Siri | Glimstad

200 Park Avenue, Seventeenth Floor, New York, NY 10166
sirillp.com | P: (212) 532-1091 | F: (646) 417-5967

VIA ELECTRONIC FILING

March 23, 2021

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR RECONSIDERATION OF CITIZEN PETITION REGARDING CLINICAL TRIAL OF Ad26.COV2.S - NCT04505722	**Docket No.** FDA-2020-P-2096

We write on behalf of our client Informed Consent Action Network ("**Petitioner**"). Petitioner submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. FDA-2020-P-2096 regarding Johnson & Johnson/Janssen's COVID-19 vaccine.

A. DECISION INVOLVED

Petitioner respectfully submits this petition to request reconsideration of the Food and Drug Administration's ("**FDA**") decision dated February 27, 2021, denying Petitioner's requested actions in the Citizen Petition ("**CP**") to amend Phase III clinical trials relating to Ad26.COV2.S (NCT04505722) on the ground that "CP does not contain facts demonstrating any reasonable grounds for the requested action." FDA Decision at 2.

B. ACTION REQUESTED

The Petitioner requests that the FDA reconsider its decision denying the action requested in the CP and require Janssen, the sponsor of Ad26.COV2.S, to amend its Phase III clinical trial protocol to provide that:

a. any and all adverse events and reactions, with the exception of minor reactions, be documented for the entire duration of the trial;

b. such documenting of adverse events and reactions shall last *at least* twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers, or such longer duration as appropriate, and in no event end prior to the subject reaching eight years of age;

c. it uses an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related, and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review[1];

d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination;

e. germline transmission tests are conducted for male participants; and

f. HIV incidence will be "monitored at the end of the study and for an appropriate follow-up period" and the trial will "evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur."

CP at 2.

In the alternative, Petitioner requests that the FDA issue a revised decision that fully explains its reasoning and its consideration of materials in the administrative docket.

C. STATEMENT OF GROUNDS

Reconsideration is warranted because the relevant information regarding safety concerns surrounding the Ad26.COV2.S, a vaccine to prevent COVID-19 by Janssen, were not adequately considered by the Commissioner.

1. Any and all adverse events and reactions documented for entire duration of the trial

The Petitioner requested that any and all adverse events and reactions to the Janssen vaccine be documented for the entire duration of the clinical trial. CP at 2. The FDA responded that the collection of certain information "would not necessarily be of value in assessing the safety" of the vaccine and "may actually have negative consequences for the clinical development of the

[1] For example, for children, the clinical trial should be properly sized and powered to determine that the vaccine is safer than a SARS-CoV-2 infection.

vaccine." FDA Decision at 13. Additionally, the FDA categorized some adverse events as "those for which there is little reason to believe that a vaccine caused the event." *Id.*

Respectfully, as a new biological product, it is unclear which events may or may not be caused by the vaccine. Petitioner reiterates its request that all adverse events, other than minor events, be tracked and documented for the entire duration of the trial. These adverse events should include any and all neurological, cardiovascular, and immunological events, among others. It is unclear from the trial protocol that these would all be considered "serious" adverse events and therefore, they would not be captured for the entirety of the trial and possibly not more than 6 months. Permitting the sponsor conducting the clinical trial to artificially carve out adverse events should be unacceptable to the FDA.

2. Documentation of adverse events and reactions shall last at least twenty-four months for adults, thirty-six months for children, and sixty months for infants and toddlers

The Petitioner further requested that adverse events be tracked for a duration of at least 24 months for adults, 36 months for children, and 60 months for toddlers. CP at 2. The FDA Decision in this regard is lacking for two reasons: (1) the FDA Decision only addresses FDA's issuance of an emergency use authorization ("EUA") to Janssen's Ad26.COV2.S vaccine candidate and does not address requirements for full licensure; and (2) the FDA Decision fails to address the specific concerns related to toddlers and children.

a. FDA Decision Only Addresses its Issuance of EUA

Petitioner's requested action of documenting adverse events and reactions for specific periods of times was addressed toward FDA licensure of Janssen's Ad26.COV2.S. CP at 3. Yet, the FDA Decision only addressed Petitioner's request in the context of the issuance of an EUA. For full licensure, these time periods for safety review are critical. With regard to adults, how will any long-term issues be identified with a novel vaccine platform if they are not tracked for longer than 6 months? The answer is they will not be.

b. FDA Decision Fails to Address the Specific Concerns Related to Toddlers and Children

Petitioner requested FDA to require Janssen to document all safety data in pediatric populations for at least thirty-six months because many "autoimmune, neurological and developmental disorders will often not be diagnosed until after children are at least a few years old and, for many conditions, not until reaching seven years of age." CP at 6. To this, the FDA Decision merely states that "FDA does not intend to authorize or license any COVID-19 vaccine until the relevant statutory requirement have been met for the population indicated in the labeling." FDA Decision at 15. The FDA Decision fails to specify the period for which the pediatric population will be tracked, if at all for developmental disorders that typically take years to be diagnosed.

The FDA also asserts that its review "is based on extensive historical experience with vaccines." However, this vaccine is a novel vaccine. Therefore, it is not scientifically appropriate to extrapolate the results of other vaccines' trials or post-marketing experience to these vaccines.

There is little to no assurance that what has been seen before with other vaccines is what will be seen with this vaccine. Indeed, one could extrapolate from prior vaccines that had serious safety and efficacy issues, either before or after licensure, just as the FDA appears to be extrapolating from vaccines that did not appear to have such issues.

Additionally, the FDA completely discounts the 2019 review, authored by researchers at the FDA and Duke University, cited by Petitioner. CP at 7. However, this study highlights that even considerably longer safety studies for drugs pediatric studies "may not provide complete safety data across all critical periods of growth and development." The FDA argues that the drugs at issue in that study are irrelevant as vaccines "are given episodically over an individual's lifespan and are not chronically or more frequently administered." However, this does not change the underlying rationale in this study for the suggested time period for reviewing safety and it is also noted that vaccines, as of the most recent CDC childhood schedule, are administered frequently. For example, the influenza vaccine is given yearly along with other vaccines. Similarly, it is anticipated that a COVID-19 vaccine will require ongoing booster shots and additional doses to address variants. Petitioner reiterates the request for long-term safety tracking in both pediatric and adult populations.

3. Adequate sample size, appropriately powered

Petitioner appreciates the acknowledgement that "all vaccines are associated with some risk." Petitioner is optimistic that the FDA would agree that the clinical trial was not properly powered because the current clinical trials even failed to identify a known risk from vaccines – anaphylaxis – as a potential serious adverse event. *See* https://jamanetwork.com/journals/jama/fullarticle/2777417 (recent Mass General Brigham study that assessed anaphylaxis in a clinical setting after the administration of COVID-19 vaccines and found "severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10,000 vaccinations." This is equivalent to 50 times to 120 times more cases than what VAERS and the CDC are reporting. According to the CDC, "Anaphylaxis after COVID-19 vaccination is **rare** and occurred in approximately 2 to 5 people per million vaccinated in the United States based on events reported to VAERS." https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html).

Additionally, the agency's response did not directly address the critical issue with children. It is unclear how pediatric trials will be designed and powered; however, it is inadequate to approve studies that are only powered to find, at best, issues that are 1 in 1,000, especially for children. Children are affected by COVID-19 at a far lesser rate than 1 in 1,000, as are young adults. It is therefore important to understand whether or not they will face a higher risk from the vaccine than from the disease.

4. Germline transmission tests are conducted for male participants

The FDA has stated that "Petitioner has not provided, and we are not aware of, data suggesting distribution of this vector to the gonads" (FDA Decision at 22) while ignoring the conclusion of the European Medicines Agency and others, as cited in the petition, that viral and non-viral vectors may be associated with a risk of vertical germline transmission of vector DNA. Moreover, Petitioner concedes that it has not, as it is not able to, provide data suggesting distribution of the vector within Janssen's vaccine to the gonads. Petitioner therefore reiterates its request that the agency require the manufacturer, which would have the capability of doing so, to

determine whether or not there is distribution to the gonads. In the event that there is evidence of same occurring, then Petitioner would request full testing for germline transmission. If the manufacturer is not required to do this testing and if the agency does not require it for full licensure, then there is likely to be an absence of any evidence determining whether or not there is a distribution of the vector within the vaccine to the gonads and therefore a need for full germline testing. The manufacturer is in the best position to gather this data.

5. Monitoring of HIV incidence

As the FDA conceded, "explanations for the apparent enhanced risk of HIV acquisition among Ad5-seropositive vaccine recipients in the Step Study remain uncertain," (FDA Decision at 26) hence, the use of adenovirus vector in a vaccine (and potential vaccine recipients who are seropositive) necessitates monitoring for effects of the vaccine on HIV acquisition. Although the "FDA does not believe that such changes to the study protocol should be a condition of the issuance of an EUA for the Janssen COVID-19 Vaccine," (FDA Decision at 26) it should be a condition of the issuance of licensure and approval.

* * *

In conclusion, Petitioner reiterates its reasonable requests: all new medical issues that arise should be tracked for sufficient time periods in pediatric and adult populations. All studies, and specifically pediatric studies, must be adequately powered to detect adverse events that happen at rates less than 1 in 1,000 in an environment where the goal is to vaccinate every one of the millions of individuals in this country. Additionally, in these novel viral vector vaccines, Petitioner requests that germline tests be conducted, and HIV incidence be monitored.

Very truly yours,

/s/ Aaron Siri

Aaron Siri
Elizabeth Brehm
Jessica Wallace
SIRI & GLIMSTAD LLP
200 Park Avenue
17th Floor
New York, NY 10166
Telephone: (212) 532-1091
Email: aaron@sirillp.com