U.S. FOOD & DRUG ADMINISTRATION

AUG 09 2018

Wendy Kramer
Director, Donor Sibling Registry
P.O. Box 1571
Nederland, CO 80466

Re: Docket Number FDA-2017-P-0052

Dear Ms. Kramer:

This letter responds to your citizen petition, received on January 3, 2017, on behalf of the Donor Sibling Registry (the "Petition"), in which you requested the Commissioner of Food and Drugs develop regulation and/or oversight of the gamete donation industry. You allege that the Food and Drug Administration (FDA) currently mandates minimal medical testing of sperm and egg donors and that no other regulation of the industry exists.

Specifically, you are requesting expanded regulation of cryobanks with regard to "medical testing and health follow-up," which would include: 1) standardizing and expanding preconception testing so that it includes, among other things, full genome sequencing (sequence testing); 2) standardizing a protocol to ensure that consumers are informed about test results and the source of the data; 3) requiring post-conception medical, genetic, and social updates; and 4) requiring electronic recordkeeping.

As we understand the Petition, you also request regulation related to "openness and transparency" as well as "recordkeeping and communication." Specifically, you request regulation that addresses the following: 1) banning anonymous gamete donation; 2) tracking all recipients, donors, and births in a central database indefinitely and making this information accessible to involved families; 3) mandating reporting of donor-conceived live births; and 4) limiting the number of births conceived with gametes from a given donor.

We appreciate your concern for the best interests of donor-conceived children and your interest in the development of further oversight of the gamete donation industry. However, after careful review and consideration, we deny the Petition for the reasons set forth below.

DISCUSSION

I. BACKGROUND

FDA is an agency within the Department of Health and Human Services (HHS) and, by delegation from the Surgeon General and the Secretary of HHS, has authority under section 361 of the Public Health Service Act (PHS Act) to:

> make and enforce such regulations as in [FDA's] 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. For purposes of carrying out and enforcing such regulations, [FDA] may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in [FDA's] judgment may be necessary.

PHS Act § 361(a), 42 U.S.C. 264(a).

Under this authority, FDA has promulgated regulations in Title 21 of the Code of Federal Regulations (CFR), part 1271 (part 1271), regarding human cells, tissues, or cellular or tissue-based products (HCT/Ps). Since HCT/Ps contain components from the human body, they pose some risk of carrying pathogens that could cause disease in health-care personnel or other handlers, recipients, and family members or other close contacts of recipients.

Included in the definition of HCT/Ps are reproductive cells and tissue, such as semen, oocytes, and embryos (see 21 CFR 1271.3(d) and 1271.3(l)). FDA generally considers reproductive cells and tissue to be HCT/Ps that meet the criteria listed in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in part 1271.[1]

As mentioned, section 361 of the PHS Act authorizes FDA to make and enforce regulations to "prevent the introduction, transmission, or spread of communicable diseases." Many of the requests in the Petition are for regulations to control the risk of transmission of genetic diseases or conditions (referred to, collectively, as "genetic diseases" for purpose of this response). Based on our current scientific understanding, we do not consider genetic diseases, such as those identified in the Petition (i.e., cystic fibrosis, polycystic kidney disease, and schizophrenia), to be "communicable diseases" within the meaning of section 361 of the PHS Act because genetic diseases do not arise as a result of an infectious agent or its toxic products.[2] Instead, genetic diseases occur as a result of a genetic defect or gene mutation that is due to a change in the

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[1] See, *e.g.*, FDA's 2007 guidance document, *Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Small Entity Compliance Guide.* https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm062592.pdf

[2] Although the term "communicable diseases" is not specifically defined in section 361 of the PHS Act, FDA interprets the term to be limited to illnesses that are due to infectious agents or their toxic products. For example, see 21 CFR 1271.150(a), which states that "[c]ommunicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents." This is also consistent with how the term "communicable diseases" is defined in other parts of FDA's regulations (see 21 CFR 1240.3(b) and 21 CFR 1250.3(b)).

sequence of DNA.[3,4,5] Some genetic diseases are caused by gene mutations that can be inherited, whereas other genetic diseases can be due to acquired gene mutations that result from either a spontaneous new mutation of a gene or environmental exposure.[6] There are also genetic disorders that are "multifactorial inheritance disorders," meaning they are caused by a combination of inherited mutations in multiple genes and exposure to certain environmental factors.[7] Since we do not consider genetic diseases to be "communicable diseases" within the meaning of section 361 of the PHS Act, we decline to issue regulations for the purpose of preventing the introduction, transmission, or spread of genetic diseases.

II. EXPANDING REGULATION OF CRYOBANKS REGARDING MEDICAL TESTING AND HEALTH FOLLOW-UP

The Petition requests that FDA develop new regulations to address what you refer to as "medical testing and health follow-up." Specifically, the Petition requests that FDA: 1) standardize and expand preconception testing so that it includes, among other things, full genome sequencing (sequence testing); 2) standardize a protocol to ensure consumers are informed about test results and the source of the data; 3) require medical, genetic, and social updates; and 4) require electronic recordkeeping.

A. Standardize and Expand Preconception Testing

The Petition requests that FDA require standardized and more comprehensive preconception testing for gamete donors. This request focuses on genetic testing and, in particular, full genome sequencing. However, as explained above, based on our current scientific understanding, we do not consider genetic diseases to be "communicable diseases" within the meaning of section 361 of the PHS Act. Since requiring genetic testing of gamete donors is unrelated to preventing the introduction, transmission, or spread of communicable diseases within the meaning of section 361 of the PHS Act, we decline to issue regulations to require such genetic testing at this time.

It is unclear whether your request that FDA expand preconception testing requirements includes a request for expanded testing requirements for communicable disease agents. Regulations are already in place with requirements to test for evidence of infection due to relevant communicable disease agents, including human immunodeficiency virus, types 1 and 2; hepatitis B virus; hepatitis C virus; and *Treponema pallidum* (see 21 CFR 1271.80 and 1271.85). Additional testing is required for donors of viable, leukocyte-rich cells or tissue (21 CFR 1271.85(b)) and for donors of reproductive cells or tissue

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[3] Iyengar SK, Elston RC. The Genetic Basis of Complex Traits: Rare Variants or "Common Gene, Common Disease?" Methods Mol Biol 2007;376:71-84. https://www.ncbi.nlm.nih.gov/pubmed/17984539

[4] Avramopoulos D. Recent Advances in the Genetics of Schizophrenia. Mol Neuropsychiatry 2018 Jun;4(1):35-51. https://www.ncbi.nlm.nih.gov/pubmed/29998117

[5] Tayoun ANA, Krock B, Spinner NB. Sequencing-based diagnostics for pediatric genetic diseases: progress and potential. Expert Rev Mol Diagn 2016 Sep;16(9):987-999. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5040519/

[6] See footnotes 3,4, and 5.

[7] See footnote 5.

(21 CFR 1271.85(c)). The testing requirements are subject to the exceptions described in 21 CFR 1271.90.

The Petition does not identify any particular types of tests for communicable disease agents that should be required in addition to those required under existing regulations, and it does not provide an explanation of why such additional testing is needed. Accordingly, we do not have a sufficient basis on which to evaluate such a request. Although we may, in the future, determine that requiring additional communicable disease testing is necessary to prevent the introduction, transmission, or spread of communicable diseases, we decline to impose additional communicable disease testing requirements at this time.

B. Standardize a Protocol to Ensure Consumers Are Informed about Test Results and the Source of the Data

You request that FDA require a standardized protocol for informing consumers of test results and sources of data. The Petition appears to focus on informing recipients of gamete donors' genetic testing results. As explained above, based on our current scientific understanding, we do not consider genetic diseases to be "communicable diseases" within the meaning of section 361 of the PHS Act. Since requiring the sharing of a gamete donor's genetic testing results is unrelated to preventing the introduction, transmission, or spread of communicable diseases within the scope of this statutory authority, we deny this request.

It is unclear whether the Petition seeks to request that FDA mandate, for communicable diseases within the scope of existing part 1271 regulations, the sharing of communicable disease testing results and the source of the data with the recipients of HCT/Ps. Although we recognize the importance of HCT/P recipients' being fully informed regarding the risks of communicable disease transmission, we decline to impose such a requirement at this time. Under current regulations, with limited exceptions, a donor with reactive results from the required testing for relevant communicable disease agents is considered ineligible, and an HCT/P from such a donor must not be used (e.g., see 21 CFR 1271.45(c) and 21 CFR 1271.50(b)(2)). In the limited situations in which an HCT/P may be used from a donor with reactive test results, the HCT/P must be prominently labeled with warnings regarding the reactive test results (21 CFR 1271.65(b); 21 CFR 1271.90(c)).[8] For example, an HCT/P from an ineligible directed reproductive donor with reactive test results must be labeled with the statement, "WARNING: Advise patient of communicable disease risks," and the statement, "WARNING: Reactive test results for (name of disease agent or disease)" (21 CFR 1271.65(b)(2)). In that case, the establishment that manufactured the HCT/P would also be required to document that it notified the physician using the HCT/P of testing and screening results (21 CFR 1271.65(b)(3)). Additionally, in the limited situations in which an HCT/P from a donor who was not tested may be used, the HCT/P

[8] These labeling requirements would not apply to an HCT/P from a donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test and who is determined to be eligible (see 21 CFR 1271.50(b)(2); 21 CFR 1271.80(d)(1)).

must be prominently labeled regarding the absence of such testing (21 CFR 1271.90(c)). We also note that physicians are under legal and ethical obligations, requiring them to discuss the risks of communicable disease transmission stemming from the use of HCT/Ps. FDA relies on physicians to meet these obligations when discussing procedures involving HCT/Ps with recipients.

C. Require Medical, Genetic, and Social Updates

The Petition requests that FDA require post-conception medical, genetic, and social updates from gamete donors as well as medical updates from donor-conceived children.

At this time, FDA declines to require post-conception genetic or social updates from gamete donors since these updates are not related to preventing the introduction, transmission, or spread of "communicable diseases" within the meaning of section 361 of the PHS Act. Although the Petition does not clearly state that it is requesting post-conception genetic and social updates from donor-conceived children, we note that these updates would also be unrelated to preventing the introduction, transmission, or spread of communicable diseases within the scope of this statutory authority.

FDA also declines, at this time, to require post-conception medical updates from gamete donors or donor-conceived children. If establishments were required to collect these updates, they would have no way to ensure that donors, offspring, or physicians would provide them with the relevant information. Moreover, even if this information were collected, post-conception medical updates from gamete donors and donor-conceived children are unlikely to provide any useful information regarding relevant communicable disease agents or diseases that the offspring may have at birth.

Although immunologic and biologic factors are specific to a particular communicable disease agent, based on available scientific data, we believe the current time frame during which a donor specimen must be collected for testing is sufficient with respect to determining the risk of transmission of a communicable disease associated with an HCT/P. According to 21 CFR 1271.80(b), for most HCT/Ps, including semen, establishments must collect the donor specimen for testing at the time of recovery of cells or tissue from the donor or up to seven days before or after recovery.[9] For donors of certain HCT/Ps, including oocytes, the donor specimen may be collected for testing up to 30 days before recovery. Further, with limited exceptions, anonymous semen donors must have repeat donor testing at least 6 months after the date of donation, as described in 21 CFR 1271.85(d). The donated semen must be quarantined under 21 CFR 1271.60(a) until retesting is complete and the donor is determined to be eligible. This allows additional time for any communicable disease agent or disease to manifest if, by chance, the donor was in the "window period" of detectability, further reducing the risk of transmission of infection.

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[9] With repeat semen donors from whom a specimen has already been collected and tested and for whom retesting is required under 21 CFR 1271.85(d), collecting a donor specimen at the time of each donation is not required (21 CFR 1271.80(b)(2)).

D. Require Electronic Recordkeeping

The Petition requests that FDA require electronic recordkeeping. Existing record retention requirements do not include a requirement that records be retained electronically but specify that "[r]ecords that can be readily retrieved from another location by electronic means are considered 'retained'" (21 CFR 1271.55(d)(3)). There are potential benefits of electronic medical records, such as a possible reduction in the rate of medical errors and the potential to improve both communication and efficiency among staff. We encourage establishments to consider the use of electronic medical records. At this time, however, we understand that requiring the use of electronic medical records would be burdensome and impractical for many tissue establishments, and it is unclear that the potential benefits would justify this burden on the regulated tissue industry. Accordingly, we deny this request.

III. OPENNESS AND TRANSPARENCY - BANNING ANONYMOUS GAMETE DONATION

You request that FDA ban anonymous gamete donation. The Petition contends that such a ban would, among other things, promote accuracy of donor information (e.g., information regarding a donor's appearance) and have psychological benefits for offspring. However, we are unaware at this time of any causal relationship between donor anonymity and transmission of "communicable diseases" within the meaning of section 361 of the PHS Act. Accordingly, we decline to prohibit anonymous gamete donation at this time.

IV. RECORDKEEPING AND COMMUNICATION

A. Track Recipients, Donors, and Births in a Central Database Indefinitely and Make Information Accessible to Involved Families

You request that FDA require the indefinite tracking of all recipients and births as well as donors, by social security number, in a central database. You also request that FDA require that this information be accessible to all involved families. In addition, you request that FDA require the indefinite safeguarding of all records in a central database.

The Petition asserts that a central database would facilitate access to and recording of information, including medical information and information regarding the number of births to a particular donor. However, the Petition does not explain why requiring the tracking of recipients, donors, and births in a central database is necessary to prevent the introduction, transmission, or spread of communicable diseases. Additionally, a central database that tracks donors by social security number and that is accessible to involved families raises concerns regarding maintaining the privacy of patient information. Such a registry may also create a significant burden on and be impractical for some tissue establishments, and such a registry does not appear, at this time, to be sufficiently related to preventing the introduction, transmission, or spread of "communicable diseases"

within the meaning of section 361 of the PHS Act. Although we encourage interested parties to explore methods of tracking donors, donations, and recipients, including the establishment of a central registry, we decline to require such a registry at this time.

The Petition also requests that FDA require that records be retained indefinitely. Under 21 CFR 1271.55(d)(4), establishments are required to "retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest." Under this existing record retention requirement, there is a possibility that records for a reproductive HCT/P would be required to be retained for decades. For example, if a reproductive HCT/P has no expiration date and is cryopreserved for long-term storage, records pertaining to that HCT/P would need to be retained for the time period between the donation and transfer of the HCT/P, which could be decades, plus an additional ten years after transfer. FDA is not aware of a standard expiration period used for cryopreserved reproductive HCT/Ps. Not assigning an expiration date increases the possibility that records pertaining to an HCT/P will need to be retained for multiple decades.

The Petition does not explain why expanding the required record retention period beyond 10 years is necessary for preventing the introduction, transmission, or spread of "communicable diseases" within the meaning of section 361 of the PHS Act. When determining that a 10-year record retention requirement would be appropriate, FDA took into account, among other considerations, that certain diseases, such as transmissible spongiform encephalopathies, appear to have long latency periods (see 69 FR 29786 at 29787 (May 25, 2004)). A requirement for retaining records indefinitely may create a significant burden on and be impractical for some tissue establishments. Accordingly, although we may, in the future, determine that extending the required record retention period is necessary to prevent the introduction, transmission, or spread of communicable diseases, we decline to expand the requirement at this time.

B. Mandate Reporting of Donor-Conceived Live Births

In the Petition, you seek to mandate the reporting of donor-conceived live births "in order to accurately track the number of donor-conceived children." We decline to impose such a requirement at this time because such a requirement is not necessary to prevent the introduction, transmission, or spread of "communicable diseases" within the meaning of section 361 of the PHS Act.

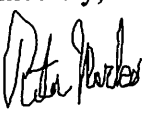
C. Limit the Number of Births Conceived with the Gametes from a Given Donor

In the Petition, you seek to limit the number of births conceived with the gametes from a given donor. We deny this request because such a limitation is unrelated to preventing the introduction, transmission, or spread of "communicable diseases" within the meaning of section 361 of the PHS Act.

V. CONCLUSION

After careful consideration of the issues raised in the Petition and based on the reasons provided above, FDA denies the Petition in its entirety.

Sincerely,



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