted reproductive technologies would be subject to the standard ethical norms of medical practice and scientific research, including informed consent. The statements of physicians at the FDA's 2002 Advisory Committee meeting indicates that physicians had already incorporated these concerns into the consent forms provided to patients who were undergoing cytoplasmic transfer. In sum, I argue for a regulatory regime in which advanced assisted reproductive technologies are not subject to subterranean regulation or any other sort of unique federal regulation.

CONCLUSION

The field of assisted reproductive technology has generated controversy since its inception.[205] When in vitro fertilization was first introduced, there was much opposition to the technique.[206] Nevertheless, today it is generally accepted ethically and legally in the United States, United Kingdom, and many other countries.[207] Mitochondrial transfer faces the same public hurdles as in vitro fertilization did in the 1970s and 1980s, in addition to additional ethical

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205 *See* CLONING HUMAN BEINGS, *supra* note 115, at 5 ("Artificial insemination by donor, for example, was considered a form of adultery when first introduced in the 1940s. . . . When prenatal diagnosis was introduced in the late 1960s, the public simultaneously welcomed the opportunity to prevent lethal disease in newborns but worried about the use of such techniques to select 'vanity' characteristics or nonmedical traits in offspring. The birth of Louise Brown, conceived via *in vitro* fertilization, in 1978 was another dramatic event, providing a new and controversial means to parenthood.").

206 *See* Connor, *supra* note 12.

207 *See* Press Release, Nobel Assembly at Karolinska Institutet, The Nobel Prize in Physiology or Medicine 2010 to Robert G. Edwards for the Development of In Vitro Fertilization (Oct. 4, 2010), https://www.nobelprize.org/nobel_prizes/medicine/laureates/2010/press.html.

hurdles related to eugenics, cloning, and germline modification.[208] CRISPR-Cas9 and other methods of gene editing will also face these public hurdles in addition to the barriers presented by subterranean regulation.

The FDA has been regulating cloning and advanced assisted reproductive technologies through letters for over twenty years, although it has never provided proof of jurisdiction. To regulate in a subterranean fashion can deter research and American patients' access to life-saving techniques. Because the FDA's interpretation of what it can regulate is contrary to researchers' and attorneys' understanding of what the FDA regulates, these letters surprise researchers by essentially asserting that their AART research protocols, which would generally not be regulated by the FDA, are essentially the same as drugs. The letters sent by the FDA to researchers do not threaten enforcement action but act as a de facto barrier to research and the clinical use of AARTs, as these letters represent an agency statement that an individual or entity is violating federal law.

In addition to regulating through letters, the FDA has structured its confidentiality regulations and recordkeeping system in a way that prevents the public from easily finding the letters that it issues to AART providers. Additionally, the Agency has promulgated regulations that make it such that if the Agency is not currently considering an application for premarket approval, then there is no docket available to the public and certainly no public access to a docket when there is an application pending. However, if the Agency is regulating through subterranean actions that have the effect of regulation, then the public needs to at least be aware of those Agency actions, and the evidence of those actions should be easily searchable. Furthermore, whether the FDA believes that advanced assisted reproductive technologies are analogous to biologics or drugs (or actually are biologics or drugs), it should be clear to the public how the FDA categorizes these technologies and why.[209]

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208 *See* Bazian, *Thousands of UK Women Could Benefit from "Three-Person" IVF*, NHS CHOICES (Jan. 29, 2015), http://www.nhs.uk/news/2015/01January/Pages/Thousands-of-UK-women-could-benefit-from-three-person-IVF.aspx; *Interview: Dr. Jamie Grifo*, PBS , http://www.pbs.org/wgbh/pages/frontline/shows/fertility/interviews/grifo.html (last visited Mar. 4, 2018); Connor, *supra* note 12; *see also* Bazian, *Draft Regulations on "Three-Parent" IVF Published*, NHS CHOICES (Feb. 28, 2014), http://www.nhs.uk/news/2014/02February/Pages/Draft-regulations-on-three-parent-IVF-published.aspx ("Opponents of these types of treatments [such as mitochondrial transfer and the use of assisted reproductive technology] cite what can be broadly summarised as the 'slippery slope' argument; this suggests that once a precedent has been set for altering the genetic material of an embryo prior to implantation in the womb, it is impossible to predict how these types of techniques might be used in the future. Similar concerns were raised, however, when IVF treatments were first used during the 1970s; today, IVF is generally accepted."); Press Release, Nobel Assembly at Karolinska Institutet, *supra* note 207.

209 Both Investigational New Drug Applications and Biologics License Applications involve

The current regulatory environment also deprives the public of a clear understanding of how the multitude of ethical and legal issues resultant from the clinical use of advanced assisted reproductive technologies are incorporated into legal regulation. The increase in the number of regulations applicable to human reproductive tissue has not corresponded with a clearly articulated understanding of how the FDA has jurisdiction over advanced assisted reproductive technologies. Currently, there is no baseline in the United States for understanding what the general consensus might be on the ethical issues related to these techniques, as an informed and national discussion of these ethical issues has not occurred. Instead, individual ethical issues, such as embryo destruction, continue to arise in the context of regulatory decisions; however, the issues are never comprehensively addressed, nor is their impact on regulatory decision-making clearly identifiable. Furthermore, to include reproductive tissues in regulations affecting all human tissue inadequately considers the unique nature of human reproductive tissue. The regulation of human reproductive tissue and reproduction in general gives rise to a number of concerns including legal concerns related to reproductive rights. Thus, not only is clear decision-making a best practice for federal agencies, but it is crucial when federal agency decisions may somehow impact reproductive rights.

APPENDIX A: LETTER TO SPONSORS / RESEARCHERS—HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL BY MEANS OTHER THAN THE UNION OF GAMETE NUCLEI

Department of Health and Human Services[210]
Public Health Service
Food and Drug Administration

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the same form; however, the applications are reviewed by different FDA staff, and different statutes govern the approval of each. *See Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm (last updated July 7, 2015) ("Whereas a new drug application (NDA) is used for drugs subject to the drug approval provisions of the FDC Act, a biologics license application (BLA) is required for biological products subject to licensure under the PHS Act. FDA form 356h is used for both NDA and BLA submissions. FDA approval to market a biologic is granted by issuance of a biologics license."); *see also* DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., FORM FDA 356H, APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE (2017), http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

210 Letter from Kathryn C. Zoon, Dir., Ctr. for Biologics Evaluation & Research, U.S. Food & Drug Admin., to Sponsors/Researchers (July 6, 2001), http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm.

1401 Rockville Pike
Rockville, MD 20852-1448

July 6, 2001

Dear Sponsor / Researcher:

We want to advise you that the Food and Drug Administration (FDA) has jurisdiction over human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei.

Examples of such genetic material include, but are not limited to:

- cell nuclei (e.g., for cloning),
- oocyte nuclei,
- ooplasm, which contains mitochondrial genetic material, and
- genetic material contained in a genetic vector, transferred into gametes or other cells.

The use of such genetically manipulated cells (and/or their derivatives) in humans constitutes a clinical investigation and requires submission of an Investigational New Drug application (IND) to FDA. We wish to inform you of the FDA regulatory process governing clinical investigations, which includes requirements applicable to manufacturing processes, the study of the safety and efficacy of such cells, and the protection of human participants in such studies. We can advise you whether or not your activities require submission of an IND. If what you are doing or plan to do does require an IND, we would be pleased to provide you with information and guidance regarding filing such an application.

FDA's regulations on investigational new drugs, including those for the submission and review of an IND are described in Title 21 of the Code of Federal Regulations (CFR), Parts 50, 56, and 312. The agency has provided notice of the applicability of these requirements to cellular and tissue-based products in many public forums and in various published documents available at http://www.fda.gov/cber, including the following:

- A Federal Register (FR) notice describing FDA's authority over cell and gene therapy products ("Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products," October 14, 1993, 58 FR 53248) (PDF - 489 KB).
- A comprehensive regulatory program for the regulation of human cellular and tissue-based products, based on a tiered, risk-based assessment ("A Proposed Approach to the

Regulation of Cellular and Tissue-Based Products," March 4, 1997, 62 FR 9721).

- A final rule that establishes the criteria for regulation of human cells, tissues, and cellular and tissue based products (HCT/Ps), including reproductive cells and tissues, published on January 19, 2001 (66 FR 5447). This rule also describes which HCT/Ps will be regulated solely under 21 CFR Part 1271, the regulations to prevent communicable disease transmission authorized by section 361 of the Public Health Service Act. HCT/Ps that do not meet the criteria under Part 1271 will be regulated as biological products, drugs, or devices under section 351 of the Public Health Service Act and/or the Food Drug and Cosmetic Act.
- "Suitability Determination for Donors of Human Cellular and Tissue-Based Products; Proposed Rule." September 30, 1999 (64 FR 52696).
- "Current Good Tissue Practice for Manufacture of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule" January 8, 2001 (66 FR 1508).

If you are unable to access the internet to obtain information on submitting an IND to the FDA, please call or write and we'll supply you with the needed information:

Center for Biologics Evaluation and Research
Office of Communication, Training & Manufacturers Assistance
Manufacturers Assistance and Technical Training Branch
1401 Rockville Pike, HFM-44
Rockville, MD 20852-1448
800-835-4709 or 301-827-1800
matt@cber.fda.gov

The specific information required in an IND will depend upon the cells under investigation and on the phase of study. For assistance in determining whether you need to file an IND submission and in preparation of a submission, please contact Wendy Aaronson, Application Administration Branch Chief, Division of Application Review and Policy, at 301-827-5101.
Sincerely,
—signature—

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation and Research
Food and Drug Administration

APPENDIX B: LETTER ABOUT HUMAN CLONING

October 26, 1998[211]
Dear Colleague:

The purpose of this letter is to confirm to institutional review boards (IRBs) that the Food and Drug Administration (FDA) has jurisdiction over clinical research using cloning technology to create a human being, and to inform IRBs of the FDA regulatory process that is required before any investigator can proceed with such a clinical investigation. This letter is being sent to IRBs at this time because of reports in the media that scientists are contemplating the use of cloning technology to create human beings. As described more fully below, the appropriate mechanism to pursue a clinical investigation using cloning technology is the submission of an investigational new drug application (IND) to FDA.

Clinical research using cloning technology to create a human being is subject to FDA regulation under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. Under these statutes and FDA's implementing regulations, before such research may begin, the sponsor of the research is required to submit to FDA an IND describing the proposed research plan; to obtain authorization from a properly constituted and functioning IRB; and to obtain a commitment from the investigators to obtain informed consent from all human subjects of the research. Such research may proceed only when an IND is in effect. Since FDA believes that there are major unresolved safety questions pertaining to the use of cloning technology to create a human being, until those questions are appropriately addressed in the IND, FDA would not permit any such investigation to proceed.

FDA may prohibit a sponsor from conducting a study proposed in an IND application (often referred to as placing the study on "clinical hold") for a variety of reasons. If the Agency finds that "human subjects are or would be exposed to an unreasonable and significant risk of illness or injury," that would be sufficient reason to put a study on clinical hold. Other reasons listed in the regulations include "the IND does not contain sufficient information required . . . to address the risks to subjects of the proposed studies," or "the clinical investigators . . . are not qualified by reason of their scientific training and experience to conduct the investigation."

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211 Nightingale, *supra* note 72.

The procedures and requirements governing the use of investigational new drugs, including those for the submission and review of INDs, are set forth in Title 21 of the Code of Federal Regulations (CFR), Part 312. Additional responsibilities of the sponsor of an IND include: selecting qualified investigators and overseeing the conduct of the investigators; ensuring that the investigations are performed in accordance with the protocols of the IND; submitting adverse experience reports and annual reports; and other duties as outlined in the regulations. The responsibilities of an investigator include: ensuring that the study is conducted in accordance with the protocols; obtaining informed consent from study subjects; and ensuring that an IRB that complies with the requirements of 21 CFR Part 56 reviews and approves the proposed clinical study and the informed consent form and procedures for obtaining informed consent, among other requirements specified in the regulations. IRBs and clinical investigators may obtain a copy of the current "Information Sheets for IRBs and Clinical Investigators" by contacting FDA's Office of Health Affairs (301-827-1685), through the world wide web (http://www.fda.gov/oha/IRB/toc.html*) or through a Fax-on-demand system (1-800-993-0098).

We hope the above information is useful to you. Please feel free to share this information with others at your institution.
Sincerely yours,

/s/
Stuart L. Nightingale, M.D.
Associate Commissioner

APPENDIX C: UNTITLED LETTER (BIOLOGIC)

March 12, 2015[212]

VIA FACSIMILE AND UPS (UNITED PARCEL SERVICE)

Samuel Simons
Regulatory Manager
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450

Re: Flublok (Influenza Vaccine)

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212 Letter from Robert A. Sausville to Samuel Simons, *supra* note 65.

BLA STN# 125285

Dear Mr. Simons:

The Advertising and Promotional Labeling Branch (APLB) at the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) has reviewed the video interview with CEO Dr. Manon Cox, entitled 'Watch us on Lifetime – The Balancing Act,' that is posted on the website www.flublok.com by your company, Protein Sciences Corporation (Protein Sciences). This promotional material is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and implementing regulations because it overstates the efficacy of Flublok (Influenza Vaccine) and omits the risks associated with Flublok. Therefore, this material misbrands Flublok under sections 502(a) and 201(n) of the Act, 21 U.S.C. § 352(a) and § 321(n), and FDA implementing regulations, *Cf.* 21 CFR 202.1(e)(6)(i) and (e)(7)(viii).

Background

According to the FDA-approved prescribing information (PI), Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 years of age and older.

The Warnings and Precautions section of the PI includes, but is not limited to, the following risks:

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Flubok.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks.

Vaccination with Flublok may not protect all vaccine recipients.

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The Adverse Reactions section includes, but is not limited to, the following:

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (15%), fatigue (15%)

and muscle pain (11%).

In adults 50 through 64 years of age, the most common (≥10%) injection site reaction was pain (32%); the most common (≥10%) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%).

In adults 65 years of age and older, the most common (≥10%) injection site reaction was pain (19%); the most common (≥10%) solicited systemic adverse reactions were fatigue (13%) and headache (10%).

Misleading Efficacy Claim

Promotional materials are misleading if they represent or suggest that a product is more effective than has been demonstrated by substantial evidence or substantial clinical experience. Your video, entitled 'Watch us on Lifetime – The Balancing Act,' presents an interview with Dr. Cox in which she states that Protein Sciences *'is able to put three times more protein in there, so it is also a high dose vaccine. More protein means your body will form more antibodies that will help you fight the flu.'* This claim misleadingly implies that the higher antigen content of Flublok translates into greater protection. Currently, there is only one licensed high-dose influenza vaccine, which is indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FDA is unaware of any adequate and well-controlled clinical trials that substantiate this claim for your product. Furthermore, in our October 20, 2014 letter to Protein Sciences on this issue, we provided advisory comments regarding the misleading implication of this claim. We reiterated our comments in a teleconference with Dr. Manon Cox on November 10, 2014.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Specifically, the video presents multiple efficacy claims for Flublok, such as '*helps you fight the flu,*' but fails to present any important safety information from the PI.

Conclusion and Requested Actions

For the reasons discussed above, your promotional material misbrands Flublok under sections 502(a) and 201(n) of the Act, 21 U.S.C. § 352(a) and § 321(n), and FDA implementing regulations, *Cf.* 21 CFR 202.1(e)(6)(i) and (e)(7)(viii).

We request that Protein Sciences immediately cease the dissemination of this violative promotional material for Flublok, as well as promotional materials with the same or similar claims and representations. Please submit a written response within ten (10) business days of the

Page 3 – STN 125285

date of this letter, stating whether you intend to comply with this request, listing all violative promotional materials for Flublok and explaining your plan for discontinuing use of such materials. Please direct your response to Lisa Stockbridge, Ph.D., Branch Chief at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, Division of Case Management, Advertising and Promotional Labeling Branch, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002. In all future correspondence regarding this matter, please refer to the BLA/STN number. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Flublok comply with each applicable requirement of the Act and FDA implementing regulations.

If you choose to revise your promotional materials, APLB is willing to assist you in assuring that your revised materials comply with applicable provisions of the Act by reviewing your revisions before you use them in promotion.

Sincerely,
Robert A. Sausville
Director, Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

APPENDIX D: WARNING LETTER ISSUED TO 23ANDME, INC.

Nov 22, 2013[213]

Ann Wojcicki
CEO
23andMe, Inc.
1390 Shoreline Way
Mountain View, CA 94043

Document Number: GEN1300666
Re: Personal Genome Service (PGS)

WARNING LETTER

Dear Ms. Wojcicki,

The Food and Drug Administration (FDA) is sending you this letter because you are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act).

This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. 321(h), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your company's website at www.23andme.com/health (most recently viewed on November 6, 2013) markets the PGS for providing "health reports on 254 diseases and conditions," including categories such as "carrier status," "health risks," and "drug response," and specifically as a "first step in prevention" that enables users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, and breast cancer. Most of the intended uses for PGS listed on your website, a list that has grown over time, are medical device uses under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions.

213 Letter from Alberto Gutierrez, Dir., Office of In Vitro Diagnostics & Radiological Health, U.S. Food & Drug Admin., to Ann Wojcicki, Chief Exec. Officer, 23andMe, Inc. (Nov. 22, 2013), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm).

Some of the uses for which PGS is intended are particularly concerning, such as assessments for BRCA-related genetic risk and drug responses (e.g., warfarin sensitivity, clopidogrel response, and 5-fluorouracil toxicity) because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these. For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist. Assessments for drug responses carry the risks that patients relying on such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome of the assessment. For example, false genotype results for your warfarin drug response test could have significant unreasonable risk of illness, injury, or death to the patient due to thrombosis or bleeding events that occur from treatment with a drug at a dose that does not provide the appropriately calibrated anticoagulant effect. These risks are typically mitigated by International Normalized Ratio (INR) management under a physician's care. The risk of serious injury or death is known to be high when patients are either non-compliant or not properly dosed; combined with the risk that a direct-to-consumer test result may be used by a patient to self-manage, serious concerns are raised if test results are not adequately understood by patients or if incorrect test results are reported.

Your company submitted 510(k)s for PGS on July 2, 2012 and September 4, 2012, for several of these indications for use. However, to date, your company has failed to address the issues described during previous interactions with the Agency or provide the additional information identified in our September 13, 2012 letter for (b)(4) and in our November 20, 2012 letter for (b)(4), as required under 21 CFR 807.87(1). Consequently, the 510(k)s are considered withdrawn, *see* 21 C.F.R. 807.87(1), as we explained in our letters to you on March 12, 2013 and May 21, 2013. To date, 23andMe has failed to provide adequate information to support a determination that the PGS is substantially equivalent to a legally marketed predicate for any of the uses for which you are marketing it; no other submission for the PGS device that you are marketing has been provided under section 510(k) of the Act, 21 U.S.C. § 360(k).

The Office of In Vitro Diagnostics and Radiological Health (OIR) has a long history of working with companies to help them come into compliance with the FD&C Act. Since July of 2009, we have been diligently working to help you comply with regulatory requirements

regarding safety and effectiveness and obtain marketing authorization for your PGS device. FDA has spent significant time evaluating the intended uses of the PGS to determine whether certain uses might be appropriately classified into class II, thus requiring only 510(k) clearance or de novo classification and not PMA approval, and we have proposed modifications to the device's labeling that could mitigate risks and render certain intended uses appropriate for de novo classification. Further, we provided ample detailed feedback to 23andMe regarding the types of data it needs to submit for the intended uses of the PGS. As part of our interactions with you, including more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications, we provided you with specific feedback on study protocols and clinical and analytical validation requirements, discussed potential classifications and regulatory pathways (including reasonable submission timelines), provided statistical advice, and discussed potential risk mitigation strategies. As discussed above, FDA is concerned about the public health consequences of inaccurate results from the PGS device; the main purpose of compliance with FDA's regulatory requirements is to ensure that the tests work.

However, even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses, which have expanded from the uses that the firm identified in its submissions. In your letter dated January 9, 2013, you stated that the firm is "completing the additional analytical and clinical validations for the tests that have been submitted" and is "planning extensive labeling studies that will take several months to complete." Thus, months after you submitted your 510(k)s and more than 5 years after you began marketing, you still had not completed some of the studies and had not even started other studies necessary to support a marketing submission for the PGS. It is now eleven months later, and you have yet to provide FDA with any new information about these tests. You have not worked with us toward de novo classification, did not provide the additional information we requested necessary to complete review of your 510(k)s, and FDA has not received any communication from 23andMe since May. Instead, we have become aware that you have initiated new marketing campaigns, including television commercials that, together with an increasing list of indications, show that you plan to expand the PGS's uses and consumer base without obtaining marketing authorization from FDA.

Therefore, 23andMe must immediately discontinue marketing the PGS until such time as it receives FDA marketing authorization for the device. The PGS is in class III under section 513(f) of the FD&C Act, 21 U.S.C. 360c(f). Because there is no approved application for premarket

approval in effect pursuant to section 515(a) of the FD&C Act, 21 U.S.C. 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), the PGS is adulterated under section 501(f)(1)(B) of the FD&C Act, 21 U.S.C. 351(f)(1)(B). Additionally, the PGS is misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because notice or other information respecting the device was not provided to FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k).

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific actions you have taken to address all issues noted above. Include documentation of the corrective actions you have taken. If your actions will occur over time, please include a timetable for implementation of those actions. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the actions will be completed. Failure to take adequate corrective action may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.

We have assigned a unique document number that is cited above. The requested information should reference this document number and should be submitted to:

James L. Woods, WO66-5688
Deputy Director
Patient Safety and Product Quality
Office of In vitro Diagnostics and Radiological Health
10903 New Hampshire Avenue
Silver Spring, MD 20993

If you have questions relating to this matter, please feel free to call Courtney Lias, Ph.D. at 301-796-5458, or log onto our web site at www.fda.gov for general information relating to FDA device requirements.

Sincerely yours,
/S/
Alberto Gutierrez
Director
Office of In vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health