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Letter

Response: First birth following spindle transfer

To the Editor

In a letter in this issue of *RBMOnline*, Norbert Gleicher and colleagues (2017) criticize a paper describing the birth of the first mitochondrial replacement therapy (MRT) baby (Zhang et al., 2017) and debate the views expressed in the accompanying editorial (Alikani et al., 2017). Here, we offer a point of discussion related to the argument of legality posed by Dr Gleicher and colleagues. Regarding the now-published details of the location of (i) IVF, egg donation and MRT procedures in New York City, (ii) blastocyst vitrification and biopsy in New York City, (iii) cryopreserved embryo transport from the USA to Mexico and (iv) embryo transfer to the patient in Dr Zhang's New Hope Clinic in Mexico, the argument is made by Gleicher and colleagues that this 'clearly established intent to breach FDA guidelines'. We would like to elaborate, as the authors of the letter appear misinformed about the USA Food and Drug Administration (FDA) guidelines in this area of research.

The only written regulation from the FDA is an archived letter issued to sponsors and researchers in July 2001 from Dr Kathryn Zoon, the then FDA director of its Center for Biologics Evaluation and Research (CBER) – https://wayback.archive-it.org/7993/20170404210748/https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm

This one-page letter asserted that the FDA could regulate cell, gamete and embryo research involving genetic alteration of the germline, under its authority to regulate drugs and biological products (i.e., the articles used in the research). The letter states that:

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

Researchers in 2001 were perplexed by the letter, which failed to address the physiology of fertilization and embryonic development and pregnancy, and seemingly required reproductive specialists to consider the altered cell, gamete or embryo as a 'new drug' or 'biological product'. The reason the FDA took this step is that it has no authority to regulate the practice of medicine under its statutory authorities (as the Agency has stated itself countless times); the proposed framework of the 'embryo as a new drug' is the only way the FDA could assert jurisdiction, which led in turn to directing physicians and researchers down the pathway to submitting an IND, the typical pathway one would use to obtain access to unapproved new drugs for clinical research in the United States. However, there are also well-accepted pathways that allow for the export of unapproved new drugs from the USA. For example, the FDA's '312 Program' was established to allow for export of unapproved new drugs for investigational use outside of the United States where no IND is in place and the research is done outside of FDA's purview.

It is our view that Gleicher and colleagues do not provide adequate background information about the definition by the FDA of the MRT embryo as an investigational new drug. The IND framework derives from a completely different set of regulations than the more logical guidelines established by UK regulators and parliamentarians. In terms of ethics and legal aspects, the comparison could be considered comical, if it were not so consequential. Performing MRT in the United States (which is, in the FDA framework, considered as the manufacturing of an investigational unapproved new drug for export), and shipping the 'product' outside the United States for research is not out of the norm, and should not be considered as an attempt to circumvent the FDA's 2001 'guidelines'.

The real focus of our attention, however, should be on the need to develop a regulatory framework for conducting clinical MRT research within the United States. In 2001, a CBER Director at FDA (at least two levels down from the Senate-confirmed FDA Commissioner) issued an ambiguous letter to IVF clinics and researchers, which, for the past 16 years has effectively stalled all clinical research in this field in the USA. This kind of governance by letter, sidestepping processes that Congress and the FDA put in

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place to help ensure thoughtful discourse and involvement of stakeholders in policy development – such as 'notice and comment' rulemaking under the Administrative Procedures Act, or development of guidelines under the FDA's Good Guidance Practices which also call for stakeholder involvement – is as inappropriate today as it was in 2001. Congress, too, shares blame by creating more impediments to the development of a cohesive and coherent regulatory framework for MRT research by prohibiting FDA expenditures on IND reviews for MRT products since 2016. It is incumbent on patients, researchers, physicians, and even lawyers, who simply believe in good governance to advocate for a framework promoting medical progress in this important area.

Declaration: Epstein, Becker & Green PC represents New Hope Fertility Center in New York City in FDA-related matters. Jacques Cohen has advised Epstein, Becker & Green PC, via James Boiani, concerning regulatory FDA matters related to MRT.

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