United States Government Accountability Office

Report to Congressional Addressees

February 2021

OPERATION WARP SPEED

Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges

GAO@100

A Century of Non-Partisan Fact-Based Work

BioNTech-Pfizer Exhibit 1176
BioNTech SE and Pfizer Inc. v. ModernaTX, Inc. IPR2023-01359
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GAO@100 Highlights

Highlights of GAO-21-319, a report to congressional addressees

February 2021

OPERATION WARP SPEED

Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges

Why GAO Did This Study

As of February 5, 2021, the U.S. had over 26 million cumulative reported cases of COVID-19 and about 449,020 reported deaths, according to the Centers for Disease Control and Prevention. The country also continues to experience serious economic repercussions, with the unemployment rate and number of unemployed in January 2021 at nearly twice their pre-pandemic levels in February 2020. In May 2020, OWS was launched and included a goal of producing 300 million doses of safe and effective COVID-19 vaccines with initial doses available by January 2021. Although FDA has authorized two vaccines for emergency use, OWS has not yet met its production goal. Such vaccines are crucial to mitigate the public health and economic impacts of the pandemic.

GAO was asked to review OWS vaccine development efforts. This report examines: (1) the characteristics and status of the OWS vaccines, (2) how developmental processes have been adapted to meet OWS timelines, and (3) the challenges that companies have faced with scaling up manufacturing and the steps they are taking to address those challenges.

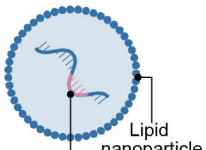
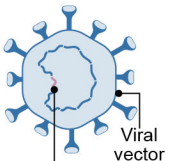
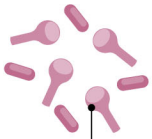
GAO administered a questionnaire based on HHS's medical countermeasures TRL criteria to the six OWS vaccine companies to evaluate the COVID-19 vaccine development processes. GAO also collected and reviewed supporting documentation on vaccine development and conducted interviews with representatives from each of the companies on vaccine development and manufacturing.

View GAO-21-319. For more information, contact Karen L. Howard and Candice N. Wright at (202) 512-6888 or howardk@gao.gov or wrightc@gao.gov.

What GAO Found

Operation Warp Speed (OWS)—a partnership between the Departments of Health and Human Services (HHS) and Defense (DOD)—aimed to help accelerate the development of a COVID-19 vaccine. GAO found that OWS and vaccine companies adopted several strategies to accelerate vaccine development and mitigate risk. For example, OWS selected vaccine candidates that use different mechanisms to stimulate an immune response (i.e., platform technologies; see figure). Vaccine companies also took steps, such as starting large-scale manufacturing during clinical trials and combining clinical trial phases or running them concurrently. Clinical trials gather data on safety and efficacy, with more participants in each successive phase (e.g., phase 3 has more participants than phase 2).

Vaccine Platform Technologies Supported by Operation Warp Speed, as of January 2021

	mRNA platform	Replication-defective live-vector platform	Recombinant-subunit-adjuvanted protein platform
			
Description	Encapsulated genetic instructions that allow vaccinated individuals to produce the spike protein of SARS-CoV-2 to stimulate immune system but cannot cause COVID-19.	Non-replicating virus that delivers genetic instructions to allow vaccinated individuals to produce the spike protein of SARS-CoV-2 to stimulate immune system but cannot cause COVID-19.	Fully-formed spike protein of SARS-CoV-2 delivered with adjuvant, which helps to stimulate immune system of vaccinated individuals but cannot cause COVID-19.
Operation Warp Speed candidates (most advanced clinical trial phase)	**Moderna** (phase 3) **Pfizer/BioNTech** (phase 3)	**Janssen** (phase 3) **AstraZeneca** (phase 3)	**Sanofi/GSK** (phase 2) **Novavax** (phase 3)

Source: GAO (analysis); Adaptation of images depicting vaccine technologies with permission from Springer Nature: *Nature* ("The Race for Coronavirus Vaccines: A Graphical Guide," Ewen Callaway) © 2020. | GAO-21-319

As of January 30, 2021, five of the six OWS vaccine candidates have entered phase 3 clinical trials, two of which—Moderna's and Pfizer/BioNTech's vaccines—have received an emergency use authorization (EUA) from the Food and Drug Administration (FDA). For vaccines that received EUA, additional data on vaccine effectiveness will be generated from further follow-up of participants in clinical trials already underway before the EUA was issued.

Technology readiness. GAO's analysis of the OWS vaccine candidates' technology readiness levels (TRL)—an indicator of technology maturity—showed that COVID-19 vaccine development under OWS generally followed traditional practices, with some adaptations. FDA issued specific guidance that identified ways that vaccine development may be accelerated during the pandemic. Vaccine companies told GAO that the primary difference from a non-pandemic environment was the compressed timelines. To meet OWS timelines,

some vaccine companies relied on data from other vaccines using the same platforms, where available, or conducted certain animal studies at the same time as clinical trials. However, as is done in a non-pandemic environment, all vaccine companies gathered initial safety and antibody response data with a small number of participants before proceeding into large-scale human studies (e.g., phase 3 clinical trials). The two EUAs issued in December 2020 were based on analyses of clinical trial participants and showed about 95 percent efficacy for each vaccine. These analyses included assessments of efficacy after individuals were given two doses of vaccine and after they were monitored for about 2 months for adverse events.

Manufacturing. As of January 2021, five of the six OWS vaccine companies had started commercial scale manufacturing. OWS officials reported that as of January 31, 2021, companies had released 63.7 million doses—about 32 percent of the 200 million doses that, according to OWS, companies with EUAs have been contracted to provide by March 31, 2021. Vaccine companies face a number of challenges in scaling up manufacturing to produce hundreds of millions of doses under OWS's accelerated timelines. DOD and HHS are working with vaccine companies to help mitigate manufacturing challenges, including:

- Limited manufacturing capacity: A shortage of facilities with capacity to handle the vaccine manufacturing needs can lead to production bottlenecks. Vaccine companies are working in partnership with OWS to expand production capacity. For example, one vaccine company told GAO that HHS's Biomedical Advanced Research and Development Authority helped them identify an additional manufacturing partner to increase production. Additionally, the U.S. Army Corps of Engineers is overseeing construction projects to expand capacity at vaccine manufacturing facilities.
- Disruptions to manufacturing supply chains: Vaccine manufacturing supply chains have been strained by the global demand for certain goods and workforce disruptions caused by the global pandemic. For example, representatives from one facility manufacturing COVID-19 vaccines stated that they experienced challenges obtaining materials, including reagents and certain chemicals. They also said that due to global demand, they waited 4 to 12 weeks for items that before the pandemic were typically available for shipment within one week. Vaccine companies and DOD and HHS officials told GAO they have undertaken several efforts to address possible manufacturing disruptions and mitigate supply chain challenges. These efforts include federal assistance to (1) expedite procurement and delivery of critical manufacturing equipment, (2) develop a list of critical supplies that are common across the six OWS vaccine candidates, and (3) expedite the delivery of necessary equipment and goods coming into the United States. Additionally, DOD and HHS officials said that as of December 2020 they had placed prioritized ratings on 18 supply contracts for vaccine companies under the Defense Production Act, which allows federal agencies with delegated authority to require contractors to prioritize those contracts for supplies needed for vaccine production.
- Gaps in the available workforce: Hiring and training personnel with the specialized skills needed to run vaccine manufacturing processes can be challenging. OWS officials stated that they have worked with the Department of State to expedite visa approval for key technical personnel, including technicians and engineers to assist with installing, testing, and certifying critical equipment manufactured overseas. OWS officials also stated that they requested that 16 DOD personnel be detailed to serve as quality control staff at two vaccine manufacturing sites until the organizations can hire the required personnel.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
BARDA	Biomedical Advanced Research and Development Authority
BLA	biologics license application
CDC	Centers for Disease Control and Prevention
CGMP	current good manufacturing practice
COVID-19	Coronavirus Disease 2019
DOD	Department of Defense
EUA	emergency use authorization
FDA	Food and Drug Administration
GLP	good laboratory practice
HHS	Department of Health and Human Services
IND	Investigational New Drug
mRNA	messenger RNA
OWS	Operation Warp Speed
R&D	research and development
TRL	technology readiness level
VRBPAC	Vaccines and Related Biological Products Advisory Committee

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February 11, 2021

Congressional Addressees

The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in catastrophic loss of life and substantial damage to the global economy, stability, and security. Worldwide, as of February 5, 2021, there were over 104 million cumulative reported cases and over 2.2 million reported deaths due to COVID-19; within the United States, there were over 26 million cumulative reported cases and 449,020 reported deaths.[1] The country also continues to experience serious economic repercussions and turmoil as a result of the pandemic.[2] In response to this unprecedented global crisis, the federal government has taken a series of actions to protect the health and well-being of Americans. Notably, in March 2020, Congress passed, and the President signed into law, the CARES Act, which provided over $2 trillion in emergency assistance and health care response for individuals, families, and businesses affected by COVID-19.[3] More recently, in December 2020, the Consolidated

[1]Worldwide data from the World Health Organization reflect laboratory-confirmed cases and deaths reported by countries and areas. Data on COVID-19 cases in the United States are based on aggregate case reporting to the Centers for Disease Control and Prevention (CDC) and include probable and confirmed cases as reported by states and jurisdictions. According to CDC, the actual number of COVID-19 cases is unknown for a variety of reasons, including that people who have been infected may have not been tested or may have not sought medical care. CDC's National Center for Health Statistics' COVID-19 death counts in the United States are based on provisional counts from death certificate data, which do not distinguish between laboratory-confirmed and probable COVID-19 deaths. Provisional counts are incomplete due to an average delay of 2 weeks (a range of 1–8 weeks or longer) for death certificate processing.

[2]U.S. Bureau of Labor Statistics, Employment Situation Summary—January 2021, (Washington, D.C.: Feb. 2021). In January, the unemployment rate was 6.3 percent and the number of unemployed persons was 10.1 million. Although both measures are much lower than their April 2020 highs, they remain well above their pre-pandemic levels in February 2020 (3.5 percent and 5.7 million, respectively).

[3]Pub. L. No. 116-136, 134 Stat. 281 (2020). As of January 1, 2021, four other relief laws were also enacted in response to the COVID-19 pandemic: the Consolidated Appropriations Act, 2021, Pub. L. No. 116-260, 134 Stat. 1182 (2020); Paycheck Protection Program and Health Care Enhancement Act, Pub. L. No. 116-139, 134 Stat. 620 (2020); Families First Coronavirus Response Act, Pub. L. No. 116-127, 134 Stat. 178 (2020); and the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, Pub. L. No. 116-123, 134 Stat. 146.

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Appropriations Act, 2021, provided additional federal assistance for the ongoing response and recovery.

The development of a COVID-19 vaccine was crucial to mitigating the public health and economic impacts of the virus. By the end of March 2020, with the initiation of the first clinical trials, the race was on in the United States to develop a vaccine. On December 14, 2020, the United States took an important step to protect the public against the virus as the first vaccine shots—developed in a shorter time than any previous vaccine—were administered.

As part of the U.S. vaccine effort, on May 15, 2020, the federal government announced Operation Warp Speed (OWS), a partnership between the Department of Defense (DOD) and Department of Health and Human Services (HHS). As stated on the HHS website, the goal was to produce 300 million doses of COVID-19 vaccines, with initial doses available by January 2021. Although FDA has authorized two vaccines for emergency use, OWS has not yet met its production goals.[4] Our November 2020 report included the following figure describing how the federal government aimed to accelerate the development of a COVID-19 vaccine (see fig. 1).[5] DOD and HHS have obligated approximately $13 billion as of December 31, 2020, to support the development, manufacture, and distribution of vaccines to help achieve this goal.[6]

[4]During an emergency, as declared by the Secretary of Health and Human Services under 21 U.S.C. § 360bbb-3(b), FDA may temporarily authorize unapproved medical products or unapproved uses of approved medical products through an emergency use authorization (EUA), provided certain statutory criteria are met.

[5]GAO, *COVID-19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations*, GAO-21-207 (Washington, D.C.: November 17, 2020).

[6]GAO, *COVID-19: Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention*, GAO-21-265 (Washington, D.C.: January 28, 2021).

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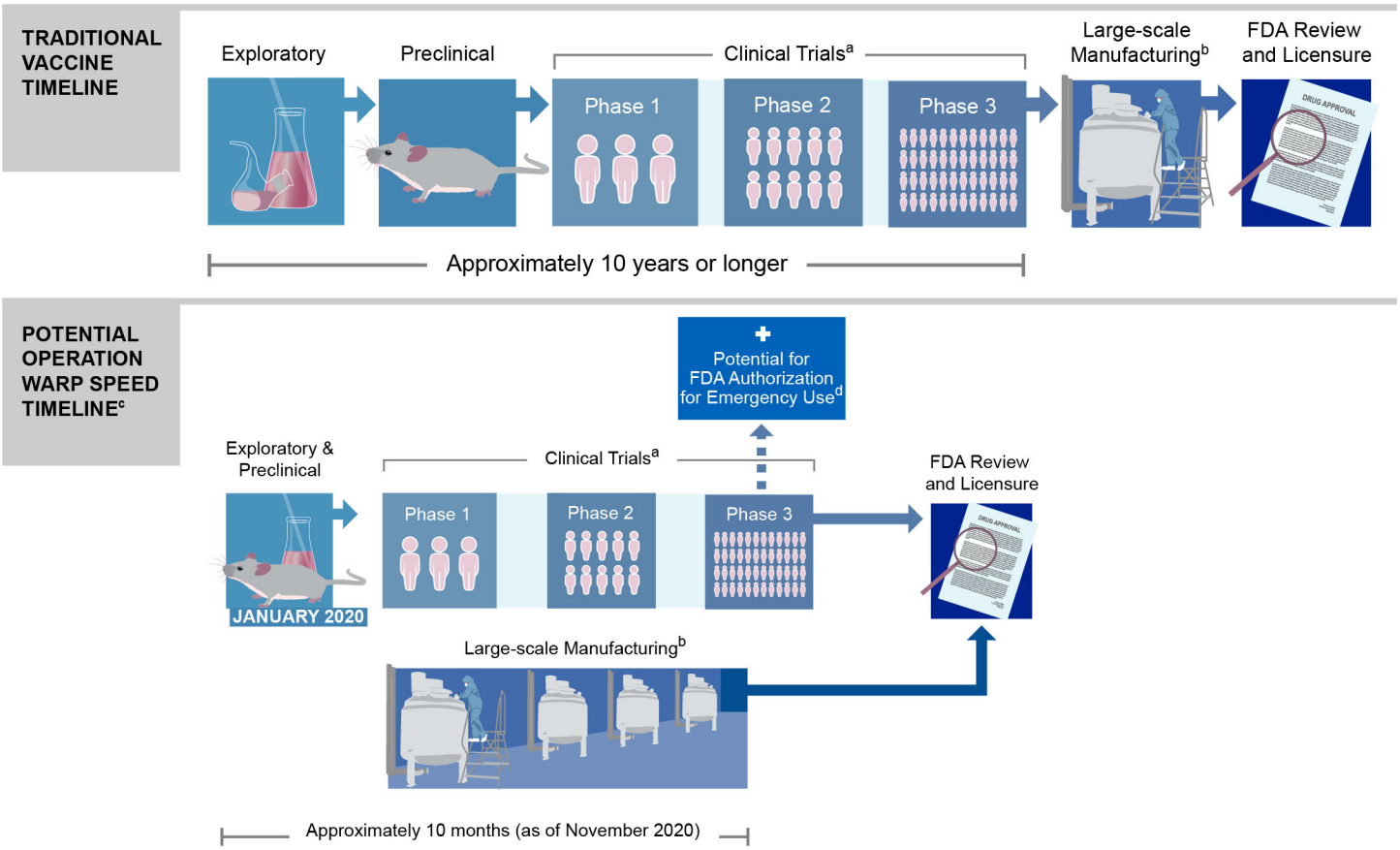
Figure 1: Traditional Vaccine Development Timeline Compared To Potential Operation Warp Speed (OWS) Timeline



Source: GAO Analysis of Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America, and Operation Warp Speed Information. | GAO-21-319

Note: The timelines for vaccine development depicted in this figure are not drawn to scale. These timelines depict examples, and the specific development steps and timelines for a given vaccine may vary from this example.

[a]Phase 1 clinical trials generally test the safety of a product with a small group of healthy volunteers (usually fewer than 100). These trials are designed to determine the product's initial safety profile and the side effects associated with increasing doses, among other things.

Phase 2 clinical trials are designed to evaluate the effectiveness of a product for a particular use and determine the common short-term side effects and risks associated with the product. These trials are conducted with a medium-size population of volunteers (usually a few dozen to hundreds).

Phase 3 clinical trials are performed after preliminary evidence suggesting effectiveness of a product has been obtained, and are intended to gather additional information about safety and effectiveness. These trials usually involve several hundred to thousands of volunteers, including participants who are at increased risk for infection. According to Food and Drug Administration (FDA) officials, these clinical trial phases may overlap.

[b]According to FDA, manufacturing processes are reviewed as part of the vaccine licensure process. Thus, even under a traditional vaccine timeline, some initial manufacturing occurs during development, so the manufacturing processes can be adequately validated. According to an OWS fact sheet, in some cases, the federal government is taking on the financial risk to enable large-scale

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manufacturing to start while clinical trials are ongoing, with the goal of having millions of doses available for distribution upon authorization or licensure of a COVID-19 vaccine.

[c]The OWS timeline depicts an example of a potential accelerated timeline for COVID-19 vaccine development. However, the development process of any given OWS vaccine candidate may vary from this example. As of January 2021, approximately 12 months have elapsed since exploratory and preclinical research began in January 2020, after the first U.S. cases of COVID-19 were reported. The timing for any remaining steps have yet to be determined as of this report. According to OWS documentation, certain steps may overlap or be shortened to accelerate the development of a COVID-19 vaccine.

[d]During an emergency, as declared by the Secretary of Health and Human Services under 21 U.S.C. § 360bbb-3(b), FDA may temporarily authorize unapproved medical products or unapproved uses of approved medical products through an emergency use authorization (EUA), provided certain statutory criteria are met. FDA has indicated that issuance of an EUA for a COVID-19 vaccine for which there is adequate manufacturing information would require the submission of certain clinical trial information from phase 3 clinical trials that demonstrate the safety and effectiveness of the vaccine in a clear and compelling manner, among other things. Any COVID-19 vaccine that initially receives an EUA from FDA is expected to ultimately be reviewed and receive licensure through a biologics license application, according to FDA guidance.

Vaccines provide protection for individuals and, more broadly, communities, to lower transmission and disease burden once a large enough portion of the population—typically 70 to 90 percent—develops immunity.[7] Reaching this "herd immunity threshold" limits the likelihood that a non-immune person will be infected. Herd immunity helps protect people who are not immune to a disease by reducing their chances of interacting with an infected individual, thereby slowing or stopping the spread of the disease. Achieving herd immunity can require a high rate of vaccination in the community, and can bring about a safe return to use of restaurants, theaters, and gyms, and the resumption of community-based activities. In this way, vaccines can save lives, reduce the sometimes debilitating effects of COVID-19, and contribute to the restoration of the economy.

You asked us to assess the technology readiness and manufacturing status of OWS vaccine candidates. This report examines (1) the characteristics and development status of the individual OWS vaccine candidates, (2) how developmental processes have been adapted to meet OWS timelines, and (3) the challenges that companies have faced with scaling up manufacturing and the steps they are taking to address those challenges.

To examine the characteristics and development status of the OWS vaccine candidates, we analyzed relevant agency documents, vaccine company documents, and journal articles. To examine how

[7]Disease burden is the impact of a health problem as measured by mortality, morbidity, financial impact, or other indicators.

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developmental processes have been adapted to meet OWS timelines, we analyzed vaccine candidates' technology readiness levels (TRL) and reviewed steps vaccine companies took to develop their vaccines. We used TRLs, a maturity scale ordered according to the required characteristics of the specific technology, similar to those specified in our GAO Technology Readiness Assessment Guide.[8] In the case of vaccine development, HHS provides development process guidelines in its integrated TRLs for medical countermeasures, which include vaccines.[9] We used the HHS TRLs to compare the OWS vaccine candidates to the standard vaccine development process. We sent a questionnaire that reflected HHS's integrated TRL criteria to all OWS vaccine companies. We also collected supporting documentation and conducted follow-up interviews with each company to clarify or further support their responses to the questionnaire, when necessary. To assign TRLs for each vaccine candidate, we reviewed questionnaire responses, and supporting documentation. When necessary, we relied on peer-reviewed studies or other public information to validate company responses. To describe how each vaccine company adapted their developmental processes to meet OWS timelines, we reviewed the supporting documents we collected and compared them against the OWS timelines. To describe the challenges in scaling up manufacturing and the steps companies are taking to address those challenges, we interviewed representatives responsible for manufacturing-related activities from each of the OWS vaccine companies, as well as representatives from the vaccine companies' manufacturing partners.[10] See appendix I for additional information on our objectives, scope, and methodology.

[8]GAO, *Technology Readiness Assessment Guide: Best Practices for Evaluating the Readiness of Technology for Use in Acquisition Programs and Projects,* GAO-20-48G (Washington, D.C.: January 7, 2020).

[9]See Department of Health & Human Services. *Integrated TRLs for Medical Countermeasure Products (Drugs and Biologics).* https://www.medicalcountermeasures.gov/trl/integrated-trls/ (accessed December 28, 2020). Medical countermeasures include drugs and biologics, such as vaccines, that can diagnose, prevent, protect from, or treat the effects of exposure to emerging infectious diseases, such as pandemic influenza, and to chemical, biological, radiological, or nuclear agents. The scope of this report is limited to vaccines.

[10]OWS vaccine companies include Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, Sanofi/GSK, and Novavax. Manufacturing partners included Emergent Biosolutions and the Texas A&M Center for Innovation in Advanced Development and Manufacturing (Texas A&M CIADM).

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We conducted this performance audit from July 2020 to February 2021 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Vaccine Selection Criteria

HHS and DOD, in support of OWS, awarded contracts and other transaction agreements to six vaccine companies to develop or manufacture vaccine doses.[11] According to the OWS Chief Advisor and the Director of Vaccines, OWS officials selected vaccine candidates from four vaccine-platform technologies that OWS considered to be the most likely to yield a safe and effective vaccine against COVID-19.[12] In addition, OWS considered whether they met the following three criteria:[13]

1. had robust preclinical data or early-stage clinical trial data supporting their potential for clinical safety and efficacy;
2. had the potential, with OWS acceleration support, to enter large phase 3 field efficacy trials in July to November 2020 and to deliver efficacy outcomes by the end of 2020 or the first half of 2021;
3. were based on vaccine-platform technologies permitting fast and effective manufacturing, with companies demonstrating the industrial

[11]Other transaction agreements are flexible agreements that allow the parties to negotiate terms and conditions specific to the project. Overall, about $8.8 billion of roughly $13 billion dollars for vaccine development and manufacturing have been obligated through other transaction agreements as of December 31, 2020.

[12]A vaccine platform is a technology for production of different vaccine antigens—proteins or other biomolecules that stimulate the immune response. A protein antigen may be produced by incorporating a gene that codes for a protein or protein subunit from the relevant virus or other pathogen (e.g., SARS-CoV-2) into another virus called a vector. The vector serves as a delivery vehicle for the genetic material, which code for the antigen. Vaccine platforms may have uniform, predictable characteristics, such as safety effects; however, each antigen in a specific platform will have different immune response characteristics.

[13]See M. Slaoui and M. Hepburn. “Developing Safe and Effective COVID Vaccines — Operation Warp Speed’s Strategy and Approach,” *New England Journal of Medicine*, Aug. 26, 2020.

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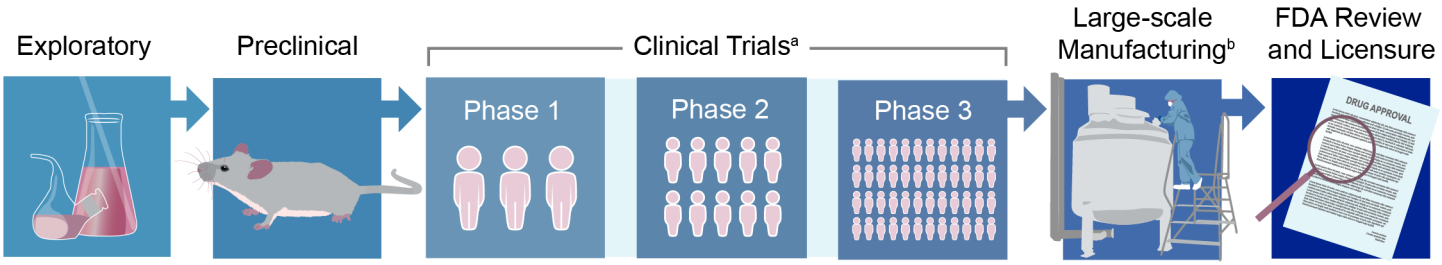
process scalability, yields, and consistency necessary to reliably produce more than 100 million doses by mid-2021.

As of January 2021, five of the six OWS vaccine companies were testing their vaccine candidates in phase 3 clinical trials. Two vaccines received emergency use authorizations (EUA) from the Food and Drug Administration (FDA) in December 2020.[14] These vaccines received EUAs in less than a year from the time the genetic code of SARS-CoV-2—the virus that causes COVID-19—was sequenced. This was considerably faster than any previous vaccine development and authorization for use in the United States.

Traditional Vaccine Development Process

The traditional process for developing a new vaccine is well established and tends to be sequential (see figure 2). Although there is sometimes overlap in phases, a longer, more sequential approach is common in non-pandemic environments. According to two vaccine companies we met with, the purpose of this approach is in part to reduce financial risk because each phase is costly—with later phases being especially costly—and each phase improves the understanding of whether the next phase will be successful.

Figure 2: Traditional Vaccine Development Process



Source: GAO Analysis of Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America. | GAO-21-319

Note: The timelines for vaccine development depicted in this figure are not drawn to scale. This timeline depicts an example, and the specific development steps and timeline for a given vaccine may vary from this example. There may be some overlap among steps.

[14]During an emergency, as declared by the Secretary of Health and Human Services under 21 U.S.C. § 360bbb-3(b), FDA may temporarily allow the use of unlicensed COVID-19 vaccines through an EUA, provided certain statutory criteria are met. For example, a company requesting an EUA must provide evidence that the vaccine may be effective and that the known and potential benefits outweigh the known and potential risks, among other requirements. Any COVID-19 vaccine that initially receives an EUA from FDA is expected to ultimately be reviewed and receive licensure through a biologics license application, according to FDA guidance.

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[a]Phase 1 clinical trials generally test the safety of a product with a small group of healthy volunteers (usually fewer than 100). These trials are designed to determine the product's initial safety profile and the side effects associated with increasing doses, among other things.

Phase 2 clinical trials are designed to evaluate the effectiveness of a product for a particular use and determine the common short-term side effects and risks associated with the product. These trials are conducted with a medium-size population of volunteers (usually a few dozen to hundreds).

Phase 3 clinical trials are performed after preliminary evidence suggesting effectiveness of a product has been obtained, and are intended to gather additional information about safety and effectiveness. These trials usually involve several hundred to thousands of volunteers, including participants who are at increased risk for infection. According to Food and Drug Administration (FDA) officials, these clinical trial phases may overlap.

[b]According to FDA, manufacturing processes are reviewed as part of the vaccine licensure process. Thus, even under a traditional vaccine timeline, some initial manufacturing occurs during development, so the manufacturing processes can be adequately validated.

In the exploratory phase, the target and candidate vaccine are identified.[15] In the preclinical phase, researchers use cells and animals to assess safety and produce evidence of clinical promise, evaluated by the candidate's ability to elicit a protective immune response. During clinical trials, more human subjects are added at each successive phase. Safety, efficacy, proposed doses, schedule of immunizations, and method of delivery are evaluated (see table 1).

Table 1: Typical Phases of Clinical Trials

Phase 1	Determines the product's initial safety profile and the side effects associated with increasing doses, among other things. These trials generally test the safety of a product with a small group of healthy volunteers (usually fewer than 100).
Phase 2	Evaluates the effectiveness of a product for a particular use and determines the short-term side effects and risks associated with the product. These trials are conducted with a medium-size population of volunteers (usually a few dozen to hundreds).
Phase 3	Performed after preliminary evidence suggesting effectiveness of a product has been obtained and are intended to gather additional information about safety and effectiveness. These trials usually involve several hundred to thousands of volunteers, including participants who are at increased risk for infection.

Source: Food and Drug Administration. | GAO-21-319

Note: According to Food and Drug Administration (FDA) documentation, these clinical trial phases may overlap. Phase 4 clinical trials may be required after licensure to obtain additional information on the product's benefits, risks, and optimal use.

The next phase is FDA review of the biologics license application (BLA) and licensure, which includes oversight of manufacturing and planning for

[15]During vaccine development, virus targets need to be identified to develop a safe and effective vaccine. In the case of COVID-19 vaccines, the SARS-CoV-2 spike protein was identified as the virus target.

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postmarket surveillance.[16] At any phase, the process can be terminated for various reasons including detection of adverse events, such as serious side effects.

HHS Integrated Technology Readiness Levels

The federal government uses TRLs to systematically review the progress of new technologies along a spectrum of technology maturity from basic research to operational implementation of a proven technology. For vaccine development, HHS tailored a set of integrated TRLs for medical countermeasures.[17] Specifically, HHS's Biomedical Advanced Research and Development Authority (BARDA) uses TRLs to make funding determinations for vaccines by requesting the information aligning with the TRL definitions from pharmaceutical companies to report progress on their research and development (R&D) programs. These TRL criteria allow a vaccine R&D program to be categorized by its degree of maturity, from basic research about the mechanisms of a disease to the evaluation of a vaccine candidate using animal studies and clinical trials in humans, and finally through licensure and large-scale manufacturing of the vaccine. We used the HHS integrated TRLs as a metric in this report because TRLs represent a widely accepted system for tracking technological progress.

The HHS integrated TRL medical countermeasure scale consists of nine levels, requiring demonstration that a vaccine has achieved incrementally higher levels of technical maturity until the final level, where a vaccine has reached post-FDA licensure activities. See Appendix II for a detailed description of the HHS integrated TRLs.

The HHS integrated TRLs include the phases of the traditional vaccine development process (exploratory phase, preclinical phase, clinical trials, BLA submission, and FDA review and licensure). Figure 3 compares the HHS integrated TRLs and the traditional vaccine development and manufacturing processes.

[16]Phase 4 clinical trials may be required after licensure to obtain additional information on the product's benefits, risks, and optimal use.

[17]HHS adapted the TRL format, originally developed by the National Aeronautics and Space Administration and DOD, to evaluate the development of medical countermeasures against both natural and man-made public health threats.

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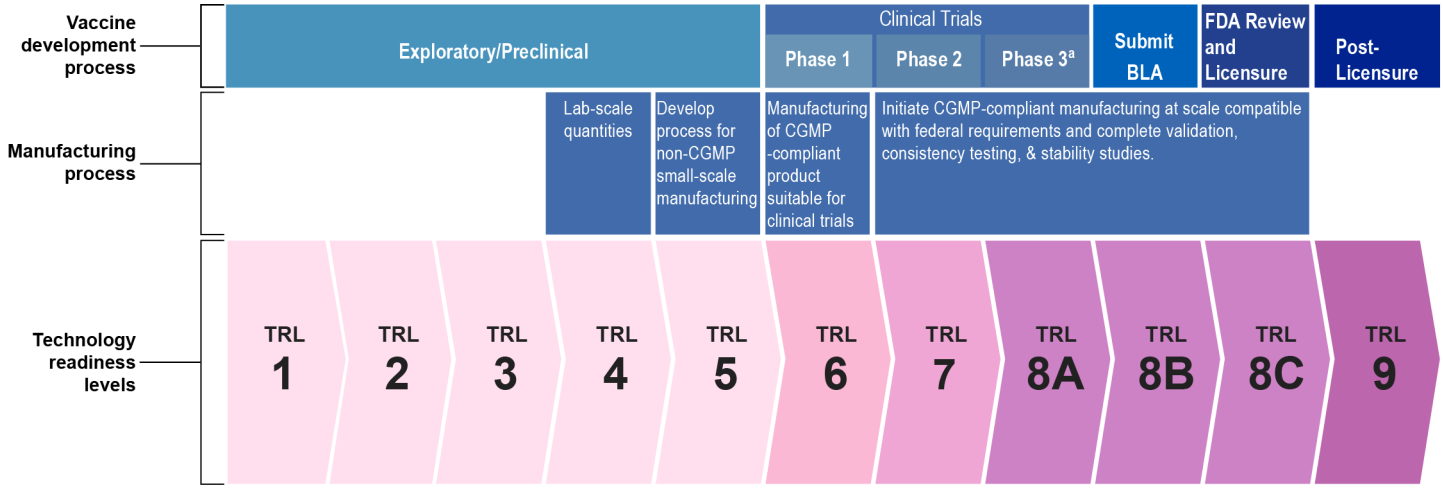
Figure 3: Department of Health and Human Services' Integrated Technology Readiness Level (TRL) Countermeasure Scale and the Traditional Vaccine Development and Manufacturing Processes



BLA = biologics license application
CGMP = current good manufacturing practice
FDA = Food and Drug Administration

Source: GAO presentation of Department of Health and Human Services criteria for Integrated Technology Readiness Levels (Drugs and Biologics) and Food and Drug Administration guidance ("Emergency Use Authorization for Vaccines to Prevent COVID-19" October 2020). | GAO-21-319

[a]Potential for FDA authorization for emergency use

OWS Supported a Range of Vaccine Approaches

To Mitigate Risk, OWS Supported Vaccines with Different Characteristics

OWS's strategy for rapid vaccine development was to build a diverse portfolio of vaccine candidates based on distinct platform technologies. According to OWS officials, this approach intended to provide a range of options, potentially accelerating development and mitigating the risks associated with the challenge of developing a safe and effective vaccine on OWS's timelines.[18] OWS officials originally planned to include four platforms in the OWS vaccine candidate portfolio: messenger RNA (mRNA), replication-defective live-vector, recombinant-subunit-adjuvanted protein, and attenuated replicating live vector (see fig. 4).

[18]*See M. Slaoui and M. Hepburn. "Developing Safe and Effective COVID Vaccines — Operation Warp Speed's Strategy and Approach," New England Journal of Medicine, Aug. 26, 2020.*

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OWS has publicly announced support for six vaccine candidates using three of those platforms.

OWS's strategy included selecting different platform technologies to mitigate the risk that any one platform or specific vaccine candidate could fail because of problems with safety, efficacy, industrial manufacturability, or scheduling factors. This strategy included two vaccine platforms that had not previously been used in a licensed vaccine, but could theoretically be quickly adapted to COVID-19 and scaled up rapidly (i.e., mRNA platform and replication-defective live-vector platform), and one platform that had been proven (i.e., recombinant-subunit-adjuvanted protein platform).

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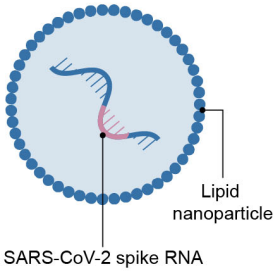
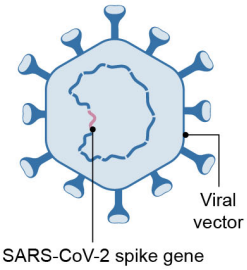
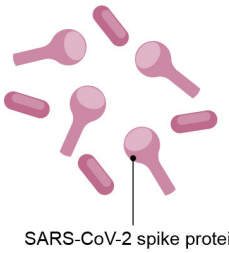
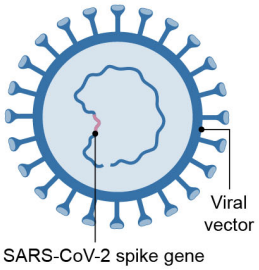
Figure 4: Overview of the Four Vaccine Platform Technologies Considered by Operation Warp Speed, as of January 2021

	mRNA platform	Replication-defective live-vector platform	Recombinant-subunit-adjuvanted protein platform	Attenuated replicating live-vector platform
				
Description	Encapsulated genetic instructions that allow vaccinated individuals to produce the spike protein of SARS-CoV-2 to stimulate immune system but cannot cause COVID-19.	Non-replicating virus that delivers genetic instructions to allow vaccinated individuals to produce the spike protein of SARS-CoV-2 to stimulate immune system but cannot cause COVID-19.	Fully-formed spike protein of SARS-CoV-2 delivered with adjuvant, which helps to stimulate immune system of vaccinated individuals but cannot cause COVID-19.	Replicating virus that delivers genetic instructions to allow vaccinated individuals to produce the spike protein of SARS-CoV-2 to stimulate immune system but cannot cause COVID-19.
Technology used in prior FDA-licensed vaccine	✗ No vaccine using this technology has ever been licensed by FDA	✗ No vaccine using this technology has ever been licensed by FDA	✓ Example: seasonal influenza vaccine (licensed by FDA)	✓ Example: Ebola vaccine (licensed by FDA)
Doses required	2	1-2	2	1 (potentially)
Operation Warp Speed candidates (most advanced clinical trial phase)	**Moderna** (phase 3)* **Pfizer/BioNTech** (phase 3)*	**Janssen** (phase 3) **AstraZeneca** (phase 3)	**Sanofi/GSK** (phase 2) **Novavax** (phase 3)	None

Source: GAO (analysis); Adaptation of images depicting vaccine technologies with permission from Springer Nature: *Nature* ("The Race for Coronavirus Vaccines: A Graphical Guide," Ewen Callaway) © 2020. | GAO-21-319

Note: Asterisk (*) indicates company has received an emergency use authorization (EUA), which allows the temporary use of an unlicensed vaccine, provided certain statutory criteria are met. As of January 2021, phase 3 clinical trials are still ongoing for these COVID-19 vaccine candidates, and the candidates are expected to ultimately be reviewed and receive licensure through a biologics license application, according to Food and Drug Administration (FDA) guidance.

Vaccine Platform Technologies Utilize Different Mechanisms for Stimulating Immune Responses

Human cells use lock-and-key-style security to allow for the necessary exchange of proteins while preventing the intrusion of disease-causing microbes, such as viruses. Before entering a cell, a protein needs to present a unique 'key'—a molecular pattern that opens a specific 'lock.' Coronaviruses, such as SARS-CoV-2, use counterfeit keys, called

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spike "S" proteins, to enter human cells.[19] All COVID-19 vaccines share a common strategy: teach the immune system to recognize the SARS-CoV-2 spike protein and neutralize the virus, providing immunity. The immune system response that neutralizes the virus is largely mediated by antibody production and associated immune cells (e.g., T cells). The OWS vaccine candidates differ in what method, or platform, they use to initiate these immune responses. There are three main platforms: mRNA, replication-defective live-vector, and recombinant-subunit-adjuvanted protein (see table 2). These three vaccine platforms, unlike other vaccine platforms, do not require researchers to grow the SARS-CoV-2 virus, which has sped the time of development and avoided safety concerns associated with using a disease-causing virus.

mRNA platform: The Moderna and Pfizer/BioNTech mRNA vaccines deliver the genetic sequence of the SARS-CoV-2 spike protein directly to the cell (see fig. 5). The mRNA molecule includes a code that causes the cell to make the spike protein. Immune system cells recognize the spike protein and a protective immune response results. The spike protein genetic code does not enter the cell's nucleus, only the cytoplasm.[20] The mRNA needs to be encased in a lipid (fat) nanoparticle to enter the cell.[21]

- **Pfizer/BioNTech** – Pfizer/BioNTech's mRNA vaccine, BNT162b2, consists of mRNA encoding the viral spike protein of SARS-CoV-2, transported inside lipid nanoparticles that allow the mRNA to enter cells. The vaccine remains shelf-stable in an ultra-low temperature freezer between -80°C to -60°C. Vials must be kept frozen between -80°C to -60°C and protected from light until ready to use. The vaccine remains shelf-stable for up to five days at standard refrigerator temperatures (between 2° and 8°C).
- **Moderna** – Moderna's mRNA-1273 vaccine also consists of mRNA encoding the viral spike protein of the SARS-CoV-2 virus transported in lipid nanoparticles. The Moderna vaccine can be stored at refrigerator temperatures (between 2° and 8°C) for 30 days, and it is stable for 6 months during shipping and long-term storage at freezer temperatures of -20°C.

[19]Coronaviruses are a family of related RNA viruses that cause mild to lethal respiratory tract diseases in mammals and birds. The SARS-CoV-2 coronavirus is the strain responsible for COVID-19.

[20]The nucleus is the inner part of the cell where the cell's DNA is located while the cytoplasm is the area outside of the nucleus, but still inside the cell membrane.

[21]mRNA is a biological molecule that codes for protein.

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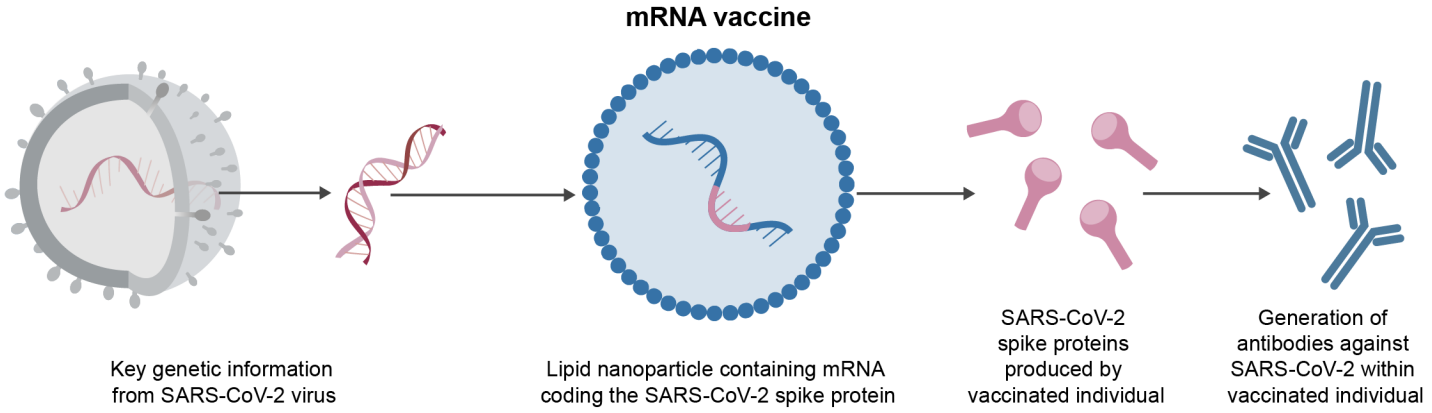
Figure 5: The Process for mRNA Vaccines Generating Antibodies to Protect Individuals from COVID-19



Sources: GAO, adapted from GAO-20-583SP; Adaptation of images depicting vaccine technologies with permission from Springer Nature: *Nature* ("The Race for Coronavirus Vaccines: A Graphical Guide," Ewen Callaway) © 2020. | GAO-21-319

Replication-defective live-vector platform: The Janssen and AstraZeneca vaccine candidates use a weakened adenovirus—a virus that can cause the common cold but that is altered so that it cannot reproduce or cause disease. Known as a viral vector, it carries a DNA code to make the SARS-CoV-2 spike protein that will stimulate the immune system to produce antibodies. The vector interacts with the target cell and delivers its genetic material into the nucleus, where cellular enzymes generate the spike protein, but not the adenovirus itself (see fig. 6). The vaccinated person will produce the spike protein, priming their immune system to target SARS-CoV-2.

- **Janssen** - Janssen's vaccine candidate uses a non-replicating human Adenovirus 26 vector platform, the same platform Janssen used to develop a vaccine for Ebola. This virus, which normally causes the common cold, contains the genetic material of the SARS-CoV-2 spike protein. This vaccine candidate can be stored between 2 and 8°C for at least three months.
- **AstraZeneca** - AstraZeneca's AZD1222 vaccine candidate consists of a non-replicating chimpanzee adenovirus, ChAdOx1, which is a weakened version of the virus that causes infections in non-human primates. This vaccine candidate can be stored between 2 and 8°C.

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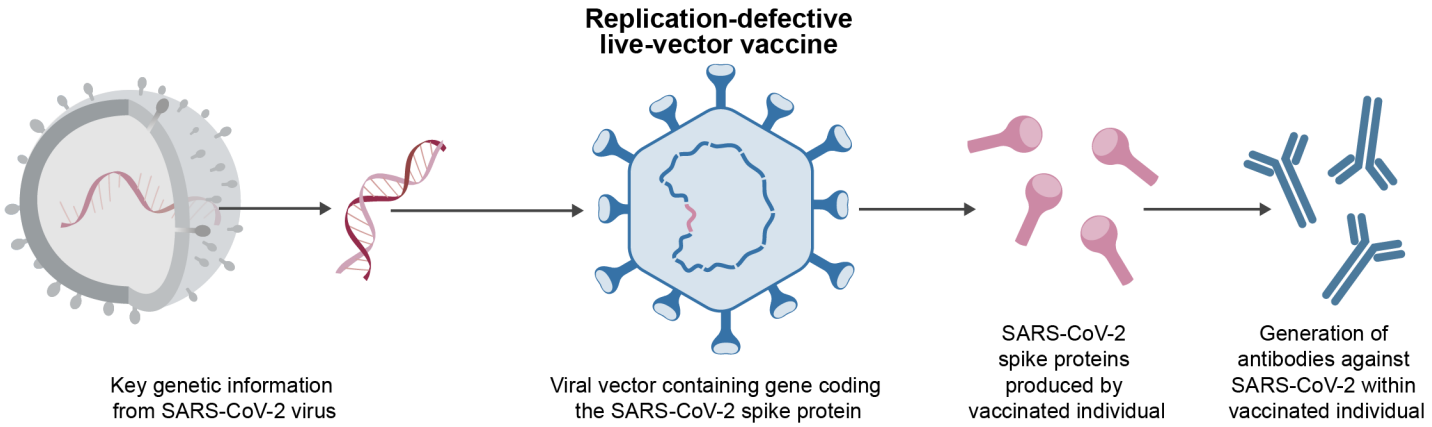
Figure 6: The Process for Replication-defective Live-vector Vaccines Generating Antibodies to Protect Individuals from COVID-19



Sources: GAO, adapted from GAO-20-583SP; Adaptation of images depicting vaccine technologies with permission from Springer Nature: *Nature* ("The Race for Coronavirus Vaccines: A Graphical Guide," Ewen Callaway) © 2020. | GAO-21-319

Recombinant-subunit-adjuvanted protein platform: The Sanofi/GSK and Novavax vaccine candidates use purified SARS-CoV-2 spike proteins to stimulate an immune response (see fig. 7). Often, recombinant-subunit adjuvanted protein platforms require an adjuvant, a component of the vaccine that helps the immune system response. Examples of the vaccines produced using this platform include Hepatitis B, human papilloma virus, and tetanus vaccines.

- **Sanofi/GSK** – Sanofi/GSK's vaccine candidate, developed in partnership by Sanofi and GSK, uses the same recombinant protein-based technology as one of Sanofi's seasonal influenza vaccines with GSK's established pandemic adjuvant technology. This vaccine candidate can be stored between 2° and 8° C.
- **Novavax** - Novavax's NVX-CoV2373 vaccine candidate is a recombinant nanoparticle spike protein vaccine candidate that includes a proprietary adjuvant to increase the immune response. It can be stored between 2° and 8°C.

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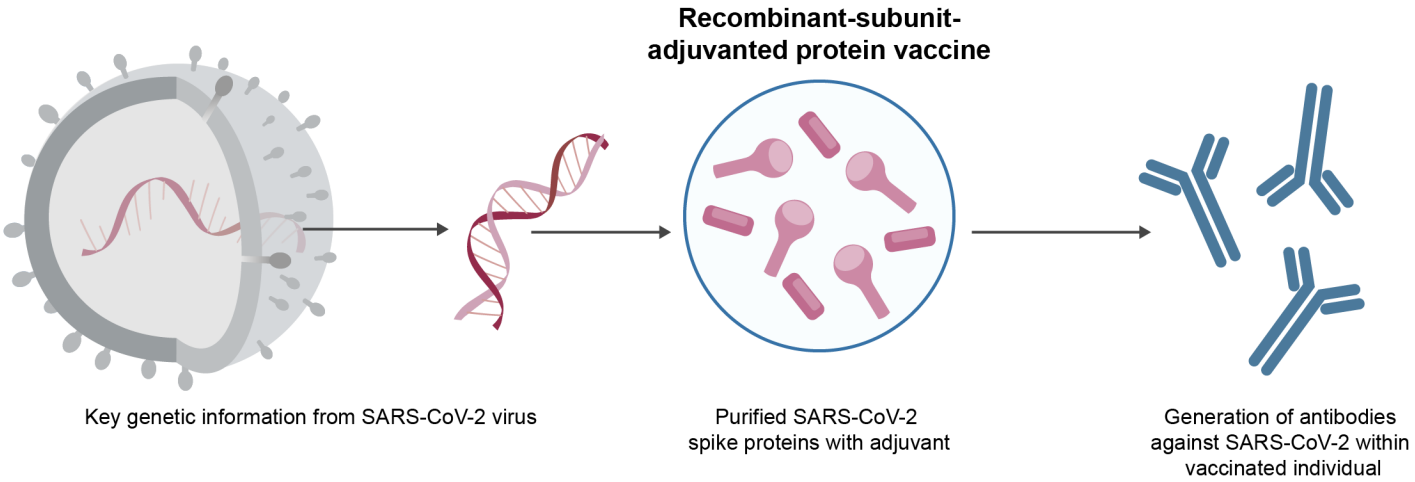
Figure 7: The Process for Recombinant-subunit-adjuvanted Protein Vaccines Generating Antibodies to Protect Individuals from COVID-19



Sources: GAO, adapted from GAO-20-583SP; Adaptation of images depicting vaccine technologies with permission from Springer Nature: *Nature* ("The Race for Coronavirus Vaccines: A Graphical Guide," Ewen Callaway) © 2020. | GAO-21-319

Attenuated replicating live-vector platform: This platform uses a genetically engineered virus with its disease-causing aspects removed. Once injected, human cells replicate the spike proteins and the virus, allowing for other cells to be infected and more spike proteins produced, triggering an immune response. No OWS vaccine candidates are using this platform.

Table 2 below summarizes key characteristics of each OWS vaccine candidate.

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Table 2: Characteristics for Each Operation Warp Speed Vaccine Candidate, as of January 2021

Vaccine identifier	Candidate company	Vaccine platform	Doses	Dose spacing (days)	Mixing required[a]	Storage temperature[b]
BNT162b2	Pfizer/BioNTech	mRNA[c]	2	21	Yes	2 to 8°C up to 5 days Longer periods -80 to -60°C
mRNA-1273	Moderna	mRNA[c]	2	28	No	2 to 8°C up to 30 days Longer periods -25 to -15°C
Ad26.COV2.S	Janssen	Replication-defective live-vector	1	N/A	No	At least 3 months at 2 to 8°C Up to 2 years at -20°C
AZD1222	AstraZeneca	Replication-defective live-vector	2	28	No	2 to 8°C up to 6 months
VAT01	Sanofi/GSK	Recombinant-subunit-adjuvanted protein	2	21	Yes	2 to 8°C
NVX-CoV2373	Novavax	Recombinant-subunit-adjuvanted protein	2	21	No	2 to 8°C

Source: GAO analysis of information from vaccine companies, Food and Drug Administration (FDA), and other government sources. | GAO-21-319.

[a]Mixing required means the addition of an adjuvant (to increase immune response) or diluent (to dilute the vaccine) is required at the time of vaccine administration.

[b]Storage temperature is the recommended temperature range for vaccine storage.

[c]Messenger RNA (mRNA)

Vaccine Clinical Trials Provide Critical Information about Safety and Efficacy for Populations Included in the Trials

As of January 2021, five of the six OWS vaccine candidates had begun phase 3 clinical trials in the United States, and two had received an EUA.[22] In November 2020, we reviewed four of the vaccine candidates' clinical trial protocols.[23] We found that they generally appeared to follow a typical clinical trial design by enrolling mostly healthy adults and excluding such groups as children, pregnant women, and those with certain

[22]Companies that have started phase 3 trials in the United States are AstraZeneca, Janssen, Moderna, Novavax, and Pfizer/BioNTech. In December 2020, FDA authorized the Moderna and Pfizer/BioNTech COVID-19 vaccines for emergency use.

[23]GAO, *COVID19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations*, GAO-21-207 (Washington, D.C.: Nov. 17, 2020).

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comorbid or unstable conditions.[24] Excluding these groups in the initial phase 3 clinical trials is not unusual, but a potential consequence is that the data on vaccine safety and effectiveness is based on mostly healthy adults and may not apply to these excluded populations.[25]

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) noted that the FDA issuance of EUAs should be used according to the evidence gathered in the phase 3 clinical trials.[26] The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) has issued interim recommendations, including vaccine dosing regimens, age restrictions, and for pregnant and lactating people.[27]

As of January 2021, the vaccines that had received EUAs had not been licensed by FDA and continue to be studied in clinical trials. For vaccines that received EUA, additional data on vaccine effectiveness will be generated from further follow-up of participants in clinical trials already underway before the EUA was issued. The two EUAs issued in December 2020 were based on analyses of clinical trial participants and showed about 95 percent efficacy for each vaccine. These analyses included assessments of efficacy after individuals were given two doses of vaccine and from follow-up for a median duration of 2 months to

[24]Three of the four companies set a minimum enrollment age of 18 years for their initial phase 3 clinical trials. The Pfizer/BioNTech vaccine is authorized for emergency use for individuals 16 years of age and older. Pfizer/BioNTech recently started trials on volunteers as young as 12 years old, and Moderna started trials on volunteers ages 12-17.

[25]In reviewing EUA requests, FDA considers the intended use of a particular vaccine and will include a contraindication in product labeling for those groups for which the risk of use clearly outweighs any benefit, according to agency officials.

[26] VRBPAC reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products which are intended for use in the prevention, treatment, or diagnosis of human diseases, and, as required, any other products for which the FDA has regulatory responsibility.

[27]According to CDC, ACIP provides advice and guidance to the Director of the CDC regarding use of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population of the United States. Recommendations made by the ACIP are reviewed by the Director, and if adopted, are published as official CDC/Health and Human Services (HHS) recommendations in the Morbidity and Mortality Weekly Report. According to CDC, people who are pregnant and part of a group recommended to receive the COVID-19 vaccine may choose to be vaccinated. If they have questions about getting vaccinated, a discussion with a healthcare provider might help them make an informed decision. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html.

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monitor for adverse events. For the two vaccines that received EUAs, Pfizer/BioNTech and Moderna, phase 3 clinical trials did not study the efficacy of a single dose regimen in a manner that allowed for definitive conclusions, according to FDA.[28]

According to FDA, a BLA typically includes safety data from the entire study population through at least 6 months of follow-up following the last vaccination, though most adverse events are observed within 1.5 months of vaccine administration. In clinical trials for the Pfizer/BioNTech and Moderna vaccines, participants reported side effects such as pain at the injection site, fatigue, and headache. These side effects are not unusual for vaccines. The initial phase 3 clinical trials for these vaccines excluded people with a history of severe adverse reactions to any vaccine or allergic reactions to any component of this vaccine. More than 20 cases of suspected anaphylaxis following vaccine administration occurred in the United States as of January, 2021.[29] FDA issued an EUA fact sheet in December 2020 (Moderna) and January 2021 (Pfizer/BioNTech) that stated there is a "remote chance" of a severe allergic reaction and recommended that people with severe allergic reactions to the first dose of the vaccine not receive the second dose and people allergic to any of the vaccine's ingredients not get the vaccine.[30] The fact sheet also notes that the two vaccines continue to be studied in additional clinical trials and that serious and unexpected side effects may occur.

[28]According to FDA, as of January 4, 2021, 98 percent of phase 3 trial participants in the Pfizer/BioNTech trial and 92 percent of participants in the Moderna trial received two doses of the vaccine at either a three- or four-week interval, respectively. Those participants who did not receive two vaccine doses at either a three-or four-week interval were generally only followed for a short period of time. Therefore, FDA determined there is not enough data to draw conclusions about the depth or duration of protection after a single dose of vaccine. See See S. Hahn, and P. Marks. Food and Drug Administration: *FDA Statement on Following the Authorized Dosing Schedules for COVID-19 Vaccines*, (Press Release Jan. 4, 2021).

[29]In January 2020, CDC reported that the Vaccine Adverse Event Reporting System detected 11.1 cases of anaphylaxis per million doses of the Pfizer/BioNTech vaccine and 2.5 cases of anaphylaxis per million doses of the Moderna vaccine. For both vaccines, greater than 70-percent of cases of anaphylaxis occurred within 15 minutes of vaccination.

[30]Food and Drug Administration, *Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Pfizer/BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 16 Years of Age and Older* (Revised January 2021); and *Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 18 Years of Age and Older* (Revised December 2020).

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COVID-19 Vaccine Development Generally Followed Traditional Practices, with Some Adaptations

The HHS integrated TRLs generally reflect the traditional process used for vaccine development. Therefore, they provide the measurement standard by which we can assess the development process to understand where and how the process may have been modified for COVID-19 vaccines.[31]

In an effort to understand the readiness of each OWS vaccine candidate, we conducted a TRL analysis, which showed that vaccine companies generally followed the traditional development process. After reviewing vaccine companies' questionnaire responses and supporting information, we assigned TRLs to each vaccine candidate based on the HHS integrated TRLs using associated FDA guidance and supporting documentation for each vaccine candidate. Table 3 shows our assigned TRL for each of the vaccine candidates as of January 21, 2021.

[31]We did not assess the extent to which the development process for OWS vaccine candidates met criteria for vaccine authorization or licensure set forth in statute and regulation.

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Table 3: Technology Readiness Levels (TRL) for Each Operation Warp Speed (OWS) Vaccine Candidate, as of January 2021

Vaccine Company	TRL	Description
Pfizer/BioNTech	8A	Vaccine has achieved completion of current good manufacturing practice (CGMP) validation and consistency lot manufacturing, and pivotal clinical trials demonstrating sufficient efficacy and safety to receive an emergency use authorization (EUA).
Moderna	8A[a]	Vaccine has achieved completion of CGMP validation and consistency lot manufacturing, and pivotal clinical trials demonstrating sufficient efficacy and safety to receive an EUA.
AstraZeneca	7B	Vaccine has achieved scale-up, initiation of CGMP process validation, and expanded clinical trials as appropriate for the product.
Janssen	7B[a]	Vaccine has achieved scale-up, initiation of CGMP process validation, and expanded clinical trials as appropriate for the product.
Novavax	6C[ab]	Vaccine has achieved CGMP pilot lot production, investigational new drug (IND) application submission, and phase 2 clinical trials that establish an initial safety, pharmacokinetics, and immunogenicity assessment as appropriate.
Sanofi/GSK	6C[a]	Vaccine has achieved CGMP pilot lot production, IND application submission, and phase 1 clinical trials that establish an initial safety, pharmacokinetics, and immunogenicity assessment as appropriate.

Source: GAO analysis of vaccine companies' questionnaire responses and vaccine development documentation. I GAO-21-319

Note: GAO assigned these TRLs based on questionnaire responses and documentation, where available.

CGMP regulations for drugs and biologics, including vaccines, contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations help to ensure that a product is safe for use, and that it has the ingredients and strength it claims to have. See 21 C.F.R. pts. 210 and 211 (2020).

An IND is a formal notice to the Food and Drug Administration (FDA) of a company's intent to begin human clinical trials. An IND must include evidence that the product is reasonably safe for proposed clinical trials, based on preclinical data, among other information. FDA has 30 days to object to an IND before it becomes effective. 21 C.F.R. pt. 312 (2020).

TRL 8A indicates that additional expanded clinical safety trials may be required for the product. In the case of a COVID-19 vaccine, we assigned a TRL 8A when an emergency use authorization (EUA) was issued for that product. During an emergency, as declared by the Secretary of Health and Human Services under 21 U.S.C. § 360bbb-3(b), FDA may temporarily authorize unapproved medical products or unapproved uses of approved medical products through an EUA, provided certain statutory criteria are met. FDA has indicated that issuance of an EUA for a COVID-19 vaccine for which there is adequate manufacturing information would require the submission of certain clinical trial information from phase 3 clinical trials that demonstrate the safety and effectiveness of the vaccine in a clear and compelling manner, among other things. Any COVID-19 vaccine that initially receives an EUA from FDA is expected to ultimately be reviewed and receive licensure through a biologics license application, according to FDA guidance.

[a]TRL based at least in part on testimonial evidence; GAO could not verify all information supporting our TRL determination through documentary evidence.

[b]Although Novavax is currently conducting phase 3 clinical trials, they reported that as of February 2, 2021, they had not completed the step to scale up and validate the CGMP manufacturing process, and therefore did not yet meet the criteria for TRL 7.

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OWS Vaccine Companies Adapted Some Practices to Accelerate Development

Each of the OWS vaccine companies we talked to told us that the primary difference between COVID-19 vaccine development and vaccine development in a non-pandemic environment was the compressed timelines under which they were working. In addition, to speed up the availability of the vaccines, companies initiated large-scale manufacturing while collecting data on clinical trial participants. In a June 2020 guidance document, FDA identified some ways that COVID-19 vaccine development may be accelerated.[32] For example, the guidance document states that companies may accelerate development by relying on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible. All OWS vaccine companies indicated that prior experience on the vaccine platform helped support key steps that would normally be conducted for each individual vaccine.

Animal Studies Were Conducted to Inform Human Studies and Not All Were Specific to the OWS Vaccine Candidates

OWS vaccine companies relied on data from animal studies to develop COVID-19 vaccines and make adaptations. Although imperfect at predicting success of a vaccine, animal studies are typically conducted to improve understanding of whether the vaccine may be safe and effective in humans before clinical trials begin. We found that all of the companies performed animal studies to investigate COVID-19 vaccine immunogenicity—including assessing the neutralizing antibodies and T-cell responses—and challenge studies that tested the potential for efficacy in preventing SARS-CoV-2 infection and/or COVID-19 in specific animal models (e.g., mice, hamsters, and/or nonhuman primates).[33] In addition, all companies indicated that they conducted animal toxicology studies for their vaccine platform, but some animal studies may not have been specific to their COVID-19 vaccines. For example, one company had more than 10 previous animal toxicology studies on the platform they were using for their COVID-19 vaccine, which showed that there were no safety concerns from any vaccine made using that platform, and, therefore, according to the company, it was not necessary to conduct separate animal studies specific to COVID-19 vaccines to proceed in developing a vaccine.

[32]Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research, *Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry* (June, 2020).

[33]A challenge study involves vaccinating animals followed by exposing them (i.e., challenge) to the SARS-CoV-2 virus and observing if they are protected from COVID-19 disease.

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At least half of the OWS vaccine companies indicated that they had not completed certain animal safety and efficacy studies before beginning phase 1 clinical trials.[34] Instead, in order to begin collecting data in clinical trials more quickly, the companies relied on data from other vaccines using the same platforms, where available, or conducted animal studies concurrently with clinical trials. As of January 2021, some animal studies are still ongoing for COVID-19 vaccines that are in late-stage (e.g., phase 3) clinical trials.

Another approach OWS vaccine companies may have used to enter clinical trials more quickly was to conduct their pre-clinical studies not in compliance with good laboratory practices (GLP), which TRL 6 and 7 criteria specify as being needed only "as appropriate."[35] One company indicated that GLP safety studies were being conducted for their COVID-19 vaccine, while others relied on non-GLP studies or GLP studies for other vaccines using that platform. One company told us that GLP efficacy studies were not possible for COVID-19 due to limitations of resources necessary to conduct such studies at the required biological safety level.

OWS Vaccine Companies Conducted Concurrent or Combined Clinical Trials

By conducting different phases of clinical trials concurrently (e.g., phase 3 clinical trials beginning as phase 1 trials are ongoing), OWS vaccine companies increased the speed of the vaccine development process.[36] One company noted that using efficient clinical trial strategies, such as concurrent or overlapping trials, is particularly important to quickly determine disease protection (i.e., vaccine efficacy) in a pandemic. For instance, this approach was successfully used during the Ebola epidemic in Africa where vaccine efficacy was assessed while the epidemic was still ongoing. Though some overlap of phases is not unusual even in traditional vaccine development, officials from two companies stated that in non-pandemic environments it can take months to review clinical trial data before starting a new phase. For example, officials from one company said they might normally take 6 months to review data from

[34]FDA recommends that vaccine manufacturers engage in early communications with FDA to discuss the type and extent of nonclinical testing required for the particular COVID-19 vaccine candidate to support proceeding to first in human clinical trials and further clinical development.

[35]GLPs define the requirements to ensure data quality and integrity of preclinical research. See 21 C.F.R. pt. 58 (2020).

[36]According to HHS, working on clinical trial phases in parallel instead of taking the traditional sequential approach to vaccine development potentially shaves months off the timeline for vaccine development.

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phase 2 trials before initiating a phase 3 trial, and they would have a meeting with FDA about the plan before proceeding. For COVID-19 vaccine development, officials from this particular company said they took 3 weeks to review data and initiate efforts to move to phase 3 trials. All six OWS vaccine companies gathered initial human safety and immunogenicity data in phase 1 or combined phase 1/2 clinical trials with a small number of participants before proceeding into trials with more participants, namely large-scale phase 3 clinical trials, consistent with traditional processes. All companies that have started phase 3 clinical trials as of January 2021 did so before completing phase 1 clinical trials (see fig. 8).

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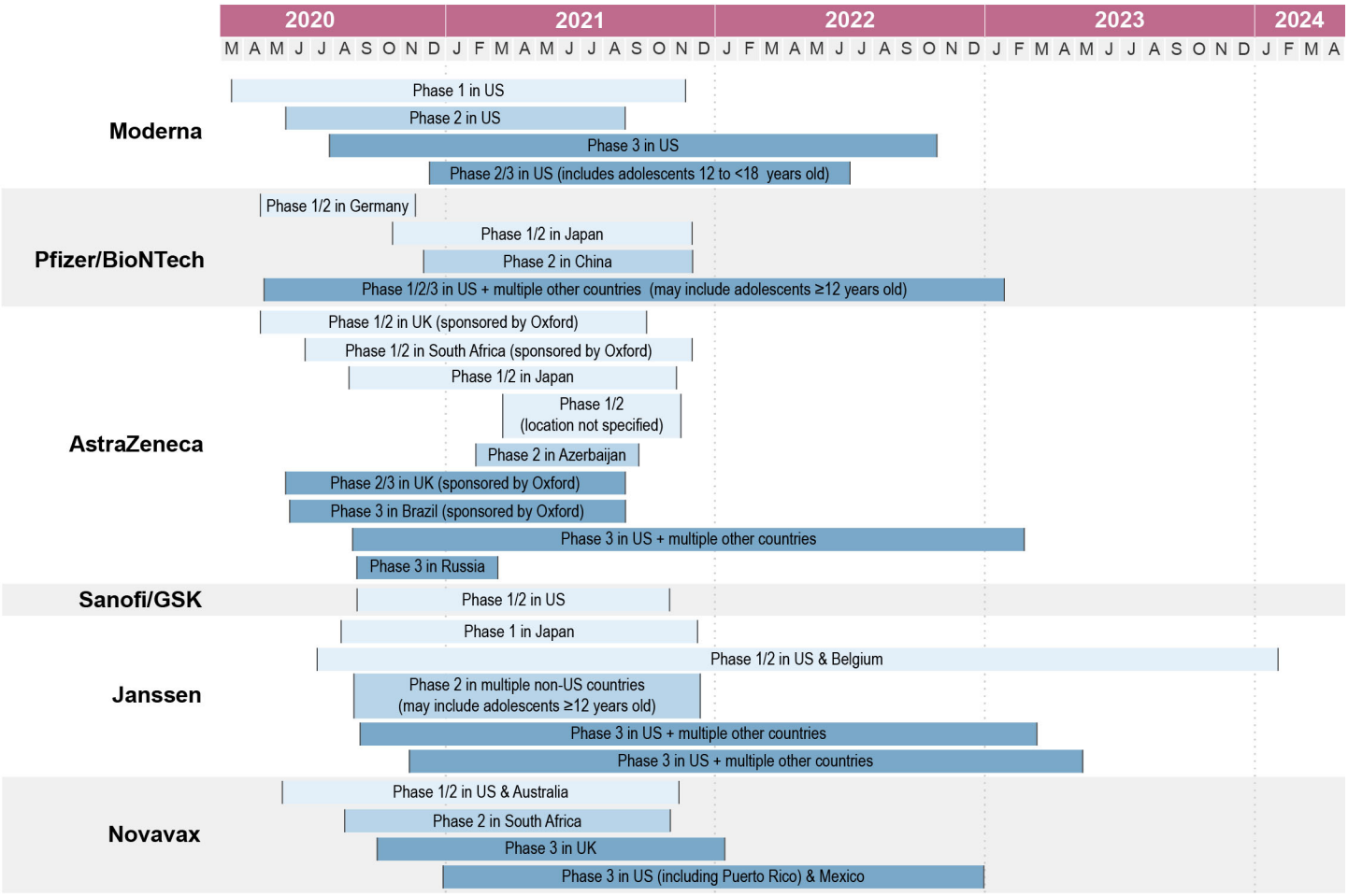
Figure 8: Operation Warp Speed Vaccine Candidates' Clinical Trials Schedule as Shown on the clinicaltrials.gov Website as of January 30, 2021



Source: GAO (analysis); clinicaltrials.gov (data). | GAO-21-319

Note: Clinical trials were listed only if they were sponsored by an Operation Warp Speed company or a collaborator and were specifically for the Operation Warp Speed vaccine candidate. Dates are study start dates and completion dates; some dates are estimates. Some of these clinical trials may not necessarily inform regulatory decisions in the United States.

At least half of the OWS vaccine companies selected a dose for phase 1 clinical trials that was based in part on disease protection data generated in animal studies for that vaccine candidate or from studies for other vaccines using the same vaccine platform. One company noted that the public health emergency precluded them from taking the time to determine the minimum effective dose. Instead, they focused on a dose that resulted in an acceptable tolerability and immunogenicity profile and

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with the greatest chance of efficacy. This company recognized that they might end up delivering a higher dose than is necessary in the short-term, but indicated they could explore a minimal dose that may be as effective, but more efficient, at a later time.

OWS Vaccine Companies Face Challenges to Scaling Up Manufacturing and Are Taking Steps to Help Mitigate Those Challenges

Several Challenges Hinder Efforts to Rapidly Scale Up Vaccine Manufacturing

As we reported in November 2020, OWS vaccine companies face several challenges with rapidly scaling up manufacturing operations to produce hundreds of millions of doses of COVID-19 vaccines, including:[37]

- **Limited manufacturing capacity.** Before the COVID-19 pandemic, most existing vaccine manufacturing capacity was already in use, according to experts we interviewed. Therefore, new capacity has been created, or production capacity shifted from other products. According to one company representative, vaccine manufacturing is highly complex and generally will ramp up at a graduated pace, rather than starting at full-scale. Additionally, once bulk quantities of vaccines are produced, they must be sealed into sterile containers, such as vials or syringes, in a process known as fill-finish manufacturing. We heard from representatives from three pharmaceutical industry groups we interviewed that there was a shortage of facilities with capacity to handle fill-finish manufacturing. That type of facilities shortage can lead to production bottlenecks.
- **Disruptions to manufacturing supply chains.** Vaccine manufacturing supply chains have been strained by disruptions caused by the global pandemic, including changes in the labor

[37]In our November 2020 report, we also reported on the difficulty associated with the technology transfer process for scaling up vaccine manufacturing. We did not include additional information on that challenge in this report because many vaccine companies we interviewed reported completing technology transfers at their large-scale manufacturing facilities.

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market, increases or decreases in the demand for certain goods, or as one DOD official noted, export restrictions implemented by some countries. For example, we heard from representatives at one facility manufacturing COVID-19 vaccines that they experienced challenges obtaining materials, including disposable reactor bags, reagents, and certain chemicals. They also said that, due to global demand, they waited 4 to 12 weeks for items that before the pandemic were typically available for shipment within one week. We also heard from one expert we interviewed that the supply of the materials used in fill-finish manufacturing, such as glass vials and pre-filled syringes, was limited.

- **Gaps in available workforce.** The ability to hire and train personnel with the specialized skills needed to run vaccine manufacturing processes can be a challenge for even experienced manufacturers. For example, we heard from representatives at a facility manufacturing COVID-19 vaccines that filling open positions for mid- to upper management had been a challenge. These positions are significant because manufacturing managers function as the technical points of contact for production questions and are responsible for managing safety, quality, and compliance with CGMPs.

OWS Vaccine Companies Are Working with the Federal Government to Help Mitigate Manufacturing Challenges

Federal officials and representatives from OWS vaccine companies described the ways that they are working together to mitigate manufacturing challenges, and as of January 2021, five of the six companies had started large-scale manufacturing. OWS officials reported that 63.7 million doses of vaccines were released to the federal government as of January 31, 2020. This represents about 32 percent of the 200 million doses, that according to OWS, the companies with EUAs are contracted to provide by March 31, 2021.[38] Additional doses of vaccines are being manufactured, but will not be releasable to the federal government unless they are authorized for emergency use, OWS officials reported. Companies reported that they are continuing to work with their manufacturing partners to ramp up vaccine production as they also work with OWS to address manufacturing challenges. For example:

- **Limited manufacturing capacity.** Some companies are working to expand production capacity. Representatives from one OWS vaccine company told us that BARDA helped them identify an additional manufacturing partner to increase production of their vaccine. The U.S. Army Corps of Engineers is also overseeing construction projects to expand capacity at vaccine manufacturing facilities. For

[38]As noted above, FDA authorized the Moderna and Pfizer/BioNTech vaccines for emergency use in December 2020.

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example, OWS officials told us in November 2020 that the Corps of Engineers provided a site assessment and oversight for a construction project that provided a manufacturing site with two additional vaccine production suites. According to OWS, the Corps of Engineers is also overseeing seven agreements to expand manufacturing capacity, including support to companies that are manufacturing products such as cell culture media and glass vials.

- **Disruptions to manufacturing supply chains.** As we reported in November 2020, representatives from a facility manufacturing COVID-19 vaccines told us that they were in frequent communication with OWS officials to coordinate on possible manufacturing disruptions and that DOD assisted them with expediting procurement and delivery of critical manufacturing equipment. Additionally, officials from BARDA said that their subject matter experts in developing and manufacturing vaccines worked with each of the six OWS vaccine companies to create a list of critical supply needs that are common across the six vaccine candidates. To address these critical supply needs, DOD and HHS officials said that as of December 2020 they had placed prioritized ratings on 18 supply contracts for vaccine companies under the Defense Production Act.[39] Furthermore, OWS officials stated that they have worked with U.S. Customs and Border Protection to expedite necessary equipment and goods coming into the United States.
- **Gaps in available workforce.** OWS officials stated that they have worked with the Department of State to expedite visa approval supporting the arrival of key technical personnel, including technicians and engineers to assist with installing, testing, and certifying critical equipment manufactured overseas. OWS officials also stated that they requested that 16 DOD personnel be detailed to serve as quality control staff at two vaccine manufacturing sites until the organizations can hire the required personnel. According to OWS, the DOD personnel were still in place at the manufacturing sites as of January 2021.

[39]The Defense Production Act, as delegated, generally provides federal agencies authority to, among other things, place priority ratings on contracts so that they receive priority treatment over any other unrated contracts or orders if necessary to meet the delivery or performance dates specified in the order. See Pub. L. No. 81-774, 64 Stat.798 (1950) (codified, as amended, at 50 U.S.C. § 4501, et seq.); Exec. Order No. 13,603, 77 Fed. Reg. 16,651 (Mar. 22, 2012); 15 C.F.R. pt. 700, Sch. 1. For additional information on agencies' use of this authority, see GAO, *Defense Production Act: Opportunities Exist to Increase Transparency and Identify Future Actions to Mitigate Medical Supply Chain Issues*, GAO-21-108 (Washington, D.C.: Nov 19, 2020).

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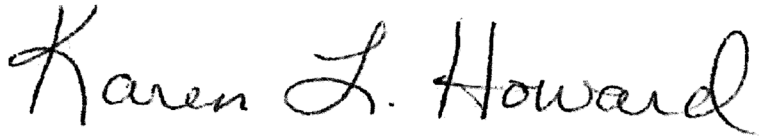
Agency Comments and Third-Party Views

We provided a draft of this report for review and comment to DOD and HHS (including the National Institutes of Health and FDA). The agencies provided technical comments, which we incorporated as appropriate. We also provided a draft of this report to the six OWS vaccine companies; four companies provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the appropriate congressional committees, the Secretary of Health and Human Services, the Secretary of Defense and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact Karen Howard at 202-512-6888 or howardk@gao.gov or Candice Wright at 202-512-6888 or wrightc@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



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List of Addressees

The Honorable Patrick Leahy
Chairman
The Honorable Richard Shelby
Vice Chairman
Committee on Appropriations
United States Senate

The Honorable Ron Wyden
Chairman
The Honorable Mike Crapo
Ranking Member
Committee on Finance
United States Senate

The Honorable Patty Murray
Chair
The Honorable Richard Burr
Ranking Member
Committee on Health, Education,
Labor, and Pensions
United States Senate

The Honorable Gary C. Peters
Chair
The Honorable Rob Portman
Ranking Member
Committee on Homeland Security
and Governmental Affairs
United States Senate

The Honorable Rosa L. DeLauro
Chairwoman
The Honorable Kay Granger
Ranking Member
Committee on Appropriations
House of Representatives

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List of Addressees Continued

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce
House of Representatives

The Honorable Bennie G. Thompson
Chairman
The Honorable John Katko
Ranking Member
Committee on Homeland Security
House of Representatives

The Honorable Carolyn B. Maloney
Chairwoman
The Honorable James Comer
Ranking Member
Committee on Oversight and Reform
House of Representatives

The Honorable Richard Neal
Chair
The Honorable Kevin Brady
Republican Leader
Committee on Ways and Means
House of Representatives

The Honorable James E. Clyburn
Chairman
Select Subcommittee on the Coronavirus Crisis
Committee on Oversight and Reform
House of Representatives

The Honorable Bill Foster
House of Representatives

The Honorable Mark E. Green, MD
House of Representatives

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Appendix I: Objectives, Scope, and Methodology

To examine the characteristics and development status of the Operation Warp Speed (OWS) vaccine candidates, we analyzed relevant agency documents, vaccine company documents, and journal articles. To describe efforts that OWS officials have taken to identify and select vaccine candidates, we reviewed the Department of Health and Human Services' (HHS) and Department of Defense's (DOD) Operation Warp Speed fact sheet and a journal article written by OWS officials, and interviewed OWS officials. To understand dosing, temperature requirements, and other vaccine characteristics, we reviewed literature from OWS vaccine companies, fact sheets from the Centers for Disease Control and Prevention (CDC), journal articles, and available clinical trial protocols on the OWS COVID-19 vaccine candidates.[1] To describe the design and status of clinical trials, we reviewed the Food and Drug Administration's (FDA) COVID-19 vaccine guidance, the available clinical trial protocols, and documentation from clinicaltrials.gov.[2]

To describe the safety and effectiveness characteristics of the Moderna and Pfizer/BioNTech vaccines—which have received emergency use authorization (EUA)—we reviewed the interim clinical considerations for use of the vaccines from the CDC's Advisory Committee on Immunization Practices (ACIP), the meeting transcripts and briefing documents from FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), FDA Letters of Emergency Use Authorization and fact sheets, and FDA guidance for Emergency Use Authorization for Vaccines to Prevent COVID-19.[3]

We analyzed vaccine candidates' technology readiness levels and reviewed steps vaccine companies took to develop their vaccines. We developed a questionnaire that reflected the HHS integrated technology readiness levels (TRL) and sent the questionnaires to all six OWS COVID-19 vaccine companies. We used TRLs, a maturity scale ordered according to the required characteristics of the specific technology. This report used the HHS integrated TRLs to assess the readiness level for

[1]We reviewed the clinical trial protocols for AstraZeneca, Janssen, Moderna, Novavax, and Pfizer/BioNTech.

[2]Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research, *Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry* (June, 2020).

[3]Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research, *Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry* (October, 2020).

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each of the six vaccine companies.[4] Other examples of TRL definitions and descriptions are provided in our GAO Technology Readiness Assessment Guide, which provides a framework for better understanding technology maturity.[5] We also collected supporting documentation and conducted follow-up interviews with companies to clarify and gather additional support for their questionnaire responses, when necessary. We used the company responses on the progress and activities conducted for each vaccine candidate, and reviewed the relevant supporting documents, such as clinical trial documents and safety and immunogenicity data evaluations conducted by research and development scientists, to verify information reported by each vaccine company.[6] To assign TRLs for each vaccine candidate, we relied on peer-reviewed or other public information to validate company responses to the greatest extent possible. When feasible, we used company documents that were created for FDA, such as components from the investigational new drug (IND) application.[7] If companies did not provide sufficient documentation to support the answers provided, we assigned a TRL noting the assumption and caveats, such as, testimonial evidence was used to support the TRL designation.

To determine how each vaccine company adapted their developmental processes to meet OWS timelines, we reviewed the documentation we collected and compared it to the HHS TRL criteria and the OWS timelines. We used information available from the questionnaire and clinicaltrials.gov to understand the different ongoing trials, such as the associated dates, including the actual study start date, and estimated study completion date. We discussed the development process, including

[4]See Department of Health & Human Services. *Integrated TRLs for Medical Countermeasure Products (Drugs and Biologics)*. https://www.medicalcountermeasures.gov/trl/integrated-trls/ (accessed December 28, 2020). Medical countermeasures include drugs and biologics, such as vaccines, that can diagnose, prevent, protect from, or treat the effects of exposure to emerging infectious diseases, such as pandemic influenza, and to chemical, biological, radiological, or nuclear agents. The scope of this report is limited to vaccines.

[5]GAO, *Technology Readiness Assessment Guide: Best Practices for Evaluating the Readiness of Technology for Use in Acquisition Programs and Projects,* GAO-20-48G (Washington, D.C.: January 7, 2020).

[6]Immunogenicity data refers to the measurement of antibodies generated against the SARS-CoV-2 spike protein antigen in clinical trial participants.

[7]An IND is a formal notice to FDA of a company's intent to begin human trials. An IND must include evidence that the product is reasonably safe for proposed clinical trials, based on preclinical data, among other information. FDA has 30 days to object to an IND before it becomes effective. 21 C.F.R. Part 312.

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the use of combined and concurrent clinical trials with the companies in our interviews. With all of these data, we were able to develop a timeline for development of each vaccine candidate.

To identify challenges in scaling up manufacturing for COVID-19 vaccine candidates and the steps OWS companies have taken to address them, we conducted a literature review and reviewed reports and journal articles about vaccine manufacturing. We interviewed or received written responses from HHS and DOD officials, including those working within OWS. We also interviewed representatives from industry groups and representatives from vaccine companies and manufacturers working with OWS for additional perspectives on vaccine development and manufacturing activities. We also reviewed information from OWS officials on the number of completed vaccine doses made available to the federal government from Moderna and Pfizer/BioNTech and the number of projected vaccine dose productions from each of the six OWS vaccine companies.

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Appendix II: The Department of Health and Human Services' (HHS) Technology Readiness Level (TRL) definitions

Table 4 shows the HHS integrated TRL medical countermeasure scale (TRL 1-9) and definitions for medical countermeasure products including drugs and biologics.[1] These TRLs are based on October 2004 Department of Defense (DOD) Medical TRLs and May 2008 HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) TRLs.

Table 4: Department of Health and Human Services' Integrated Technology Readiness Level (TRL) Scale and Definitions

TRL 1	**Review of Scientific Knowledge Base.** Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies.
TRL 2	**Development of Hypotheses and Experimental Designs.** Scientific "paper studies" to generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues. Focus on practical applications based on basic principles observed. Use of computer simulation or other virtual platforms to test hypotheses.
TRL 3	**Target/Candidate Identification and Characterization of Preliminary Candidate(s).** Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterization of candidate(s). Preliminary efficacy demonstrated in vivo. **3A** Identify target and/or candidate. **3B** Demonstrate in vitro activity of candidate(s) to counteract the effects of the threat agent. **3C** Generate preliminary in vivo proof-of-concept efficacy data [non-good laboratory practice (GLP)].
TRL 4	**Candidate Optimization and Non-GLP In Vivo Demonstration of Activity and Efficacy.** Integration of critical technologies for candidate development. Initiation of animal model development. Non-GLP in vivo toxicity and efficacy demonstration in accordance with the product's intended use. Initiation of experiments to identify markers, correlates of protection, assays, and endpoints for further non-clinical and clinical studies. **Animal Models:** Initiate development of appropriate and relevant animal model(s) for the desired indications. **Assays:** Initiate development of appropriate and relevant assays and associated reagents for the desired indications. **Manufacturing:** Manufacture laboratory-scale [i.e., non-good manufacturing practice (GMP)] quantities of bulk product and proposed formulated product. **4A** Demonstrate non-GLP in vivo activity and potential for efficacy consistent with the product's intended use (i.e., dose, schedule, duration, route of administration, and route of threat agent challenge). **4B** Conduct initial non-GLP toxicity studies and determine pharmacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable). **4C** Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).

[1]Medical countermeasures include drugs and biologics that can diagnose, prevent, protect from, or treat the effects of exposure to emerging infectious diseases, such as pandemic influenza, and to chemical, biological, radiological, or nuclear agents.

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TRL 5	**Advanced Characterization of Candidate and Initiation of GMP Process Development.** Continue non-GLP in vivo studies, and animal model and assay development. Establish draft Target Product Profiles. Develop a scalable and reproducible manufacturing process amenable to GMP. **Animal Models:** Continue development of animal models for efficacy and dose-ranging studies. **Assays:** Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality, as appropriate. **Manufacturing:** Initiate process development for small-scale manufacturing amenable to GMP. **Target Product Profile:** Draft preliminary Target Product Profile. Questions of shelf life, storage conditions, and packaging should be considered to ensure that anticipated use of the product is consistent with the intended use for which approval or licensure will be sought from FDA[a]. **5A** Demonstrate acceptable absorption, distribution, metabolism, and elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing. **5B** Continue establishing correlates of protection, endpoints, and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose once clinical data are obtained.
TRL 6	**GMP Pilot Lot Production, IND Application, and Phase 1 Clinical Trial(s).** Manufacture GMP-compliant pilot lots. Prepare and submit Investigational New Drug (IND) package to FDA and conduct phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article. **Animal Models:** Continue animal model development via toxicology, pharmacology, and immunogenicity studies. **Assays:** Qualify assays for manufacturing quality control and immunogenicity, if applicable. **Manufacturing:** Manufacture, release, and conduct stability testing of GMP-compliant bulk and formulated product in support of the IND and clinical trial(s). **Target Product Profile:** Update Target Product Profile as appropriate. **6A** Conduct GLP non-clinical studies for toxicology, pharmacology, and immunogenicity as appropriate. **6B** Prepare and submit IND application to FDA to support initial clinical trial(s). **6C** Complete phase 1 clinical trial(s) that establishes an initial safety, pharmacokinetics, and immunogenicity assessment as appropriate.
TRL 7	**Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s**). Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate. Conduct phase 2 clinical trial(s). **Animal Models:** Refine animal model development in preparation for pivotal GLP animal efficacy studies. **Assays:** Validate assays for manufacturing quality control and immunogenicity if applicable. **Manufacturing:** Scale-up and validate GMPs at a scale compatible with USG[b] requirements. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production. **Target Product Profile:** Update Target Product Profile as appropriate. **7A** Conduct GLP animal efficacy studies as appropriate for the product at this stage.[c] **7B** Complete expanded clinical safety trials as appropriate for the product (e.g., phase 2).

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TRL 8	**Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Phase 3 Clinical Trials, and FDA Approval or Licensure.** Finalize GMP manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit a new drug application (NDA) or biologics license application (BLA). **Manufacturing:** Complete validation and manufacturing of consistency lots at a scale compatible with federal requirements. Complete stability studies in support of label expiry dating. **Target Product Profile:** Finalize Target Product Profile in preparation for FDA approval or licensure. **8A** Complete pivotal GLP animal efficacy studies or pivotal clinical trials (e.g., phase 3), and any additional expanded clinical safety trials as appropriate for the product. **8B** Prepare and submit NDA or BLA to FDA. **8C** Obtain FDA approval or licensure.
TRL 9	**Post-Licensure and Post-Approval Activities.** **9A** Commence post-licensure/post-approval and phase 4 studies (post-marketing commitments), such as safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate. **9B** Maintain manufacturing capability as appropriate.

Source: The Department of Health and Human Services' (HHS) TRL medical countermeasure scale. I GAO-21-319

[a]FDA = Food and Drug Administration

[b]USG = United States Government

[c]These could include GLP animal efficacy studies required by FDA at this stage in support of an emergency use authorization (EUA). During an emergency, as declared by the Secretary of Health and Human Services under 21 U.S.C. § 360bbb-3(b), FDA may temporarily authorize unapproved medical products or unapproved uses of approved medical products through an EUA, provided certain statutory criteria are met. The scientific evidence required for issuance of an EUA will be handled on a case-by-case basis and will depend on, among other things, the nature and extent of the threat at any point during the product development timeline, from the initiation of phase 1 studies through licensure or approval. GLP animal efficacy study requirements may also vary by product type (e.g., vaccine, therapeutic, prophylactic) and U.S. government agency program office.

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Appendix III: Operation Warp Speed Dashboard

In connection with the issuance of this report, GAO has produced an interactive dashboard that integrates multiple data sources to visualize the status of vaccine development.[1] This dashboard brings together timely data on OWS-supported vaccines, assesses their maturity using technology readiness levels, and provides insight into OWS vaccine development, manufacturing, leadership, funding, and lessons learned.[2] Data displayed in the online dashboard will be updated periodically. Data metrics may be added to the dashboard after the issuance of this report. Taken together, these resources provide readers with the information they need to better understand and respond to the ongoing pandemic.

[1]The interactive dashboard may be found at https://ows.gaoinnovations.gov/.

[2]The data published in this report and on the dashboard as of Feb 11, 2021 is the latest data available at the time of our analyses.

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Appendix IV: GAO Contacts and Staff Acknowledgments

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In addition to the contacts named above, Laura Holliday (Assistant Director), Christopher Murray (Assistant Director), Darnita Akers (Analyst-in-Charge), Anna Irvine (Analyst-in-Charge), Angelica Aboulhosn, Nora Adkins, Mike Dickens, Maya Dru, Lorraine Ettaro, Cory Gerlach, Ryan Han, Anika McMillon, John Ortiz, and Benjamin Shouse made key contributions to this report. Other staff contributing include Tim DiNapoli Kaitlin Farquharson, Katheryn Hubbell, Alyssa Hundrup, Tom Lombardi, Jeff Mayhew, Miranda Riemer, Will Simerl, and Jennifer Weber.

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