August 4, 2017

VIA FACSIMILE AND UPS

John Zhang, PhD, MD
Chief Executive Officer
Darwin Life, Inc. and New Hope Fertility Center
4 Columbus Circle, 4th Floor
New York, NY 10019

Dear Dr. Zhang:

As explained in your recent article in Reproductive Biomedicine Online, available at http://www.rbmojournal.com/article/S1472-6483(17)30041-X/pdf, your firm used mitochondrial replacement technology (hereinafter, MRT) to form a genetically modified embryo in the United States. Your article further claims that you then exported that genetically modified embryo to Mexico for implantation to prevent the transmission of mitochondrial disease. Thereafter, you submitted a written request, dated April 22, 2016, for a pre-investigational new drug (IND) meeting for a clinical investigation of a "spindle transfer for assisted pregnancy in patients with mitochondrial disease."

Since December 2015, the United States Food and Drug Administration (FDA) has been prohibited by Congress in provisions in annual federal Appropriations Acts from using funds to accept IND submissions for clinical investigations that involve "a human embryo . . . intentionally created or modified to include a heritable genetic modification." *See, e.g.*, The Consolidated Appropriations Act, 2017, Pub. L. No. 115-31; H.R. 244, 115th Cong. § 736 (2017) (enacted). Consistent with this prohibition, FDA declined your pre-IND meeting request, because your proposed human subject research would involve the intentional creation of a genetically modified embryo.

Your April 2016 letter further informed FDA that "until an effective IND is in place, and a clinical trial is authorized by FDA, Darwin [L]ife will not use its spindle transfer technology again within the United States to support ex-US studies or procedures." Despite that commitment, you continue to market MRT to prevent the transmission of mitochondrial disease and to treat infertility. For example, among other claims, you, Darwin Life, Inc., and/or the New Hope Fertility Center promote MRT:

- As "the first proven treatment for certain genetic disorders," including mitochondrial disease, "and a successful solution to age-related infertility," *see* http://darwinlife.com/about-us/; http://darwinlife.com/mitochondrial-disease/;

- As "prolonging natural fertility," *see* http://darwinlife.com/technology/;

- To "prevent maternally transmitted diseases, like Mitochondrial Disease, in an unprecedented way" potentially "yield[ing] the removal of this disease forever," *see* http://darwinlife.com/technology/;

- To "prevent the inheritance of diseased mitochondria. Mitochondrial Disease, also known as Mito-disease, is the primary disorder currently addressed. Other applications will be discussed in the future." *see* http://www.newhopefertility.com/her-ivf-3-parent/; and

- As "a cure for Mitochondrial Disease." *See* http://drjohnzhang.com/3-parent-ivf-a-big-leap-for-humankind/?__hstc=137128623.8567c34ebd7f737558febdb3abdb2467.1497886916521.1497886916521.1497886916521.1&__hssc=137128623.2.1497886916522&__hsfp=328184882l.

Please be advised that you are using MRT to form a genetically modified embryo, which is subject to FDA's regulations with respect to human cells, tissues, or cellular or tissue based products (HCT/Ps) under 21 CFR Part 1271, issued under authority of section 361 of the Public Health Service Act (PHS Act [42 U.S.C. 264]). HCT/Ps that do not meet all of the criteria in 21 CFR 1271.10(a) and do not qualify for any exceptions in section 1271.15, are subject to additional regulation, including appropriate premarket review.

The genetically modified embryo that you formed using MRT does not meet all the criteria in 21 CFR 1271.10(a) and does not qualify for any exceptions. Therefore the HCT/P is not regulated solely under section 361 of the Public Health Service Act (PHS Act) [42 U.S.C. 264] and the regulations in 21 CFR Part 1271, but is also regulated as a drug as defined under section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 321(g)], and a biological product as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i). Specifically, your processing constitutes more than minimal manipulation of cells or nonstructural tissues, as defined in 21 CFR 1271(f)(2).

To lawfully market a drug that is also a biologic, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a demonstration of safety, purity, and potency. While in the development stage, such biological drugs may be distributed for clinical use in humans only if the sponsor has an IND application in effect as specified by FDA regulations (21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312). The MRT-produced HCT/P is not the subject of an approved biologics license application (BLA) nor is there an IND in effect. Moreover, as noted above, FDA cannot accept an IND for a clinical investigation

involving your HCT/P, and such human subject research cannot legally be performed in the United States. Nor is exportation permitted unless it meets the requirements of an applicable export exemption.

In general, there are several exemptions from the licensing requirement for a drug that is also a biological product when that drug is for export, specifically under section 802 of the Act [21 U.S.C. 382], 21 CFR 312.110(b)(1), and 21 CFR 312.110(b)(4). However, your export at issue here did not meet the requirements of any of these export exemptions. For example, there is not an IND in effect as required by 21 CFR 312.110(b)(1), you did not provide the written certification to FDA as required by 21 CFR 312.110(b)(4), and you did not provide the written notification to FDA as required by section 802(g) and 21 CFR 1.101(d). Although the written notification to FDA is not required when a drug is exported under section 802(c) or 802(d), these export exemptions do not apply here because, among other things, export was not to a country described in section 802(b)(1)(A)(i) or (ii).

This letter is not intended to be an all-inclusive list of violations. It is your responsibility to ensure full compliance with the FD&C Act and the PHS Act and their implementing regulations.

We request that you notify this office, in writing, of the steps you have taken or will take to address the violation noted above and to prevent recurrence. Any response to this letter should be sent to me, in writing, at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 10903 New Hampshire Avenue, Bldg. 71, Silver Spring, MD 20993. Please be advised that only written communications are considered official.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research