Why we petitioned the FDA to refrain from fully approving any covid-19 vaccine this year

Description

USA: We are part of a group of clinicians, scientists, and patient advocates who have lodged a formal "Citizen Petition" with the United States Food and Drug Administration (FDA), asking the agency to delay any consideration of a "full approval" of a covid-19 vaccine. The message of our petition is "slow down and get the science right—there is no legitimate reason to hurry to grant a license to a coronavirus vaccine." We believe the existing evidence base—both pre- and post-authorization—is simply not mature enough at this point to adequately judge whether clinical benefits outweigh the risks in all populations.

The covid-19 vaccines in widespread use have emergency authorizations (EUA), not actual approvals, a crucial regulatory distinction that reflects major differences in the level of regulatory scrutiny and certainty about the risk-benefit balance.

Our petition doesn't argue that risks outweigh benefits—or that benefits outweigh risks. Rather, we focus on methods and processes, outlining the many remaining unknowns about safety and effectiveness—and suggest the kinds of studies needed to address the open questions.

If the FDA listens to us, they won't give serious consideration to approving a covid-19 vaccine until 2022. Our first request is that the FDA require manufacturers to submit data from completed Phase III trials—not interim results. Trials by vaccine manufacturers were designed to follow participants for two years, and should be completed before they are evaluated for full approval, even if they are now unblinded and lack placebo groups. These Phase III trials are not simply efficacy studies; they also are necessary and important safety studies (as the study titles say), and all collected data remain invaluable.

We also call on FDA to require a more thorough assessment of spike proteins produced *in-situ* by the body following vaccination—including studies on their full biodistribution, pharmacokinetics, and tissue-specific toxicities. We ask the FDA to demand manufacturers complete proper biodistribution studies that would be expected of any new drug and request additional studies to better understand the implications of mRNA translation in distant tissues. We call on data demonstrating a thorough

investigation of **all** serious adverse events reported to pharmacovigilance systems, carried out by independent, impartial individuals, and for safety data from individuals receiving more than two vaccine doses, in consideration of plans for future booster shots. We ask the FDA to request necessary studies in specific populations, including those previously infected with SARS-CoV-2, pediatric subjects, and those with immunological or other underlying medical complexities. Given the nature of the novel vaccine platforms, our petition asks for experts in gene therapy to be included among the external committee advising the FDA.

These are several of our major requests. The petition has been signed by a group of 27 clinicians, researchers, and consumer advocates with diverse experiences and thoughts about the pandemic. We all agree that there remain many open, unanswered questions surrounding the efficacy and safety of covid-19 vaccines that must be answered before the FDA gives serious consideration to granting full approval.

These are the reasons why we lodged our petition. There is no need to rush approval to help stop the pandemic because the vaccines already have Emergency Use Authorization. Yet a rushed process is the very possibility that now confronts us. In the past month, Pfizer and Moderna submitted formal applications for “full approval.”

Covid-19 vaccines are already fully accessible to all Americans who want one. EUAs have enabled their widespread use, and can remain in place even after the expiry of the SARS-CoV-2 public health emergency declaration, as is the case for various Zika products. Even without full approval, covid-19 vaccines will remain available for all who want them under EUA.

Some surveys suggest that vaccine hesitancy in the United States is due, in part, to lack of full FDA approval. While approval might lead to increased public confidence in covid-19 vaccines, as well as provide legal support for employer-instituted vaccine mandates, to approve a medical product for these reasons is outside FDA’s regulatory purview. Approval decisions must be driven by the safety and efficacy data. The potential unintended consequences of a rushed approval may contribute to growing mistrust of the US public health and regulatory institutions.

Finally, regarding the elephant in the room: publicly raising any element of hesitation about covid-19 vaccines will be seen by some as irresponsible, stoking unfounded fears in the public’s mind and contributing to the “vaccine hesitancy” problem trumpeted every day. But the alternatives—privately raising concerns or simply remaining silent—are arguably more detrimental to public trust in the long run. Staying silent is not the responsible option. And the implications of only privately raising concerns to regulatory bodies are murky—most would probably not be acted upon, and if they were, it would promulgate the baggage of insufficient accountability and transparency in decision making.

To us, the Citizen Petition seemed the most responsible approach: voice our concerns in our own words, in a professional and transparent manner, through a formal mechanism that can promote accountability in regulatory decision making.

Approving a covid-19 vaccine now risks setting a precedent of lowered standards for future vaccine approvals. The “FDA approved” seal must represent a high bar—and premature licensure of a covid-19 vaccine could seriously damage public confidence in regulatory authorities, particularly if long-term safety issues were to emerge following licensure. Keeping covid-19 vaccines under EUA regulations would also encourage vaccine manufacturers to continue investing resources in completing the

necessary safety and efficacy studies for a potential FDA consideration of full licensure in the future.

For each covid-19 vaccine, the benefits may ultimately outweigh the harms. Or not. Or we may end up in a more nuanced position, finding that benefits outweigh harms for some populations, but not others. Only time—and better evidence—will tell. And so it is vital we allow the scientific process the time required to gather and assess the evidence to be confident in the decisions we ultimately have to make.

Our citizen petition and supporting documents are filed under Docket ID FDA-2021-P-0521 on regulations.gov. Anybody can comment on the petition, or read others' comments, including the FDA's official reply once it arrives.

See also:

Linda Wastila is Professor and Parke-Davis Endowed Chair of Geriatric Pharmacotherapy at the University of Maryland Baltimore School of Pharmacy. She has conducted policy and epidemiological research focusing on intended and unintended outcomes of clinical and policy interventions involving medications and their safety over the past 30 years.

***Peter Doshi** is an associate professor of pharmaceutical health services research at University of Maryland Baltimore School of Pharmacy and senior editor at* The BMJ*. He has been calling for greater independence and transparency in covid-19 vaccine related decision making.*

***Hamid Merchant** is a subject lead in pharmacy at The University of Huddersfield and has experience in pharmaceutical research and development both from industry and academia. His clinical knowledge and expertise in pharmaceutical formulation helps in understanding the clinical and therapeutic principles underpinning drug delivery and the science of dosage-form design.*

***Kim Witczak** is a global drug safety advocate with over 25 years of advertising and marketing experience. She co-founded Woodymatters, an organization started after the death of her husband due to undisclosed side effects of antidepressants. Kim is currently Consumer Representative on the FDA Psychopharmacologic Drugs Advisory Committee.*

***Competing interests:** PD has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-20), and is an editor at The BMJ. None further declared.*

The views and opinions expressed here are those of the authors and do not necessarily reflect official policy or position of the University of Maryland or the University of Huddersfield.

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