U.S. FOOD & DRUG ADMINISTRATION

December 14, 2023

Joseph A. Ladapo, MD, PhD
State Surgeon General
Florida Department of Health
4052 Bald Cypress Way, Bin A-00
Tallahassee, FL 32399-1710

Dear Dr. Ladapo,

This is in response to your letter of December 6, 2023, regarding the mRNA COVID-19 vaccines. In your letter, you raise the concern that SV40 promoter/enhancer DNA is present in these vaccines and that this raises safety concerns.[1] **We would like to make clear that based on a thorough assessment of the entire manufacturing process, FDA is confident in the quality, safety, and effectiveness of the COVID-19 vaccines.** The agency's benefit-risk assessment and ongoing safety surveillance demonstrate that the benefits of their use outweigh their risks. Additionally, with over a billion doses of the mRNA vaccines administered, no safety concerns related to residual DNA have been identified. Responses to each of your three specific questions follow below:

1. **In response to the question regarding potential genotoxicity of the mRNA COVID-19 vaccines:** No SV40 proteins are encoded for or are present in the vaccines. On first principle, it is quite implausible that the residual small DNA fragments located in the cytosol could find their way into the nucleus through the nuclear membrane present in intact cells and then be incorporated into chromosomal DNA.[2] Additionally, studies have been conducted in animals using the modified mRNA and lipid nanoparticle together that constitute the vaccine, including the minute quantities of residual DNA fragments left over after DNAse treatment during manufacturing, and demonstrate no evidence for genotoxicity from the vaccine.[3] Pharmacovigilance data in hundreds of millions of individuals also indicate no evidence indicative of genotoxicity.

2. **Regarding whether FDA considers the lipid nanoparticle delivery system in setting the safe levels of DNA in the mRNA vaccine:** The agency has taken into account the totality of the mRNA COVID-19 vaccine product, including the lipid nanoparticles, as it reviewed the manufacturers' specifications for residual DNA fragments present. Any contamination with residual DNA fragments is monitored routinely as a product specification.

3. **Regarding concern for possible integration of the residual DNA fragments into reproductive cells:** Please see the response to the first question above regarding the implausibility that the minute amounts of small DNA fragments present could find their way into the nucleus of these cells. Additionally, reproductive toxicology studies have been conducted to evaluate the mRNA COVID-19 vaccines and have found no concerns.

[1] In your letter, you raise questions, citing to the 2007 Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications. This guidance was developed for DNA vaccines themselves, not for DNA as a contaminant in other vaccines, and is not applicable to the mRNA COVID-19 vaccines.

[2] The Nuclear Envelope and Traffic between the Nucleus and Cytoplasm - The Cell - NCBI Bookshelf (nih.gov);

[3] https://www.fda.gov/media/151733/download?attachment; https://www.fda.gov/media/155931/download?attachment

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Perpetuating references to this information about residual DNA without placing it within the context of the manufacturing process is misleading. Therefore, we hope the following general explanation of the manufacturing process for these vaccines will be helpful.

The starting material for the manufacture of the mRNA portion is a DNA template. As part of the purification process during production, the mRNA is treated with DNAse to digest residual DNA. There are internationally agreed upon recommendations for the quantity of residual DNA present in all biological products, including the mRNA vaccines.[4] The specification for the COVID-19 mRNA vaccines for residual DNA following DNAse treatment results in the presence of DNA fragments at a quantity that is less than three orders of magnitude lower than the quantity of the RNA dose by weight. This has been determined (and continues to be determined during production of lots) with a validated quantitative PCR assay.

No SV40 proteins are encoded by the nucleotide sequences present in the mRNA vaccines. The treatment of the products with DNAase also fragments any residual DNA template that might be present after other manufacturing steps. Thus, as noted above, following manufacture of the mRNA COVID-19 vaccines, no DNA encoding SV40 proteins is present in the residual DNA remaining in the products.

Additionally, animal studies with the mRNA delivery technology done over the past decade show no evidence of genotoxicity. Moreover, we now have access to global surveillance data on over one billion doses of the mRNA vaccines that have been given, and there is nothing to indicate harm to the genome, such as increased rates of cancers.

FDA takes its responsibility for ensuring the safety, effectiveness and manufacturing quality of all vaccines licensed in the U.S., including the mRNA COVID-19 vaccines, very seriously. We stand firmly behind our regulatory decision making with the authorizations and approvals of the COVID-19 vaccines, which have a highly favorable safety profile, and which have saved, and continue to save, many lives.

The challenge we continue to face is the ongoing proliferation of misinformation and disinformation about these vaccines which results in vaccine hesitancy that lowers vaccine uptake. Given the dramatic reduction in the risk of death, hospitalization and serious illness afforded by the vaccines, lower vaccine uptake is contributing to the continued death and serious illness toll of COVID-19.

We hope the information provided addresses your concerns and those of your constituents.

Sincerely,

Peter Marks

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

[4] WHO (World Health Organization) Meeting Report Study group on cell substrates for production of biologicals. June 11 and 12, 2007; 1–30; FDA Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications | FDA. U.S. Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research, February, 2010.

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