A Growing Multi-Billion-Dollar Pharmaceutical Industry Fueled by the HEK293 Cell

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Catholics and the Catholic Church have made the argument that embryonic stem cells (ESC) have never cured any disease and, at the same time, pose scientific challenges. Yet, there are still ongoing clinical trials in type 1 diabetes and Parkinson's disease that are pursuing the use of ESC. The Food and Drug Administration (FDA) has yet to approve any therapeutic from ESC. This lack of therapeutic success with ESC to date has seemingly provided some level of comfort and a level of complacency among pro-life individuals that there is little concern to worry about the future impact of morally-illicit cells on healthcare. However, therapeutics is not the only market segment for ESC. ESC are used in drug discovery for screening drugs; for developing diagnostics; and manufacturing research reagents. The total market for ESC is 1.06 billion dollars as of 2021 and is anticipated to grow at a compound annual growth rate (CAGR) of 9.2 percent. Although ESC represented the first described pluripotent stem cells, these cells pose specific shortcomings. ESC exhibit a neoplastic propensity and display genetic instability. Additionally, they pose a risk of immune rejection from the human leukocyte antigen (HLA) mismatch between donor and recipient, which requires the need for immunosuppressant drugs that pose important adverse medical risks. Yet, more importantly, ESC are not representative of the true impact of morally illicit cells on the total global market from the biopharmaceutical industry.

In 1970, Dr. Frank Graham, a scientist at the University of Leiden in the Netherlands, successfully cultured a cell line in a way that made it possible for it to be used for future medical research. The cell line was manufactured from the kidney cells of a first trimester unborn female child whose parents were unknown. It is presumed that this unborn child was electively aborted. Also, it is not known whether informed consent from the parents was ever obtained. That cell line received the abbreviated name HEK293 – which stands for human embryonic kidney. The 293 designation refers to the number of attempts required to create this immortalized cell line. Unfortunately, this sad story does not end in a lab in the Netherlands in the 1970's. Fifty years later, the HEK293 cell line represents the backbone of countless therapeutics, diagnostics and research reagents, which generate billions of dollars for the biopharmaceutical industry. There have been several previous articles that have focused on the bioethics of the HEK293 cell line. In this essay, we take a different approach by examining the scientific and economic impact of the HEK293 cell line on Catholic consumers, healthcare providers and the Catholic hospital system.

The HEK293 cell line plays an integral part in gene therapies, representing up to 70% of the current gene therapies in development. HEK293 cells are used to produce a weakened and non-replicating virus (a term called viral vectors) that contain an important gene that is missing in genetic diseases. The virus is administered into a patient and delivered to a targeted tissue to provide a normal gene to correct genetically-defective cells. While gene therapy is still an emerging field, the FDA has already approved several gene therapies. According to market

research, the gene therapy market was worth approximately 5.33 billion dollars in 2022 with a CAGR of 30.1%, which should be worth approximately 19 billion dollars by 2027 (Table 1).

Gene therapies are not the only FDA-approved drugs in which HEK293 are used to manufacture advanced medicines. HEK293 is used in the manufacturing of chimeric antigen receptor (CAR) -T cells for the treatment of refractory hematological malignancies. T-cells are specialized white blood cells that are harvested from cancer patients and genetically transformed with a virus that carries the CAR gene. The genetically created virus is produced from HEK293 cells. The final CAR-T cell is administered back into the patient whereby the cell then targets and kills tumor cells. The global market for CAR-T cells is 3.8 billion dollars as of 2022 and is growing at a CAGR of 30 percent (Table 1). By 2027, the global market is estimated to reach 21 billion dollars and 75 percent of CAR-T therapies will require HEK293 cells. However, there are several challenges to personalized CAR-T therapies. First, there is batch to batch variability due to inter-subject differences in available T-cells caused from low numbers of T-cells or from defective cells in cancer patients. The manufacturing process is expensive and labor intensive – costing hundreds of thousands of dollars to create an individualized treatment. These challenges result in delays in critical life-saving treatments. Additionally, the FDA recently issued a warning of reported secondary T-cell malignancies in CAR-T treated patients probably caused from the use of integrating viral vectors produced from HEK293 cells. Thus, there is a scientific and public economic need to develop a novel approach to create CAR-T cell therapies that are universal and free of viruses. If such methods were created without viruses, then HEK293 cells would not be necessary for this treatment.

Vaccines represent a large fraction of medicines that are manufactured from either morally-illicit cells or are required in the design and testing of these medicines. Prior to COVID, the global market for non-COVID vaccines in 2020 was 55 billion dollars and growing at a 10 percent CAGR with an estimated future market of 107 billion dollars by 2027 (Table 1). Many vaccines have been manufactured from aborted fetal cells that include Wi-38 and MRC-5. There is no evidence that the HEK293 cell line is used to manufacture non-COVID vaccines. However, there is no available public data to determine whether the pharmaceutical industry uses the HEK293 cell line in routine testing of vaccine efficacy and safety. In contrast, there is ample available public data to support the role of HEK293 in the design and testing of COVID-19 mRNA vaccines. The global market for mRNA COVID-19 vaccines in 2022 from Moderna was 18.4 billion dollars and from Pfizer was 38.7 billion dollars, adding up to a sum of 57 billion dollars (Table 1). However, subsequent COVID vaccine acceptance has significantly declined because, in part, from a lack of efficacy in preventing viral transmission and numerous safety reports in the VAERS system.

Biologics or proteins represent the largest fraction of products that are produced from HEK293 cells. The global market for biologics in the form of therapeutics is 327 billion dollars as of 2022 with a 7.8 percent CAGR. Thirty percent of the biologic market is produced from HEK293 cells (Table 1). Taken together, the current global market for biopharmaceutical products that are derived from HEK293 cells is over 100 billion dollars as of 2022 (Table 1),

which does not include the COVID-19 vaccines. When one considers the CAGR of CAR-T cells, biologics and gene therapy, the estimated future global market for products derived from HEK293 cells is approximately 200 billion dollars by 2027 (Table 1). To put this market into perspective, Planned Parenthood generates 1.5 billion dollars annually from their provided abortion services.

To further put the global market of HEK293-dependent products into perspective to other non-healthcare consumer market segments, the global breakfast cereal market is 36 billion dollars in 2021. The 2023 global watch market is 102 billion dollars. The global pet food market is 103 billion dollars in 2023. The global biopharmaceutical industry generated 1.5 trillion dollars of revenue as of 2022. Thus, approximately 7 percent of the total global biopharmaceutical market requires the HEK293 cell line.

In 2005, the *Pontifical Academy for Life* issued its first official position for Catholics regarding the criteria when a vaccine that is morally tainted can be morally acceptable. First, the medical condition must be grave. Second, there must be no ethical alternative medicine. Third, a Catholic is still permitted to exercise their conscience and reject the medicine on moral grounds. Fourth, Catholics have the responsibility to use every legal means to urge the pharmaceutical industry to develop ethical alternative medicines without using morally-illicit cells. Subsequently in 2008, the *Congregation for the Doctrine of Faith* reaffirmed this position into official Church doctrine in a document entitled *Dignitas Personae*, which additionally emphasized that Catholic researchers and doctors should avoid the use of morally-illicit cells in their profession.

The impact of HEK293 cell-dependent biotechnologies will greatly affect religious consumers, Catholic hospitals and pro-life healthcare providers. These medicines are more complex, which require specialized care in transportation, storage and administration. These medicines are not going to be formulated as pills that will be dispensed by community pharmacies. They will require administration in a hospital setting. These medicines frequently treat grave medical conditions. Pro-life patients will have to make tough decisions on whether they will reject such treatments out of their moral conscience. Otherwise, patients will need to accept the drugs that are in contradiction to a person's religious and moral beliefs. Catholic hospitals and pro-life healthcare providers will have to make the choice on whether to refuse administration of these drugs at the risk of lost revenue and healthcare market share. Otherwise, they will have to ignore the moral dilemma and offer morally tainted treatments at the risk of violating their Catholic identity.

Unfortunately, no Catholic university, hospital or foundation conducted medical research since the HEK293 cell line was introduced to develop an alternative ethical human cell line for the biopharmaceutical industry to consider adopting. Notwithstanding that the HEK293 cell line represents an ethically controversial cell line, it poses scientific deficiencies that are noteworthy. HEK 293 cells have an abnormal karyotype with 64 chromosomes. HEK 293 cells were generated by genetic transformation of cultured human embryonic kidney cells with sheared adenovirus 5'DNA. Subsequent analysis has shown that the transformation was created by

inserting 4,500 nucleic acid base pairs from an adenovirus strain that was incorporated into chromosome 19. Thus, HEK293 cells pose a small infectious risk of introducing a replicate competent virus when producing viral vectors or producing trace amounts of contaminating viral proteins when producing a biologic. As previously mentioned, the FDA has issued a warning that CAR-T therapies pose a risk of secondary T-cell malignancies, which is likely attributed to the use of viral vectors. Also, there are differences in the posttranslational modification (PTM) process of proteins between HEK293 cells and proteins that are naturally found in human plasma. The PTM process confers important pharmacological properties in the efficacy and safety of biologics.

Thus, the HEK293 cell represents a double-edged sword for religious consumers and the Catholic healthcare system. On one side, the cell line represents a significant threat in which religious consumers and Catholic hospitals do not have access to ethical non-controversial medicines for grave diseases. Also, the size of the global market in which the biopharmaceutical industry exploits the dignity of an unborn child fifty years ago is unsettling. Yet, there is a silver lining to the other side of that sword to the extent that there is a tremendous future economic opportunity to develop alternative biotechnologies to HEK293 cell-derived medicines that offer scientific advantages, and which can finally address a large unmet market for religious consumers and the Catholic healthcare system.

Therapeutic Area	Market Size 2022 (billions)	5-year CAGR	Estimated percentage of market requiring HEK293	Estimated market size in 2027 (billions)	Estimated market need for HEK293 in 2027 (billions)
Gene Therapy	$5.33	30.1%	70%	$19.88	$13.3
mRNA COVID Vaccines	$57.1		100%	-	-
Other Vaccines	$55	10%		$107	_
CAR-T Cell Therapy	$3.8	30%	75%	$21	$15.8
Biologics	$393.5	7.8%	30%	$569.9	$170

Table 1