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Development and Regulation of Medical Countermeasures for COVID-19 (Vaccines, Diagnostics, and Treatments): Frequently Asked Questions

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SUMMARY

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Agata Dabrowska
Analyst in Health Policy

Frank Gottron
Specialist in Science and Technology Policy

Amanda K. Sarata
Specialist in Health Policy

Kavya Sekar
Analyst in Health Policy

Development and Regulation of Medical Countermeasures for COVID-19 (Vaccines, Diagnostics, and Treatments): Frequently Asked Questions

In recent months, the Coronavirus Disease 2019 (COVID-19) pandemic has spread globally, with the United States now reporting the highest number of cases of any country in the world. Currently, there are few treatment options available to lessen the health impact of the disease and no vaccines or other prophylactic treatments to curb the spread of the virus.

The biomedical community has been working to develop new therapies or vaccines, and to repurpose already approved therapeutics, that could prevent COVID-19 infections or lessen severe outcomes in patients. In addition, efforts have been underway to develop new diagnostic tools (i.e., testing) to help better identify and isolate positive cases, thereby reducing the spread of the disease. To this end, Congress has appropriated funds for research and development into new *medical countermeasures* (MCMs) in several recent supplemental appropriations acts. MCMs are medical products that may be used to treat, prevent, or diagnose conditions associated with emerging infectious diseases or chemical, biological, radiological, or nuclear (CBRN) agents. MCMs include biologics (e.g., vaccines, monoclonal antibodies), drugs (e.g., antimicrobials, antivirals), and medical devices (e.g., diagnostic tests).

This report answers frequently asked questions about current efforts related to research and development of medical countermeasures, their regulation, and related policy issues. Although several efforts are underway, medical product research, development, and approval is a difficult and high-risk endeavor that takes years in typical circumstances. In response to COVID-19, this process has been expedited, including through several federal programs and mechanisms covered in this report. However, expedited medical product development can carry certain risks, such as a more limited safety profile for new products upon approval.

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In recent months, the Coronavirus Disease 2019 (COVID-19) pandemic has spread globally, with the United States now reporting the highest number of cases of any country in the world. Currently, there are few treatment options available to lessen the health impact of the disease and no vaccines or other prophylactic treatments to curb the spread of the virus. Treatment of severe COVID-19 cases can require significant health care resources, such as ventilators for patients with serious respiratory complications. A portion of severe cases are fatal.

The biomedical community has been working to develop new therapies or vaccines, and to repurpose already approved therapeutics, that could prevent COVID-19 infections or lessen severe outcomes in patients. In addition, efforts have been underway to develop new diagnostic tools (i.e., testing) to help better identify and isolate positive cases, thereby reducing the spread of the disease. To this end, Congress has appropriated funds for research and development into new *medical countermeasures* (MCMs) in several recent supplemental appropriations acts.

On May 15, the Trump Administration announced Operation Warp Speed, the major federal effort to accelerate and coordinate the development, manufacturing, and distribution of MCMs. The public-private partnership involves several federal agencies (including those covered in this report), as well as private firms. A key feature of the initiative is greater federal involvement and coordination in research, development, and manufacturing for selected MCM candidates than is typical for most U.S. pharmaceutical research and development (R&D).

This report summarizes current efforts related to research and development of medical countermeasures (including studying novel uses of already approved MCMs), their regulation, and related policy issues. Although several efforts are underway, medical product research, development, and approval is a difficult and high-risk endeavor that takes years in typical circumstances. In response to COVID-19, this process has been expedited, including through several federal programs and mechanisms covered in this report. However, expedited medical product development can carry certain risks, such as a more limited safety profile for new products upon approval. Particularly in the context of a pandemic, regulators are faced with the challenge of weighing the benefits and risks in introducing any new product into the market on a rapid timeline. This report focuses on therapeutics, vaccines, and diagnostics for COVID-19 and generally does not discuss other types of medical devices relevant to the treatment of COVID-19 (e.g., ventilators, personal protective equipment). This report also does not discuss MCM affordability, coverage, or supply chain issues.

Background

What are MCMs?

MCMs are medical products that may be used to treat, prevent, or diagnose conditions associated with emerging infectious diseases or chemical, biological, radiological, or nuclear (CBRN) agents. MCMs include biologics (e.g., vaccines, monoclonal antibodies)[1], drugs (e.g., antimicrobials, antivirals), and medical devices (e.g., diagnostic tests).[2]

[1] Monoclonal antibodies are preparations of a specific type of antibody designed to bind to a single target. See NIH, "Monoclonal antibodies crucial to fighting emerging infectious diseases, say NIH officials," March 8, 2018, https://www.nih.gov/news-events/news-releases/monoclonal-antibodies-crucial-fighting-emerging-infectious-diseases-say-nih-officials.

[2] Food and Drug Administration (FDA), "What Are Medical Countermeasures?," accessed April 15, 2020, https://www.fda.gov/emergency-preparedness-and-response/about-mcmi/what-are-medical-countermeasures. Personal

How are medical products like MCMs typically developed?

Developing any new medical product typically requires several stages of research:

- basic research to understand the fundamental mechanisms of a disease;
- identification of a potential product (i.e., a drug);
- preclinical testing in the laboratory, often using animals, tissue samples, and/or computer models;
- testing in several stages (typically three phases) of human clinical trials in progressively larger groups of human subjects to assess products for safety and effectiveness.

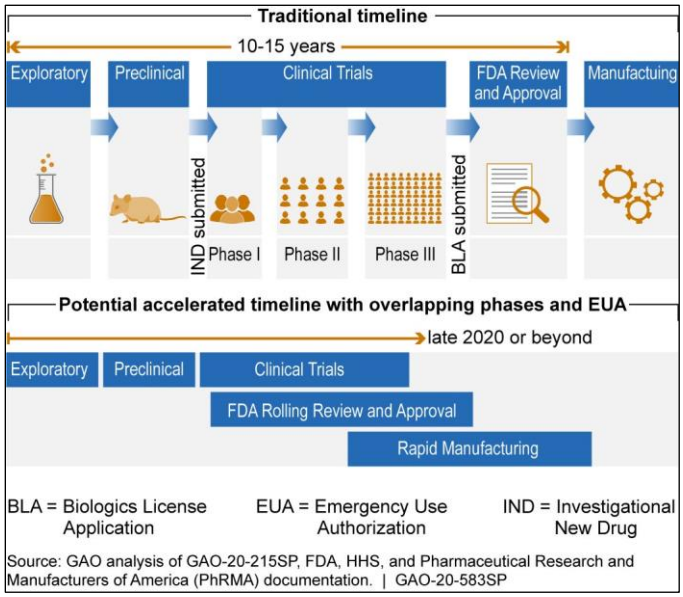
In addition, companies must develop the manufacturing capabilities to produce a new product at scale. In most cases, medical products must be approved by the U.S. Food and Drug Administration (FDA) before being marketed in the United States. In typical circumstances, the development and approval of new drugs takes an average of 10-15 years from discovery to approval.[3] This process may be abbreviated in the case of an already approved therapeutic whereby safety has been established, but clinical testing is still needed to evaluate its effectiveness for a new use. This is sometimes referred to as drug repurposing. Additional safety studies may be needed if the route of administration or dosage of the therapeutic for the new use differs from that previously approved.

To make products available for the COVID-19 pandemic, the federal government is aiming to accelerate and coordinate various elements of the process, as shown in the Government Accountability Office (GAO) graphic below (see **Figure 1**).

protective equipment is also a type of medical device and MCM; however, a discussion of these products is outside the scope of this report.

[3] CRS Infographic IG10013, *The Pharmaceutical Drug Development Process*.

Figure 1. Traditional Pharmaceutical R&D Timeline Versus an Accelerated Timeline



Source: Government Accountability Office (GAO), "The Reward and Risk of Expediting COVID-19 Testing and Vaccine Development," May 28, 2020, https://blog.gao.gov/2020/05/28/the-reward-and-risk-of-expediting-covid-19-testing-and-vaccine-development/.

In typical circumstances, the public sector generally finances much of the basic research and some preclinical testing and clinical research of new pharmaceutical products—such as through research supported by the National Institutes of Health (NIH)—mostly in the early stage of R&D, such as Phase 1 clinical trials.[4] The private sector tends to support much of the later-stage R&D of new medical products, such as late-stage and large-scale Phase 3 clinical trials, and the development of manufacturing capabilities.[5]

The federal government has recognized that countermeasures to some public health threats, such as emerging infectious diseases or bioterrorism agents, may have fewer market incentives than other pharmaceutical products, such as those treating chronic diseases. Manufacturers generally lack a profit incentive to develop products or capabilities in anticipation of a potential pandemic disease. As a result, the federal government has invested in agencies and programs that support the development of new MCMs. For example, the Biomedical Advanced Research and Development Authority (BARDA) can specifically support later-stage R&D and the manufacturing capabilities of new MCMs. Other incentives, such as regulatory exclusivity and tax incentives, can also support the development of new products.[6]

[4] Gillian K. Gresham, Stephan Ehrhardt, and Jill L. Meinhert, "Characteristics and Trends of Clinical Trials Funded by the National Institutes of Health Between 2005 and 2015," *Clinical Trials*, vol. 15, no. 1 (2018), pp. 65-74.

[5] National Academies of Sciences, Engineering, and Medicine, *Making Medicines Affordable: A National Imperative*, 2018, pp. 31-70.

[6] The sponsor of an new drug application (NDA) or biologics license application (BLA) for a new MCM may receive, upon approval, a period of exclusivity during which FDA may not approve an NDA or BLA from another sponsor for a certain number of years. For example, provided that statutory criteria are met, a drug that contains a new chemical entity is eligible for five years of data exclusivity.

Which federal agencies are usually involved in MCM development?

Several federal agencies, some of which are listed below, support medical and health R&D, while the FDA regulates the marketing of medical products in the United States. These agencies can contribute to and facilitate the development of new medical products, particularly in the event of an infectious disease threat.

The **National Institutes of Health (NIH)** within the Department of Health and Human Services (HHS) is the primary federal agency that supports medical and health research. NIH funds much of the basic biomedical science research in the United States, and it supports some development of new medical products.[7] One NIH institute, the National Institute of Allergy and Infectious Diseases (NIAID), aids in the response to new infectious disease threats as a part of its mission—supporting both basic scientific research and the development of new MCMs.[8]

The **Centers for Disease Control and Prevention (CDC)** within HHS generally supports public health and laboratory research related to new infectious disease threats. In the event of emerging infectious disease outbreaks, CDC has been the first to develop a diagnostic testing kit for use in U.S. public health laboratories—a model followed during the H1N1 influenza pandemic, the 2016 Zika outbreak, and now during the COVID-19 pandemic.[9] Aside from diagnostic test development, the agency supports a limited amount of MCM R&D; for example, past clinical trials for pre-exposure prophylaxis (PrEP) for HIV infections.[10] CDC also supports postmarket surveillance (i.e., data collection) on the safety and effectiveness of certain MCMs on the market, such as for vaccines.[11]

The **Biomedical Advanced Research and Development Authority (BARDA)** under the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) supports MCM development for use against emerging infectious diseases; pandemic influenza; and chemical, biological, radiological, and nuclear threat agents. Its efforts focus on supporting the transition from basic research to advanced development, clinical testing, FDA approval, and acquisition of some MCMs into the Strategic National Stockpile (SNS).[12]

FDA within HHS regulates the safety, effectiveness, and quality of MCMs through premarket review and postmarket requirements (e.g., adverse event reporting). FDA provides guidance, regulatory advice, and technical assistance to entities developing MCMs. The agency also conducts intramural and funds extramural regulatory science research to support the development

[7] CRS Report R41705, *The National Institutes of Health (NIH): Background and Congressional Issues*.

[8] National Institute of Allergy and Infectious Diseases (NIAID), "NIAID Strategic Plan 2017," https://www.niaid.nih.gov/sites/default/files/NIAIDStrategicPlan2017.pdf.

[9] Centers for Disease Control and Prevention (CDC), "The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," 2010, https://www.cdc.gov/h1n1flu/cdcresponse.htm.

[10] CDC, "CDC U.S. Extended PrEP Safety Trial: Quick Facts on Trial Design," July 2010, https://www.cdc.gov/nchhstp/newsroom/docs/US-PrEP-Study-7-15-10-508.pdf.

[11] CDC, "Vaccine Safety Monitoring," https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/index.html.

[12] The Strategic National Stockpile (SNS) refers to the supply of medicine and medical supplies maintained by the U.S. government to respond to a public health emergency severe enough to deplete local supplies (e.g., hurricane, infectious disease outbreak, or terrorist attack). The SNS includes antibiotics, intravenous fluids, and other medical supplies such as PPE and ventilators, as well as certain medicines, such as anthrax and smallpox vaccines and treatments that may not be otherwise available for public use. For additional information, see CRS In Focus IF11574, *National Stockpiles: Background and Issues for Congress*, by G. James Herrera and Frank Gottron.

of tools, standards, and approaches for assessing and developing MCMs.[13] In addition, FDA has created the Coronavirus Treatment Acceleration Program (CTAP), which seeks to accelerate clinical testing of potential therapeutics and move new treatments to patients as quickly as possible.[14]

The **Department of Defense (DOD)** operates several medical research and MCM development efforts, including through the Congressionally Directed Medical Research Program (CDMRP), the U.S. Army Medical Research and Development Command (USAMRDC), and the Defense Advanced Research Projects Agency (DARPA). For example, DARPA's Pandemic Prevention Platform program is focused on developing a platform that would aid in the rapid development of new MCMs in response to the identification of any known or unknown infectious threat.[15]

CDC, NIH, and FDA participate in the **Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)**, along with DOD, the U.S. Department of Veterans Affairs (VA), the Department of Homeland Security (DHS), and the U.S. Department of Agriculture (USDA). The PHEMCE, under the leadership of ASPR, facilitates interagency coordination and strategy for the development, regulation, and availability of medical countermeasures in preparation for public health emergencies such as infectious disease outbreaks. As required by Public Health Service Act (PHSA) Section 2811,[16] the PHEMCE assesses and updates a strategy plan annually for MCM preparedness.[17]

Research and Development (R&D)

What mechanisms are available for agencies to accelerate MCM R&D?

Several federal agencies have mechanisms to support rapid MCM R&D in the context of an infectious disease threat. Typically, agencies' grant-making, contract, and procurement processes can take several months when conducted pursuant to laws and regulations. However, several agencies have other transaction (OT) authority—additional authorities that provide flexibility and allow for expedited research funding and product procurement—particularly during a public health emergency. In addition, several agencies have existing research efforts or partnerships that can be mobilized to address emerging infectious disease threats.

NIH supports both intramural research in NIH-operated facilities and extramural research conducted by scientists at research institutions (i.e., universities, medical centers, and nonprofits). During a public health emergency, NIH has authority to award supplemental extramural research funding to existing research projects and to expedite the review process for new research proposals.[18] NIH also has several OT authorities that allow for expedited and flexible funding of

[13] FDA, "MCM Regulatory Science," https://www.fda.gov/emergency-preparedness-and-response/medical-countermeasures-initiative-mcmi/mcm-regulatory-science.

[14] FDA, "Coronavirus Treatment Acceleration Program (CTAP)," https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.

[15] Defense Advanced Research Projects Agency (DARPA), "Pandemic Prevention Platform," https://www.darpa.mil/program/pandemic-prevention-platform.

[16] 42 U.S.C. §300hh-10.

[17] The Assistant Secretary for Preparedness and Response (ASPR), "2017-2018 PHEMCE Strategy and Implementation Plan," 2017, https://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx.

[18] Public Health Service Act (PHSA) §494.

new projects. In particular, NIH has OT authority for projects involving "high impact cutting-edge research that fosters scientific creativity and increases fundamental biological understanding leading to the prevention, diagnosis, or treatment of diseases and disorders, or research urgently required to respond to a public health threat."[19]

NIH intramural researchers can shift efforts to address a new public health threat, such as the current work by the NIAID Vaccine Research Center on COVID-19 vaccines.[20] NIAID was able to redirect existing intramural research efforts related to other coronaviruses to the virus causing COVID-19.[21] In addition, NIH can leverage private funding through the Foundation for the NIH[22] to support MCM development, such as announced on April 17, 2020, for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership aimed at accelerating the development of new vaccines and therapeutic candidates.[23]

BARDA supports MCM development through funding, technical assistance, and other core services. Funding support includes contracts with product developers (e.g., pharmaceutical and biotechnology companies) for advanced development, including preclinical and clinical testing and manufacturing scale-up. COVID-19-related supplemental appropriations have increased the number of promising vaccine and therapeutic candidates that BARDA can support. Prior to the COVID-19 pandemic, BARDA used its OT authority to form partnerships with several companies to develop MCMs against threats such as pandemic influenza and Ebola.[24] In February, BARDA used the OT authority flexibility to redirect these efforts to speed the development of COVID-19 countermeasures.[25] BARDA's core services program can provide technical and regulatory assistance for countermeasure developers. These services include the Centers for Innovation in Advanced Development and Manufacturing, which is a public-private partnership that provides infrastructure for domestic production of MCMs; the Fill Finish Manufacturing Network, which assists MCM developers with final drug product manufacturing (e.g., vial filling); and the Clinical Studies Network which provides clinical study services from designing clinical protocols to managing clinical trial sites.[26]

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[19] 42 U.S.C. §282(n)(1)(C).

[20] NIH, "NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins," press release, March 16, 2020, https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins.

[21] NIH, "New Coronavirus Stable for Hours on Surfaces," press release, March 17, 2020, https://www.nih.gov/news-events/news-releases/new-coronavirus-stable-hours-surfaces.

[22] The Foundation for the NIH is a not-for-profit organization established by Congress in 1990 to raise private funds in support of the NIH's mission and facilitate public-private partnerships. See CRS Report R46109, *Agency-Related Nonprofit Research Foundations and Corporations*.

[23] NIH, "NIH to Launch Public-Private Partnership to Speed COVID-19 Vaccine and Treatment Options," press release, April 17, 2020, https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options.

[24] Department of Health and Human Services (HHS), "HHS, Janssen Research & Development join forces on innovative influenza products," press release, September 15, 2017, https://www.phe.gov/Preparedness/news/Pages/janssen-flu.aspx.

[25] The Biomedical Advanced Research and Development Authority (BARDA), "HHS, Regeneron Collaborate to Develop 2019-nCoV Treatment," press release, February 4, 2020, https://www.hhs.gov/about/news/2020/02/04/hhs-regeneron-collaborate-to-develop-2019-ncov-treatment.html; and BARDA, "HHS, Janssen Collaborate To Develop Coronavirus Therapeutics," press release, February 18, 2020, https://www.hhs.gov/about/news/2020/02/18/hhs-janssen-collaborate-to-develop-coronavirus-therapeutics.html.

[26] HHS Public Health Emergency, "Core Services," accessed June 23, 2020, https://www.medicalcountermeasures.gov/barda/core-services.aspx. See also, "Department of Health and Human Services' Centers for Innovation in Advanced Development and Manufacturing," https://www.medicalcountermeasures.gov/barda/core-services/ciadm/.

What is Operation Warp Speed and how does it differ from typical R&D?

Operation Warp Speed is a new national program to "accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics."[27] The program is intended to coordinate MCM efforts "between components of HHS, including CDC, FDA, NIH, and BARDA; the Department of Defense; private firms; and other federal agencies." Its stated goal is to accelerate selected MCM testing while developing manufacturing infrastructure to allow mass distribution faster than would be possible otherwise (see **Figure 1**). Not all government-supported countermeasures will participate in Operation Warp Speed.

Aside from Operation Warp Speed, how is the federal government supporting the development of MCMs for COVID-19?

BARDA has used supplemental appropriations to support preclinical and clinical testing of more than 20 diagnostic, vaccine, and therapeutic candidates.[28] In addition, BARDA created the CoronaWatch portal to serve as a single point of entry that enables potential medical countermeasure developers to connect with the most appropriate potential federal funding source.[29]

NIH is supporting both extramural and intramural research related to COVID-19 and the development of MCMs. NIH, particularly NIAID, has issued several funding opportunity announcements for emergency research funding related to COVID-19, including for the development of new diagnostic tests, therapeutic candidates, and vaccine candidates. NIH supports basic scientific research on the virus and disease that will help inform the development of new products.[30] NIH can support both basic and laboratory research, as well as clinical research with humans, such as for clinical testing of new MCMs.

NIH has announced two major research initiatives related to COVID-19. Announced on April 17, 2020, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) is a public-private partnership with several companies and federal agencies that aims to accelerate research and development on new vaccines and therapeutics by prioritizing vaccine and drug candidates, streamlining clinical trials, coordinating regulatory processes, and leveraging the assets of partners for new products.[31] The Rapid Acceleration of Diagnostics (RADx) initiative announced on April 29 is a prize competition that aims to incentivize the development of new diagnostics for COVID-19.[32]

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[27] HHS, "Trump Administration Announces Framework and Leadership for 'Operation Warp Speed,'" press release, May 15, 2020, https://www.hhs.gov/about/news/2020/05/15/trump-administration-announces-framework-and-leadership-for-operation-warp-speed.html.

[28] HHS Public Health Emergency, https://www.medicalcountermeasures.gov/newsroom/.

[29] HHS Public Health Emergency, "Request a USG CoronaWatch Meeting," https://www.medicalcountermeasures.gov/Request-BARDA-TechWatch-Meeting/.

[30] NIH, "Notice of Special Interest (NOSI) regarding the Availability of Emergency Competitive Revisions for Research on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19)," March 25, 2020, https://grants.nih.gov/grants/guide/notice-files/NOT-AI-20-034.html.

[31] NIH, "NIH to Launch Public-Private Partnership to Speed COVID-19 Vaccine and Treatment Options," press release, April 17, 2020, https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options.

[32] NIH, "NIH Mobilizes National Innovation Initiative for COVID-19 Diagnostics," press release, April 29, 2020,

DOD has reported research efforts into new vaccines and treatments that complement those of NIH and BARDA.[33]

FDA is working with MCM developers to provide regulatory advice and technical assistance with respect to development programs and testing.[34]

What is the state of MCM development in the COVID-19 response?

Currently, no FDA-approved MCMs are available to treat COVID-19. Federal agencies, pharmaceutical and biotech companies, nongovernmental organizations, and global regulators have been working to develop MCMs for COVID-19. Examples of such efforts are provided below.

Therapeutics

Researchers have initiated studies examining unapproved drug candidates, as well as unapproved uses of already approved drugs. NIH has issued COVID-19 treatment guidelines, which identify several therapeutic options currently under investigation,[35] and the federal clinical trials database maintained by the National Library of Medicine at NIH lists more than 1,000 clinical trials for COVID-19.

With respect to already approved drugs, on March 28, 2020, FDA issued the first emergency use authorization (EUA) for a COVID-19 therapeutic, authorizing the emergency use of hydroxychloroquine and chloroquine, two FDA-approved anti-malarial drugs. The EUA specifically authorized the use of hydroxychloroquine and chloroquine donated to the SNS by drug manufacturers and distributed to states to treat patients hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible.[36] According to the EUA letter that has since been revoked, FDA determined that based on the totality of scientific evidence, it was reasonable to believe that these drugs may be effective in treating COVID-19, and that when used in accordance with the conditions of the EUA, the known and potential benefits outweigh the known and potential risks. Some stakeholders—including several former FDA officials—expressed concern regarding the EUA, stating that the available data on the safety and effectiveness of these drugs for treatment of COVID-19 was largely anecdotal and that expanding access may jeopardize research into the drugs.[37] On April 24, 2020, FDA issued a drug safety communication warning against the use of these drugs for treatment of COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.[38] On June 15, 2020, FDA

https://www.nih.gov/news-events/news-releases/nih-mobilizes-national-innovation-initiative-covid-19-diagnostics.

[33] Department of Defense (DOD), "Defense Department Press Briefing Investigating and Developing Vaccine Candidates Against COVID-19," March 5, 2020, https://www.defense.gov/Newsroom/Transcripts/Transcript/Article/2104736/defense-department-press-briefing-investigating-and-developing-vaccine-candidat/.

[34] FDA, "MCM Regulatory Science," https://www.fda.gov/emergency-preparedness-and-response/medical-countermeasures-initiative-mcmi/mcm-regulatory-science. FDA, "Coronavirus Treatment Acceleration Program (CTAP)," https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.

[35] NIH, "COVID-19 Treatment Guidelines," accessed June 17, 2020, https://covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/.

[36] FDA, Letter of Authorization, March 28, 2020, https://www.fda.gov/media/136534/download.

[37] C. Piller, "Former FDA leaders decry emergency authorization of malaria drugs for coronavirus," *Science*, April 7, 2020, https://www.sciencemag.org/news/2020/04/former-fda-leaders-decry-emergency-authorization-malaria-drugs-coronavirus.

[38] FDA, "FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems," April 24, 2020, https://www.fda.gov/drugs/drug-safety-and-

revoked its EUA, determining that the statutory standard for EUA issuance was no longer met.[39] More specifically, FDA determined that based on emerging scientific data, hydroxychloroquine and chloroquine are unlikely to be effective in treating COVID-19, and that in light of serious cardiac adverse events and other potential serious side effects, the known and potential benefits of the drugs no longer outweigh the known and potential risks for this use. NIH updated its treatment guidelines to recommend against the use of hydroxychloroquine and chloroquine for the treatment of COVID-19, except in a clinical trial.[40]

Researchers are investigating the potential of other approved drugs. For example, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial at the University of Oxford in the United Kingdom is evaluating a range of potential treatments, including the HIV drug lopinavir-ritonavir, the steroid dexamethasone, and the antibiotic azithromycin.[41] Early results reported from the trial found that low-dose dexamethasone reduced deaths by one-third in ventilated patients with COVID-19.[42] Domestically, FDA has partnered with the Critical Path Institute (C-Path) and NIH's National Center for Advancing Translational Sciences (NCATS) on the CURE Drug Repurposing Collaboratory (CDRC), which includes a COVID-19 pilot project.[43] The CDRC aims to capture real-world clinical outcome data (e.g., data on off-label use captured by electronic medical records) to advance drug repurposing and inform future clinical trials for diseases of unmet medical need.

With respect to unapproved drug candidates, some therapeutics are further along in clinical testing (e.g., Gilead's antiviral drug remdesivir) than others. Gilead initiated two Phase 3 clinical studies evaluating the safety and effectiveness of its experimental drug in adults diagnosed with COVID-19.[44] In addition, on February 21, 2020, NIAID launched a randomized, double-blind, placebo-controlled trial of remdesivir as a potential treatment for hospitalized adult patients diagnosed with COVID-19.[45] NIH reported early results on April 29, 2020, finding that based on a preliminary analysis of the trial data, hospitalized patients with severe COVID-19 who received remdesivir recovered faster than similar patients who received placebo.[46] Other clinical studies of remdesivir are being carried out internationally. On the basis of data from the NIAID trial (NCT04280705) and a Gilead-sponsored Phase 3 trial (NCT04292899), on May 1, 2020, FDA

availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.

[39] FDA, "Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine," June 15, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.

[40] NIH, "COVID-19 Treatment Guidelines," as updated June 16, 2020, https://www.covid19treatmentguidelines.nih.gov/whats-new/.

[41] RECOVERY, Randomised Evaluation of COVID-19 Therapy, accessed June 17, 2020, https://www.recoverytrial.net/.

[42] University of Oxford, "Dexamethasone reduces death in hospitalised patients with severe respiratory complications of COVID-19," June 16, 2020, http://www.ox.ac.uk/news/2020-06-16-dexamethasone-reduces-death-hospitalised-patients-severe-respiratory-complications.

[43] FDA, "Coronavirus (COVID-19) Update: Daily Roundup," news release, June 23, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-june-23-2020. See also, Critical Path Institute, CURE Drug Repurposing Collaboratory, https://c-path.org/programs/cdrc/.

[44] Gilead, Remdesivir Clinical Trials, NCT04292730 and NCT04292899, https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials.

[45] NLM, Clinicaltrials.gov, NCT04280705, accessed April 15, 2020, https://clinicaltrials.gov/ct2/show/NCT04280705.

[46] NIH, "NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19," April 29, 2020, https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19.

granted EUA for remdesivir, determining that it is reasonable to believe that the known and potential benefits of the drug outweigh the known and potential risks for treatment of patients hospitalized with severe COVID-19.[47]

Two investigational blood-derived therapies also are being studied for the treatment of COVID-19: convalescent plasma and hyperimmune globulin.[48] *Convalescent plasma* refers to blood plasma collected from an individual who has recovered (i.e., "convalesced") from a disease, and thus presumably has developed antibodies against the virus that causes the disease—in this case SARS-CoV-2—that is then administered to a patient actively sick with COVID-19 for treatment. A related therapy is *hyperimmune globulin*, a manufactured biological product containing concentrated antibodies collected from convalescent plasma. Although convalescent plasma units vary in antibody specificities and levels based on the plasma donor, hyperimmune globulin preparations are typically standardized.[49] FDA has announced the availability of an expanded access protocol for convalescent plasma for patients across the United States—limited to those with severe or life-threatening COVID-19, or those judged by the treating provider to be at high risk of progression to severe or life-threatening disease.[50] More than 2,000 sites and over 8,000 physicians have signed on to participate in the expanded access protocol, with the Mayo Clinic acting as the Institutional Review Board (IRB).[51] Plasma transfusions are generally safe; however, they are not without risk and can cause allergic reactions and other side effects in some patients. Data are limited regarding the safety and effectiveness of convalescent plasma in treating COVID-19, but anecdotal evidence suggests the treatment may be safe and effective for some patients.[52]

The antibody-based therapies mentioned above have many different antibodies in them, only some of which might be effective against COVID-19. At least 50 companies and academic laboratories are trying to identify and isolate antibodies that specifically bind parts of the coronavirus and stop the infection process.[53] Once isolated, these monoclonal antibodies can be mass produced. This approach has led to successful treatments for diseases as diverse as cancer and Ebola. Some groups are also testing whether monoclonal antibodies can confer temporary immunity from COVID-19 infection so that they could be used prophylactically until the development of a safe and effective vaccine.

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[47] FDA, Letter of Authorization to Gilead Sciences, Inc., May 1, 2020, https://www.fda.gov/media/137564/download.

[48] FDA, "Coronavirus (COVID-19) Update: FDA Coordinates National Effort to Develop Blood-Related Therapies for COVID-19," April 3, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19. FDA, "Investigational COVID-19 Convalescent Plasma," April 2020, updated May 1, 2020, https://www.fda.gov/media/136798/download.

[49] J. D. Roback and J. Guarner, "Convalescent Plasma to Treat COVID-19 Possibilities and Challenges," *JAMA* (March 27, 2020).

[50] Ibid.

[51] FDA, "Coronavirus (COVID-19) Update: FDA Encourages Recovered Patients to Donate Plasma for Development of Blood-Related Therapies," April 16, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-encourages-recovered-patients-donate-plasma-development-blood.

[52] FDA, "Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions," April 3, 2020, https://www.fda.gov/media/136470/download. JD Roback and J Guarner, "Convalescent Plasma to Treat COVID-19 Possibilities and Challenges," *JAMA* (March 27, 2020). A Joseph, "Everything we know about coronavirus immunity and antibodies—and plenty we still don't," *STAT News*, April 20, 2020, https://www.statnews.com/2020/04/20/everything-we-know-about-coronavirus-immunity-and-antibodies-and-plenty-we-still-dont/. See also CRS Report R46375, *The U.S. Blood Supply and the COVID-19 Response: In Brief*, by Jared S. Sussman and Agata Dabrowska.

[53] Jon Cohen, "The Race is on for Antibodies that Stop the New Coronavirus," *Science*, May 5, 2020, https://www.sciencemag.org/news/2020/05/race-antibodies-stop-new-coronavirus.

Vaccines

Researchers and product developers are testing numerous types of vaccines—both in the laboratory and in some early-stage testing in humans. As of June 12, 2020, at least 120 experimental vaccines are known to be in development around the world.[54] The experimental vaccines rely on different platforms, or technologies, that aim to induce an immune response to protect against COVID-19 virus infection. Some rely on technology that has traditionally been used in vaccines to date, such as inactivated viruses or preparations of proteins involved in the immune response.[55] Others involve novel approaches such as viral vectors, where an existing virus is weakened so it cannot cause disease and is genetically engineered to produce COVID-19 proteins—an approach used for the recently approved Ebola vaccine.[56]

Some of the proposed vaccine technologies have never been used before in FDA-licensed vaccines, such as the nucleic-acid based vaccines. For example, the NIAID-supported Moderna vaccine uses messenger RNA (mRNA) as a genetic platform to induce cells to produce a protein involved in the immune response against the virus.[57] The new mRNA and DNA-based vaccines build on epidemic preparedness efforts by DARPA[58] and groups such as the Coalition for Epidemic Preparedness (CEPI)[59] that have worked to develop flexible vaccine platforms that could be used to quickly develop a new vaccine in the event of an epidemic, regardless of the specific pathogen.[60] These vaccines have also built on efforts to develop vaccines for other coronaviruses such as SARS-CoV-1 and MERS-CoV.[61]

As of early June 2020, several vaccines are in various stages of clinical trials in several countries, including the United States, Germany, China, and the United Kingdom.[62] Several Phase 1 trials have been completed, with various vaccines moving onto Phase 2, Phase 3, or combined Phase 2/3 phases. Scientists and product developers are planning innovative clinical trial designs and coordination or harmonization of multiple trials with the goal of expediting the development process for COVID-19 vaccines, such as through the efforts by NIH's ACTIV program.[63] As a

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[54] Jonathan Corum and Carl Zimmer, "Coronavirus Vaccine Tracker," *New York Times*, June 12, 2020, https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.

[55] Jon Cohen, "With Record-Setting Speed, Vaccinemakers Take Their First Shots at the New Coronavirus," *Science*, March 31, 2020, https://www.sciencemag.org/news/2020/03/record-setting-speed-vaccine-makers-take-their-first-shots-new-coronavirus; and Fatima Amanat and Florian Krammer, "SARS-CoV-2 Vaccines: Status Report," *Cell*, vol. 52 (April 14, 2020), pp. 583-589, https://www.cell.com/immunity/pdf/S1074-7613(20)30120-5.pdf.

[56] Ewen Callaway, "The Race for Coronavirus Vaccines: A Graphical Guide," *Nature*, April 28, 2020, https://www.nature.com/articles/d41586-020-01221-y.

[57] NIH, "NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins," March 16, 2020, https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins.

[58] Moderna, "DARPA Awards Moderna Therapeutics a Grant for up to $25 Million to Develop Messenger RNA Therapeutics™," press release, October 2, 2013, https://investors.modernatx.com/news-releases/news-release-details/darpa-awards-moderna-therapeutics-grant-25-million-develop.

[59] The Coalition for Epidemic Preparedness (CEPI) is a public-private global partnership that finances vaccine development for emerging infectious diseases. See https://cepi.net/about/whoweare/.

[60] Tung Thanh Le, Zacharias Andreadakis, and Arun Kumar, "The COVID-19 Vaccine Development Landscape," *Nature Reviews Drug Discovery*, April 9, 2020.

[61] NIH, "NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins," press release, March 16, 2020, https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins.

[62] Jonathan Corum and Carl Zimmer, "Coronavirus Vaccine Tracker," *New York Times*, June 12, 2020, https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.

[63] Jocelyn Kaiser, "To Streamline Coronavirus Vaccine and Drug Efforts, NIH and Firms Join Forces," *Science*, April 17, 2020, https://www.sciencemag.org/news/2020/04/tame-testing-chaos-nih-and-firms-join-forces-streamline-

part of Operation Warp Speed, the Trump Administration has selected five companies with candidate vaccines for investment, and those companies have received more than $2 billion from the Administration.[64] Moving forward, a challenge for large-scale vaccine trials is the shifting geography of the pandemic. Locations affected by the virus are changing; therefore, planning a clinical trial in a given location is difficult.[65]

Vaccine development is usually a long, complex, and risky process—most existing vaccines took 10 to 30 years to go from the beginning of clinical trials to licensure. Most vaccines fail in preclinical and clinical trials; less than 1 in 15 vaccine candidates that enter Phase 2 clinical trials gain FDA licensure.[66] The claims that a COVID-19 vaccine will be available within one year would represent the fastest development time of any vaccine to date.[67] The Trump Administration has announced intentions to accelerate the development of AstraZeneca's vaccine, with the first doses available in October.[68] Some experts express skepticism that this timeline is feasible, given that many vaccines have faced unexpected challenges during development.[69] Other experts posit that a COVID-19 vaccine should be easier to develop than vaccines for other diseases, such as HIV and Hepatitis C, which have posed greater challenges in development in part because a respiratory virus may be easier to develop a vaccine for than for blood-borne viruses.[70] Scientists continue to learn about the biology of COVID-19 and robust data on the efficacy of any vaccine candidate in protecting against COVID-19 is likely months away.[71]

Still unknown is whether vaccination or antibodies raised in response to infection with SARS-CoV-2 will confer immunity at all, and if so, to what extent. Current estimates for potential duration of immunity come from other coronaviruses, which suggest that immunity may wane after one or more years.[72] Despite anecdotal reports of reinfection with the virus, it is uncertain

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coronavirus-vaccine-and-drug; and Lawrence Corey, John R. Mascola, and Anthony S. Fauci, et al., "A Strategic Approach to COVID-19 Vaccine R&D," *Science*, May 29, 2020, pp. 948-50, https://science.sciencemag.org/content/368/6494/948/tab-figures-data.

[64] Noah Weiland and David E. Sanger, "Trump Administration Selects Five Coronavirus Vaccine Candidates as Finalists," *The New York Times*, June 9, 2020, https://www.nytimes.com/2020/06/03/us/politics/coronavirus-vaccine-trump-moderna.html.

[65] Jon Cohen, "'It's Really Complicated.' United States and Others Wrestle with Putting COVID-19 Vaccines to the Test," *Science*, June 12, 2020

[66] R. Gordon Douglas and Vijay B. Samant, "The Vaccine Industry," in *Plotkin's Vaccines*, 7th ed. (Elsevier, 2017), pp. 41-50.

[67] Tung Thanh Le, Zacharias Andreadakis, and Arun Kumar, "The COVID-19 Vaccine Development Landscape," *Nature Reviews Drug Discovery*, April 9, 2020.

[68] HHS, "Trump Administration's Operation Warp Speed Accelerates AstraZeneca COVID-19 Vaccine to be Available Beginning in October," press release, May 21, 2020, https://www.hhs.gov/about/news/2020/05/21/trump-administration-accelerates-astrazeneca-covid-19-vaccine-to-be-available-beginning-in-october.html.

[69] Holden and Thorp, "Underpromise, Overdeliver," *Science*, March 27, 2020, https://science.sciencemag.org/content/367/6485/1405; and Jon Cohen, "Doubts Greet $1.2 Billion Bet by United States on a Coronavirus Vaccine by October," *Science*, May 22, 2020, https://www.sciencemag.org/news/2020/05/doubts-greet-12-billion-bet-united-states-coronavirus-vaccine-october.

[70] Jon Cohen, "With Record-Setting Speed, Vaccinemakers Take Their First Shots at the New Coronavirus," *Science*, March 31, 2020, https://www.sciencemag.org/news/2020/03/record-setting-speed-vaccine-makers-take-their-first-shots-new-coronavirus.

[71] Jon Cohen, "'It's Really Complicated.' United States and Others Wrestle with Putting COVID-19 Vaccines to the Test," *Science*, June 12, 2020, https://www.sciencemag.org/news/2020/06/it-s-really-complicated-united-states-and-others-wrestle-putting-covid-19-vaccines-test.

[72] Daniel M. Altmann, Daniel C. Douek, and Rosemary J. Boyton, "What Policy Makers Need to Know About COVID-19 Protective Immunity," *The Lancet*, April 27, 2020, https://thelancet.com/journals/lancet/article/PIIS0140-6736(20)30985-5/fulltext, and Fatima Amanat and Florian Krammer, "SARS-CoV-2 Vaccines: Status Report," *Cell*,

whether patients reporting reinfection may have simply never cleared the virus, despite negative diagnostic test results. The accuracy of results of diagnostic testing where the virus is at or close to the limit of detection is not robust. Additionally, positive test results after an initial resolution of symptoms may indicate the presence of inactive virus leftover from the original infection, rather than a new unique active infection.

Diagnostics

Generally, coronavirus diagnostics (in vitro diagnostics, or IVDs) may be molecular, serological, or antigen tests. Tests are characterized by their methods—molecular tests are based on nucleic acid amplification techniques—as well as by the substance they directly identify—antigens, antibodies, or viral nucleic acid. To date, development of COVID-19 tests has been largely focused on molecular tests—specifically on a test using Polymerase Chain Reaction (PCR)—and serology tests—those tests that identify the presence of antibodies to the SARS-CoV-2 virus. PCR is a fairly time-intensive and expensive technique, and for this reason, other techniques have been employed and are being researched, including loop-mediated isothermal amplification (which, unlike PCR, does not require temperature cycling), CRISPR-based tests, and, most recently, next generation sequencing (NGS)-based tests. Loop-mediated isothermal amplification, for example, was used in diagnostics during the outbreak of SARS, and it was found to be faster, less expensive, and simpler than other molecular methods, while maintaining comparable sensitivity and specificity.[73] The FDA-EUA-authorized Abbott IDNow test uses this technique. Although the test has encountered some accuracy issues in its roll-out, and FDA now requires negative results to be considered to be presumptive negatives until they are confirmed using an authorized high sensitivity molecular test, the test is used at the point of care and helps with access issues in certain cases.[74]

CRISPR-based systems are typically used to edit genetic sequences, but they are also an effective tool for identifying a specific genetic sequence.[75] Such systems rely on a combination of (1) an enzyme that cuts DNA (a nuclease) and (2) a guiding piece of genetic material (guide RNA) to target a location in a genome for cleavage. Cleaving the genetic material releases a signal that is detectable by simple methods. Diagnostics using CRISPR can provide for "high sensitivity (can detect as few as 10 gene copies), specificity, portability, easy read-out (e.g., colorimetric with paper strips), speed (~45 min), and low cost (few dollars per sample)."[76] Researchers recently published details of a CRISPR-based test, the SARS-CoV-2 DETECTR test, clinical validation of which the authors report is ongoing in response to FDA guidance for COVID-19 diagnostics.[77] In addition, FDA granted its first EUA for a CRISPR-based test in early May, for a test called Sherlock CRISPR SARS-CoV-2 Kit.[78] This test is for use only in clinical laboratories certified to

vol. 52 (April 14, 2020), pp. 583-589, https://www.cell.com/immunity/pdf/S1074-7613(20)30120-5.pdf.

[73] The National Academies Press, "Rapid Expert Consultation on SARS-CoV-2 Laboratory Testing for the COVID-19 Pandemic," April 8, 2020 https://www.nap.edu/catalog/25775/rapid-expert-consultation-on-sars-cov-2-laboratory-testing-for-the-covid-19-pandemic-april-8-2020.

[74] FDA, "Abbott IDNow COVID-19 EUA Letter of Authorization," updated June 1, 2020, https://www.fda.gov/media/136522/download.

[75] See CRS Report R44824, *Advanced Gene Editing: CRISPR-Cas9*, by Marcy E. Gallo et al., for more information.

[76] The National Academies Press, "Rapid Expert Consultation on SARS-CoV-2 Laboratory Testing for the COVID-19 Pandemic," April 8, 2020 https://www.nap.edu/catalog/25775/rapid-expert-consultation-on-sars-cov-2-laboratory-testing-for-the-covid-19-pandemic-april-8-2020.

[77] J. P. Broughton et al., "CRISPR–Cas12-based detection of SARS-CoV-2," *Nature Biotechnology*, April 16, 2020, https://www.nature.com/articles/s41587-020-0513-4.

[78] FDA, "Sherlock CRISPR SARS-Cov-2 Kit Letter of Authorization," May 6, 2020, https://www.fda.gov/media/

perform high complexity testing per the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations (not for use at the point of care),[79] returns results in one hour, and requires no specialized instruments.

Because CRISPR-based tests do not necessarily require specialized laboratory equipment and use inexpensive components in addition to leveraging a fast and portable read-out, they have the potential to be used as a point-of-care test.[80] Specifically, the DETECTR test "can be performed with portable heat blocks, readily available reagents, and disposable lateral flow strips."[81] In addition, this test uses different reagents than those used in PCR tests, and it might eventually be able to be used without RNA extraction, both of which might ease certain supply chain stressors. Finally, test manufacturers are developing tests that use next-generation sequencing techniques—also referred to as *massively parallel sequencing*—that are both highly accurate and may be used to monitor changes in the virus's genetic code over time, because they sequence the partial or complete viral genome as part of the testing. FDA recently authorized the first COVID-19 diagnostic that uses next-generation sequencing technology.[82] In addition, this type of testing platform is being investigated as a way to support the high-volume testing capacity that many expect to be needed as employers and schools undertake large-scale screening initiatives.

In addition to research into different molecular techniques for carrying out testing, manufacturers and clinical laboratories are working to develop testing components and tests that may be used in decentralized settings, including near-patient settings, such as urgent care centers and emergency rooms, and in the home. In particular, FDA has authorized a kit for at-home specimen collection developed by EverlyWell[83] and has authorized modifications to existing EUAs to accommodate the use of at-home collection kits. For example, LabCorp developed a home sample collection kit, and FDA reissued the EUA for LabCorp's PCR test to allow for use of samples self-collected by patients at home.[84] In addition, the use of different sample types is also under investigation—specifically saliva, which would offer benefits including ease of sample collection and a reduction in supply shortages (e.g., a shortage of swabs used by current tests to collect samples from the nose and throat). FDA has authorized a Rutgers University PCR-based laboratory-developed test (LDT) to permit testing of saliva samples self-collected by patients at home.[85] FDA has not

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[79] Point-of-care testing may be defined as follows, "Point-of-care testing means that results are delivered to patients in the patient care settings, like hospitals, urgent care centers and emergency rooms, instead of samples being sent to a laboratory." See https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-first-emergency-use-authorization-point-care-diagnostic.

[80] Science Magazine, "CRISPR Gene Editing May Help Scale Up Coronavirus Testing," April 23, 2020, https://www.scientificamerican.com/article/crispr-gene-editing-may-help-scale-up-coronavirus-testing/.

[81] 360dx.com, "UCSF, Mammoth Bio Develop Rapid Coronavirus Diagnostic Using CRISPR-Cas12 Method," April 16, 2020, https://www.360dx.com/gene-silencinggene-editing/ucsf-mammoth-bio-develop-rapid-coronavirus-diagnostic-using-crispr-cas12#.XqiK4GhKg4k.

[82] FDA, "Coronavirus (COVID-19) Update: FDA Authorizes First Next Generation Sequence Test for Diagnosing COVID-19," https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-next-generation-sequence-test-diagnosing-covid-19.

[83] FDA, "Everlywell COVID-19 Test Home Collection Kit Letter of Authorization," May 15, 2020, https://www.fda.gov/media/138144/download.

[84] FDA, "Coronavirus (COVID-19) Update: FDA Authorizes First Test for Patient At-Home Sample Collection," https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-test-patient-home-sample-collection.

[85] FDA, "Coronavirus (COVID-19) Update: FDA Authorizes First Diagnostic Test Using At-Home Collection of Saliva Specimens," https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-diagnostic-test-using-home-collection-saliva.

granted EUA to any complete at-home tests, but many are under development, and the agency has stated that it expects to authorize this type of test in the future.[86]

Regulation and Approval

How are MCMs regulated?

FDA—under the Federal Food, Drug, and Cosmetic Act (FFDCA) and the PHSA—regulates the safety and effectiveness of MCMs domestically. The statutory and regulatory requirements governing MCMs vary depending on whether a product meets the definition of a drug, biologic, or medical device.

Drugs and biologics

Drugs are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"[87] and generally include biologics such as monoclonal antibodies and vaccines.[88] While drugs are typically chemically synthesized, small molecule compounds with well-defined structures, biologics are relatively large and complex molecules derived from living organisms or made in living systems. An MCM that meets the definition of a drug, including a biologic, must receive approval or licensure from FDA prior to marketing.[89] Except under limited circumstances, to support approval or licensure, FDA requires a sponsor (typically the drug manufacturer) to submit data from clinical trials—formally designed, conducted, and analyzed studies in which the investigational drug or biologic is administered to human subjects to provide evidence of a drug's safety and effectiveness, or in the case of a biologic, safety, purity, and potency.[90] The requirements regarding approval and submission of clinical trial data generally apply regardless of whether the drug is a new molecular entity (i.e., contains a new active ingredient not previously approved by FDA) or whether the drug has been approved by FDA for one use and is to be repurposed for a new use.

Before beginning clinical testing, a sponsor must file with FDA an investigational new drug application (IND), which is a request for permission to administer an investigational drug or biologic to humans prior to approval or licensure.[91] An IND must include information about the investigational drug or biologic and its chemistry, manufacturing, and controls; the proposed clinical study design; completed animal test data; and the lead investigator's qualifications,

[86] FDA, "FAQs on Diagnostic Testing for SARS-CoV-2," https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2.

[87] FFDCA §201(g)(1) [21 U.S.C. §321(g)(1)].

[88] PHSA §351(i)(1) [21 U.S.C. §262(i)(1)] defines a biologic as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." For additional information, see CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*, by Agata Dabrowska.

[89] FFDCA §505(a) [21 U.S.C. §355(a)]; PHSA §351(a) [42 U.S.C. §262(a)].

[90] PHSA 351(a)(2)(C) [42 U.S.C. §262(a)(2)(C)]. While FDA approves drugs that are *safe and effective*, the equivalent terminology for biologics is *safe, pure, and potent*. In an April 2015 FDA guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, the agency states that the standard for licensure of a biologic as potent has long been interpreted to include effectiveness (under 21 C.F.R. §600.3(s)). In guidance, FDA often uses the terms *safety and effectiveness* and *safety, purity, and potency* interchangeably.

[91] FFDCA §505(i) [21 U.S.C. §355(i)]; PHSA §351(a)(3) [21 U.S.C. §262(a)(3)]. 21 C.F.R. Part 312.

among other things.[92] The investigator also must provide assurance that an Institutional Review Board (IRB) will provide initial and continuous review and approval of each of the studies in the clinical investigation to ensure that participants are aware of the drug's investigative status and that any risk of harm will be necessary, explained, and minimized.[93] FDA has 30 days to review an IND, after which a manufacturer may begin clinical testing if FDA has not objected and imposed a clinical hold. Clinical trials are typically conducted in three phases. Phase 1 clinical trials assess safety—and for biologics, safety and immunogenicity[94]—in a small number of volunteers. Phase 2 trials assess dosing and side effects and may enroll hundreds of volunteers. Phase 3 trials assess effectiveness and continue to monitor safety and typically enroll hundreds to thousands of volunteers.[95]

Once a sponsor completes clinical trials, it submits the results of those investigations, along with other information, to FDA in a new drug application (NDA) or a biologics license application (BLA).[96] While drugs are approved via an NDA under the FFDCA, biologics—including vaccines—are licensed for marketing via a BLA under the PHSA. The requirements and review pathways for NDAs and BLAs are generally similar, and biologics are subject to various FFDCA provisions. In reviewing an NDA or BLA, FDA considers whether the drug is safe and effective—or whether the biologic is safe, pure, and potent—for its *intended use*; whether the proposed labeling is appropriate; and whether the methods and controls used to manufacture the product are adequate to preserve its identity, strength, quality, and purity.[97]

Diagnostics

In vitro diagnostic devices (IVDs) are devices used in the laboratory analysis of human samples. IVDs include commercial test kits, laboratory-developed tests (LDTs), and instruments used in testing, among other things. LDTs are a class of IVD that is designed, manufactured, and used within a single laboratory. LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new strains of known infectious diseases) or that are the subject of rapidly advancing scientific research (e.g., genomic testing for cancer).[98] Traditionally, LDTs have been regulated by FDA differently than commercial test kits. IVDs may be used in a variety of settings, including a clinical laboratory, a physician's office, or in the home. IVDs used in the clinical management of patients fall under the definition of medical "device" in the FFDCA[99] and

[92] 21 C.F.R. §312.23.

[93] 21 C.F.R. §312.23(a)(1)(iv) and 21 C.F.R. Part 56.

[94] *Immunogenicity* refers to an immune response to a therapeutic that may have the potential to affect product safety and effectiveness. One FDA guidance document specifically defines immunogenicity (for the purpose of the guidance) as "the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events." See *Immunogenicity Assessment for Therapeutic Protein Products*, August 2014, https://www.fda.gov/media/85017/download.

[95] FDA, "Vaccine Product Approval Process," https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process.

[96] FFDCA §505(b) [21 U.S.C. §355(b)] and 21 C.F.R. §314.50.

[97] For additional information, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Agata Dabrowska and Susan Thaul.

[98] For more information, see CRS In Focus IF11389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*, by Amanda K. Sarata.

[99] The term "device" is statutorily defined as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro reagent*, or other similar or related article, including any component, part, or accessory" (emphasis added) that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or is intended to affect the structure or any function of the body of man or other

therefore are subject to regulation by FDA. As with other medical devices, the application of FDA regulatory requirements to IVDs depends on the IVD's risk classification according to its intended use.

Medical devices are grouped into three classes: Class I (low risk, generally no premarket review required); Class II (usually requires premarket notification and may require special controls, such as specific labelling); and Class III (usually requires premarket approval prior to marketing). Generally, Class II devices require 510(k) clearance demonstrating that a device is substantially equivalent to a device already on the market (i.e., a predicate device). A 510(k) application typically does not require submission of clinical data. Generally, Class III devices require a premarket approval application (PMA), with some exceptions. FDA issues an approval order when a PMA demonstrates reasonable assurance that a device is safe and effective for its intended use(s). Effectiveness must be based on well-controlled investigations, which generally means clinical trial data. Unless specifically excluded by regulation, all devices must meet general controls, which include premarket and postmarket requirements; for example, registration, labeling, and compliance with current good manufacturing practices (CGMPs) as set forth in FDA's quality system regulations (QSRs).[100]

IVDs are defined in regulation as a specific subset of medical devices that include "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions ... in order to cure, mitigate, treat, or prevent disease ... [s]uch products are intended for use in the collection, preparation, and examination of specimens taken from the human body."[101] As indicated by this definition, an IVD may be either a complete test or a component of a test. In either case, an IVD comes under FDA's regulatory purview. Regulated test components include both non-diagnostic ingredients, called general purpose reagents (GPRs), and the active ingredient(s) in a diagnostic test, referred to as the analyte specific reagent (ASR). LDTs, as opposed to commercially manufactured and distributed test kits, have traditionally been exempt from FDA's premarket review requirements.

In some limited cases, IVDs may fall under the statutory definition of a biological product. In those cases, the IVD would be subject to the requirements of the PHSA for the licensure of biological products.[102] Such IVDs include, for example, blood donor screening tests for infectious agents (HIV, hepatitis B and C).

What FDA pathways are available to expedite availability of MCMs?

Because clinical testing and the FDA review process typically take several years, FDA and Congress have established mechanisms to (1) expedite the premarket development and review processes for new products coming onto the market, and (2) expand access to products that are still under investigation.[103] As used in this section, the term *drugs* generally includes biologics, unless noted otherwise.

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animals." FFDCA §201(h); 21 U.S.C. §321.

[100] For more information, see CRS In Focus IF11083, *Medical Product Regulation: Drugs, Biologics, and Devices*, by Agata Dabrowska and Victoria R. Green.

[101] 21 C.F.R. §809.3(a); Definitions.

[102] PHSA §351 [42 U.S.C. §262]; Regulation of Biological Products.

[103] CRS In Focus IF11379, *Medical Product Innovation and Regulation: Benefits and Risks*.

Expedited development and review programs for MCMs

FDA uses several formal mechanisms to expedite the development and review processes for drugs that address unmet medical need in the treatment of a serious or life-threatening condition. These four programs are fast track product designation, breakthrough therapy designation, accelerated approval, and priority review.[104] An already approved drug being studied for a new use (e.g., a drug approved for the treatment of HIV being studied for COVID-19) may be eligible for one of these expedited programs provided the applicable statutory criteria are met, and drugs may be designated to more than one program. Separately, there is a breakthrough device designation for medical devices.

Breakthrough therapy and fast track product designation are both intended to streamline the drug development process, but the qualifying criteria and features of these programs differ. To qualify for *fast track product designation*, a drug must be intended to treat a serious condition and nonclinical or clinical data must demonstrate the drug's potential to address an unmet medical need.[105] A drug (but not a biologic) also may qualify for fast track if it has been designated as a qualified infectious disease product (QIDP).[106] The sponsor of a fast track-designated drug is eligible for frequent interactions with the FDA review team, priority review, and rolling review (i.e., FDA reviews portions of an NDA or BLA before a complete application is submitted).[107] To qualify for *breakthrough designation*, a drug must be intended to treat a serious condition, and preliminary clinical evidence must indicate that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. Features of breakthrough therapy designation include rolling review; intensive FDA guidance on designing an efficient drug development program; involvement of "senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review" to expedite the development and review of a breakthrough therapy; and eligibility for other expedited programs. An interested sponsor must submit to FDA a request for fast track product or breakthrough therapy designation; a request may be submitted either with the IND or any time after,[108] as further specified in FDA guidance.[109]

The *accelerated approval* pathway allows a drug to be approved based on its effect on a surrogate endpoint (e.g., a laboratory measurement) that predicts the effectiveness of a new treatment, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality. Postmarketing confirmatory studies generally must be completed to demonstrate actual effectiveness.[110] To qualify for accelerated approval, a drug must (1) treat a serious condition, (2) generally provide a meaningful advantage over available therapies, and (3) demonstrate an effect on an endpoint that is reasonably likely to predict clinical benefit.

A *priority review* designation means FDA's goal is to take action on an application within six months of its filing, in contrast to 10 months for standard review. An NDA or BLA may qualify

[104] FFDCA §506 [21 U.S.C. §356]. FDA, "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics," May 2014, https://www.fda.gov/media/86377/download.

[105] FFDCA §506(b) [21 U.S.C. §356(b)].

[106] A qualified infectious disease product (QIDP) is an antibacterial or antifungal drug for human use that is intended to treat serious or life-threatening infections. FFDCA §505E(g) [21 U.S.C. §355E(g)].

[107] FFDCA §506(a) [21 U.S.C. §356(a)].

[108] FFDCA §506(a)(2) & (b)(2) [21 U.S.C. §356(a)(2) & (b)(2)].

[109] FDA, "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics," May 2014, https://www.fda.gov/media/86377/download.

[110] FFDCA §506(c) [21 U.S.C. §356(c)].

for priority review designation if, for example, it is for a drug that treats a serious condition and that, if approved, would provide a significant improvement in safety or effectiveness. An NDA or BLA also may qualify for priority review if submitted with a priority review voucher[111] or if the drug (but not biologic) is designated as a QIDP.

The 21st Century Cures Act (P.L. 114-255) and the FDA Reauthorization Act of 2017 (P.L. 115-52) established a new *breakthrough device* category allowing FDA to expedite development and prioritize review of devices that (1) provide more effective diagnosis or treatment of a life-threatening or irreversibly debilitating condition, and (2) represent breakthrough technologies for which no approved alternatives exist, offer significant advantages over existing alternatives, or are in the best interest of patients.[112] The Breakthrough Device Program, a voluntary program, expedites development, assessment, and review of breakthrough devices as they go through premarket approval, 510(k) clearance, or marketing authorization via the de novo classification process.

Enabling access to investigational MCMs

In general, a drug, biologic, or medical device may be provided to patients only if FDA has approved, licensed, or cleared its marketing application or authorized its use in a clinical trial under an IND or Investigational Device Exemption (IDE). In certain circumstances, however, patients may access investigational MCMs outside this framework through expanded access (i.e., compassionate use) programs and through emergency use authorization (EUA).

Expanded Access

Individuals who are not eligible for participation in a clinical trial (e.g., because they do not meet the study criteria, or because the trial is not enrolling new patients) may request, through their physician, access to an investigational product through an expanded access protocol,[113] provided that an IND or IDE is submitted to FDA and

- the physician determines (1) that the patient has no comparable or satisfactory alternative, and (2) that the probable risk from the investigational product is not greater than the probable risk from the disease or condition; and
- FDA determines (1) there is sufficient evidence of safety and effectiveness and (2) that provision of the investigational product will not interfere with "the initiation, conduct, or completion of clinical investigations to support marketing approval."[114]

A physician also may request an emergency IND (eIND) for an individual patient.[115] The provision of an investigational product in a clinical trial is intended to generate evidence of safety and effectiveness to support marketing approval. In contrast, expanded access protocols are not

[111] Currently, three priority review voucher programs are authorized in the FFDCA: (1) the tropical disease priority review program, (2) the rare pediatric disease priority review program, and (3) the material threat MCM priority review voucher program. Under each of these programs, the sponsor of an NDA or BLA that meets the statutory requirements of the specific program is eligible to receive, upon approval, a transferable voucher, and the sponsor may either use that voucher for the priority review of another application or sell it to another sponsor to use.

[112] FFDCA §515B [21 U.S.C. §360e-3].

[113] FFDCA §561(b) [21 U.S.C. §360bbb(b)].

[114] FFDCA §561(b)(3) [21 U.S.C. §360bbb(b)(3)].

[115] 21 C.F.R. §312.310.

primarily intended to be used to obtain safety and effectiveness data; instead, they are intended to provide investigational therapies to patients who have exhausted all other options.[116] FDA approves the majority of expanded access requests it receives.[117]

For FDA to grant permission, a manufacturer must have agreed to provide the investigational product. Manufacturers are not always willing to provide an investigational product outside of a clinical trial for various reasons, including supply constraints, liability concerns, and lack of clarity regarding how FDA may use adverse event or outcome data when considering approval in the future.

Due to perceived limitations with FDA's expanded access program, in 2018, the Right to Try (RTT) Act (P.L. 115-176) was enacted. The RTT Act created a pathway for eligible patients to access an eligible investigational drug (but not a device) without FDA's authorization. The manufacturer must still agree to provide the drug. An *eligible patient* is a patient who has (1) been diagnosed with a life-threatening disease or condition; (2) exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug; and (3) provided written informed consent to the treating physician regarding the eligible investigational drug.[118] An *eligible investigational drug* is an investigational drug that meets the following criteria: (1) a Phase 1 clinical trial has been completed; (2) the drug has not been approved or licensed by FDA for any use; (3) an NDA or BLA has been filed, or the drug is under investigation in a clinical trial, as specified; and (4) the active development or production of the drug is ongoing, and FDA has not placed a clinical hold on the trial.[119] FDA does not approve or review RTT Act requests and, with limited exceptions, FDA may not use a clinical outcome associated with the use of an eligible investigational drug to delay or adversely affect its review or approval.[120] Given interest in generating safety and effectiveness data and resource and supply constraints, the RTT pathway is unlikely to be used to provide access to COVID-19 investigational therapies.

Emergency Use Authorization (EUA)

FDA may enable access to unapproved MCMs by granting EUA, if the HHS Secretary declares that circumstances exist to justify the emergency use of an unapproved product or an unapproved use of an approved medical product.[121] This emergency declaration by the HHS Secretary is authorized under FFDCA Section 564, is distinct from the Public Health Emergency (PHE) declaration made pursuant to PHSA Section 319, and may be made in the absence of a PHE declaration made pursuant to PHSA Section 319.[122] The HHS Secretary's declaration must be

[116] FDA, Guidance for Industry, *Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers*, p. 3, June 2016, https://www.fda.gov/media/85675/download.

[117] FDA, "Expanded Access (compassionate use) submission data," updated March 16, 2020, https://www.fda.gov/news-events/expanded-access/expanded-access-compassionate-use-submission-data.

[118] FFDCA §561B(a)(1) [21 U.S.C. §360bbb-0a(a)(1)].

[119] FFDCA §561B(a)(2) [21 U.S.C. §360bbb-0a(a)(2)].

[120] FFDCA §561B(c) [21 U.S.C. §360bbb-0a(c)].

[121] FFDCA §564 [21 U.S.C. §360bbb-3]. For additional information, see CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

[122] For example, on August 5, 2014, the HHS Secretary declared, pursuant to FFDCA Section 564, that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection of Ebola virus. The HHS Secretary's declaration was made in the absence of a PHE declaration under PHSA Section 319. Instead, the HHS Secretary's declaration was made on the basis of a determination by the Secretary of the Department of Homeland Security that the Ebola virus presents a material threat against the U.S. population sufficient to affect national security.

based on one of four determinations; for example, a determination that there is an actual or significant potential for a public health emergency that affects or has significant potential to affect national security or the health and security of U.S. citizens living abroad.[123] Following the HHS Secretary's declaration, FDA, in consultation with ASPR, NIH, and CDC, may issue an EUA authorizing the emergency use of a specific drug, device, or biologic, provided that the following criteria are met:

- the agent that is the subject of the EUA can cause a serious or life-threatening disease or condition;
- based on the totality of the available scientific evidence, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such disease or condition, and that the known and potential benefits of the product outweigh its known and potential risks; and
- there is no adequate, approved, or available alternative to the product.[124]

FDA must impose certain conditions as part of an EUA to the extent practicable (e.g., distributing certain information to health care providers and patients) and may impose additional discretionary conditions where appropriate.[125] FDA may waive or limit current good manufacturing practices (e.g., storage and handling) and prescription dispensing requirements for products authorized under EUA. FDA also may establish conditions on advertisements and other promotional printed matter that relates to the emergency use of a product. An EUA remains in effect for the duration of the emergency declaration made by the HHS Secretary under FFDCA Section 564, unless revoked at an earlier date.

On February 4, 2020, the HHS Secretary determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves COVID-2019.[126] On the basis of this determination, the HHS Secretary subsequently declared that circumstances exist justifying the authorization of emergency use of unapproved in vitro diagnostics for the detection and/or diagnosis of COVID-19; personal respiratory protective devices; medical devices, including alternative products used as medical devices; and therapeutics. Pursuant to these declarations, FDA subsequently issued numerous EUAs authorizing the emergency use of specific diagnostics, drugs, and other medical devices during the COVID-19 outbreak.[127]

[123] FFDCA §564(b)(1) [21 U.S.C. §360bbb-3(b)(1)].

[124] FFDCA §564(c) [21 U.S.C. §360bbb-3(c)]. These criteria are explained in more detail in the FDA guidance *Emergency Use Authorization of Medical Products and Related Authorities*, January 2017, p. 7, https://www.fda.gov/media/97321/download.

[125] FFDCA §564(e) [21 U.S.C. §360bbb-3(e)].

[126] 85 *Federal Register* 13907, publication date March 10, 2020, effective date February 4, 2020.

[127] FDA "Emergency Use Authorizations," accessed April 15, 2020, https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.

Availability

How are MCMs in development for COVID-19 available to U.S. patients?

In the absence of approved MCMs for COVID-19, patients can access investigational, unapproved MCMs in several ways, including through EUA, by participating in clinical trials, and through expanded access programs. In addition, FDA-approved drugs may be prescribed off-label (i.e., for unapproved uses) by physicians for treatment of COVID-19.

Emergency Use Authorization (EUA)

Patients hospitalized with severe COVID-19 may obtain access to products granted EUA. For therapeutics, as of the date of this report, remdesivir is the only drug subject to an EUA.[128] Hydroxychloroquine and chloroquine were subject to an EUA that has since been revoked by FDA. However, physicians may still prescribe these drugs off-label for individual patients. To date, FDA has not granted EUA to any COVID-19 vaccines. However, numerous clinical trials are underway, and some experts and industry members think that if a vaccine shows adequate results from the first trials, it may be made available to certain populations (such as health care workers) before clinical trials are completed via an EUA.[129]

Diagnostics are available for clinical use through authorized marketing pursuant to an EUA during the COVID-19 emergency. EUAs have been granted for more than 100 molecular diagnostics (both commercial test kits and LDTs), as well as for several serology tests and one antigen test.[130] The EUA tests include several that may be used at the point of care, including for example, the Abbott IDNow molecular test. In addition, Quidel's antigen test is authorized for use in point-of-care settings. Thus far, no serology test has been authorized for use in point-of-care settings. The vast majority of EUAs have been granted for tests that must be carried out in a centralized clinical laboratory environment (i.e., higher complexity tests).

Through guidance, FDA has taken steps to liberalize the EUA process to expand access to tests.[131] Specifically, the agency has allowed, in specified cases, tests to be marketed and clinically used prior to being granted EUA but after validation and notification to FDA. In addition, the FDA initially allowed serology tests to be made available and marketed without EUA. While these policies have improved access, they have also resulted in access to diagnostics with less robust performance characteristics in some cases.

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[128] FDA, Letter of Authorization to Gilead Sciences, Inc., May 1, 2020, https://www.fda.gov/media/137564/download.

[129] Jon Cohen, "With Record-Setting Speed, Vaccinemakers Take Their First Shots at the New Coronavirus," *Science*, March 31, 2020, https://www.sciencemag.org/news/2020/03/record-setting-speed-vaccine-makers-take-their-first-shots-new-coronavirus.

[130] A COVID-19 serology test identifies antibodies to the SARS-CoV-2 virus, usually in an individual blood sample. Antibodies are proteins generated by the immune system in response to an antigen, or foreign substance. An antigen may be a pathogenic virus or bacteria, for example, or generally any substance that is recognized by the immune system as both foreign and harmful. An antigen test uses antibodies to a specific antigen (e.g., SARS-CoV-2 virus) to identify the virus in a patient's sample. A COVD-19 serology test may determine prior infection, whereas an antigen test may determine an active infection, because the serology test identifies a product of the immune response whose generation lags infection, whereas the antigen test directly identifies the actual virus.

[131] See, generally, FDA, "Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised)," May 11, 2020, https://www.fda.gov/media/135659/download.

Expanded access

Patients may enroll in one of various clinical trials studying the safety and effectiveness of new drugs and vaccines for COVID-19. If participation in a clinical trial is not feasible—because the trial is not enrolling new subjects or because the patient does not meet criteria for enrollment—patients may be able to receive the experimental drug through an expanded access program. In the case of convalescent plasma, for example, patients may access the Mayo Clinic-led expanded access protocol, which has more than 2,000 sites and over 8,000 physician investigators participating.[132] The federal clinical trials database maintained by the National Library of Medicine at NIH lists several expanded access programs for COVID-19 treatments, and it is likely not an exhaustive list.[133] In cases where access to a clinical trial or the expanded access protocol is not available, a physician may request an eIND for an individual patient for a specific investigational drug.

Postmarket Surveillance

In light of efforts to expedite access to MCMs for COVID-19, questions have been raised about postmarket monitoring of adverse events and the continued collection of safety and effectiveness data. While premarket studies are designed to identify common safety risks associated with a drug or biologic, they may not identify all long-term or rare adverse events. As such, FDA may request that sponsors conduct additional studies once a drug or biologic is on the market to further provide information about its risks, benefits, and optimal use.[134] These studies may be particularly useful when one of the expedited pathways is used because it allows for the marketing and benefits of a product to be realized sooner, while at the same time allowing for a fuller safety and effectiveness profile to be developed. FDA also may require a sponsor to conduct a postapproval study or clinical trial to assess a known serious risk or in response to signals of serious risk related to use of the drug or biologic.[135]

FDA has several systems for monitoring medical product safety following approval or licensure. For example, drug and biologic manufacturers must report all serious and unexpected adverse events to the FDA Adverse Event Reporting System (FAERS) within 15 days of becoming aware of them, and they must report other adverse events in mandated periodic reports to the agency.[136] The reports are made publicly available through the FAERS public dashboard. For vaccines, adverse events must be reported to the Vaccine Adverse Event Reporting System (VAERS), which is co-sponsored by FDA and CDC. For medical devices, manufacturers must report device-related deaths, serious injuries, and malfunctions within 30 days of becoming aware of them; medical device reports (MDRs) are stored in the FDA's Manufacturer and User Facility Device

[132] FDA, "Coronavirus (COVID-19) Update: FDA Encourages Recovered Patients to Donate Plasma for Development of Blood-Related Therapies," April 16, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-encourages-recovered-patients-donate-plasma-development-blood.

[133] NLM, "Clinical Trials," accessed April 15, 2020, https://clinicaltrials.gov/ct2/results?cond=COVID-19&age_v=&gndr=&type=Expn&rslt=&Search=Apply.

[134] 21 C.F.R. §312.85. FFDCA §506(c)(2) [21 U.S.C. §356(c)(2)].

[135] PHSA §351(a)(2)(D) [42 U.S.C. §262(a)(2)(D)] and FFDCA §505(o)(3) [21 U.S.C. §355(o)(3)].

[136] 21 C.F.R. §314.80(c) and 21 C.F.R. §600.80(c). FDA Adverse Event Reporting System (FAERS) Public Dashboard, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Safety reporting is required during clinical testing and in expanded access programs (21 C.F.R. §312.32).

Experience (MAUDE) database. Under typical circumstances, patients and health care providers are encouraged, but not required, to report adverse events to FDA through MedWatch.[137]

However, FDA may impose, as part of an EUA, conditions for monitoring and reporting adverse events associated with the emergency use of a product, including mandatory reporting by health care providers.[138] For example, the EUAs for hydroxychloroquine and chloroquine and for remdesivir require health care facilities and providers who administer the drugs to track and report any serious adverse events to FDA through MedWatch.[139] Similarly, EUAs for diagnostics require, as a condition of authorization, the manufacturer or laboratory granted the EUA to track adverse events (specifically false results) and report them to FDA. Adverse events also may be reported to the HHS Safety Reporting Portal (SRP), which is intended to streamline the process of reporting product safety issues to both FDA and NIH.[140]

FDA conducts active postmarket surveillance through its Sentinel System, which uses data obtained from electronic health records, patient registries, and other sources to provide information about the safety of a drug, medical device, vaccine, or biologic. FDA's Sentinel System is involved in several COVID-19-related activities, including "monitoring the use of drugs, describing the course of illness among hospitalized patients, and evaluating the treatment impact of therapies actively being used under real-world conditions."[141] One component of Sentinel is the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program—established in 2009 as part of vaccine safety surveillance during the H1N1 influenza pandemic—which uses electronic health records from insurance providers and state immunization registries to monitor adverse events following vaccination.[142] FDA uses safety information and data generated from FAERS, VAERS, Sentinel, and other sources to inform regulatory action.

Ongoing surveillance and research may be particularly important when drugs or diagnostics are made available via EUA or expanded access, as the standard of evidence for authorizing early access to investigational products is different than that required for FDA clearance, approval, or licensure. EUA issuance, for example, is based on FDA's determination that the totality of the available scientific evidence suggests that a product may be effective in diagnosing, treating, or preventing a disease or condition and that the known and potential benefits of the product outweigh its known and potential risks. This determination is different from the standard required for FDA approval of a drug or biologic, which is based on *substantial evidence* of effectiveness derived from adequate and well-controlled studies.[143] Following issuance of the March 2020 EUA for hydroxychloroquine and chloroquine, and based on analysis of case reports in FAERS, the published medical literature, and poison control centers data, in April 2020, FDA published a

[137] FDA, "MedWatch: The FDA Safety Information and Adverse Event Reporting Program," https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.

[138] FFDCA §564(e).

[139] FDA, Letter of Authorization to Gilead Sciences, Inc., May 1, 2020, https://www.fda.gov/media/137564/download. FDA, Letter of Authorization to BARDA, March 28, 2020, https://www.fda.gov/media/136534/download.

[140] HHS, The Safety Reporting Portal, https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx.

[141] Sentinel, FDA Sentinel System's Coronavirus (COVID-19) Activities, https://sentinelinitiative.org/drugs/fda-sentinel-system-coronavirus-covid-19-activities.

[142] PRISM is the vaccine component of FDA's Sentinel Initiative. The Sentinel system was implemented as an "Active Post-Market Risk Identification and Analysis program" under FFDCA §505(k)(3), as amended by §905 of the FDA Amendments Act, P.L. 110-85.

[143] FDA, "Understanding the Regulatory Terminology of Potential Preventions and Treatments for COVID-19," https://www.fda.gov/consumers/consumer-updates/understanding-regulatory-terminology-potential-preventions-and-treatments-covid-19.

Drug Safety Communication cautioning against use of these drugs outside the hospital or clinical trial setting due to risk of heart rhythm problems.[144] Data obtained by FDA further led the agency to revoke the EUA in June 2020.[145] Diagnostic EUAs require manufacturers, laboratories, and authorized laboratories carrying out testing to "collect information on the performance of their product," and, more specifically, false positives, false negatives, and other deviations from a test's performance characteristics—all of which must be reported to FDA. In addition, in some cases, FDA will require a post-authorization clinical evaluation study as a condition of the authorization, with a requirement to update labelling based on the results of the study.[146]

Funding

What funding is available for COVID-19 MCM development and approval?

Recently enacted supplemental appropriations have included funding for several accounts that can be used to support the development and approval of COVID-19 MCMs, or to support scientific research that can aid in MCM development (as summarized in **Table 1**). The table below shows funding that can be used for MCM R&D or approval activities as provided in the three coronavirus supplemental appropriations acts:[147]

- Division A, Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020 (P.L. 116-123), enacted on March 6, 2020.
- Division B, Coronavirus Aid, Relief, and Economic Security Act (P.L. 116-136), enacted on March 27, 2020.
- Division B, Paycheck Protection Program and Health Care Enhancement Act (P.L. 116-139), enacted on April 24, 2020.

Table 1 shows accounts from which funding can be used by FDA, NIH, DOD Defense Health Research, and components within the HHS Office of the Secretary (including BARDA). In some cases, funds are appropriated to those accounts; in others, transfers or set-asides to relevant agencies or accounts are either directed or allowed. (This transfer authority in several instances is either "not more than" or "not less than" a specified amount.) Funds to be transferred are shown in the account to which they were appropriated, not in the account to which they are to be transferred.

The purpose of the funds indicates their allowed uses as specified in the respective appropriations acts. Additional contextual information is included where appropriate. The period of availability is either the date after which funds are no longer available for obligation, or "until expended."

[144] FDA, "FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems," April 24, 2020, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.

[145] FDA, "Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine," June 15, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.

[146] See for example FDA, "Cue COVID-19 Test: Letter of Authorization," https://www.fda.gov/media/138823/download.

[147] The second supplemental appropriations measure, The Families First Coronavirus Response Act (P.L. 116-127) did not include available funding for MCM R&D.

In some cases, funds are provided to accounts that are mostly for activities related to MCMs, such as funding for FDA, DOD Defense Health Program, or NIH accounts. In other cases, funds appropriated to the listed account may be allocated to MCM R&D-related activities at the discretion of the funded agency. For example, funds have been appropriated to the Public Health and Social Services Emergency Fund (PHSSEF) for a broad array of HHS emergency preparedness and response activities related to COVID-19, particularly those conducted by ASPR, where BARDA is based. The HHS Secretary generally has broad discretion to allocate the PHSSEF account amounts listed below to BARDA, except where set-asides or transfers are specified.

Table 1. Funding for MCM R&D in Coronavirus Supplemental Appropriations

Accounts with specific funding available for MCM R&D

Account	Amount	Purpose	Availability
Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020 (P.L. 116-123)[a]			
FDA—Salaries and Expenses	$61 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally, including the development of necessary medical countermeasures and vaccines, advanced manufacturing for medical products, the monitoring of medical product supply chains, and related administrative activities."	Until expended
NIH—NIAID	$836 million (less specified transfer of not less than $10 million)[b]	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
HHS Office of the Secretary (OS)—Public Health and Social Services Emergency Fund (PHSSEF; parent account for BARDA)	$3.1 billion and $300 million in contingent appropriations (less specified transfers of not more than $102 million)[c]	"to prevent, prepare for, and respond to coronavirus, domestically or internationally, including the development of necessary countermeasures and vaccines, prioritizing platform-based technologies with U.S.-based manufacturing capabilities, and the purchase of vaccines, therapeutics, diagnostics, necessary medical supplies, medical surge capacity, and related administrative activities." The HHS Secretary may direct funding from this account to BARDA.	September 30, 2024
CDC—CDC-Wide Activities and Program Support—Transfer to Infectious Disease Rapid Response Reserve Fund (IRRRDF)	Transfer of not less than $300 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally." Funding from IDRRRF is transferrable to NIH and PHSSEF accounts by the CDC Director pursuant to 42 U.S.C. §247d-4a.	September 30, 2022
Coronavirus Aid, Relief, and Economic Security Act (CARES Act) (P.L. 116-136)[d]			
DOD—Defense Health Program	$415 million	"Research, development, test and evaluation to prevent, prepare for,	September 30, 2021

Account	Amount	Purpose	Availability
		and respond to coronavirus, domestically or internationally."	
FDA—Salaries and Expenses	$80 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally, including funds for the development of necessary medical countermeasures and vaccines, advanced manufacturing for medical products, the monitoring of medical product supply chains, and related administrative activities."	Until expended
NIH—National Heart, Lung, and Blood Institute (NHLBI)	$103 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
NIH—NIAID	$706 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally." Not less than $156 million of the total is for "the study of, construction of, demolition of, renovation of, and acquisition of equipment for, vaccine and infectious diseases research facilities of or used by NIH, including the acquisition of real property."	September 30, 2024
NIH—National Institute of Biomedical Imaging and Bioengineering (NIBIB)	$60 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
NIH—National Library of Medicine (NLM)	$10 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
National Center for Advancing Translational Sciences (NCATS)	$36 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
NIH—Office of the Director	$30 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally."	September 30, 2024
OS—PHSSEF (parent account for BARDA)[e]	$27 billion including the BARDA set-aside below (less other specified set-asides or transfers of roughly $16.5 billion)[g]	"to prevent, prepare for, and respond to coronavirus, domestically or internationally, including the development of necessary countermeasures and vaccines, prioritizing platform-based technologies with U.S.-based manufacturing capabilities, the purchase of vaccines, therapeutics, diagnostics, necessary medical supplies, as well as medical surge capacity, addressing blood supply chain, workforce modernization, telehealth access and	September 30, 2024

Account	Amount	Purpose	Availability
		infrastructure, initial advanced manufacturing, novel dispensing, enhancements to the U.S. Commissioned Corps, and other preparedness and response activities." The HHS Secretary may direct funding from this account to BARDA.	
Set-aside to BARDA (non-add)	*Set-aside of not less than $3.5 billion*	*"for necessary expenses of manufacturing, production, and purchase, at the discretion of the Secretary, of vaccines, therapeutics, diagnostics, and small molecule active pharmaceutical ingredients, including the development, translation, and demonstration at scale of innovations in manufacturing platforms."*	*As above*
CDC—CDC-Wide Activities and Program Support- Transfer to IRRRDF	Transfer of $300 million	"to prevent, prepare for, and respond to coronavirus, domestically or internationally." Funding from IDRRRF is transferrable to NIH and PHSSEF accounts by the CDC Director pursuant to 42 U.S.C. §247d-4a.	September 30, 2024
Paycheck Protection Program and Health Care Enhancement Act (P.L. 116-139)[h]			
OS—PHSSEF[i]	$25 billion including transfers below (less other specified set-asides or transfers of not less than $13.8 billion)[i]	"to prevent, prepare for, and respond to coronavirus, domestically or internationally, for necessary expenses to research, develop, validate, manufacture, purchase, administer, and expand capacity for COVID–19 tests to effectively monitor and suppress COVID–19, including tests for both active infection and prior exposure, including molecular, antigen, and serological tests, the manufacturing, procurement and distribution of tests, testing equipment and testing supplies, including personal protective equipment needed for administering tests, the development and validation of rapid, molecular point-of-care tests, and other tests, support for workforce, epidemiology, to scale up academic, commercial, public health, and hospital laboratories, to conduct surveillance and contact tracing, support development of COVID–19 testing plans, and other related activities related to COVID–19 testing."	Until expended

Account	Amount	Purpose	Availability
Transfer to NIH National Cancer Institute (non-add)	*Transfer of not less than $306 million*	*"to develop, validate, improve, and implement serological testing and associated technologies."*	*As above*
Transfer to NIH NIBIB (non-add)	*Transfer of not less than $500 million*	*"to accelerate research, development, and implementation of point of care and other rapid testing related to coronavirus."*	*As above*
Transfer to NIH Office of the Director (non-add)	*Transfer of not less than $1 billion*	*"to develop, validate, improve, and implement testing and associated technologies; to accelerate research, development, and implementation of point of care and other rapid testing; and for partnerships with governmental and non-governmental entities to research, develop, and implement the activities outlined in this proviso."*	*As above*
Set-aside to BARDA (non-add)	*Transfer of not less than $1 billion*	*"for necessary expenses of advanced research, development, manufacturing, production, and purchase of diagnostic, serologic, or other COVID–19 tests or related supplies, and other activities related to COVID–19 testing at the discretion of the Secretary."*	*As above*
Transfer to FDA (non-add)	*Transfer of $22 million*	*"to support activities associated with diagnostic, serological, antigen, and other tests, and related administrative activities."*	*As above*

Notes: Funding in other accounts not included in this table could potentially be used for activities related to MCM R&D, such as funding for Global Health, National Science Foundation and others. However, such funding is excluded from this presentation because MCM R&D is not a primary purpose of these accounts. Amounts shown rounded to first decimal place. The second supplemental appropriations measure, The Families First Coronavirus Response Act (P.L. 116-127) did not include available funding for MCM R&D.

Acronyms: FDA= Food and Drug Administration; NIH= National Institutes of Health; NIAID= National Institute of Allergy and Infectious Diseases; HHS= Department of Health and Human Services; BARDA= Biomedical Advanced Research and Development Authority; DOD= Department of Defense.

a. HHS may transfer nearly all the funds appropriated to it in Title III, Division A, of P.L. 116-123 among accounts at CDC, NIH, or PHSSEF, provided the transfers are made to prevent, prepare for, and respond to the COVID-19 pandemic, domestically or internationally (see §304). HHS is to notify the House and the Senate appropriations committees 10 days in advance of such a transfer.

b. Transfer to the National Institute of Environmental Health Sciences (NIEHS) for "worker-based training to prevent and reduce exposure of hospital employees, emergency first responders, and other workers who are at risk of exposure to coronavirus through their work duties."

c. Transfers specified are $100 million to the Health Resources and Services Administration (HRSA) and up to $2 million to the HHS Office of Inspector General (OIG).

d. HHS may transfer nearly all the funds appropriated to it in Title VIII, Division B, of P.L. 116-136 among accounts at CDC, PHSSEF, NIH, Administration for Children and Families (ACF), and the Administration for Community Living (ACL), provided the transfers are made to prevent, prepare for, and respond to the COVID-19 pandemic, domestically or internationally (see §18111). HHS is to notify the House and the Senate appropriations committees 10 days in advance of such a transfer.

e. Not more than $4 million per Title VIII, Division B, Section 8113, is to be transferred to the HHS Office of the Inspector General (OIG) from the $127.29 billion total appropriated to PHSSEF for oversight of all

f. activities supported with funds appropriated to HHS to prevent, prepare for, and respond to the COVID-19 pandemic.

g. Transfers specified are not more than $16 billion for the Strategic National Stockpile; not less than $250 million for grants or cooperative agreements with existing grantees or sub-grantees of the Hospital Preparedness Program; not more than $289 million to other federal agencies for care of persons under federal quarantine; and $1.5 million for a National Academies of Science, Engineering, and Medicine (NASEM) study on the security of the U.S. medical supply chain.

h. HHS may transfer certain funds appropriated to it in Title I, Division B, of P.L. 116-139 among accounts at CDC, NIH, PHSSEF, and FDA, provided the transfers are made to prevent, prepare for, and respond to the COVID-19 pandemic (see §102). HHS is to notify the House and the Senate appropriations committees 10 days in advance of such a transfer.

i. Not more than $6 million per Title I, Division B, Section 103, of P.L. 116-139 is to be transferred to the HHS Office of the Inspector General (OIG) from the $127.29 billion total appropriated to PHSSEF for oversight of all activities supported with funds appropriated to HHS to prevent, prepare for, and respond to the COVID-19 pandemic.

j. Other specified transfers include not less than $11 billion for grants and cooperative agreements with states, localities, territories, tribes, and other jurisdictions/entities; not less than $1 billion to CDC-wide activities and program support; $600 million to HRSA for community health centers; $225 million for rural health clinics; and $1 billion for the cost of testing for the uninsured.

Author Information

Agata Dabrowska
Analyst in Health Policy

Amanda K. Sarata
Specialist in Health Policy

Frank Gottron
Specialist in Science and Technology Policy

Kavya Sekar
Analyst in Health Policy

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