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Via email: mitochondriareview@hfea.gov.uk

To the Mitochondria Review Policy Team, HFEA:

We are writing in response to the "Call for evidence: Update to scientific review of the methods to avoid mitochondrial disease." As you know, the US Food and Drug Administration's Cellular, Tissue and Gene Therapies Advisory Committee Meeting held a public meeting about these proposed methods on February 25-26, 2014.

The FDA's 35-page briefing document about the scientific, technologic, and clinical issues related to what it terms "mitochondrial manipulation technologies" previews some of the issues that were discussed at the meeting. The document notes that "the full spectrum of risks… has yet to be identified," and offers a list of known safety concerns regarding both the women involved and the potential resulting children. These include damage caused to the egg or embryo by the manipulations, nuclear-mitochondrial incompatibility, epigenetic modification of nuclear DNA, and the impact of the chemicals and drugs used at various points throughout the procedure.

Further, the briefing document states that none of the existing data, which it terms "preliminary evidence," should be seen as traditional proof-of-concept studies because with one exception, none of the studies used eggs or embryos containing abnormal mitochondria. In other words, the studies were not conducted with models of mitochondrial disease. Because of this, the document states, "it is not clear whether these data provide any support for the potential effectiveness of these methods in humans."

In some eleven and a half hours of presentations and deliberations on February 25 and 26, the committee members heard and discussed these and other serious concerns about the safety and efficacy of pro-nuclear transfer, maternal spindle transfer, and related oocyte and embryo modification techniques. Some of these concerns involved the inadequacy of the preclinical evidence that has been presented to date, both in animal models and in vitro. Some addressed the insufficient understanding of the basic science of mitochondrial disease and of the methods under consideration. Some applied to the daunting challenges of designing meaningful clinical trials, or indeed of safe clinical trials since pregnancy itself poses serious health risks for many women with mitochondrial diseases.

In his summary statement after the first day's session, committee chair Dr. Evan Y. Snyder noted that although some committee members found the preclinical data intriguing,

"There was a sense of the committee that at this particular point in time there is probably not enough data either in animals or in vitro to conclusively move on to human trials without…answering a few additional questions…..The concerns revolved around the preclinical data with regard to fundamental translation, but also with regard to the basic science" [transcribed from the meeting video, posted here].

We urge you to carefully examine and thoroughly review and follow up on the wide range of safety and efficacy concerns raised by the FDA committee, and by others, in order to fulfill your mandate of providing an accurate summary of the current state of expert and scientific understanding.

We also draw your attention to the fact that the phrase "mitochondrial replacement techniques" used in your Terms of Reference paragraph is misleading: no mitochondria are replaced in pro-nuclear and maternal spindle transfer protocols, which instead replace the nuclear genome of an egg. We therefore urge that you avoid this formulation, which has the effect of minimizing the magnitude of the manipulations, in future documents.

In addition, we note the very short time that was provided for responses to the "Call for evidence," and we request that you extend the deadline in order to allow others to communicate their concerns.

Sincerely,

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