FOOD AND DRUG LAW JOURNAL

Analyzing the Laws, Regulations, and Policies Affecting FDA-Regulated Products

Sperm Banking as a Strategy to Reduce Harms Associated with Advancing Paternal Age

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FDLI GEORGETOWN LAW O'NEILL INSTITUTE FOR NATIONAL & GLOBAL HEALTH LAW GEORGETOWN LAW

VOLUME 70 NUMBER 4 2015

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William C. Hudson*

I. Introduction

> *...the greatest mutational health hazard in the human population at present is fertile old males.*
>
> James Crow, 1997[1]

Conventional medical practice is to refer men to sperm banks when their fertility is at risk, such as before chemotherapy or certain surgical procedures. But there is another plausible reason for men to bank their sperm. Medical studies associate advanced paternal age (APA) with an increase in disorders among offspring. Because sperm banking lowers effective paternal age at the time of conception, it may thereby reduce the risk of these disorders.

Federal law does not restrict the use of sperm banking services, such as by requiring a prescription or diagnosed condition, so sperm-generating persons (SGPs)[2] can bank their sperm for the purpose of lowering effective paternal age at conception. However, should sperm banks or cryopreservation equipment manufacturers attempt to *promote* their services or devices for the explicit purpose of reducing the risk of disorders in offspring, the regulatory questions become more complicated—the issues presented, unsettled. In short, promotional claims of this kind, in claiming that cryopreservation would prevent disorders in offspring, would seem to make the preserved semen into a statutory drug, or the cryopreservation equipment into a new medical device; both would be being promoted as "articles intended for use in the . . . prevention of disease."[3]

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* William C. Hudson is a second-year JD candidate at Yale Law School. He gives special thanks to Professor Aaron S. Kesselheim for his instruction in FDA Law. This article was awarded the Florence M. Kelley '37 Family Law Prize for the 2014-2015 academic year at Yale Law School.

[1] James F. Crow, *The High Spontaneous Mutation Rate: Is it a Health Risk?*, 94 Proc. Nat'l. Acad. Sci. 8380, 8382 (1997), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC33757/.

[2] A sperm-generating person (SGP) is anyone whose body conducts spermatogenesis: the process of producing spermatozoa. I introduce this term here because, though it may sound overly technical, it is both eminently precise and inclusive of all gender identities and sexes. I continue the use of "paternal" and other gendered terms where it is a term of art within the medical literature, e.g., "the paternal age effect" and "advanced paternal age," and where I am quoting or referring to other sources, such as medical studies, that used a particular term. I generally use the pronoun "they" to refer to persons in the singular and the plural.

[3] 21 U.S.C. § 321(g)(1)(B) (2012). While sperm banks currently promote cryopreservation of semen for patients facing infertility, they are not promoting "the diagnosis, cure, mitigation, treatment, or prevention" of the infertility itself. They are merely preserving sperm in its current state, perhaps making it available for assisted reproduction medical procedures leading to conception.

Currently, FDA does classify cryopreservation equipment,[4] along with other "assisted reproduction accessories," as Class II (special controls) medical devices,[5] but their indications are for the limited purpose of preserving cells during the freezing process.[6] By contrast, a hypothetical evidence-supported indication that cryopreservation reduces the risk of harms associated with APA would seem to require evidence establishing much more, namely, that:

1. Advanced paternal age is a cause of disorders in offspring;
2. The mechanism by which advanced paternal age increases the risk of disorders is manifest in the sperm itself (i.e., not a social effect);
3. Cryopreservation successfully freezes sperm that can remain viable after thawing (already established);
4. The cryopreservation of sperm does not introduce additional risks to offspring.

This article does not aim to establish which of these factors could be sufficiently satisfied by current medical evidence—these factors are only a first sketch. Instead, this article raises and addresses the anterior question: as a matter of law, would a cryopreservation equipment manufacturer need to receive an indication in order to make lawful claims that its product reduces the risk of disorders in offspring? The article then extends this analysis to consider whether another stakeholder—the sperm banks—would, in the absence of a manufacturer's indication, require an approved[7] indication of their own in order to make such claims. Finally, the article makes policy recommendations to FDA and Congress.

These issues are not merely hypothetical or academic; at least one sperm bank has already taken to promoting its services for advancing paternal age. In responding to a written inquiry by the author as to why they do not already include paternal age risk reduction as a suggested reason (among a list of commonly offered reasons[8]) for

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[4] In practice, long-term cryopreservation tanks are not reviewed by FDA and do not carry an FDA-approved or FDA-cleared indication, but more specialized cryopreservation equipment such as controlled-rate freezers used in the initial freezing process, the medium in which cells are frozen, and storage containers do have indications.

[5] 21 C.F.R. § 884.6120 (2015).

[6] *See, e.g.*, Letter from Richard Miller, Manager of Regulatory Compliance, Thermo Forma, Inc., to Food & Drug Admin. (Mar. 28, 2002), http://www.accessdata.fda.gov/cdrh_docs/pdf2/K021042.pdf ("intended to be used to freeze gametes and/or embryos at a user determined rate"); Letter from Food & Drug Admin. to NidaCon Int'l (Nov. 8, 2002), http://www.accessdata.fda.gov/cdrh_docs/pdf2/K023206.pdf ("for protecting human sperm during cryopreservation"); Letter from Brenda Davis, Regulatory Affairs Technical Writer, Cook Urological Inc., to Food & Drug Admin. (May 10, 2006), http://www.accessdata.fda.gov/cdrh_docs/pdf6/K061371.pdf ("intended for use as a buffer to prevent damage to sperm samples during cryopreservation and thawing").

[7] Technically, "FDA-approved" is a term of art, distinguishable from, for example, "FDA-cleared." This article, however, will refer simply to "approved" indications, meaning any indication that FDA has agreed can be lawfully marketed.

[8] *See, e.g.*, CAL. CRYOBANK, http://fertile-future.com/services/fertile-future-sperm-storage-program (last visited Nov. 5, 2015) ("Sperm banking may be considered under a number of circumstances": "Prior to cancer-related therapies," "Prior to testicular or prostate surgery," "Prior to a vasectomy," "Prior to hormone replacement therapy," "Prior to an upcoming fertility procedure," "For high-risk occupational exposures," "For oligospermia (low sperm count) patients"); NEW ENG. CRYOGENIC CTR., INC., http://www.necryogenic.com/sperm-banking-faqs.php (last visited Nov. 5, 2015) ("Why should I bank my sperm?": "at risk for sterility through surgery or medical treatments like chemotherapy / radiation therapy," "in an occupation that exposes you to dangerous chemicals, radiation or physical activity which may decrease fertility, including athletes, police, fire fighters, and military personnel," "attempting assisted reproductive procedures such as in vitro fertilization," "frequently separated from your partner during ovulation"); SPERM BANK CAL., https://www.thespermbankofca.org/about-storing-sperm (last visited Nov. 5, 2015) (listing *in toto* under heading "Who

consumers to utilize sperm banking services,[9] some sperm banks indicated that such a use simply "was not really on [their] mind"[10]—despite fifteen years of extensive media coverage[11]—but one, ReproTech, after receiving the inquiry updated its webpage

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stores their sperm?": "A recent diagnosis," "Upcoming treatment or surgery," "Transitioning MTF," "Fertility preservation," "Frequent travel while trying to conceive," "You are storing for someone you know," "You are storing for the use with a surrogate," "Storing now for an unknown reproductive partner in the future"); SPERM BANK INC., http://www.spermbankcalifornia.com/bank-sperm.html (last visited Nov. 5, 2015) (listing *in toto* "Reasons to Cryopreserve Sperm" as "Medical Reasons," "Pre-Vasectomy Sperm Banking," and "Military & Hazardous Occupation Fertility Preservation").

[9] The term "sperm bank" is descriptively under-inclusive. Sperm banks store semen samples, not isolated sperm; moreover, FDA regulations refer to semen, not sperm. This paper will therefore generally refer to semen, except when intending to refer specifically to sperm, or when referring to a sperm bank.

[10] Email from ReproTech, Ltd., to author (June 8, 2015, 3:24 PM EST) (on file with the Food and Drug Law Journal) ("I would say the only reason that we don't list that is due to it being a much more infrequent use and therefore not really on our mind when we discussed that section with our web developer. As you point out, it is a real issue and thus we will add it to the next revisions."); Email from Suzanne Seitz, Certified Genetic Counselor, Fairfax Cryobank & Cryogenic Labs., Inc., to author (June 9, 2015, 11:50 AM EST) (on file with the Food and Drug Law Journal) (concluding that "it would be reasonable to say that if a man knows he will be postponing having children into his later years, the option of storing sperm when he is younger does make sense. I will look into this and hope to have something posted soon that addresses this new field of study."). Other sperm banks responded to the inquiry that men are not interested enough in prospective sperm banking for it to be worth their effort. This explanation is somewhat surprising. There is no marginal cost to at least mentioning—again, in a list of reasons for sperm banking that already appears on a website—one additional reason. In fact, it is odd that this reason, until ReproTech made the addition, has been uniformly absent. *See, e.g.*, Email from Ole Schou, Managing Dir., Cryos Int'l, to author (Apr. 13, 2015, 3:13 AM EST) (on file with the Food and Drug Law Journal) ("[M]en are not very focused on reproduction, so from a business point of view, it is waste of time. The market is not really there.").

[11] *See, e.g.*, HARRY FISCH, THE MALE BIOLOGICAL CLOCK: THE STARLING NEWS ABOUT AGING, SEXUALITY, AND FERTILITY IN MEN 25 (2008) ("There has been a dramatic rise in the age of parents in the past few decades, which could be considered a public health concern because of the increased risk of birth defects that the rise entails."); Nicholas Bakalar, *Bipolar Disorder Tied to Age of Fathers*, N.Y. TIMES, Sept. 8, 2008, http://www.nytimes.com/2008/09/09/health/09bipo.html; Nicholas Bakalar, *Older Paternal Age Seen as Factor in Some Birth Defects*, N.Y. TIMES, June 6, 2006, http://www.nytimes.com/2006/06/06/health/06sper.html; Sandra G. Boodman, *The Mutant Sperm Theory of Schizophrenia; Study Finds Children of Older Fathers Are More Likely to Be Afflicted*, WASH. POST, Apr. 17, 2001; Benedict Carey, *Father's Age Is Linked to Risk of Autism and Schizophrenia*, N.Y. TIMES, Aug. 22, 2012, http://www.nytimes.com/2012/08/23/health/fathers-age-is-linked-to-risk-of-autism-and-schizophrenia.html; Benedict Carey, *Mental Illness Risk Higher for Children of Older Fathers, Study Finds*, N.Y. TIMES, Feb. 26, 2014, www.nytimes.com/2014/02/27/health/mental-illness-risk-higher-for-children-of-older-parents-study-finds.html; Faye Flam, *Delaying Fatherhood Has Risks, Too*, PHIL. INQ., Sept. 25, 2006; Judy Foreman, *Risk of Birth Defects Linked to Father's Age*, L.A. TIMES, July 23, 2001, http://articles.latimes.com/2001/jul/23/health/he-25555; Erica Goode, *Father's Age Linked to Risk of Schizophrenia in Child*, N.Y. TIMES, Apr. 12, 2001, http://www.nytimes.com/2001/04/12/us/father-s-age-linked-to-risk-of-schizophrenia-in-child.html; Nicole Gray, *Father Time: Children with Older Dads at Greater Risk for Mental Illness*, SCI. AM., Aug. 29, 2011, http://www.scientificamerican.com/article/children-with-older-dads-at-greater-mental-illness-risk/; Roni Rabin, *It Seems the Fertility Clock Ticks for Men, Too*, N.Y. TIMES, Feb. 27, 2007, http://www.nytimes.com/2007/02/27/health/27sper.html?pagewanted=all; Kári Stefánsson, *Men Shouldn't Delay Fatherhood*, N.Y. TIMES, July 9, 2013, http://www.nytimes.com/roomfordebate/2013/07/08/should-women-delay-motherhood/men-shouldnt-delay-fatherhood; *Study Links Older Dads, Kids' Psychiatric Problems*, USA TODAY, Feb. 26, 2014, http://www.usatoday.com/story/news/nation/2014/02/26/fathers-older-children-psychiatric-problems/5850171/; Shankar Vedantam, *Autism Risk Rises with Age of Father*, WASH. POST, Sept. 5, 2006, www.washingtonpost.com/wp-dyn/content/article/2006/09/04/AR2006090400513.html; *CBS Evening News* (CBS News television broadcast Aug. 24, 2012), http://www.cbsnews.com/videos/autism-risk-could-rise-with-fathers-age/; Todd B. Nippoldt, *How Does Paternal Age Affect a Baby's Health?*, MAYO CLINIC, http://www.mayoclinic.org/healthy-lifestyle/getting-pregnant/expert-answers/paternal-age/faq-20057873 (last visited Nov. 5, 2015); William Hudson, *Study: Children of Older Fathers Face Higher Risk of Psychiatric Disorders*, CNN, Feb. 27, 2014, http://thechart.blogs.cnn.com/2014/02/27/study-children-of-older-fathers-at-much-higher-risk-of-psychiatric-disorders; Maanvi Singh, *More Hints That Dad's Age at Conception Helps Shape a Child's Brain*,

to include the words "advancing paternal age" under the heading "Who Uses Sperm Freezing?"[12] This appears to be the first sperm bank to list this reason for banking sperm.[13] And yet, it is also a limited, ambiguous statement for anyone not familiar with medical research in this field. For example, "advancing paternal age" could be interpreted to describe only the risk of male fertility declining with age. These three words say nothing of what the specific risks to offspring may be (e.g., autism, schizophrenia, ADHD), nor do they say anything about how effective sperm banking is in reducing these risks, who should consider this preventive measure, and when. This article imagines a future in which sperm banks would want to communicate—i.e., promote—this type of information to consumers, and considers whether such promotion would be permissible under FDA law.

There is some anecdotal evidence that young men are increasingly banking their own sperm for "age-related reasons."[14] These men would seem to have the support of one geneticist writing in *Nature* that "if the paternal-age effect . . . does lead to substantially impaired health in the children of older fathers, then collecting the sperm of young adult men and cold-storing it for later use could be a wise individual decision."[15] Meanwhile, the average age of SGPs upon birth of their offspring continues to climb. In 2013, the number of births attributable to fathers aged 35–39, 40–44, and 45–49 all reached record highs, while births to fathers aged 15–19, 20–24, and 25–29 reached record lows.[16] How common personal sperm banking becomes in the future, one could reasonably assume, will be a function of several inter-related factors including, among others, the results

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NPR, Feb. 26, 2014, http://www.npr.org/blogs/health/2014/02/26/283081784/more-hints-that-dads-age-at-conception-helps-shape-a-childs-brain; *Today Show* (NBC News television broadcast Mar. 13, 2007), http://www.nbcnews.com/video/today-show-health/17589427#17589427.

[12] Email from ReproTech, Ltd., to author (June 12, 2015, 3:14 PM EST) (on file with the Food and Drug Law Journal) ("ReproTech's website now includes Advancing Paternal Age . . . ").

[13] The following sperm banking websites were reviewed for this article: CRYOCHOICE, http://www.cryochoice.com/who_should_bank_sperm.html; CAL. CRYOBANK, http://fertile-future.com/services/fertile-future-sperm-storage-program; CRYOS INT'L, http://usa.cryosinternational.com/sperm-storage/; CRYOGAM COLO., http://www.cryogam.com/; CRYOGENIC LABORATORIES, http://www.cryolab.com/; FERTILITY CTR. CAL. (FCC), SPERM BANK INC. http://www.spermbankcalifornia.com/; SEATTLE SPERM BANK (EUROPEAN SPERM BANK USA), https://www.europeanspermbankusa.com/why-use-us/; FAIRFAX CRYOBANK, http://www.fairfaxcryobank.com/; MANHATTAN CRYOBANK, http://www.manhattancryobank.com/sperm-storage/; M.A.Z.E. LABORATORIES, INC., http://www.mazelabs.com/index.php; NEW ENG. CRYOGENIC CTR., INC., http://www.necryogenic.com/; NW CRYOBANK, https://www.nwcryobank.com/sperm-storage/; PAC. REPRODUCTIVE SERVS., https://www.pacrepro.com/index.php?main_page=contact_us (does not offer personal storage); REPRODUCTIVE TECHNOLOGIES, https://www.thespermbankofca.org/; XYTEX CRYOS INT'L, https://www.xytex.com/sperm-donor-bank-become-donor/.

[14] Deborah Kotz, *Why Have More Men Chosen to Freeze Their Sperm?*, BOS. GLOBE, Dec. 2, 2014, http://www.bostonglobe.com/lifestyle/health-wellness/2014/12/02/why-have-more-men-chosen-freeze-their-sperm/a0QVfDcP81FH2qNOezhOEK/story.html. However, it is ambiguous the degree to which "age-related reasons" includes APA risks specially versus other age-related reasons, such as infertility.

[15] Alexey Kondrashov, *Genetics: The Rate of Human Mutation*, 488 NATURE 467, 468 (2012), http://www.nature.com/nature/journal/v488/n7412/full/488467a.html#auth-1.

[16] Joyce A. Martin et al., *Births: Final Data for 2013*, NAT'L VITAL STAT. REP., Jan. 15, 2015, http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_01.pdf (explaining that in 2013 there were 101.8 births per 1,000 men aged 30–34 (down slightly from a peak of 110.3 in 2007), up from 91 births per 1,000 in 1980; 66.6 births per 1,000 men aged 35–39, up from 42.8 per 1,000 in 1980; 27 births per 1,000 men aged 40–44, up from 17.1 per 1,000 in 1980; and 8.8 births per 1,000 men aged 45–49, up from 6.1 per 1,000 in 1980. By contrast, birth rates for men under age 30 have fallen steeply. In 2013 there were 12.3 births per 1,000 men aged 15–19, down from 18.8 per 1,000 in 1980 (and a peak of 24.7 in 1991); there were 55.7 births per 1,000 men aged 20–24, down from 92 per 1,000 in 1980; and 90.6 births per 1,000 men aged 25–29, down from 123.1 in 1980.).

of on-going medical research, consensus among the medical community, population-level rates of associated conditions, the pricing of sperm-banking services, and the promotional claims that sperm-banking manufacturers can make to shape consumer awareness, perceptions, and norms.

And if preventive sperm banking does become more common, what type of social norm might it become? "Will doctors begin asking men if they've begun considering their 'reproductive options' at their annual checkups as they enter their 30s?" asks KJ Dell'Antonia in the *New York Times*.[17] Perhaps sperm cryopreservation becomes something that nearly everyone in certain privileged circles does around a certain age, like attending college after high school. Or it could become (more or less) equitably distributed, routine preventive medical care covered by health insurance, akin to maternity care.[18]

A higher degree of medical certainty and specificity as to sperm banking's benefits is likely a necessary condition, without which public-private cost-sharing models of allocating sperm-banking services (e.g., a guaranteed insurance benefit) will have insufficient popular support. Sperm banking as a *premium* service, however, is a different story.[19] Among *this* market, consumer awareness would seem to be the most important limiting factor. Parents of higher socioeconomic status, seeking to confer every possible advantage onto their children, would appear to be a fertile target audience for sperm-banking services.

Consider this sales pitch template: "Sperm banking is quick and easy. Sperm banking will preserve your fertility for life, but the longer you wait the more you age, and the more likely your children and even grandchildren are to suffer from life-altering disorders." One could imagine sperm banks tailoring this basic message, for example, to parents of teenagers on the cusp of adulthood, or to young professionals who intend to delay parenthood (perhaps indefinitely). Moreover, individuals of higher socioeconomic status would likely perceive a greater need for these services, as they tend to have children later in life.[20] Indeed, sperm banking could itself become a status symbol.

This article therefore is situated within the context of the following premises: that advanced paternal age (APA) at the time of conception is associated with an increased risk of disorders in offspring; that banking sperm well in advance of conception could reduce these risks by lowering the relevant paternal age; that more SGPs would choose

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[17] KJ Dell'Antonia, *The Clock Ticks for Men as Well*, N.Y. TIMES, Aug. 24, 2012, http://www.nytimes.com/2012/08/26/fashion/autism-study-starts-clock-for-prospective-fathers.html.

[18] *See Health Coverage if You're Pregnant or Plan to Get Pregnant*, U.S. CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.healthcare.gov/what-if-im-pregnant-or-plan-to-get-pregnant/ (last visited June 2, 2015).

[19] *Cf.* John A. Robertson, *Commerce and Regulation in the Assisted Reproduction Industry*, 85 TX. L. REV. 665 (2007), *reprinted in* BABY MARKETS: MONEY AND THE NEW POLITICS OF CREATING FAMILIES 191, 192 (Michele Bratcher Goodwin ed., 2010) ("Some countries treat [assisted reproductive technology] and infertility as a needed medical service that the national health system should pay for. Others treat it like a luxury good available only to those who are able to purchase it. One may legitimately ask whether such an investment to produce a child is worth it, and whether society should subsidize it. That inquiry would look at the costs and benefits of coverage, what it does to others in the health insurance pool, and whether it is worth subsidizing in a national health system. If not covered, obtaining such children becomes a luxury good of sorts . . . .").

[20] *See* Lori Reeder, *Parental Income, College Attendance, and First Birth Timing*, PRINCETON U. (2014), http://paa2014.princeton.edu/papers/142280. *See generally* Tomáš Sobotka, OOCYTE CRYOPRESERVATION AS AN INSURANCE STRATEGY: A SOCIO-DEMOGRAPHIC VIEWPOINT (2013), http://www.socialfreezing.org/wp-content/uploads/2013/02/symposium_2013.pdf (discussing the relationship between oocyte cryopreservation and a shift towards later age at childbearing in rich countries).

to bank their sperm if they had this information or were exposed to promotional advertising; and therefore, there is at present an underserved market for the preventive use of sperm banking services.[21]

II. HOW FDA REGULATES SEMEN

The most important distinction to draw between the many FDA-regulated products is between those products that must be shown only to be safe (e.g., food, cosmetics, dietary supplements), and those products that must be both safe[22] *and effective*,[23] that is, that they do what they claim to do (e.g., drugs, medical devices[24]).[25] Biological products straddle this divide in a unique way. Whereas all food must be only safe, and all new drugs must be both safe and effective, some biologics, such as reproductive tissue, need only be safe, but other biologics, such as vaccines, must also demonstrate efficacy.[26] In some cases, the same biologic can require different efficacy standards based on the intended recipient; for example, cord blood for autologous use requires only safety standards, whereas cord blood for allogeneic use in an unrelated patient must have a condition-specific indication based on demonstrated efficacy.[27]

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[21] Of course, one or all of these premises may be incorrect. While studies have shown an association between paternal age and mental disorders in children, the relationship may not be causal, or may not be due to paternal biological age per se.

[22] *See* 21 U.S.C. § 355(d)(1) (2012) (requiring that new drug applications be supported by "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof").

[23] *See* 21 U.S.C. § 355(d)(5) (2012) (requiring that new drug applications show "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"); 21 U.S.C. § 360j(e)(1)(B) (2012) (allowing that the Secretary "may by regulation require that a device be restricted to sale, distribution, or use" if "the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness").

[24] However, Class I medical devices are sometimes an exception to the rule that medical devices must have demonstrated efficacy. A Class I medical device may have "insufficient information from which to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness" if "the device is not life-supporting or life-sustaining or for a use which is of substantial importance in preventing impairment of human health, and which does not present a potential unreasonable risk of illness of injury." 21 C.F.R. § 860.3(c)(1) (2015).

[25] One may argue that tobacco products, recently added to the FDA regulatory portfolio by the Family Smoking Prevention and Tobacco Control Act (2009), is an exception in that FDA ensures neither safety nor efficacy. While recognizing that tobacco products like cigarettes are always harmful, FDA is authorized to reduce the amount of harm that these products cause, thereby increasing their relative safety. The Act requires, *inter alia*, pre-market approval for new tobacco products not substantially equivalent to products on the market on or before February 15, 2007, 21 U.S.C. § 387j (2012), the "testing and reporting of tobacco product constituents, ingredients, and additives," 21 U.S.C. § 387o (2012), and regulations prescribing good manufacturing practices including "the testing of raw tobacco for pesticide chemical residues," 21 U.S.C. § 387f (2012).

[26] By statute, licensed biologics must be "safe, pure, and potent." *See* 42 U.S.C. § 262(a)(2)(C)(i)(I) (2012) (explaining that "Potent" carries the same legal meaning as effective); 21 § C.F.R. 600.3(s) (2015) ("The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.").

[27] *See Cord Blood Banking—Information for Consumers*, FOOD & DRUG ADMIN. (July 23, 2012), http://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Consumers/ucm236044.htm ("Cord blood stored for potential future use by a patient unrelated to the donor meets the definition of 'drug' under the Food, Drug & Cosmetic Act and 'biological product' under Section 361 of the Public Health Service Act. Cord blood in this category must meet additional requirements and be licensed under a biologics license application (BLA), or subject to an investigational new drug application (IND) before use.").

In general, FDA divides the biological products "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) into two separate categories for purposes of determining the applicable promotional claims regulatory regime. So-called "361 Products" or "361 HCT/Ps" are exempt from FDA's advertising and promotional claims regulations, and subject only to Section 361 of the Public Health Service Act, which is concerned with preventing the transmission of communicable diseases.[28] To qualify as a "361 HCT/P," an HCT/P must satisfy four criteria: (1) minimally manipulated (relates to the nature and degree of processing); (2) intended for homologous use only (the product performs the same basic function in the donor as in the recipient); (3) not combined with another article (with some exceptions, like a freezing agent), and (4) intended for autologous use, use by a first- or second-degree blood relative, or for reproductive use.[29] FDA considers semen stored for use in conception an example of a "361 HCT/P," as is skin used in skin grafts and heart valves used in allografts.[30] Much turns on whether a product maintains its status as a 361 HCT/P. Products failing to satisfy any of these four criteria are instead regulated as drugs, medical devices, or biological products,[31] or as a combination of these products,[32] and thereby generally requiring FDA approval before marketing.

It remains an open question how FDA would attempt to classify a semen storage device promoted to reduce the risk of disorders in offspring.[33] Of the four criteria a product must satisfy to qualify as a "361 HCT/P," it is the "homologous use" requirement that is most uncertain in this use. FDA defines "homologous use [to mean] the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with

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[28] *See* 42 U.S.C. § 264 (2012) ("Regulations to control communicable diseases. (a) Promulgation and enforcement by Surgeon General. The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.").

[29] 21 C.F.R. § 1271.10(a) (2015).

[30] *FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm150485.htm (last visited Nov. 9, 2015).

[31] Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment, Registration, and Listing, 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001) (to be codified at 21 C.F.R. pt. 207) ("HCT/P's that do not meet FDA's criteria set forth in part 1271 for regulation solely under section 361 of the PHS Act are regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act.").

[32] 21 C.F.R. § 3.2(e) (2015) ("Combination product includes: (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologics, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, or strength, route of administration, or significant change in dose; or (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.").

[33] FDA's Tissue Reference Group provides non-binding guidance to industry queries seeking clarification as to whether certain uses of human products would qualify as "361 HCT/Ps." In January 2015, the author submitted an inquiry to the Tissue Reference Group seeking clarification as to whether the cryopreservation of semen to reduce the risk of psychiatric disorders in children would qualify as a "361 HCT/P." In March 2015, the Tissue Reference Group responded to the inquiry without providing a determination.

an HCT/P that performs the same basic function or functions in the recipient as in the donor."[34] Whether an HCT/P meets this definition turns on the producer's intent "as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."[35] The logic underlying the homologous use prong is that when nature has fashioned the human body to perform some function, there is no need to demonstrate efficacy. Replacement skin will perform the function that skin performs; replacement heart valves will perform the function that heart valves perform.

It should be noted that *any* reproductive use of semen would seem to push the textual limits of the homologous use definition, as semen obviously functions very differently in the "recipient as in the donor." Nonetheless, semen, as currently promoted, satisfies all four 361 HCT/P criteria, and, a priori, the homologous-use only criterion. This follows naturally from the intent and spirit of the law[36] to not impose regulations on human tissue products being used for "the same basic function" as they would normally be used absent any medical intervention. Whether promoting semen storage for the purpose of reducing risks in offspring moves semen beyond the confines of this homologous-use exception will be considered below.

III. THE RISK TO OFFSPRING OF ADVANCING PATERNAL AGE

An association between APA and schizophrenia was first identified in the 1950s.[37] Epidemiological studies have further supported the association[38] and linked APA to an increased risk of many other negative health outcomes in offspring including autism

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[34] 21 C.F.R. § 1271.3(c) (2015).

[35] 21 C.F.R. § 1271.10(a)(2) (2015).

[36] Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment, Registration, and Listing, 66 Fed. Reg. at 5449 ("The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on the research, development, or the availability of new products . . . . We have determined that some HCT/P's may be effectively regulated solely by controlling the infectious disease risks they present.").

[37] *See* Ian Gregory, *An Analysis of Family Data on 1000 Patients Admitted to a Canadian Mental Hospital*, ACTA GENETICA ET STATISTICA MEDICA 54 (1959), https://www.karger.com/Article/Abstract/151085; Eva Johanson, *A Study of Schizophrenia in the Male: A Psychiatric and Social Study Based on 138 Cases with Follow Up*, 33 ACTA PSYCHIATRICA SCANDIAVICA 7 (1958), http://www.ncbi.nlm.nih.gov/pubmed/13594594; *see also* Dolores Malaspina, *Paternal Factors and Schizophrenia Risk: De Novo Mutations and Imprinting*, 27 SCHIZOPHRENIA BULL. 379, 382 (2001), http://schizophreniabulletin.oxfordjournals.org/content/27/3/379.long.

[38] *See* Brian Miller et al., *Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring*, 37 SCHIZOPHRENIA BULL. 1039 (2011), http://www.ncbi.nlm.nih.gov/pubmed/20185538/; Attila Sipos et al., *Paternal Age and Schizophrenia: A Population Based Cohort Study*, 329 BRIT. MED. J. 1070 (2004), http://dx.doi.org/10.1136/bmj.38243.672396.55.

spectrum disorders,[39] bipolar disorder,[40] congenital disorders,[41] eating disorders,[42] leukemia and other childhood cancers,[43] breast cancer,[44] impaired neurocognition,[45] and all-cause childhood mortality.[46] These studies typically use statistical controls to account

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[39] *See* Lisa A. Croen et al., *Maternal and Paternal Age and Risk of Autism Spectrum Disorders*, 161 ARCH. PEDIATRIC & ADOLESCENT MED. 334 (2007), http://www.ncbi.nlm.nih.gov/pubmed/17404129?dopt=Abstract; Judith K. Grether et al., *Risk of Autism and Increasing Maternal and Paternal Age in a Large North American Population*, 170 AM. J. EPIDEMIOLOGY 1118 (2009), http://aje.oxfordjournals.org/content/170/9/1118.abstract?ijkey=a2c16e9864a3fdb77136596f8b5dba7f5f370e34&keytype2=tf_ipsecsha; Christina M. Hultman et al., *Advancing Paternal Age and Risk of Autism: New Evidence from a Population-based Study and a Meta-analysis of Epidemiological Studies*, 16 MOLECULAR PSYCHIATRY 1203 (2011), http://www.nature.com/mp/journal/v16/n12/full/mp2010121a.html; Abraham Reichenberg et al., *Advancing Paternal Age and Autism*, 63 ARCH. GEN. PSYCHIATRY 1026 (2006), http://archpsyc.jamanetwork.com/article.aspx?articleid=668208; Sven Sandin et al., *Autism Risk Associated with Paternal Age and with Increasing Difference in Age between the Parents*, MOLECULAR PSYCHIATRY (2015), http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201570a.html.

[40] *See* Emma M. Frans et al., *Advancing Paternal Age and Bipolar Disorder*, 65 ARCH. GEN. PSYCHIATRY 1034 (2008), http://archpsyc.jamanetwork.com/article.aspx?articleid=210144.

[41] *See* Camilla Bille et al., *Parent's Age and the Risk of Oral Clefts*, 16 EPIDEMIOLOGY 311 (2005), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2839123/; Jagteshwar Grewal et al., *Paternal Age and Congenital Malformations in Offspring in California, 1989–2002*, 16 MATERNAL & CHILD HEALTH J. 385 (2011), http://link.springer.com/article/10.1007%2Fs10995-011-0759-z; Zhi-Hao Lian et al., *Paternal Age and the Occurrence of Birth Defects*, 39 AM. J. OF HUM. GENETICS 648 (1986), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1684057/; Steven Singer et al., *Craniosynostosis in Western Australia, 1980–1994: A Population-based Study*, 83 AM. J. MED. GENETICS 382 (1999), http://www.ncbi.nlm.nih.gov/pubmed/10232748 (linking paternal age to craniosynostosis); Marie M. Tolarova et al., *Birth Prevalence, Mutation Rate, Sex Ratio, Parents' Age, and Ethnicity in Apert Syndrome*, 72 AM. J. MED. GENETICS 394 (1997), http://www.ncbi.nlm.nih.gov/pubmed/9375719 (linking paternal age to Apert syndrome); Jin Liang Zhu et al., *Paternal Age and Congenital Malformations*, 20 HUM. REPROD. 3173 (2005), http://humrep.oxfordjournals.org/content/20/11/3173.abstract?ijkey=58a1d03bb805a1dcce27ea4ec33f3fbf8b1f3dd9&keytype2=tf_ipsecsha.

[42] *See* Sarah E. Racine et al., *Advanced Paternal Age at Birth: Phenotypic and Etiologic Associations with Eating Pathology in Offspring*, 44 PSYCHOL. MED. 1029 (2014), http://www.ncbi.nlm.nih.gov/pubmed/23795717/.

[43] *See* Kari Hemminki et al., *Parental Age as a Risk Factor of Childhood Leukemia and Brain Cancer in Offspring*, 10 EPIDEMIOLOGY 271 (1999), http://www.ncbi.nlm.nih.gov/pubmed/10230837?dopt=Abstract; Liam Murray et al., *Association of Early Life Factors and Acute Lymphoblastic Leukaemia in Childhood: Historical Cohort Study*, 86 BRIT. J. CANCER 356 (2002), http://www.ncbi.nlm.nih.gov/pubmed/11875699?dopt=Abstract; Benjamin H. Yip et al., *Parental Age and Risk of Childhood Cancers: A Population-Based Cohort Study From Sweden*, 35 INT'L J. EPIDEMIOLOGY 1495 (2006), http://www.ncbi.nlm.nih.gov/pubmed?term=17008361. *See also* Greta Bunin et al., *Paternal Age and Sporadic Neurofibromatosis 1: A Case-control Study and Consideration of the Methodologic Issues*, 14 GENETIC EPIDEMIOLOGY 507 (1997), http://www.ncbi.nlm.nih.gov/pubmed/9358268; Qian Liu et al., *Parental Age and Neurofibromatosis Type 1: A Report from the NF1 Patient Registry Initiative*, 14 FAMILIAL CANCER 317 (2015), http://www.ncbi.nlm.nih.gov/pubmed/25523354; Marta Snajderova et al., *The Importance of Advanced Paternal Age in the Origin of Neurofibromatosis Type 1*, 158A AM. J. MED. GENETICS 519 (2012), http://www.ncbi.nlm.nih.gov/pubmed/22302476.

[44] *See* Ji-Yeob Choi et al., *Association of Paternal Age at Birth and the Risk of Breast Cancer in Offspring: A Case Control Study*, 5 BMC CANCER 143 (2005), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1291359/; Inbal Wiess-Salz et al., *Ethnic Ancestry and Increased Paternal Age Are Risk Factors for Breast Cancer Before the Age of 40 Years*, 16 EUR. J. CANCER PREVENTION 549 (2007), http://www.ncbi.nlm.nih.gov/pubmed/18090128?dopt=Abstract.

[45] *See* Sukanta Saha et al., *Advanced Paternal Age Is Associated with Impaired Neurocognitive Outcomes During Infancy and Childhood*, 6 PLOS MED. (2009), http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000040*; see also* Anna C. Svensson et al., *Implications of Advancing Paternal Age: Does it Affect Offspring School Performance?*, 6 PLOS ONE e24771 (2011), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0024771.

[46] *See* Stine Kjaer Urhoj et al., *Advanced Paternal Age and Mortality of Offspring Under 5 Years of Age: A Register-based Cohort Study*, 29 HUM. REPROD. 343 (2014), http://www.ncbi.nlm.nih.gov/pubmed/24316515;

for confounding factors such as birth year, socioeconomic status, and maternal age. APA has also been linked to an increased risk of miscarriage, and many miscarriages are attributable to genetic abnormalities in the embryo making it non-viable.[47] Moreover, APA may harm multiple generations;[48] grandparental age has been associated with both schizophrenia[49] and autism.[50]

In 2014, D'Onofrio et al. published the most comprehensive study to date on the paternal age effect.[51] The study included 2.6 million people born to 1.4 million SGPs, using birth data from the Swedish Medical Birth Register, biological relationship information from the Multi-Generation Register, and outcome data from seven additional national databases.[52] The dataset represents 89.6% of everyone born in Sweden from 1973 to 2001. The study authors compared the offspring of SGPs aged 20–24 with the offspring of SGPs aged 25–29, 30–34, 35–39, 40–44, and over 45. The results generally show a modest, linear increase in risk with increasing paternal age, but a striking increase in risk when comparing only paternal siblings, that is, children born to the same SGP. This quasi-experimental design is intended to help rule out confounding genetic and environmental factors (for example, possible differences in personality traits associated with postponing parenthood) because sibling pairs are expected to share those confounders.[53] The study found a 24-fold increased risk of bipolar disorder, a 13-fold increased risk of ADHD, a 3-fold increased risk of autism and suicide attempts, and a 2-fold increased risk of psychosis, substance use problems, failing a grade, and low

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Jin Liang Zhu et al., *Paternal Age and Mortality in Children*, 23 EUR. J. EPIDEMIOLOGY 443 (2008), http://www.ncbi.nlm.nih.gov/pubmed/18437509.

[47] *See* Anne-Marie Nybo Andersen et al., *Advanced Paternal Age and Risk of Fetal Death: A Cohort Study*, 160 AM. J. EPIDEMIOLOGY 1214, 1217 (2004), http://www.ncbi.nlm.nih.gov/pubmed/15583374; Karine Kleinhaus et al., *Paternal Age and Spontaneous Abortion*, 108 OBSTETRICS & GYNECOLOGY 369, 369 (2006), http://www.ncbi.nlm.nih.gov/pubmed/16880308?dopt=Abstract; Elise de La Rochebrochard & Patrick Thonneau, *Paternal Age and Materal Age are Risk Factors for Miscarriage; Results of a Multicentre European Study*, 17 HUM. REPROD. 1649, 1650 (2002), http://www.ncbi.nlm.nih.gov/pubmed/12042293; Rémy Slama et al., *Does Male Age Affect the Risk of Spontaneous Abortion? An Approach Using Semiparametric Regression*, 157 AM. J. EPIDEMIOLOGY 815 (2003), http://www.ncbi.nlm.nih.gov/pubmed/12727675; Rémy Slama et al., *Influence of Paternal Age on the Risk of Spontaneous Abortion*, 161 AM. J. EPIDEMIOLOGY 816, 817 (2005), http://www.ncbi.nlm.nih.gov/pubmed/15840613.

[48] *See* Julia Schroeder et al., *Reduced fitness in progeny from older parents in a natural population*, 112 PROC. NAT'L ACAD. SCI. 4021, 4021 (2015), http://www.pnas.org/content/112/13/4021.short.

[49] *See* Emma M. Frans et al., *Advanced Paternal and Grandpaternal Age and Schizophrenia: A Three-Generation Perspective*, 133 SCHIZOPHRENIA RES. 120, 120 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3660090/.

[50] *See* Emma M. Frans et al., *Autism Risk Across Generations: A Population-Based Study of Advancing Grandparental and Paternal Age*, 70 JAMA PSYCHIATRY 516, 517 (2013), http://archpsyc.jamanetwork.com/article.aspx?articleid=1666654.

[51] Brian M. D'Onofrio et al., *Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity*, 71 JAMA PSYCHIATRY 432, 437 (2014), http://www.ncbi.nlm.nih.gov/pubmed/24577047 ("[T]he findings suggest APA represents a risk for numerous public health and societal problems.").

[52] *Id.* at 433 (explaining databases used in the study include: (1) Patient Register ("which provides diagnosis for all inpatient psychiatric hospital administrations in Sweden"), (2) Cause of Death Register, (3) National Crime Register, (4) National School Register ("which includes grades in all subjects for all students at the end of grade 9"), (5) Education Register ("which contains information on the highest level of completed formal education"), (6) Military Conscription Register ("which includes cognitive assessments for all 18-year-old men in Sweden between 1970 and 2009"), and (7) Longitudinal Integration Database for Health Insurance and Social Studies ("which contains yearly assessments of income, marital status, employment status, social welfare status, and education for all individuals 15 years or older")).

[53] *Id.* at 435.

educational attainment. Paternal age may therefore be a clinically significant risk factor for many conditions, some of which are increasing in prevalence.[54]

The hypothesis most widely suggested to account for the effects of APA is that as SGPs age, as their sperm replicates continuously, the increasing number of de novo mutations ultimately has adverse effects on their offspring's health—especially mental health and brain function, which "depends on the functionality of a very high number of genes and non-coding regulatory regions, and therefore the mutational target size is large."[55] Kong et al. found that while SGPs aged 20 passed on an average of 25 new point mutations, SGPs aged 40 passed on 65 mutations, an increase of 2 new mutations per year.[56] Epigenetic alterations in gene expression caused by environmental exposures have also been proposed as a cause of APA risks.[57]

Finally, even though "advanced paternal age is often defined as 40 years and older," write Emma Frans et al., "there is no consistent evidence for a dramatic increase in risk for these disorders in offspring of fathers over 40. Instead, the risk increases linearly with paternal age."[58] If true, the potential risks of APA may not accrue only to the offspring of those having advanc*ed* paternal age per se; the risks may apply in some degree to all with advanc*ing* paternal age, that is, all parents.

It should be noted, however, that long-term cryopreservation of sperm could in theory carry its own risks to offspring.[59] While children conceived using assisted

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[54] Lars Vedel Kessing et al., *Are Rates of Pediatric Bipolar Disorder Increasing? Results from a Nationwide Register Study*, 2 INT'L J. BIPOLAR DISORDERS 1, 1 (2014), http://www.journalbipolardisorders.com/content/2/1/10 ("The rate of diagnosis of mania/bipolar disorder increased from 1995 to 2014, which did not seem to be explained by more diagnostic attention."). In reporting on the risks of autism spectrum disorders and other conditions of increasing prevalence, as when reporting on risks associated with APA, it is common practice to remind readers that the overall risk of these conditions remains "low." For example, in reporting on the D'Onofrio study, the *New York Times* reported that "[a] threefold increase [in autism risk] would put the odds at about one in 100, still very low. The same goes for the risk of psychosis. The baseline rate is tiny for the children of young, healthy parents, and remains quite low even when doubled." Benedict Carey, *Mental Illness Risk Higher for Children of Older Fathers, Study Finds*, N.Y. TIMES, Feb. 26, 2014, http://www.nytimes.com/2014/02/27/health/mental-illness-risk-higher-for-children-of-older-parents-study-finds.html?_r=0 (While acknowledging that many perceive, for example, a 1 in 68, or 1.5% overall risk of autism to be low, a claim that any given risk should be viewed as being low or high is a normative claim beyond the scope of this article); *Attention-Deficit/Hyperactivity Disorder (ADHD) Data & Statistics*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/ncbddd/adhd/data.html (last visited Sept. 5, 2015) ("The percentage of children with an ADHD diagnosis continues to increase, from 7.8% in 2003 to 9.5% in 2007 and to 11.0% in 2011."); *Autism Spectrum Disorder (ASD) Data & Statistics*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/ncbddd/autism/data.html (last visited Sept. 5, 2015) (explaining the prevalence of autism spectrum disorders increased from 1 in every 150 children in surveillance year 2000 to 1 in every 68 children in surveillance year 2010, which is the most recent year where data is available).

[55] Emma Frans et al., *Advancing Paternal Age and Psychiatric Disorders*, 14 WORLD PSYCHIATRY 91, 92 (2015), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329902/#b18.

[56] Augustine Kong et al., *Rate of De Novo Mutations, Father's Age, and Disease Risk*, 488 NATURE 471, 472 (2012), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3548427/.

[57] *See* James Curley et al., *Epigenetics and the Origins of Paternal Effects*, 59 HORMONES & BEHAV. 306, 311 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2975825/; Mary Perrin et al., *Aberrant Epigenetic Regulation Could Explain the Relationship of Paternal Age to Schizophrenia*, 33 SCHIZOPHRENIA BULL. 1270, 1270 (2007), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2779878/.

[58] Frans, *supra* note 55, at 91.

[59] Gregory M. Fahy & Brian Wowk, *Principles of Cryopreservation by Vitrification*, 1257 METHODS MOLECULAR BIOLOGY 21, 61 (2015) ("[Cryoprotectant agents] have been shown to elevate membrane phase transition temperatures; rearrange the cytoskeleton, including most significantly the meiotic spindle; cause membrane blistering; fuse cell membranes; change gene expression; alter RNA polymerase; weaken DNA-nucleosome binding; destabilize nucleic acid duplexes; impair ribosome assembly; and induce many other

reproductive technologies (ART) are generally at greater risk for negative health outcomes, it is particularly difficult to determine the cause, as persons using ART very often have confounding medical issues.[60] Moreover, there are many different combinations of ART, including intrauterine insemination (ICI), in vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI), and involving the use of cryopreserved semen, oocytes, or embryos. It would require a substantial investment of resources to conduct a study sufficiently powered to find minor increases in risk arising specifically from the cryopreservation of semen in a way that would permit a direct comparison of cryopreservation risks (if any) to APA risks.

IV. PROMOTIONAL CLAIMS

A. *By Cryopreservation Equipment Manufacturers*

As it applies to cryopreservation equipment manufacturers, this issue is straightforward. Although recent case law regarding off-label promotion may relax restrictions on statements that are "not false or misleading,"[61] cryopreservation equipment manufacturers still could not claim wholesale an entirely new indication for their products with all the concomitant benefits of an approved indication. A manufacturer's claim that the use of cryopreservation equipment reduces the risk of disorders in offspring would place these products squarely within the definition of a new medical device: "articles intended for use in the . . . prevention of disease."[62] A company that introduces an article into interstate commerce with an unapproved intended use violates the Food, Drug, and Cosmetic Act.[63] Therefore, under current law, cryopreservation equipment manufacturers would need to seek a new indication.

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adverse changes, but for the most part, the relevance of these observed changes, if any, to most cells being prepared for cryopreservation is currently unknown."); Roger Hart & Robert J. Norman, *The Longer-term Health Outcomes for Children Born as a Result of IVF Treatment: Part I—General Health Outcomes*, 19 HUM. REPROD. UPDATE 232, 240 (2013), http://humupd.oxfordjournals.org/content/19/3/232.long ("The use of cryoprotectants for the practice of sperm, testicular tissue and embryo cryopreservation may add a further potential insult to the developing embryo, and represent a potential mechanism for a long-term influence on fetal development.").

[60] *See* Yue-hong Lu et al., *Long-term Follow-up of Children Conceived Through Assisted Reproductive Technology*, 14 J. ZHEIJIANG U. SCI. 359, 359 (2013), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3650450/ ("In brief, there are still a number of unanswered questions, and further, well-designed studies on the topics described above are urgently needed."); *see also* ESHRE Capri Workshop Group, *Birth Defects and Congenital Health Risks in Children Conceived Through Assisted Reproduction Technology (ART): A Meeting Report*, 31 J. ASSISTED REPROD. & GENETICS 947, 954 (2014), http://www.ncbi.nlm.nih.gov/pubmed/24870703.

[61] *See, e.g.*, United States v. Caronia, 703 F.3d 149, 165 (2d Cir. 2012); Amarin Pharma, Inc. v. FDA, No. 153588, 2015 WL 4720039, at *3 (S.D.N.Y Aug. 7, 2015).

[62] 21 U.S.C. § 321(g)(1)(B) (2012). *See also* 21 U.S.C. § 321(g)(1) (2012) (giving three additional, independently sufficient definitions of "drug"); 21 U.S.C. § 321(g)(1)(A) has been largely written out by case law; 21 U.S.C. § 321(g)(1)(C) provides for "articles (other than food) intended to affect the structure or any function of the body"; 21 U.S.C. § 321(g)(1)(D) simply provides for the inclusion of "components" of the other definitions, and similarly, a "biological product" is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention treatment, or cure of a disease or condition of human being"; 42 U.S.C. § 262(i) (2012) (codified as 21 C.F.R. § 600.3(h) (2015)).

[63] 21 U.S.C. § 355(a) (2012) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug."); *see also* 21 U.S.C. § 331(d) (2012).

B. *By Sperm Banks*

The matter becomes more complicated in the context of sperm banks. On the one hand, sperm banks may be considered only to be providing a service or medical care, over which FDA does not have jurisdiction. On the other hand, sperm banking for this purpose could be considered the creation of a new biologic product or a combination device/biologic product requiring an approved indication. Accordingly, this section considers legal arguments as to whether FDA would have jurisdiction to regulate promotional claims by sperm banks.

To be clear, at present there are no FDA promotional claim restrictions or guidelines for sperm banks. As noted above, the uses of sperm banking heretofore have all been considered "361 Products," intended for "mere functional replacement," even though promotional claims made by sperm banks today arguably go well beyond the mere functional replacement of the 361 Product regulations, offering instead access to elite genetic material.[64] If the purpose of homologous use is really to replace "the same basic function," it is unclear in the context of these claims where mere quality control ends and another type of service begins.[65]

Note, however, that despite ensuring "the best of the best," these claims make no explicit statements regarding expected outcomes. It is the reproductive equivalent of being sold "the most premium, nutritious tomato" on the market. Customers are led to infer that the health outcomes will be better as compared to a less-premium, less-nutritious tomato, but how so and to what degree is left unstated.[66] Yet some sperm banks may wish to go further, making specific claims such as: "banking sperm now could reduce the risk of autism in your offspring." It is this type of specific claim that would arguably move semen beyond the pale of the 361 HCT/P regulations.

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[64] *Donor Selection: Your Ideal Donor is Just a Few Clicks Away*, CAL. CRYOBANK, https://cryobank.com/Why-Use-Us/Donor-Selection/ (last visited June 4, 2015) (For example, a representative claim by the California Cryobank (CCB) states that: "Whether it is education, athleticism, religion, ethnicity, build, complexion, musicality, facial features, or artistry you are interested in (or any combination), [California Cryobank] has the right donor for you . . . . CCB's four donor labs . . . recruit from many of the country's top universities (UCLA, USC, Stanford, Harvard, MIT) . . . Our sperm bank donors are hand-picked and screened intensely before being accepted into our donor program. The quality of our donors is the foundation of our service, with less than 1% of all applicants making it through the selection process. Potential donors are subjected to an exhaustive medical, genetic, and psychological screening—as well as a detailed examination of their background and family medical history . . . Our screening is detailed and far-reaching to ensure that our clients are provided the best of the best."); *Donor Program*, CAL. CRYOBANK, http://www.cryobank.com/ (last visited June 4, 2015).

[65] *See also* KARA W. SWANSON, BANKING ON THE BODY: THE MARKET IN BLOOD, MILK, AND SPERM IN MODERN AMERICA 231–32 (2014) ("Rather than fungible market commodities, the therapeutic merchandise provided by sperm banks are highly individuated frozen semen ampoules tied to a cluster of preferred donor traits. In sperm banking, folk beliefs, expressed as popular eugenics, are not discouraged as unscientific and disruptive to the flows of inventory through body banks but are encouraged through the free market.").

[66] FDA requires pre-market approval for food labeling that makes "health claims," i.e., claims that a substance affects a particular disease or health-related condition, but no pre-marketing approval is required for "dietary guidance statements" and "structure/function claims," which make more generalized statements. *See Label Claims for Conventional Foods and Dietary Supplements*, FOOD & DRUG ADMIN., http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm111447.htm (last visited June 7, 2015).

1. *Argument against FDA Jurisdiction: "361 HCT/P" Classification Should Continue to Apply because the "Intended Use" Has Not Changed*

As discussed above, "361 HCT/Ps" do not require evidence of efficacy, as they are intended to simply perform the biological function that they evolved to perform. Nor are they subject to the labeling, advertising, and promotional claim regulations that pertain to other medical products. The requirement that "361 HCT/Ps" be "intended for homologous use only,"[67] that is, "the product performs the same basic function," would seem to be the most vulnerable factor to the claim that semen, when intended to reduce the risks of disorders in offspring (as opposed to merely conceiving offspring), should continue to qualify as a "361 HCT/P."

There is an argument to be made, however, that this prong of the test is duly satisfied even when there is an objective intent not just to fertilize an egg at a later time, but also to prevent disease in offspring. The argument is as follows: the primary, basic function of the stored semen has not changed at all—that is, its function is to fertilize an egg. To promote the preventive aspect of storage is merely to inform about an *associated* and secondary benefit (i.e., increased safety) realized from choosing this method of insemination. For example, many types of minimally manipulated skin products qualify as 361 HCT/Ps, and although their primary function is to replace skin, these products have associated benefits making them preferable to "un-manipulated" skin grafts, such as lower rates of rejection and faster healing times. Companies making these 361 HCT/P skin products are permitted to compete by advertising their associated benefits both to medical professionals and the general public without any premarket review of safety and efficacy by FDA.[68] Giving this argument full force would mean that sperm banks could make all the claims they wish about the benefits of freezing to reduce risks of APA, as long as those claims are cast as contributing to increased safety and better performance of a product for which the intended use has not changed in the slightest.

2. *Argument against FDA Jurisdiction: Sperm Banking Is a Service. It Does Not Produce a New Article*

FDA regulations clearly state that "semen is considered an HCT/P"—that is, semen is a human cell or tissue *product*.[69] This leads to somewhat odd linguistic results, as when, in 2010, FDA ordered Trent Arsenault, who was selling his own sperm online, "to cease

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[67] 21 C.F.R. § 1271.10(a) (2015).

[68] HEALTH & HUM. SERVS., Final Report, TECHNOLOGY ASSESMENT: SKIN SUBSTITUTES FOR TREATING CHRONIC WOUNDS 27, 37 (Dec. 18, 2012), http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/skinsubs/HCPR0610_skinsubst-final.pdf (identifying thirteen skin graft HCT/Ps sold without premarket review, i.e., "361 HCT/Ps")*; see, e.g.*, *AlloDerm Regenerative Tissue Matrix*, LIFECELL, http://www.lifecell.com/health-care-professionals/lifecell-products/allodermr-regenerative-tissue-matrix/ (last visited June 6, 2015) ("AlloDerm Tissue Matrix promotes tissue regeneration by supporting rapid revascularization, white cell migration and cell repopulation, all of which may lead to increased resistance to risk of infection at the surgical site. AlloDerm Tissue Matrix ultimately transitions into host tissue for a strong, natural repair."); *Puros Dermis Features and Benefits*, ZIMMER DENTAL, http://www.zimmerdental.com/Products/Regenerative/rg_puDermisOverView.aspx (last visited June 6, 2015) ("Puros Dermis exhibits superb soft tissue response and maturation, ideal for aesthetic case requirements." "Excellent handling, rapid hydration, five-year shelf life and room temperature storage."); *Theraskin Description*, SOLUBLE SYSS., http://www.solublesystems.com/Products/TheraSkin (last visited June 6, 2015) ("TheraSkin provides, upon application, an 'at ready' supply of growth factors/cytokins, and a robust collagen scaffold to jumpstart healing in recalcitrant, non-healing chronic wound.").

[69] 21 C.F.R. § 1271.3(d)(3) (2015).

manufacturing" his sperm.[70] However, a sperm bank may argue that it is promoting the preventive benefits of its *services* without making any statements whatsoever about the function of the original semen product. The service argument follows this basic logic: cryopreservation is what allows semen ejaculate from T_0 to fertilize an egg at T_1. In promoting the preventive-use of its services, sperm banks are speaking to the relative benefits of using T_0 sperm at T_1 as compared to using T_1 sperm at T_1, not to any per se benefits of the T_0 semen product. As result, the thing being promoted is not a product but rather a medical service or procedure, and therefore falls outside of FDA's regulatory jurisdiction.[71] In fact, this argument would be consistent with how states view tissue banking; the American Law Institute finds that "legislation in almost all jurisdictions limits the liability of sellers of human blood and human tissue to the failure to exercise reasonable care, often by providing that human blood and human tissues are not 'products' or that their provision is a 'service.'"[72]

3. *Argument in Favor of FDA Jurisdiction: Sperm Banks Would Be Creating New Biologic or New Device/Biologic Combination Products*

As discussed above, biologic products may be regulated solely under Section 361 of the Public Health Service Act ("361 Products"), as equivalents to drugs that require an approved Biologics License Application (BLA), or both. Combination products[73] are medical products that include two or more drugs, devices, or biologics; two or more articles intended to prevent, treat, or cure a disease or health condition, or intended to affect the structure and function of the human body. Because there would be a clear intention to prevent disorders in offspring via cryopreservation of semen, such claims could satisfy the statutory definition's clear meaning of an article "applicable to the prevention, treatment, or cure of a disease or condition of human beings,"[74] and FDA could therefore plausibly classify the cryopreserved semen as a biologic requiring a Biologics License Application or the cryopreservation equipment and semen together as a single Combination Product.

On its face, it may seem odd to classify semen as a medical product equivalent to a drug. The "product's" contents vary by person and by sample; it does not have the

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[70] *Order to Cease Manufacturing of HCT/Ps—Trent*, FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm232852.htm (last visited Nov. 1, 2010).

[71] Drugs and devices are defined by statute as "articles," and biologics as "products." *See* 21 U.S.C. § 321(g)(1) (2012) (defining drugs); 21 U.S.C. § 321(h) (2012) (defining devices); 42 U.S.C. § 262 (2012) (defining biologics).

[72] RESTATEMENT (THIRD) OF TORTS: PROD. LIAB. § 19 (AM. LAW INST. 1998)*; see also* Cryolife v. Superior Court, 110 Cal. App. 4th 1145, 1154 (2003) (finding "that the collection, processing and storage of human tissue for transplantation" is a "service" under California state law); Condos v. Musculoskeletal Transplant Found., 208 F. Supp. 2d 1226, 1230 (D. Utah 2002) (finding "that human bone tissue is not a 'product'" under Utah state law).

[73] FDA's Office of Combination Products, a small nine-person office, reviews and then assigns an application for a combination product to either the Center for Drug Evaluation and Research (CDER), the Center for Device and Radiological Health (CDRH), or the Center for Biologics Evaluation and Research (CBER) based on "the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." 21 C.F.R. § 3.2(m) (2015). *See generally About FDA: Office of Combination Products*, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm (last visited June 11, 2015).

[74] 42 U.S.C. § 262(i) (2012).

uniformity expected of a pharmaceutical. But in fact this is exactly how FDA regulates both cord blood intended for unrelated, allogeneic use[75] and fecal microbiota for transplantation (FMT).[76] Both products, like semen, are drawn or excreted from humans with obvious variability.

Of the above legal arguments, it should be acknowledged that none are completely satisfactory or dispositive. The third argument—that sperm banks are creating a new product—would seem to be sufficient to establish FDA jurisdiction; the first and second arguments are valid reasons for FDA to decline to take action. Thus, either outcome—requiring a new indication, or not—would seem to be reasonable, and the agency's decision to require or not require an indication would likely receive *Chevron* deference.[77] The question then is simply what policy should FDA pursue.

V. RECOMMENDATIONS

A. *For FDA*

One of the primary purposes for requiring approved indications is to incentivize the generation of new knowledge about safety and efficacy.[78] Unfortunately, for sperm banks, these incentives may never materialize. Incentivizing research through intellectual property rights requires exclusion: such a regime would grant monopoly powers to whichever sperm bank earned the indication. But unlike in a traditional pharmaceutical or medical device context in which the manufacturer is both the exclusive promoter and the exclusive supplier, in the sperm banking and cryopreservation equipment context, even if they were limited in how they advertise, all sperm banks and cryopreservation equipment manufacturers could continue to supply demand indirectly, because after learning that sperm banking may reduce the risk of disorders in offspring, customers could still use any sperm bank to that end. In this way, incentives to invest in new

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[75] *Cord Blood Banking, supra* note 27.

[76] FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT *Clostridium difficile* INFECTION NOT RESPONSIVE TO STANDARD THERAPIES (July 2013), http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf. *See generally* Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396 (2015).

[77] Chevron v. Nat. Res. Def. Council, 467 U.S. 837, 843 (1984) ("If the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute.").

[78] *See* Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 483 (2009) ("The real value of government limits on off-label promotional activities is that they give manufacturers an incentive to sponsor the research needed to determine whether off-label uses are safe and effective."); Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 101, 144 (2014) ("There is no need for companies to design these studies to meet the FDA's standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use, but rather intend to use the study findings only in marketing communications."); Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 560–61 (2014) ("In this realm, truth or falsity is not knowable a priori. Any knowledge of truth or falsity emerges from our economic and temporal investments, by those who have incentives to make those investments, in legal and institutional context that define those incentives . . . In this sense, the [Food, Drug, and Cosmetic Act] does not exist to police the truth. Instead, the [Food, Drug, and Cosmetic Act] exists to provide and protect an epistemic and economic process of research and discovery, one that helps physicians make more rational decisions.").

research may be crippled by a limited power to meaningfully exclude others. Rather than generate new knowledge meant to satisfy the evidentiary barrier to a new indication, firms may rationally decide simply to not pursue the indication.

Recognizing this limitation, FDA should present the issue to its Cellular, Tissue, and Gene Therapies Advisory Committee, asking whether, based on safety and efficacy data already in the public domain, it would approve sperm banking for the purpose of reducing the risk of disorders associated with APA, and if so, which disorders. If the advisory committee recommends the approval of such an indication,[79] then this "indication" could apply globally to all sperm banks and cryopreservation equipment manufacturers through informal guidance creating a safe harbor for such promotion. If the advisory committee would not recommend approval it could provide direction as to what evidentiary gaps would likely need to be filled for an indication to be approved. In theory, if the costs of generating the additional requisite evidence were less than the projected increases in revenue, firms, unable to truly exclude each other from the market, may instead invest in the research through collective action, even though new market entrants could still hamper their return on investment.

B. *For Congress*

Separately, Congress should give FDA broader authority to regulate the safety of sperm banking, such that FDA could address APA safety concerns regardless of whether an affirmative indication or safe harbor is appropriate. As noted above, the agency currently regulates semen as a "361 HCT/P" under its authority to prevent the transmission of communicable diseases as provided by 42 U.S.C. § 264. The agency could not likely promulgate age-related safety regulations under this statutory authority for communicable diseases.

Under a new statute, however, the agency could extend to the issue of age its current bifurcation of sperm banking safety standards for communicable diseases based on whether the use is between sexually intimate partners or for allogeneic use by third parties.[80] If the agency determines that APA is a significant risk to offspring, then sperm banks that provide sperm for allogeneic use should have to meet certain donor age requirements; for example, the agency could set a ceiling on the age of eligible donors, as both the American Society of Reproductive Medicine and the American Association of Tissue Banks recommend their members do voluntarily.[81] But in the intimate partner

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[79] Note that biologics do not technically require controlled clinical investigations for approval. 21 C.F.R. § 601.25(d)(2) (2012) (requires that, for biologics, "proof of effectiveness shall consist of controlled clinical investigations" except that this requirement may be "waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness"). *See generally* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS (May 1998), http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf.

[80] 21 C.F.R. § 1271.75 (2015) requires that sperm donors be screened for communicable diseases unless, pursuant to 21 C.F.R. § 1271.90 (2015), the sperm is "donated by a sexually intimate partner of the recipient for reproductive use."

[81] The American Society of Reproductive Medicine (ASRM) recommends that "[s]perm donors should be of legal age and ideally less than 40 years of age to minimize the potential hazards of aging." AM. SOC'Y OF REPROD. MED., THIRD-PARTY REPRODUCTION: A GUIDE FOR PATIENTS 10 (2012), https://www.asrm.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/thirdparty.pdf. Similarly, the American Association of Tissue Banks' *Standards for Tissue Banking* states that "[s]emen donors shall be younger than 40 years of age to minimize the risk of genetic anomalies except with the written agreement of the user physician." AM. ASS'N OF TISSUE BANKS, STANDARDS FOR TISSUE BANKING 12 (13th ed. 2012), http://www.aatb.org/aatb/files/ccLibraryFiles/Filename/000000000495/Overview%20

context there would be no such requirement: individuals could continue to bank their sperm at any age without restriction.

VI. CONCLUSION

This article sought to identify an emerging regulatory issue relating to both the public health and individual family planning, and to make recommendations for how FDA and Congress should address it. The question remains as to why sperm banks have not already attempted to promote their services for this purpose. Some may legitimately have not thought to promote this use of sperm banking; that was ReproTech's explanation, and their subsequent inclusion of this reason on their website would seem to validate that explanation. It may be significant, however, that ReproTech offers only personal and directed-donor services, not general donor services like most sperm banks. Indeed, most sperm banks, the ones selling donor sperm, may in fact have an interest in maintaining silence. Full acknowledgement of the risks associated with APA would likely be bad business for those sperm banks for which the primary source of revenue comes from clients seeking donor sperm. For these sperm banks, self-storage is only an ancillary business. Their primary source of revenue comes from delivering the more premium service of banking donor sperm for third-party use. This premium service involves finding desirable and varied sperm donors, conducting detailed family histories and required infectious disease screenings,[82] collecting a sufficient number and quality of samples, and then presenting these many worthwhile options to clients at a considerable markup.[83] If sperm banks were to concede to *these* clients, the sperm *buyers*, that a 20-year-old donor's sperm may be inherently safer than a 35-year-old donor's sperm, it seems to follow that much of a sperm bank's inventory would necessarily lose value. Furthermore, there would be increased competition for an even narrower range of sperm donors (likely requiring higher financial incentives and recruitment costs). There are, therefore, potential financial incentives in favor of some sperm banks not "over-educating" clients about the goods in this market. If true, this account of the current market for sperm banking services further supports Congress and FDA treating APA as a safety concern requiring mandatory age restrictions on allogeneic sperm donations, as the industry is not likely to seek a novel indication that simultaneously disrupts its own business model.

In conclusion, it should be noted that failing to provide timely guidance on the use of cryopreservation to reduce APA risks could harm the public health regardless of whether such use is deemed safe and effective, or not. If such use is safe and effective, then SGPs would have continued to advance in their years without knowing that a product

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and%20Updates%20-%2013th%20edition%20of%20Standards.pdf. *See also* British Andrology Society, *UK Guidelines for the Medical and Laboratory Screening of Sperm, Egg, and Embryo Donors*, 11 HUM. FERTILITY 201, 202 (2008), http://informahealthcare.com/doi/pdf/10.1080/14647270802563816 ("The recommended upper age limit for [sperm] donation is 40 for males.").

[82] 21 C.F.R. §§ 1271.75–1271.90 (2015).

[83] *See Current Prices as of January 2015*, CAL. CRYOBANK, http://www.cryobank.com/Services/Pricing/#DonorSemen_box (last visited Apr. 12, 2015) (one vial of semen by an open donor for intrauterine insemination costs $840); *Cryobank Sperm Donor Pay & Benefits*, CAL. CRYOBANK, http://www.spermbank.com/why-donate/sperm-donor-pay (last visited Apr. 12, 2015) (Donors are compensated up to $125 per semen sample, which produces several vials.)*; see also* KARA W. SWANSON, BANKING ON THE BODY: THE MARKET IN BLOOD, MILK, AND SPERM IN MODERN AMERICA 225 (2014) (taking note of "a markup by the bank that can reach 2,000 percent").

or service, used sooner, could have reduced risks to their offspring. If this use is not safe and effective, then SGPs may be doing harm to their offspring directly, such as through toxic cryoprotectant agents, or indirectly, by delaying childbearing with undue reliance on cryopreservation. Thus, here, as in most of medicine, FDA has an important role to play in protecting the public health.