September 16, 2022

Explanation of this document

Following the August 31, 2022 publication of our peer-reviewed study, we learned that FDA had distributed a critique of our study to media outlets (see table at end of this document). A reporter shared the FDA's full statement with us. FDA's statement contains two sections: one labeled "on the record," the other "on background."

The "on the record" statement is almost entirely about VAERS, which was puzzling as our study is not an analysis of VAERS; our analysis was limited to the Pfizer and Moderna randomized trials that supported the Dec 2020 EUAs.

The "on background" section of FDA's statement was the same critique FDA provided our group by email on May 10, 2022 following its review of a version of manuscript that we shared with the agency on March 14, 2022 (about 3 months prior to the preprint). Thus, FDA's statement to media outlets did not recognize or reflect the extensive changes to our analysis and discussion that occurred in the intervening 5 months (March to August), many of which arose in response to the original FDA critique as well as others we received.

Response to FDA's critique

Below, we provide responses to the FDA's full critique. The FDA response appears indented and in bold, purple font. It is reproduced verbatim; the only editing we have done is to break it up. Our responses are in red font.

> **On the Record:**
>
> **The FDA takes seriously and investigates reports of any adverse events. The Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system that receives unverified reports of adverse events following immunization with both licensed (approved) vaccines and those that are FDA-authorized for use. The FDA and CDC place a high priority on vaccine safety and are committed to the integrity and credibility of our vaccine safety monitoring efforts. Anyone can report an adverse event to VAERS. Patients, parents, caregivers and healthcare providers are encouraged to report adverse events after vaccination even if it is not clear that the vaccine caused the adverse event. In addition, healthcare providers are required to report certain adverse events (such as a severe allergic reaction) after vaccination, and vaccine manufacturers are required to report all adverse events brought to their attention. Accurate and honest reporting play an important role in this process.**
>
> **It's important to note that reports of adverse events to the Vaccine Adverse Event Reporting System (VAERS) following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. In fact, reviews by FDA and CDC have determined that the vast majority of the deaths reported are not directly attributable to the vaccines. FDA requires healthcare providers**

to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem.

Reports of death after COVID-19 vaccination are rare. As reported on CDC's website, More than 592 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, through June 21, 2022. During this time, VAERS received 15,193 preliminary reports of death (0.0026%) among people who received a COVID-19 vaccine. CDC and FDA clinicians review reports of death to VAERS including death certificates, autopsy, and medical records.

To put into perspective the approximate number of doses of vaccine administered during a specific time frame after authorization of COVID-19 vaccines we suggest that you reference CDC's data at https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total. CDC clinicians review reports of death to VAERS including death certificates, autopsy, and medical records.

***Response to the above four paragraphs**: These paragraphs are not about our paper, as our study is not an analysis of VAERS. Our paper is instead an analysis of serious adverse events in the Pfizer and Moderna phase III clinical trials using available data summaries. Our analysis is limited by the fact that the individual patient data from the trials have not been made public by Pfizer or Moderna; VAERS has no bearing on this problem.*

FDA continues to find the three authorized and approved COVID-19 vaccinations meet the agency's rigorous standards for safety, effectiveness, and manufacturing quality. These vaccines have proven to be an important tool for fighting the COVID-19 pandemic.

***Response**: This is not a criticism of our paper. The importance of the vaccines does not in any way lessen requirements for detailed and subgroup-specific consideration of harm and benefit. Our analysis shows the need for public release and reconsideration of the participant level trial datasets as part of meeting this requirement.*

FDA disagrees with the conclusions in the paper from Doshi et.al. Based on the agency's thorough evaluation of the safety and effectiveness data for the mRNA COVID-19 vaccines, as well as the ongoing safety surveillance of the vaccines, we continue to find their benefits far outweigh their risks in preventing COVID-19, including its most serious outcomes of hospitalization and death.

***Response:** Unfortunately, the FDA does not state which conclusion they disagree with. Our results raise concerns that the mRNA COVID-19 vaccines are associated with higher adverse event risks than initially estimated at the time of emergency authorization. We also found that the excess risk of serious AESIs exceeded the reduction in COVID-19 hospitalizations in both Pfizer and Moderna trials. We went on to explain that the harm-*

benefit ratio is not a fixed constant over time, but rather a variable dependent upon a number of factors that would shift the ratio towards overall benefit or overall harm. Waning vaccine effectiveness, decreased viral virulence, and increasing degree of immune escape from vaccines would presumably all reduce the benefit from what we saw in the trials. In addition, patient characteristics such as natural immunity or low risk of severe COVID-19, would affect harm-benefit calculations. Thus our actual conclusions were that (1) additional analyses are needed to determine under what circumstances the benefits of the vaccine outweigh the harms, which would be aided by the individual level patient data from the trials, (2) the analysis datasets from the trials that were used for authorization of the vaccines must be made publicly available, and (3) there should be a coordinated effort to compare side effects of different vaccines.

> **On background:**
> **The primary conceptual limitation of the publication is that an analysis of this nature (pooling disparate events and performing statistical significance testing to identify an imbalance between arms) can't provide new information about product safety beyond what is documented in the FDA clinical review memo, statistical safety review memo, and other public documents.**

Response: *The FDA criticism does not pertain to either the posted preprint or the published article, as neither document based their conclusions on statistical significance testing. In addition, the FDA's own safety analysis pooled seemingly disparate events multiple times (e.g., adverse events, severe adverse events, and serious adverse events) as seen in the FDA briefings.*

> **If an imbalance on pooled events were observed in a clinical trial, the next step would be to investigate the events in more detail, including breaking them down by system organ class (SOC), by preferred term (PT), confirming the clinical narratives, investigating relatedness and alternate explanations, and incorporating event types with possible causal linkage to the investigational agent into benefit-risk assessments. Please see FDA's Clinical Review Memos that are posted on the agency's website (under "Supporting Documents" for Comirnaty and Spikevax). All of these steps have already been performed by FDA for both COMIRNATY (see especially pages 56-81 of the FDA Clinical Review Memo dated August 23, 2021) and SPIKEVAX (see especially pages 60-91 of the FDA Clinical Review Memo dated January 28, 2022).**

Response to the above: *We have reviewed those memos and do not find any mention of FDA documenting an imbalance on SAEs. For example, our study found 36% more SAEs in the vaccine arm than the placebo arm in the Pfizer trial, but this result is not reported in the FDA clinical review memo (even though an imbalance can be seen in Table 14 of the FDA's Dec 11, 2020 decision memo). It thus seems to us that the FDA was mistaken in concluding that SAEs were "balanced" (Pfizer) and "without meaningful imbalances" (Moderna) between treatment arms.*

> **In addition to the conceptual limitation noted above, these analyses have inherent statistical limitations. Clearly, these are post hoc analyses, not**

planned in trial protocols/statistical analysis plans, and performed after at least casual inspection of the data tables.

Response: *This criticism seems to assume that post hoc analyses should not be done. We disagree: No analysis or data should be immune from reconsideration in light of new concerns or questions. In particular, we believe it is incumbent on the FDA to investigate and rectify as necessary any oversights of the original pre-specified analyses.*

Additionally, to FDA's knowledge, it appears that no protocol was pre-registered for this secondary analysis.

Response: *Pre-specified protocols are important for analyses that will be used to make determinative decisions such as authorization and approval. Our analyses were not proposed for that purpose, but instead aimed to evaluate whether there is evidence to justify re-opening the investigation of side effects and harm-benefit using the trial data. As a reanalysis based on publicly available data, our paper concludes that there is evidence of an important safety signal. This concern can be addressed in part with the trial data held by the FDA, which has not been made available to researchers or the public. We have not claimed our results to be definitive, and instead wrote: "We emphasize that our investigation is preliminary, to point to the need for more involved analysis." The critical next step is warning the public of our findings (including their limitation), and replication of our work using the individual patient data.*

This raises concerns of researcher degrees of freedom and potential for bias.

Response: *We have documented our methods in the paper, posted the data we used, and are happy to assist FDA if the published manuscript leaves anything unclear. FDA's concerns of potential bias are another good reason FDA should replicate our study and extend it using the individual patient data they possess.*

In particular, certain unusual analytic choices were made, each of which would have led to non-significant results if a more natural choice were made. The most notable of these is the choice to analyze number of events rather than number of subjects with an event, ignoring the dependence of events within subjects.

Response: Our published paper addressed this criticism as follows: "Because we did not have access to individual participant data, to account for the occasional multiple SAEs within single participants, we reduced the effective sample size by multiplying standard errors in the combined SAE analyses by the square root of the ratio of the number of SAEs to the number of patients with an SAE. This adjustment increased standard errors by 10% (Pfizer) and 18% (Moderna), thus expanding the interval estimates." More accurate standard errors could be calculated from the individual patient data set used for authorization, which should be publicly released.

Also of note are the decisions to use outdated emergency use authorization (EUA) tables instead of updated tables from biologics license application (BLA) reviews

Response: *Our published paper explained why we used the EUA dataset instead of BLA: the unblinding process created "self-selection processes [that] may have introduced nonrandom differences between the vaccine and unvaccinated participants, thus rendering the post-authorization [post-EUA] data less reliable."*

and the decision to remove COVID-19 from the SAE tables.

Response: *We do not understand FDA's concern about our decision to remove COVID-19 related efficacy outcomes from the SAE tables. Such removal is common in safety analyses. Our approach (in removing efficacy outcomes) is consistent with what Pfizer did (see section 8.3.7 of Pfizer's protocol), which the FDA did not object to but instead repeated in its analysis.*

Moderna, by contrast, included COVID-19 in the SAE table. Despite the differing approach taken by Pfizer and Moderna in compiling their SAE tables, FDA's method for analyzing the two trials was the same. We could find no rationale for this treatment in the FDA review memos and suggest this may have been an oversight in the FDA analysis. We do not think it is unreasonable that such oversights would occur, especially given the volume of details and documents that the FDA had to review under extraordinary pressure. It would only be unreasonable to fail to address concerns about such oversights once they were noted, whether by parties inside or outside the agency.

It is worth noting that the three statistically significant comparisons reported in the publication may not survive a multiplicity correction even for the four comparisons reported, setting aside researcher degree of freedom issues. Again, we stress that, while serious, these are secondary concerns; the primary issue is the irrelevance of the significance testing in the first place.

Response: *To repeat, this appears to be an irrelevant comment because neither our preprint nor our published article used significance testing to derive their conclusions.*

Finally, interpreting line items in SAE tables in the context of the Brighton Collaboration list of adverse events of special interest (AESI) cannot be done in a reliable way. To take just one example, three cases of chest pain reported in the Moderna EUA briefing document SAE table have been classified as pericarditis in the analysis in the publication. In fact, as documented in the clinical review memo, there were five cases of pericarditis in the Moderna trial (two in the vaccine arm and three in the placebo arm), and there is little overlap between these five cases and the three cases of chest pain in the EUA tables. Chest pain can, of course, have many different etiologies.

Response: *We fail to see how the cited numbers make chest pain irrelevant or its use unreliable. The criticism does however point to a problem that arose from the fact that individual participant data (IPD) was not publicly available to resolve such problems.*
We share FDA's concern about the possible impact that clinical judgements had on the final results. To address this uncertainty, we performed a sensitivity analysis that excluded SAEs for which subjective decisions were made to include them (including chest pain). The

findings were consistent with the original analysis, suggesting these subjective decisions were not the major driver of the differences between groups. The sensitivity analysis is publicly available in our Zenodo repository here.

The original FDA text (without our interwoven comments) is reproduced in the table below.

Table. FDA response distributed to media outlets

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It's important to note that reports of adverse events to the Vaccine Adverse Event Reporting System (VAERS) following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. In fact, reviews by FDA and CDC have determined that the vast majority of the deaths reported are not directly attributable to the vaccines. FDA requires healthcare providers to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem.

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In addition to the conceptual limitation noted above, these analyses have inherent statistical limitations. Clearly, these are post hoc analyses, not planned in trial protocols/statistical analysis plans, and performed after at least casual inspection of the data tables. Additionally, to FDA's knowledge, it appears that no protocol was pre-registered for this secondary analysis. This raises concerns of researcher degrees of freedom and potential for bias. In particular, certain unusual analytic choices were made, each of which would have led to non-significant results if a more natural choice were made. The most notable of these is the choice to analyze number of events rather than number of subjects with an event, ignoring the dependence of events within subjects. Also of note are the decisions to use outdated emergency use authorization (EUA) tables instead of updated tables from biologics license application (BLA) reviews and the decision to remove COVID-19 from the SAE tables. It is worth noting that the three statistically significant comparisons reported in the publication may not survive a multiplicity correction even for the four comparisons reported, setting aside researcher degree of freedom issues. Again, we stress that, while serious, these are secondary concerns; the primary issue is the irrelevance of the significance testing in the first place.

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