Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Pathway to a Vaccine: Efforts to Develop a Safe, Effective and Accessible COVID-19 Vaccine"

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The Honorable Frank Pallone, Jr. (D-NJ):

1. Completion of Phase III clinical trials will be critical to ensuring the safety and efficacy of any future COVID-19 vaccine. The U.S. Food and Drug Administration's guidance suggests that a Phase III clinical trial must enroll thousands of individuals in order to generate robust data to support an authorization or approval. Historically experts have suggested Phase III trials enroll upwards of 60,000 patients. How many patients does Merck intend to enroll in Phase III trials for a COVID-19 vaccine, and how will the company work to ensure that this goal is achievable given other competing trials?

   Historically Phase III vaccine studies have been designed to provide sufficient information to test stringent efficacy or safety hypotheses. For example, the Phase III efficacy study for our product Gardasil 9® enrolled approximately 14,000 subjects, the Phase III efficacy study for Zostavax® enrolled approximately 38,000 subjects, and the Phase III safety and efficacy study for RotaTeq® enrolled approximately 70,000 subjects. Merck is currently considering the appropriate trial design for its two SARS-CoV-2 investigational vaccines, V590 (VSV platform used for the licensed Ebola vaccine, Ervebo) and V591 (measles platform vaccine used for investigational vaccines for MERS and Chikungunya).

   Current assumptions regarding the incidence of SARS-CoV-2 disease and infection and the approach to hypothesis testing suggest that approximately 31,000 subjects will need to be enrolled to accrue the number of COVID-19 cases needed to provide sufficient power to test a stringent primary efficacy hypothesis. In order to enroll such a large number of subjects in a short period of time – approximately 3 months – Merck is making investments in these large clinical trials at risk, before obtaining the results of early stage studies. Merck plans to use its large global network of experienced clinical trial sites and has already begun collecting information on study site interest and capacity for these trials.

2. You stated in your testimony that, "Under normal circumstances, manufacturing and distributing a vaccine is exceedingly complex … When we think about what will be needed to address this pandemic, we are talking about orders of magnitude beyond what we as an industry are currently doing."

a. What challenges remain to be able to drastically ramp up manufacturing capacity for a COVID-19 vaccine?

b. What steps is Merck taking now to achieve this goal?

As announced in 2018, Merck was already investing significantly to expand our vaccine production capacity. In fact, to meet growing demand for Merck's medicines and vaccines and enable Merck to invest in R&D, Merck had already planned to invest $20 billion in capital projects from 2019 to 2023.

For SARS-CoV-2 specifically, we are already working to scale up manufacturing capacity to produce hundreds of millions of vaccine doses. This involves refitting or repurposing our global manufacturing network, which includes technology appropriate manufacturing sites in the U.S. and Europe, while also identifying additional opportunities to supplement this network.

We are focusing substantial resources on getting our vaccines and therapeutics, if successful, to market as fast as possible.

The Honorable Brett Guthrie (R-KY):

1. Through Operation Warp Speed and the efforts of your companies and many more, we are seeing an unprecedented effort to quickly develop a safe and effective vaccine. What lessons or changes from this process should we consider making permanent in an effort to fundamentally change the traditional, years-long process for vaccine development going forward?

   The SARS-CoV-2 vaccine programs have been enabled by pre-investment in vaccine platform processes that allowed existing pre-clinical safety and manufacturing knowledge to be leveraged for rapid construction of vaccine candidates with antigens selected through the emerging scientific understanding of SARS-CoV-2. In addition, the establishment of effective public-private partnerships based on complementary capabilities and aligned goals have encouraged access to critical reagents and knowledge sharing that has furthered the development of critical research tools such as animal models and laboratory tests. Frequent and expedient engagement with regulatory agencies, resulting in rapid alignment on endpoint definitions and laboratory testing standards, are expected to decrease the cycle time for protocol planning while assuring that the different vaccine candidates undergo consistent stringent scientific assessments.

   Through cooperative efforts, many vaccine programs have proceeded at unprecedented speed while still assuring rigorous safety and efficacy testing. Cooperative aligned efforts will be needed in the future to ensure successful vaccines will reach the public. For example, innovative regulatory review processes and global regulatory agency harmonization that acknowledges the importance of equitable access and the dependence of vaccines on global supply chains will be required for broad approval in the U.S. and around the globe. These and additional steps are critical to allow for broad access while preserving healthy market

dynamics that drive incremental, value-added improvements to vaccine product characteristics, as well as investments toward increased capability to address future infectious disease risks.

Specific to V590 which uses the VSV virus backbone, the flexibility and co-operation of the U.S. Department of Commerce was essential to enable rapid development of this vaccine candidate, as clinical development and manufacturing of this nature requires international co-operation. The VSV virus backbone itself is a controlled technology subject to Bureau of Industry and Security (BIS) license for export outside of the U.S. Normally, this would mean that a new license application would have been required for every third party outside of the U.S., including Merck sites. This is a major limiting factor for a vaccine we intend to be licensed, manufactured, and distributed globally. However, the U.S. Department of Commerce granted a general exemption for the purposes of developing a vaccine.

The development of future vaccines against currently known as well as unforeseen infectious threats will benefit greatly from continued investments in vaccine technologies that can be rapidly applied to new problems, further strengthening of collaborative partnerships, and enhanced regulatory science and alignment between countries.

2. How did investments into platform technology help speed up the vaccine development process?

   Investment in platform technologies allows for the rapid production of clinical material with minimal process development time. As a result of our experience with Ervebo, our licensed vaccine for Zaire Ebola virus infection, materials for our SARS-CoV-2 vaccine candidate V590 (using the VSV platform) were generated within a quarter once the vaccine construct was finalized. Experience with Ervebo allowed V590 to undergo focused pre-clinical assessment. In addition, the initial Phase I formulation and subsequent improvement were informed based on prior experience with the VSV platform.

   For our vaccine candidate V591 (using the measles platform), the fact that the Coalition for Epidemic Preparedness Innovations (CEPI) had already funded a MERS coronavirus vaccine using the measles platform allowed for the rapid pivoting of the program to SARS-CoV-2. Again, this permitted clinical material to be generated within a few months and streamlined the pre-clinical program.

   Unfortunately, these platform technologies take many years to develop, so continual investment is critical to assure availability of promising technologies in the future.

3. Do any of your companies have recommendations about how to further innovate clinical trials?

   We are optimistic that future vaccine trials will build on the innovations that we are seeing with respect to SARS-CoV-2, which will enhance public interest in and ability to participate in clinical trials. These types of innovations include greater utilization of remote monitoring and data collection for trial subjects.

4. COVID-19 has been with us for about seven months. There is still much we don't know about the antibody response and how long it lasts. Is there anything from the last seven months that has been learned that provides any insights into immune responses, and why it might suggest that our vaccine enterprise is on the right track?

   Over the last several months the scientific understanding of the immune response to SARS-CoV-2, the various modes of transmission, and risk factors for severe disease manifestations have evolved. Moving forward, additional knowledge will inform important modeling and simulation exercises to better understand whether immune responses are likely to translate into clinical protection, as well as how population immunity might impact the epidemic.

   To apply these principles to the Merck SARS-CoV-2 vaccine candidates, ongoing and planned pre-clinical studies will assess the ability of these candidates to protect animals from SARS-CoV-2 infections as well as the immune response associated with protection in these animal models. Our planned clinical studies will assess the candidates' ability to elicit robust neutralizing antibodies and T-cell immunity among clinical study participants. Immunogenicity observed following administration of these vaccine candidates will be assessed in light of observations among COVID-19 survivors to determine if late stage clinical trials are warranted. In the absence of established immune correlates of protection, efficacy will be confirmed in large Phase III clinical efficacy trials. These studies will also be sufficiently large to confirm that the safety and reactogenicity profile are suitable for use in large healthy populations.

5. Do you have plans to have human challenge studies where you will take healthy individuals, immunize them with your vaccine candidate, and then challenge them with an infectious dose of COVID-19?

   a. If yes, how is this ethical, and will your human challenge studies include participants over 55 years of age?

   b. If nobody under 55 will be enrolled, will there be a gap in our knowledge about vaccine effectiveness in the 55 years and older age group?

   No, Merck is currently not planning human challenge studies of its SARS-CoV-2 vaccine candidates.

6. Could your vaccine candidate(s) be used with an adjuvant? If so, how many additional doses could be generated from the use of an adjuvant.

   a. If not, are there other ways your vaccine could be boosted to strengthen the immune response in patients?

   Both Merck SARS-CoV-2 vaccine candidates, V590 and V591, are replicating virus constructs and are currently not designed to be used with an adjuvant.

With additional time and resources, other methods of delivery, such as microarray nano-patches, could potentially provide for dose sparing, though this would need to be investigated further. This delivery technology offers the advantages of rapid dissemination of an approved product. In addition, investment into new formulation technologies focused on end-to-end processing can improve dose targeting and thus reduce overage requirements per dose, increasing the total amount of doses available.

The Honorable David B. McKinley (R-WV):

1. When H.R. 3, the Lowering Drug Costs Now Act, was being considered in the House, members of this Committee raised concerns about what such legislation could do to innovation and drug development in the U.S., and Dr. Gerberding mentioned in her testimony how a robust biopharmaceutical research network has contributed to the accelerated development of a vaccine. H.R. 3 would undermine the important role of private-sector R&D in the U.S., as countries with price controls have suffered a decline in pharmaceutical R&D.

   Do you all have concerns about impacts on your research and development efforts, should such legislation become law in the U.S.? Why or why not?

   We believe that H.R. 3 is the wrong approach to address patient affordability. Patients deserve common-sense solutions that will lower their out-of-pocket costs while maintaining access to innovative medicines. Instead of making these types of practical changes, H.R. 3 upends the current competition-based system in favor of government price setting that will have a devastating impact on innovation and limit access to the newest and most innovative medicines. We agree that we must address patient affordability and the misaligned incentives in our current health care system, but H.R. 3 would not achieve these objectives. We will continue to work on solutions to help patients with their drug costs while still supporting the innovation ecosystem to produce the medical advancements that Americans need and desire.

2. Most of you have accepted awards from the U.S. Department of Health and Human Services (HHS) to assist with the development and manufacturing of a COVID-19 vaccine?

   a. Are each of you on schedule and on budget?

   b. If you are behind schedule, do you plan to invest your own capital if the government grant runs out before you are finished with development?

   c. If you are ahead of schedule and you have grant money left over, what are your plans for those funds?

   For our vaccine candidate V590 (our rVSV vaccine being developed in collaboration with the International AIDS Vaccine Initiative (IAVI)), Merck has signed an agreement with the Biomedical Advanced Research and Development Authority (BARDA), part of the office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health

and Human Services, to provide initial funding support for this effort. These efforts are on schedule and the resources provided by BARDA are only a small fraction of the investment Merck is making to pursue development of this vaccine candidate.