

PATHWAY TO A VACCINE: ENSURING A SAFE AND EFFECTIVE VACCINE PEOPLE WILL TRUST

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Chairwoman DeGette, Ranking Member Guthrie, and members of the House Energy and Commerce Subcommittee on Oversight and Investigations: I'm Mark McClellan, Director of the Robert J. Margolis, MD, Center for Health Policy at Duke University. I previously had the privilege to serve as Commissioner of the U.S. Food and Drug Administration, and I currently serve on the board of directors of Johnson & Johnson, which is engaged in an effort to develop a vaccine to COVID. I appreciate the opportunity to join you today to discuss the path forward as we work together to develop, approve, and distribute safe and effective vaccines to overcome the global COVID-19 pandemic.

The development of safe and effective vaccines, in conjunction with other therapeutic interventions and non-medical measures like masks and physical distancing, represents our best path for containing and moving beyond the pandemic. The impact of a vaccine depends on its safety and effectiveness, and also on public confidence in the vaccine. Guided by the health care providers they trust, Americans will need to choose to get a vaccine, both to protect themselves and to reduce spread to people around them. Critical to achieving the benefits of safe and effective vaccination are the actions of our Federal government's public health scientists and regulators, in particular the expert staff at the U.S. Food and Drug Administration (FDA). The FDA has set the global gold standard on issues of medical product safety and effectiveness, and has unparalleled experience and expertise in regulating vaccines that are used safely and effectively by hundreds of millions of Americans.

It was my privilege to serve as FDA Commissioner from 2002 to 2004. During that time, among many other issues, the agency dealt with containing the Severe Acute Respiratory Syndrome (SARS) coronavirus outbreak. We also worked on a bipartisan basis with this committee to enact FDA's authority for emergency use authorization (EUA), which has since been augmented based on experience with the H1N1 pandemic. While at the agency, and subsequently in our work related to FDA issues at Duke University, I have experienced first-hand the integrity, expertise, and commitment of the FDA's career staff – particularly in responding to public health emergencies with timely and science-based

actions. The vaccine experts in FDA's biologics center are globally respected for their decades of experience in overseeing all aspects of vaccine development, manufacturing, and post-market monitoring, and I appreciate the FDA staff's explicit commitments to the public to ensure that these processes are followed. I continue to have full confidence in FDA's guidance of the COVID-19 vaccine development process, as reflected in the agency's actions to date and its expectations for the path forward for vaccine development from here. FDA's approach to COVID-19 vaccines has been scientifically sound and remains on track.

I would like to describe that path for the committee, with an emphasis on key steps that FDA is taking to support the science-based assessment of candidate COVID-19 vaccines, as part of the well-developed systems of independent checks that have been put in place over decades to build a reliable and robust infrastructure for assuring vaccine safety and effectiveness.

The approach is designed to ensure that any vaccine that is approved or authorized will be safe and effective for use, which is the only basis for the trust needed for patients and providers to use it. There's great urgency in a pandemic. Speed matters given all of the lives lost daily. We must make sure that we are doing everything that can safely be done in parallel, like scaling up manufacturing and assuring its quality even as we conduct clinical trials. But when it comes to the assurance of clinical safety and effectiveness as part of these steps, there are no shortcuts. The fastest way to success is through good science that delivers a confident result.

The Administration deserves credit for launching Operation Warp Speed, which has led to extraordinary progress in advancing multiple promising vaccine platforms by converting what is typically a long and uncertain sequential development process to a hyper-parallel process. FDA has provided industry and researchers with early and frequent guidance in this process, including written guidance documents for preclinical and clinical development, as well as safe manufacturing practices. The National Institutes of Health (NIH) has similarly helped to set up and monitor well-designed, very large-

scale randomized clinical trials. Manufacturers supported by the Biomedical Advanced Research and Development Authority (BARDA) are taking financial risk to produce hundreds of millions of doses before we know whether the vaccines work. And the Centers for Disease Control (CDC) has initiated collaborative planning with state, local, and private sector partners for the extensive operational steps needed to support timely distribution and administration of any vaccines that prove safe and effective.

Some recent statements from the White House have implied that FDA's plan to release additional written guidance on its expectations for emergency use authorization of a vaccine is unnecessarily raising the bar on regulatory standards for authorization. That is not the case. FDA's standards are based on decades of experience with vaccines routinely used by millions of Americans as well as extensive experience with the development of urgently needed countermeasures during public health emergencies. FDA's guidance to product developers is intended to help them develop the totality of evidence needed for FDA to support a decision about benefits and risks of using a treatment or vaccine. FDA has been sharing its regulatory guidance directly with vaccine manufacturers and researchers, and its guidance is reflected in the design and conduct of the large-scale clinical trials and other development activities already underway. The agency's further written guidance in development on expectations for an emergency use authorization for a vaccine simply reflects FDA's ongoing feedback to sponsors. Vaccine manufacturers have already committed to following FDA's guidance, including in writing and in statements to Congress. Releasing the written guidance doesn't change that but would add to transparency about it. Indeed, manufacturers routinely request written guidance from FDA to reduce the time and increase clarity around the development process.

Written guidance or not, FDA has been clear in public statements that its emergency use authorization standards for vaccines are different and much higher than those for currently-available therapeutic products like convalescent plasma. Convalescent plasma has been used for a century as a treatment for many infections, and it has already been used in tens of thousands of seriously ill COVID-

19 patients without evidence of any significant safety problem. It may not have much or any benefit – clinical trials are underway now to help answer that question – but this is a very different context from vaccine use in people who aren't sick. COVID-19 vaccines in development are entirely new products intended for use by potentially hundreds of millions of healthy Americans to prevent them from developing infections and serious complications. Consequently, FDA is requiring very large, well-designed, randomized clinical trials that have meaningful clinical endpoints of significant reductions in infections and serious COVID-19 complications. FDA is also requiring the trials to produce large safety databases to monitor for side effects that extend past the month or two during which most serious side effects from a vaccine generally occur. In addition, FDA has also made clear that it intends emergency use authorization powers to require substantial postmarket data collection on any populations who get relatively early access to an authorized vaccine. Such data would further augment the evidence collected in the clinical trials.

Vaccine use is a very different context for the application of emergency use authorization compared to convalescent plasma, requiring a much higher evidence standard on safety and effectiveness. Congress designed the emergency use authorization process to provide FDA with exactly this flexibility to set standards that are appropriate to the different contexts that arise in a pandemic.

Whether or not any further guidance is published, FDA's current guidance coupled with well-established clinical development processes and supports provide a very clear idea of what we should expect in the coming weeks to assure safe and effective vaccines. In particular, we should expect multiple independent checks and public review opportunities built into a well-developed approach that generates the needed evidence on vaccine safety and effectiveness.

First, the large randomized clinical trials underway now, or getting underway soon, must continue until they establish whether the vaccines cause a meaningful reduction in the likelihood and severity of COVID-19 infections without significant safety problems. It is well-established practice for

such pivotal trials to be monitored by independent experts who make up a data safety monitoring board (DSMB). They, and not politicians, should determine when there is sufficient evidence from the trial, leading to a report on the trial's findings. These independent advisors backed by FDA's established standards on good trial practices are also critical to identifying potential safety issues during a trial. FDA has already demonstrated its willingness to use its authority to suspend a vaccine trial, if the trial's safety monitoring suggests a concern.

Second, in consultation with FDA, companies will need to submit their evidence to the FDA in an application for emergency use or approval. The FDA scientific staff will review this evidence and provide a written assessment, which will be shared publicly at a meeting of the FDA's independent expert advisory committee on vaccines, the Vaccines and Related Biological Products Advisory Committee (VRBPAC). This committee will independently review the evidence and answer questions from FDA staff as to whether the standards for an emergency authorization have been met. The FDA has committed to such a public advisory committee meeting for each new vaccine.

Next, the FDA will take what it has learned from this public airing of evidence to make a decision about emergency authorization or approval. The decision will be reflected in a detailed written report. The report should include a specific plan for learning more about the vaccine's safety as it begins to be used. This plan will include Federal and state vaccine databases to track who has been vaccinated, and mechanisms for drug manufacturers, clinicians, and patients to report whether they had a significant health issue or other adverse event arise following vaccination. Such systems for monitoring infections and potential vaccine side effects in early-use populations should be augmented using secure linkages to electronic databases from medical records, insurance claims, and other sources for timely detection and analysis of further data related to safety. In addition, health care workers who may be first to receive the vaccine could participate in a registry to assess infections and side effects, such as the HERO registry

supported by the Patient-Centered Outcomes Research Network (PCORNet) that is tracking other COVID-related data on health care professionals who volunteered to share it via a secure mobile app.

Finally, the Advisory Committee on Immunization Practices (ACIP) at the CDC will publicly review the evidence and the FDA's authorizations to recommend how the vaccine should be distributed. If the FDA expands its authorization, the CDC's independent advisers will likely meet again to provide a basis for updating their guidance.

Given all of these steps and the FDA's high bar for authorizing a vaccine, it has never been likely that a vaccine would be approved before the election. We shouldn't use that single point in time as a yardstick to measure success. The bottom line is that this process is proceeding at a historic pace, and if we are able to deliver a safe and effective vaccine sometime this fall or winter, it will be a monumental achievement for all of those who supported these endeavors, including the patients who entered trials, the providers on the frontlines, the sponsors who developed products, the administration that stood up Operation Warp Speed, and the members of Congress who had the foresight to provide the foundational regulatory authorities, research infrastructure, and funding and impetus to make it possible.

If this process stays on track, it is possible that one or more vaccines may be authorized for initial use in certain populations before the end of the year. Unless a clinical trial shows overwhelming evidence of effectiveness, and especially since the supply of a vaccine will initially be limited, it's likely that this vaccine access will occur in a staged process. This would start with the people most likely to benefit from a vaccine based on available evidence – potentially including health care workers, high-risk essential workers, older individuals and those with comorbidities. The data on infections and potential adverse events collected from the early-use groups would add substantially to the evidence collected in the clinical trials, including longer-term follow-up on additional patients to address more remote

potential long-term safety risks. Additional studies might also be conducted in groups not well represented in the current trials, such as children and young people.

The EUA allows FDA to enable this very staged market entry of a product like a vaccine, where the vaccine can initially be made available to a smaller group of patients based on their much higher risk of contracting COVID, suffering a bad outcome, or transmitting it to others at high risk. In such a group, the benefits may outweigh the risks, even in a setting where the long-term uncertainties aren't as well understood. As more data is collected, and more and longer-term follow-up is completed, access can be expanded to other groups of patients based on their risk and their likelihood of achieving benefits that outweigh any rare and theoretical safety issues. These further steps would provide the foundation for a broader emergency authorization or approval, and broader use of a vaccine, which is more likely to happen in the second quarter of 2021 or perhaps later.

Given everything I have outlined here - the well-established practices for good clinical trials; independent expert review and public transparency; written commitment of companies to follow the FDA-guided process; and particularly the FDA's experience and commitment to a well-developed, science-based process – I am confident in the path ahead for developing safe and effective vaccines – so long as FDA's expert staff continues to guide it. Science-based decisions like those coming for COVID-19 vaccines are complex, and there will always be some differences of scientific viewpoints among experts and the broader public. But with more than a century of experience in making science-based decisions, a long-established culture of independence and professionalism, independent advisory groups, and the best collection of expertise on COVID-19 vaccines in the world, the FDA is the best equipped place to consider the evidence and views and make these decisions. We're lucky to have such resources in the midst of this public health emergency, so that we can develop and make available safe and effective vaccines at a rapid pace.

All of these well-established systems are hard to disrupt, and they have kept the COVID-19 vaccine development process robust and on track. This is despite a range of political actions, including steps from the White House to influence FDA's process as well as proposed actions by governors to set up some kind of new and untested vaccine review process. Despite the fact that vaccine development continues to follow FDA's long-held standards and guidance, such political actions have created uncertainty for the public that has diminished confidence in the FDA and in vaccine development. Recent public opinion surveys have shown a concerning shift in American attitudes toward potential COVID-19 vaccination. A [recent Pew Research Center](#) poll found 49% of respondents unwilling to be vaccinated today if a new vaccine were available. That's a 22% increase in unwillingness to be vaccinated since Pew surveyed vaccine attitudes in May. For COVID-19 vaccines to have an impact, they must be safe and effective – and Americans must be confident in using them progressively more widely. So it's particularly important for Americans to know that the FDA and the other public health agencies involved in vaccine development and use are following their well-established science-based processes.

Thanks to the instrumental steps in Operation Warp Speed to accelerate vaccine development, coupled with the hard work and professionalism of the FDA, academic experts, industry scientists, public health experts, and others, it is possible that we will have safe and effective vaccines available on a limited basis later this year and much more widely during 2021. But vaccines are only effective to the extent they are used. Over the years, this committee has provided strong bipartisan resources and support for an effective FDA and a science-based development process for products to address unmet medical needs. We need that today more than ever, to avoid ending up prolonging the pandemic and all of its health and economic consequences.

Finally, it's worth emphasizing that for some time to come, we will need to rely on the entire playbook of steps to contain this pandemic. Vaccines will not provide a short-term silver bullet under any plausible circumstances but will hopefully soon become an increasingly important component of

that response. Even as we begin to use vaccines, we will still need the other proven steps that work – masks, distancing, avoiding large groups especially indoors, and personal hygiene like hand washing and sanitizing. We also need to keep working on potential therapeutics, another critical part of Operation Warp Speed and the NIH’s ACTIV trial network.

The return to normalcy will happen gradually. We will still be grappling with COVID-19 next year. But with the right tools, we can accelerate this return, allowing us to significantly reduce the burden of COVID-19 while reopening more effectively and saving lives. To achieve these shared goals, we need to agree on some common principles. These include supporting the steps to efficiently advance the development and use of a safe and effective vaccine, based on FDA’s trusted and scientifically sound guidance. Thank you for your time and continued efforts to address the challenges to the health of the nation and the world.