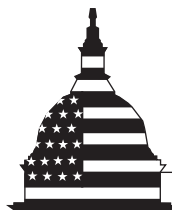


June 2011

INFLUENZA VACCINE

Federal Investments in Alternative Technologies and Challenges to Development and Licensure



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Why GAO Did This Study

Production delays for the 2009 H1N1 pandemic vaccine using the current egg-based production technology heightened interest in alternative technologies that could expand the supply or accelerate the availability of influenza vaccine. Within the federal government, the Department of Health and Human Services (HHS) and the Department of Defense (DOD) support the development of technologies that can be used in producing influenza vaccines. HHS's Food and Drug Administration (FDA) reviews licensing applications for new vaccine, and the Department of State is the U.S. diplomatic liaison to the international entity that declares worldwide pandemics.

GAO was asked to review federal activities for the development of alternative technologies used in producing influenza vaccine. This report examines (1) federal funding from fiscal year 2005 through March 2011 for alternative technologies and the status of manufacturers' efforts, (2) challenges to development and licensure identified by stakeholders, and (3) how HHS is addressing those challenges.

GAO reviewed HHS and DOD documents and funding data. GAO also interviewed stakeholders, including manufacturer representatives, industry associations, and other experts on challenges to development and licensure. GAO interviewed HHS officials on how they are addressing those challenges.

INFLUENZA VACCINE

Federal Investments in Alternative Technologies and Challenges to Development and Licensure

What GAO Found

From fiscal year 2005 through March 2011, HHS and DOD provided about \$2.1 billion in funding for the development of alternative technologies that could potentially expand the supply or accelerate the availability of influenza vaccine. Specifically, HHS and DOD have funded two alternative production technologies—cell-based and recombinant technologies, which produce vaccine in cells instead of eggs—and adjuvants, which can reduce the amount of vaccine needed to stimulate an immune response. HHS's funding supports the development of a new influenza vaccine using alternative technologies with the goal of manufacturers submitting licensing applications to FDA. DOD's funding supports the research and development of a technology that can make various vaccines, including influenza vaccines. HHS awarded \$1 billion in contracts to manufacturers to develop cell-based technology, with manufacturers making progress toward licensure. HHS and DOD funded \$296.5 million in contracts and \$86.9 million in technology investment agreements, respectively, for the development of recombinant technology. HHS also awarded about \$152 million in contracts for the development of adjuvanted influenza vaccines. Two manufacturers receiving HHS funds plan to submit licensing applications for their adjuvanted vaccines to FDA within the next 2 years.

Some stakeholders said low demand, high research and development costs, and regulatory challenges can hinder the development and licensure of new vaccines using alternative technologies. For example, despite the United States using more seasonal vaccine than any other country, some stakeholders told us that low vaccination rates can decrease incentives for manufacturers to develop new influenza vaccines using alternative technologies because there is not sufficient demand for new products. Some stakeholders said high research and development costs can also decrease manufacturers' incentives; however, HHS noted that increased investments in this area have generated a significant interest in this type of research and development. Some stakeholders also told us that some of FDA's guidance documents are not sufficiently comprehensive. FDA officials told us that their guidance documents cannot cover all possible scenarios; thus, they regularly meet with manufacturers to discuss issues and provide advice.

HHS is addressing challenges in the development and licensure of new influenza vaccines using alternative technologies. For example, HHS intends to fund the establishment of specialized facilities that will provide support and expertise to manufacturers. Additionally, through FDA, HHS plans to facilitate the review of licensing applications for new influenza vaccines using alternative technologies and to enhance FDA's staff expertise.

HHS, DOD, and the Department of State reviewed a draft of this report. In commenting on a draft of this report, HHS and DOD agreed with GAO on its findings. The Department of State did not provide comments. HHS provided suggestions to clarify the discussion.

Contents

Letter		1
	Background	7
	The Federal Government Has Provided about \$2.1 Billion in Funding for the Development of Alternative Technologies that Can Be Used in Producing Influenza Vaccines, and Manufacturers Are Demonstrating Progress toward Licensure	15
	Some Stakeholders Identified Challenges to the Development and Licensure of Influenza Vaccines Using Alternative Technologies	22
	HHS Is Addressing Challenges in the Development and Licensure of Influenza Vaccines Using Alternative Technologies	30
	Agency Comments	35
Appendix I	The Research, Development, and Review of Licensing Applications for New Influenza Vaccine in the United States	37
Appendix II	Influenza Vaccine Production Process Using Egg-Based Technology	38
Appendix III	Egg-Based and Alternative Technologies for Use with Influenza Vaccines	40
Appendix IV	Comments from the Department of Health and Human Services	45
Appendix V	Comments from the Department of Defense	49
Appendix VI	GAO Contact and Staff Acknowledgments	50

Related GAO Products

51

Tables

Table 1: Federal Government's Role in the Research and Development of Alternative Technologies and the Licensure and Regulation of Influenza Vaccines	10
Table 2: Alternative Technologies and Their Potential to Expand the Supply or Accelerate the Availability of Influenza Vaccine	13
Table 3: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of Cell-Based Influenza Vaccine, Fiscal Year 2005 through March 2011	17
Table 4: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of Recombinant Influenza Vaccine, Fiscal Year 2009 through March 2011	19
Table 5: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of an Adjuvanted Influenza Vaccine, Fiscal Year 2007 through March 2011	21
Table 6: Number of U.S.-Licensed Manufacturers of Seasonal Influenza Vaccine and Number of Doses Produced and Distributed for the 2000–01 through 2010–11 Influenza Seasons	24
Table 7: Influenza Vaccine Production Process Using Egg-Based Technology	38
Table 8: Additional Potential Benefits of Adjuvants	43

Figure

Figure 1: Estimated Timeline for the Research, Development, and Review of Licensing Applications for New Influenza Vaccine for the United States	37
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Abbreviations

CDC	Centers for Disease Control and Prevention
DOD	Department of Defense
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NIH	National Institutes of Health
PCAST	President's Council of Advisors on Science and Technology

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United States Government Accountability Office
Washington, DC 20548

June 27, 2011

The Honorable Fred Upton
Chairman
The Honorable Henry A. Waxman
Ranking Member
Committee on Energy and Commerce
House of Representatives

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

The Honorable Roy Blunt
United States Senate

The Honorable Joe Barton
House of Representatives

Influenza, in both its seasonal and pandemic forms, is an ongoing public health concern. Seasonal influenza may begin as early as August and generally diminishes by April in the northern hemisphere. It has been associated with 3,000 to nearly 50,000 deaths each year in the United States in recent decades, according to the Department of Health and Human Services's (HHS) Centers for Disease Control and Prevention (CDC).¹ Pandemic influenza, which periodically causes a global outbreak of serious illness with the potential for many more deaths than seasonal influenza, has occurred four times in the past 100 years.² In the late 1990s and early 2000s, detection of the H5N1 avian influenza (also known as "bird flu") virus in animals raised concerns among experts that it or another influenza virus might mutate into a strain that could lead to a

¹CDC, "Estimates of Deaths Associated with Seasonal Influenza—United States, 1976-2007," *Morbidity and Mortality Weekly Report*, vol. 59, no. 33 (2010): 1057-1062.

²These pandemics include the "Spanish flu" of 1918, which killed an estimated 675,000 people in the United States; the "Asian flu" of 1957, which caused approximately 70,000 deaths in the United States; the "Hong Kong flu" of 1968, which caused an estimated 34,000 deaths in the United States; and the recent 2009 H1N1 pandemic, which caused from 8,870 to 18,300 deaths in the United States. Influenza pandemics can have successive "waves" of disease and last for up to 3 years.

human influenza pandemic.³ The recent 2009 H1N1 influenza pandemic reinforced the need to be prepared for future influenza pandemics.

The federal government, specifically HHS and the Department of Defense (DOD), funds the research and development of alternative technologies that can be used in producing human influenza vaccines as a part of its pandemic influenza preparedness efforts.⁴ According to HHS, HHS's and DOD's funding represents virtually all of the federal government's investment in this type of research and development. Vaccines are considered the first line of defense against seasonal and pandemic influenza, as they can prevent infection and control the spread of the disease. Furthermore, influenza vaccines are—along with diagnostic tools and treatments such as antiviral drugs—a type of medical countermeasure that can be used to protect the population during public health emergencies.⁵ In 2005, HHS issued the *HHS Pandemic Influenza Plan* (Plan) for responding to an influenza pandemic.⁶ One of the goals stated in the Plan is to have sufficient domestic capacity to produce enough pandemic vaccine to cover the United States' population within 6 months

³According to the United Nations' World Health Organization, since 2003, 553 cases of human H5N1 influenza have appeared in 15 countries, resulting in a total of 323 deaths as of May 13, 2011.

⁴Alternative technologies for influenza vaccines can also be referred to as non-egg based technologies or next generation technologies. However, for this report, we use alternative technologies. Examples of these technologies include cell-based technology or adjuvants, described later in this report. Other examples include quadravalent vaccine, that is, a vaccine made using four strains of influenza virus.

⁵Medical countermeasures are drugs, biological products, or devices that treat, identify, or prevent harm from a biological and other agent that may cause a public health emergency. Medical countermeasures for use during an influenza pandemic may include vaccine, antiviral drugs, personal respirators, and influenza diagnostic tests. Antiviral drugs are medications that can prevent or reduce the severity of a viral infection, such as influenza. This report focuses on influenza vaccine.

⁶HHS, *HHS Pandemic Influenza Plan* (Washington, D.C., 2005), 24. HHS's Plan is only part of the federal government's planning efforts for responding to a pandemic. The President of the United States released two documents for a broader response: (1) the *National Strategy for Pandemic Influenza*, which provides a framework for future planning efforts for how the country will prepare for, detect, and respond to a pandemic, and (2) the *National Strategy for Pandemic Influenza Implementation Plan* (Implementation Plan), which further clarifies the roles and responsibilities of governmental and nongovernmental entities and provides preparedness guidance for all segments of society. This Implementation Plan includes 324 action items, some of which are related to enhancing domestic production capacity and supporting the development of alternative technologies for use in producing influenza vaccine.

of a pandemic declaration.⁷ These global declarations are made by the United Nations' World Health Organization, to which the Department of State is the United States' diplomatic liaison.⁸ HHS also laid out its intent to support the development of new influenza vaccines using alternative technologies that could help achieve this goal. DOD plays an active role in pandemic influenza preparedness in order to maintain the military's readiness and ongoing military operations abroad, such as stockpiling antiviral drugs for use during a pandemic and developing other countermeasures.⁹ In addition to ensuring the military's readiness, DOD's pandemic preparedness goals include being able to support U.S. government efforts to save lives, reduce human suffering, and slow the spread of infection.¹⁰

Challenges in the production of 2009 H1N1 pandemic vaccines caused fewer doses of vaccine to be available early in the pandemic than manufacturers had initially estimated; this heightened interest in the status of vaccine technologies that provide alternatives to egg-based technology. Egg-based technology is used to make all influenza vaccine currently licensed for the U.S. market by the Food and Drug Administration (FDA), the agency within HHS responsible for licensing and regulating influenza

⁷According to HHS, there was an overabundance of 2009 H1N1 pandemic vaccine available 6 months after the declaration of the 2009 H1N1 pandemic. However, some experts we spoke with noted that the egg-based technology currently used to make influenza vaccine and the limited U.S. production capacity hindered the delivery of the 2009 H1N1 pandemic vaccine during the pandemic's peak—the time when it was most needed and in greatest demand. According to CDC, the first wave of the 2009 H1N1 pandemic peaked in the United States in May and June, with a second wave peaking in October 2009. Additionally, one federal report on influenza vaccine research and development from a presidential advisory committee noted that the pandemic vaccine continued to be unavailable in sufficient quantities during the second wave of the pandemic that began in August 2009. In fact, first doses of the 2009 H1N1 pandemic vaccine did not become available until early October 2009.

⁸As part of its overall mission to protect public health, the United Nations' World Health Organization is the international entity that monitors global influenza outbreaks and declares pandemics based on the pattern of outbreaks in its regions. The *National Strategy for Pandemic Influenza* assigned the lead for the U.S. government's diplomatic role in international efforts to address a pandemic influenza to the Department of State.

⁹The vulnerability of the U.S. armed forces to an influenza pandemic was demonstrated during World War I when at least 43,000 U.S. servicemembers died—about half of all the deaths of U.S. servicemembers during World War I—because of influenza or influenza-related complications, and another 1 million servicemembers were hospitalized.

¹⁰DOD, Office of the Assistant Secretary of Defense, *Department of Defense Implementation Plan for Pandemic Influenza* (Washington, D.C., 2006).

vaccines for the U.S. market. It is a well-established technology that has been in use for decades; however, it has demonstrated certain limitations in speed and efficiency in producing influenza vaccine as evidenced in the delay in producing the 2009 H1N1 pandemic vaccine supply. Given the limitations of egg-based technology and the vulnerability of chicken flocks to infectious diseases, the federal government has funded the development of alternative technologies that can be used to produce new influenza vaccines. Vaccines produced using these alternative technologies may be used during the annual influenza season or during a pandemic in order to respond faster or to create a greater supply than is possible with the current technology and production capacity. New influenza vaccines using alternative technologies are being pursued by influenza vaccine manufacturers that have egg-based influenza vaccines currently licensed for marketing and distribution in the United States or internationally, as well as by manufacturers that currently only have products in development. No influenza vaccines using alternative technologies have yet been licensed in the United States.

You asked us to review the federal government's actions regarding the research and development of alternative technologies that can be used in producing new influenza vaccines. In this report, we examine (1) federal funding from fiscal year 2005 through March 2011 in alternative technologies that can be used in producing influenza vaccines and the status of manufacturers' efforts, (2) the challenges identified by stakeholders to the development and licensure of influenza vaccines using alternative technologies, and (3) how HHS is addressing challenges to the development and licensure of influenza vaccines using alternative technologies.

To examine federal funding from fiscal year 2005 through March 2011 in alternative technologies that can be used in producing influenza vaccines and the status of manufacturers' efforts, we reviewed documents pertaining to HHS's and DOD's funding for this purpose. According to HHS, HHS's and DOD's funding represents virtually all of the federal government's investment in this type of research and development. We reviewed documents from HHS on its funding from fiscal year 2005 through March 2011. These documents included semiannual reports prepared by HHS that were submitted to Congress on the department's contracts to develop influenza vaccines using alternative technologies. We also interviewed HHS officials who oversee contracts with manufacturers to assist with the research and development of influenza vaccine for the federal government. We reviewed HHS's proposals for funding the research and development of these technologies and interviewed HHS

budget officials to discuss and clarify the department's efforts. Additionally, we reviewed information from DOD on its technology investment agreements from fiscal year 2005 through fiscal year 2010. We interviewed DOD officials on the department's support of alternative technologies and the status of these development efforts. To assess the reliability of HHS's contracting data, we reviewed published data across multiple years to ensure relative consistency and interviewed knowledgeable officials to clarify questions regarding the department's funding. For DOD, we compared data on its funding provided by different sources within the department. We also asked officials about its data sources and how the department validates its data. Although we did not independently verify the information provided by HHS or DOD, based on our reviews of the data and interviews with federal officials, we concluded that these data were sufficiently reliable for the purposes of our work. Additionally, to better understand these technologies we conducted site visits to three influenza vaccine manufacturing facilities, each utilizing a different production technology, and attended national conferences on influenza vaccine research and development.

To examine challenges to the development and licensure of influenza vaccines using alternative technologies, we interviewed a judgmental sample of stakeholders, which included representatives from industry associations and manufacturers and other experts. Specifically, we interviewed 15 representatives of the vaccine industry, including those from three associations that represent pharmaceutical manufacturers—the Biotechnology Industry Organization, the International Federation of Pharmaceutical Manufacturers & Associations, and the Pharmaceutical Research and Manufacturers of America. We also interviewed officials representing 12 vaccine manufacturers—which included those manufacturers pursuing the research and development of influenza vaccines using alternative technologies, as well as those that have chosen to forgo such research and development—about the factors influencing their decisions. Of these 12 manufacturers, 8 have received funding from HHS to pursue the research and development of influenza vaccines using alternative technologies, and 1 received funds from DOD. Additionally, we interviewed a judgmental sample of 12 other experts in vaccine technology on challenges to research and development and licensure. We selected these other experts, in part, based on recommendations from an initial round of interviews with members of associations representing researchers and scientists, such as the American Society for Microbiology and the Infectious Disease Society of America. Other experts we interviewed included those from provider groups—specifically the American Academy of Pediatrics, the American Congress of Obstetricians

and Gynecologists, and the American Medical Association. We interviewed representatives from these provider groups about the public's and providers' concerns about influenza vaccine safety and their understanding of alternative technologies. We also reviewed peer-reviewed journal articles and federal reports on challenges to the development and licensure of influenza vaccines using alternative technologies, including HHS's medical countermeasure review and the President's Council of Advisors on Science and Technology's (PCAST) report on influenza vaccine production.¹¹ We also interviewed officials representing manufacturers with influenza vaccines licensed for use in other countries and officials from the Department of State, the diplomatic liaison to the United Nations' World Health Organization—the international body that declares worldwide pandemics.

To examine how HHS is addressing challenges to the development and licensure of influenza vaccines using alternative technologies, we interviewed HHS officials on their assessments of challenges to research, development, and licensure identified by stakeholders. We also interviewed HHS officials on their efforts to address these challenges, including plans to use funds available for this purpose. Additionally, we reviewed federal documents, such as a report by FDA on its plans to improve its oversight of new products, including influenza vaccines using alternative technologies.¹²

We conducted this performance audit from March 2010 through June 2011 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings based on our audit objectives.

¹¹HHS, *The Public Health Emergency Medical Countermeasures Enterprise Review* (Washington, D.C., 2010), and PCAST, *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (Washington, D.C., 2010).

¹²FDA, *A Framework for FDA's Regulatory Science Initiative: Advancing Regulatory Science for Public Health* (Washington, D.C., 2010).

Background

Influenza is a contagious respiratory illness caused by a number of different influenza virus strains and can range in severity from mild to lethal.¹³ Symptoms can include cough, muscle or body aches, and fatigue. Vaccination is the primary method for preventing infection with strains of the influenza virus and controlling the disease.¹⁴ In order for a vaccine to be most effective, it needs enough well-matched antigen to stimulate a protective immune response, antigen being the active substance in a vaccine that provides immunity by causing the body to produce protective antibodies to fight off a particular influenza strain.¹⁵ The vaccine's antigen needs to be derived from a strain that is well-matched to a specific influenza strain—in wide circulation in humans—so that the antibodies formed in response to the vaccine protect against infection from that strain. Because multiple influenza strains are in constant circulation, seasonal vaccine is produced and administered annually to protect against the three influenza strains expected to be most prevalent that year (i.e., a trivalent vaccine). In contrast, the 2009 H1N1 pandemic vaccine was formulated to match the single pandemic-causing strain (i.e., a monovalent vaccine).

¹³There are three types of influenza viruses: A, B, and C. However, only influenza A viruses cause pandemics. Influenza A viruses are further categorized into subtypes according to differences in the outer surfaces of the virus. These influenza A subtypes are further characterized into strains, which can mutate, or change genetically, over time. Small mutations result in seasonal or common influenza; more substantial changes can result in a pandemic.

¹⁴Vaccination is one part of a multilayered prevention strategy against influenza that also includes treatment with antiviral drugs and nonpharmaceutical countermeasures, such as regular hand washing and social distancing actions.

¹⁵Antibodies are molecules produced by the immune system that help fight infections.

Federal Government's Role in the Research and Development of Alternative Technologies and the Licensure and Regulation of Influenza Vaccines

Within the federal government, HHS is the department responsible for leading and coordinating preparedness and medical response activities to public health emergencies, per the 2006 Pandemic and All-Hazards Preparedness Act.¹⁶ Additionally, as the principal department for protecting the public's health, HHS is the primary department funding the research and development of influenza vaccines. HHS enters into contracts with manufacturers for the development of new influenza vaccines using alternative technologies.¹⁷ DOD also makes some investments through its technology investment agreements for the research and development of alternative technologies that can be used in producing influenza vaccine as part of its preparedness efforts in order to maintain the military's readiness.¹⁸ Manufacturers with which these agencies have entered into contracts or technology investment agreements include large-scale influenza vaccine manufacturers that have vaccines licensed for use in the United States and internationally as well as manufacturers that currently only have vaccines in research and development. Influenza vaccines—both seasonal and pandemic—are biological products. Within HHS, FDA is the federal agency responsible for the licensure and regulation of biological products for use in the U.S. market (see app. I for additional information on the research and development and review of licensing applications for new influenza vaccines in the United States). These responsibilities include issuing

¹⁶Pub. L. No. 109-417, § 101, 120 Stat. 2831, 2832. Public health emergencies may include influenza pandemics.

¹⁷According to HHS, the National Institutes of Health (NIH) has a history of supporting the research and development of alternative technologies for use in producing influenza vaccine. For example, as early as 2000, NIH awarded \$4.93 million in grants to three manufacturers for the research and development of influenza vaccines using alternative technologies. In addition to supporting the testing of influenza vaccines using alternative technologies in preclinical studies in animals and clinical trials, NIH has supported many collaborative projects with academia and industry. These projects have an emphasis on applied research and early stage assessment of new and improved technologies for influenza vaccines, such as the use of adjuvants, and evaluating alternative vaccine technologies, such as recombinant technology. According to NIH officials, the agency's efforts are intended to further scientific knowledge and to provide services and expertise to enable the translation of new technological ideas into products which benefit public health.

¹⁸The Defense Advanced Research Projects Agency within DOD enters into and funds these technology investment agreements. A technology investment agreement is a type of financial assistance instrument meant to increase the involvement of commercial firms in the department's research, development, and demonstration programs. Technology investment agreements are not considered contracts, cooperative agreements, or grants. See 10 U.S.C. § 2371(a).

guidance for existing and new vaccines and consulting with manufacturers on the development of their new vaccines, such as on how manufacturers conduct clinical trials required for licensure of new vaccines.¹⁹ Until FDA has approved its licensing application, no manufacturer can market its biological product in the United States.²⁰ Table 1 summarizes the federal government's role in the research and development of alternative technologies and the licensure and regulation of influenza vaccines.

¹⁹Clinical trials are used to test the safety and efficacy of potential treatments in human volunteers. They occur in multiple phases, which vary based on the size and objective of the study. Studies range in size from a small number of closely monitored volunteers to thousands of volunteers. In most cases, before clinical trials can be conducted in human volunteers, researchers conduct preclinical studies in animals.

²⁰However, after the HHS Secretary declares a public health emergency and under certain circumstances, FDA, as delegated by the HHS Secretary, may authorize the emergency use of licensed pharmaceutical products, such as vaccines, for unapproved uses or the emergency use of unlicensed pharmaceutical products through emergency use authorizations. *See* 21 U.S.C. § 360bbb-3.

Table 1: Federal Government’s Role in the Research and Development of Alternative Technologies and the Licensure and Regulation of Influenza Vaccines

Department	Agency
Department of Health and Human Services (HHS)	• The Biomedical Advanced Research and Development Authority within the Office of the Assistant Secretary for Preparedness and Response contracts with manufacturers for influenza vaccine research and development with the goal of manufacturers submitting licensing applications to the Food and Drug Administration (FDA) for new vaccines and establishing domestic production capacity for these new vaccines. • The National Institutes of Health supports the research and development of vaccines using alternative technologies through various activities, including conducting basic and clinical research. • FDA is responsible for the licensure and regulation of influenza vaccine—including the approval of facilities in which influenza vaccine is produced—for the U.S. market. Its responsibilities include issuing guidance for new and existing vaccines and consulting with manufacturers on the development of their new vaccines. Until FDA has approved its licensing application, no manufacturer can market its influenza vaccine in the United States.^a Once FDA issues a license for an influenza vaccine, it continues to regulate the vaccine's production and use. For example, FDA must review and approve the seasonal vaccine annually because the influenza strains included in it frequently change from one year to the next.^b
Department of Defense (DOD)	• The Defense Advanced Research Projects Agency within DOD funds programs focused on unique and innovative research and development efforts—including the early stage research and development of alternative technologies that can be used in producing influenza vaccines—and that accelerate the discovery and research and development of medical countermeasures, in part, through the use of novel technologies.^c

Source: GAO analysis of HHS and DOD documents.

^aAfter the HHS Secretary declares a public health emergency and under certain circumstances, FDA, as delegated by the HHS Secretary, may authorize the emergency use of licensed pharmaceutical products, such as vaccines, for unapproved uses or the emergency use of unlicensed pharmaceutical products through emergency use authorizations. See 21 U.S.C. § 360bbb-3.

^bEach manufacturer of a U.S.-licensed influenza vaccine annually submits a supplement to its initial licensing application, noting the new influenza strains selected for a given influenza season. This same process of submitting a supplement to an existing, approved licensing application was used in the licensure of vaccine for use in the United States for the 2009 H1N1 pandemic.

^cMedical countermeasures are drugs, biological products, or devices that treat, identify, or prevent harm from a biological or other agent that may cause a public health emergency. Medical countermeasures for use during an influenza pandemic may include vaccine, antiviral drugs, personal respirators, and influenza diagnostic tests. Antiviral drugs are medications that can prevent or reduce the severity of a viral infection, such as influenza. This report focuses on influenza vaccine.

HHS Efforts to Enhance Domestic Production Capacity to Expand the Supply or Accelerate the Availability of Influenza Vaccine

Given its responsibilities for national seasonal influenza and pandemic preparedness and response, HHS has an interest in enhancing domestic production capacity—that is, enhancing the nation’s overall infrastructure for influenza vaccine production—and expanding the supply or accelerating the availability of influenza vaccine. HHS began awarding contracts to enhance domestic production capacity for the current egg-based technology as early as fiscal year 2005.²¹ Since fiscal year 2005, HHS has supported a program to ensure a year-round, secure, domestic egg supply; prior to this funding, manufacturers maintained a 9-month supply of eggs—enough for production only during the influenza season without any additional capacity for emergencies, such as an influenza pandemic.

Despite HHS’s initial efforts to maintain a year-round egg supply, other events have occurred that highlighted the need for HHS to increase domestic production capacity for influenza vaccine and to support the introduction of influenza vaccines produced using alternative technologies. First was the unexpected loss of almost half of the influenza vaccine supply because of potential contamination during the 2004–05 season and the reliance on two domestic influenza vaccine manufacturers to supply enough vaccine for that year.²² Second was the recognition by HHS that one of the greatest challenges to preparing for an influenza pandemic and implementing its strategy for using vaccines was the lack of production capacity within the United States. As we noted in prior work, the lack of U.S. production capacity is cause for concern among experts because it is possible that countries without domestic production capacity will not have access to influenza vaccine in the event of a pandemic if countries where vaccine is produced prohibit the export of the pandemic vaccine until their own needs are met.²³ As a result, HHS continued its funding of egg-based technology for the production of influenza vaccine to enhance domestic production capacity using this technology. For

²¹Egg-based technology is a complex process that involves growing seed strains in millions of fertilized chicken eggs. This process involves a sequence of steps that can take approximately 4 to 5 months to complete. Egg-based technology is used to produce both seasonal and pandemic influenza vaccines for the U.S. market.

²²GAO, *Influenza Vaccine: Shortages in 2004–05 Season Underscore Need for Better Preparation*, [GAO-05-984](#) (Washington, D.C.: Sept. 30, 2005), 1.

²³GAO, *Influenza Pandemic: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic*, [GAO-08-92](#) (Washington, D.C.: Dec. 21, 2007), 26. This situation occurred during the 2009 H1N1 pandemic when CSL Biotherapies in Australia and GlaxoSmithKline, plc in Canada were required to fulfill their domestic orders for the pandemic vaccine prior to releasing vaccine to the United States.

example, in fiscal year 2007, HHS entered into contracts with two manufacturers for the retrofitting of existing domestic egg-based production facilities for the production of pandemic influenza vaccine. Some of the completed facilities were used in the 2009 H1N1 pandemic, and according to HHS, when all the retrofitting is complete, one of these facility's production capacity will double and the other will triple. Third, concerns about strains of the H5N1 virus that had reemerged in the early 2000s, and continues to cause severe infection in humans, further prompted interest in alternative technologies to egg-based technology for producing influenza vaccine.²⁴ Strains of the H5N1 virus have infected chicken flocks and other poultry, resulting in the culling of these flocks, raising concern that the egg supply for influenza vaccine was at risk. Thus, HHS began a more concerted effort to fund the research and development of influenza vaccines using three alternative technologies. Specifically, HHS has funded the development of vaccines using two alternative production technologies—cell-based and recombinant technologies—and vaccines using a third alternative technology—antigen-sparing technology (adjuvants).

Each of these three alternative technologies has the potential to expand the supply or accelerate the availability of both seasonal and pandemic influenza vaccines (see app. II for a description of the production process for influenza vaccine using the current, egg-based technology). Expanding the supply or accelerating the availability of influenza vaccine is particularly important when there is a perceived shortage of seasonal vaccine—when vaccine is not available and demand is highest—or during a pandemic when demand increases because of increased risk of disease and death. Expanding the supply or accelerating the availability of influenza vaccine can be done in two ways. The first is to increase the overall amount of vaccine available at the end of the production process; the second is to speed up the production process itself by, for example, reducing or eliminating step(s) in the process. Table 2 describes these three alternative technologies and their potential to expand the supply or accelerate the availability of influenza vaccines (see app. III for more information on these alternative technologies).

²⁴Human infections from strains of the H5N1 virus first occurred in 1997 in Hong Kong, Special Administrative Region.

Table 2: Alternative Technologies and Their Potential to Expand the Supply or Accelerate the Availability of Influenza Vaccine

Alternative technologies	Description of technology	Potential expansion of the supply or acceleration of the availability of influenza vaccine	
		Increase the overall amount of vaccine available	Speed up the production process
Cell-based technology	An alternative production technology, cell-based technology involves a production process similar to egg-based technology. For example, as with egg-based technology, the vaccine's antigen—that is, the active substance of the vaccine that stimulates a protective immune response—is produced from the influenza virus. However, rather than using fertilized eggs as the medium for producing the influenza vaccine, cell-based technology typically uses cells infected with the influenza virus for the production of vaccine. This technology for influenza vaccines typically relies on the use of well-established cell lines, such as those originally derived from the kidney cells of monkeys or canines.	X	
Recombinant technology ^a	A second type of alternative production technology, recombinant technology uses specific protein(s) or genes from the influenza virus instead of the entire virus, as used in egg-based and cell-based technologies, as the antigen for the vaccine. This technology can use cells from mammals as the medium for producing the influenza vaccine as well as cells from other sources, such as from bacteria, yeast, insects, or plants.	X	X
Adjuvants ^b	A type of antigen-sparing technology, adjuvants are substances that may be added to an influenza vaccine to enhance the immune response, resulting in a dose-sparing capability because less antigen is needed per dose to stimulate a protective immune response. This technology can be included with influenza vaccines made using different production technologies, such as egg-based, cell-based, or recombinant technology.	X	

Source: GAO analysis of President's Council of Advisors on Science and Technology report.

^aThe Department of Health and Human Services (HHS) refers to this technology as recombinant/molecular technology. According to HHS, this technology is also used for researching and developing a universal influenza vaccine. The National Institutes of Health, which is conducting research on a universal vaccine, defines it as a vaccine that would theoretically provide protection against any strain of influenza without needing to be updated or administered every year to protect against newly emerging annual or pandemic strains.

^bIn this report, we are referring to adjuvants made using a combination of oil and water; there are different types of adjuvants that can be used with vaccines.

HHS Funding for the Development of Influenza Vaccines Using Alternative Technologies

In fiscal year 2005, with funds available from that year's appropriation, HHS funded the research and development of an influenza vaccine produced using cell-based technology.²⁵ Following the release of the Plan, numerous additional appropriations became available for the acquisition and development of pharmaceutical interventions for pandemic-related purposes, including approximately \$3.2 billion dedicated for vaccines.²⁶ HHS has since used these funds, as well as funds available from previous appropriations, for multiyear contracts for the development of influenza vaccine using cell-based technology, recombinant technology, and adjuvants. In response to the 2009 H1N1 pandemic, Congress provided HHS with a supplemental appropriation to prepare for and respond to an influenza pandemic.²⁷ In addition to making \$1.85 billion immediately available to HHS, the 2009 supplemental appropriation made \$5.8 billion available contingent upon one or more presidential notifications to Congress.²⁸ In August 2010, after the 2009 H1N1 pandemic had ended, HHS notified Congress of its plan to direct some of the remaining funds toward pandemic and related preparedness activities. Specifically, HHS proposed spending \$1.98 billion in a variety of vaccine-related activities, including the development of alternative technologies, such as recombinant technology.²⁹ According to HHS, it also uses funding available from annual

²⁵See Consolidated Appropriations Act, 2005, Pub. L. No. 108-447, 118 Stat. 2809, 3112, 3138. During this fiscal year, other appropriations were also available for the acquisition and development of pharmaceutical interventions for pandemic-related purposes, including vaccines. See Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, 118 Stat. 3, 251, and Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief 2005, Pub. L. No. 109-13, 119 Stat. 231, 276, 280. Many of these appropriations are available without fiscal year limitation.

²⁶See Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-149, 119 Stat. 2833, 2857; Department of Defense, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006, Pub. L. No. 109-148, 119 Stat. 2680, 2783, 2786; Emergency Supplemental Appropriations Act for Defense, the Global War on Terror and Hurricane Recovery, 2006, Pub. L. No. 109-234, 120 Stat. 479; and Revised Continuing Appropriations Resolution, 2007, Pub. L. No. 110-5, 121 Stat. 8, 33. Many of these appropriations are available without fiscal year limitation.

²⁷Supplemental Appropriations Act, 2009, Pub. L. No. 111-32, 123 Stat. 1859, 1884-86.

²⁸Each such presidential notification must designate amounts as emergency funds required to address critical needs related to emerging influenza viruses.

²⁹HHS, *Amended Spending Plan for 2009 Supplemental Funding* (Washington, D.C., 2010), as reported to Congress in August 2010. According to HHS, the amended spending plan will provide funding for further development of medical countermeasures as recommended in *The Public Health Emergency Medical Countermeasures Review*.

appropriations, such as its fiscal year appropriations for 2009 and 2010, for pandemic-related activities.³⁰

The Federal Government Has Provided about \$2.1 Billion in Funding for the Development of Alternative Technologies that Can Be Used in Producing Influenza Vaccines, and Manufacturers Are Demonstrating Progress Toward Licensure

From fiscal year 2005 through March 2011, the federal government awarded approximately \$2.1 billion in contracts and technology investment agreements for the research and development of cell-based and recombinant technologies and adjuvants, which can be used in producing influenza vaccines. Manufacturers are demonstrating progress toward licensure.

³⁰ See Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2009, Pub. L. No. 111-8, 123 Stat. 524, 779, and Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2009, Pub. L. No. 111-117, 123 Stat. 3034, 3255. Portions of these appropriations are available without fiscal year limitation.

HHS Has Primarily Funded the Development of Cell-Based Technology, with Two Manufacturers Completing Clinical Trials and One Manufacturer Constructing a Domestic Facility

In fiscal year 2005, HHS awarded the most funding through contracts to manufacturers to develop cell-based technology.³¹ With these funds, two manufacturers are demonstrating progress toward licensure of a vaccine by completing clinical trials required to file for licensure with FDA, and one of these two manufacturers has also constructed a domestic cell-based influenza vaccine facility. HHS awarded contracts to six manufacturers—one manufacturer in fiscal year 2005 and five manufacturers in fiscal year 2006—worth a total of approximately \$1 billion for the development of an influenza vaccine produced using cell-based technology (see table 3). According to HHS, it awarded multiple contracts because it expected some attrition by manufacturers as the development of new influenza vaccines progressed. Cell-based technology has the potential to increase the overall amount of vaccine available at the end of the production process. As of March 2011, two of the manufacturers to which HHS had awarded contracts—DynPort Vaccine Company LLC (with Baxter International Inc.) (DynPort/Baxter)³² and Novartis Vaccines and Diagnostics Inc. (Novartis Vaccines)—have completed clinical trials required to file for licensure with FDA. While Novartis Vaccines anticipates submitting a licensing application for its seasonal influenza vaccine using cell-based technology to FDA in 2011, DynPort/Baxter anticipates submitting its licensing application to FDA in 2012. Additionally, GlaxoSmithKline plc (GlaxoSmithKline) is currently conducting clinical trials with its adjuvanted cell-based pandemic influenza vaccine, and MedImmune, LLC is conducting preclinical studies in animals on its cell-based pandemic influenza vaccine. The remaining two contracts with sanofi pasteur³³ and Solvay Pharmaceuticals were terminated by HHS.

³¹According to HHS, the required criteria for manufacturers to receive this funding were (1) develop cell-based influenza vaccine technology, (2) obtain FDA licensure of cell-based influenza vaccine, and (3) construct a domestic cell-based influenza vaccine facility.

³²HHS contracted with DynPort Vaccine Company LLC (DynPort), which collaborated with Baxter International Inc. (Baxter) to develop a seasonal and a pandemic influenza vaccine using cell-based technology. Baxter oversaw the development of the vaccine, including supporting licensure efforts for the seasonal vaccine. Baxter also oversaw the completion of clinical trials for the pandemic vaccine. DynPort managed the overall project as well as clinical trials. For the purposes of this report, we refer to this contract as DynPort/Baxter because of the collaboration between the two manufacturers.

³³The policy of sanofi pasteur is to spell its name without capital letters.

Table 3: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of Cell-Based Influenza Vaccine, Fiscal Year 2005 through March 2011

Manufacturer	Fiscal year of award	Total obligations (in millions) ^a	Development status as of March 2011
sanofi pasteur ^b	2005	\$77.0 ^c	The manufacturer concluded that cell-based technology was not more advantageous than egg-based technology, lacked a clear path for further development, and thus chose to forgo pursuit of cell-based technology. According to HHS, it terminated this contract for the development of a cell-based influenza vaccine.
GlaxoSmithKline	2006	274.8	The manufacturer completed early-stage clinical trials of its cell-based seasonal influenza vaccine in 2009 and is currently conducting early-stage clinical trials of its cell-based, adjuvanted pandemic influenza vaccine.
Novartis Vaccines	2006	220.5	The manufacturer completed clinical trials required to file for licensure and anticipates resubmitting a licensing application for its cell-based seasonal influenza vaccine to the Food and Drug Administration (FDA) in 2011. ^d
DynPort/Baxter ^e	2006	242.3 ^f	The manufacturer completed clinical trials required to file for licensure and anticipates submitting a licensing application for its cell-based seasonal influenza vaccine to FDA in 2012.
MedImmune, LLC	2006	169.5	As directed by HHS, the manufacturer halted development of its cell-based seasonal and pandemic influenza vaccine in March 2009. The manufacturer resumed development of its cell-based pandemic influenza vaccine in June 2010 and is conducting preclinical studies in animals.
Solvay Pharmaceuticals ^g	2006	48.6 ^h	The manufacturer discontinued plans for the construction of a cell-based influenza vaccine production facility in the United States because of lack of commercial viability. HHS terminated the contract for the development of a cell-based influenza vaccine in June 2009.
Total		\$1032.7	

Source: GAO analysis of HHS and manufacturer data.

^aObligations are definite commitments that establish the legal liability of a federal agency to make payments for goods or services ordered or received, immediately or in the future. Because payments are typically made as goods or services are received, the funds listed may not have been expended. Upon termination of a contract, unexpended funds may be deobligated and, depending on the terms of their appropriation, may remain available to the agency.

^bThe policy of sanofi pasteur is to spell its name without capital letters.

^cThis amount reflects a \$20 million deobligation in fiscal year 2009. A deobligation refers to the cancellation or downward adjustment of previously incurred obligations.

^dAccording to Novartis Vaccines, it submitted a licensing application for its cell-based seasonal influenza vaccine to FDA in April 2009. However, in agreement with FDA, Novartis Vaccines subsequently withdrew the application in order to incorporate efficacy data at FDA's request.

^eHHS contracted with DynPort Vaccine Company LLC (DynPort), which collaborated with Baxter International Inc., (Baxter) to develop a seasonal and a pandemic influenza vaccine using cell-based technology. Baxter oversaw the development of the vaccine, including supporting licensure efforts for the seasonal vaccine. Baxter also oversaw the completion of clinical trials for the pandemic vaccine. DynPort managed the overall project as well as clinical trials. For the purposes of this report, we refer to this contract as DynPort/Baxter because of the collaboration between the two manufacturers.

^fThis amount includes a modification of \$201.3 million made in fiscal year 2007 to the existing contract. The original contract was awarded for \$41 million.

^gAbbott Laboratories purchased Solvay Pharmaceuticals in February 2010.

^hThis amount reflects a \$250 million deobligation in fiscal year 2009.

In addition to the six contracts awarded for the research and development of cell-based influenza vaccine, HHS also entered into a \$486.6 million contract with Novartis Vaccines in fiscal year 2009 for the construction of a cell-based influenza vaccine production facility in the United States to enhance domestic production capacity.³⁴ According to HHS, Novartis Vaccines completed construction of this facility in November 2009 and will have qualified the facility for producing pandemic vaccine using cell-based technology, if needed, by the end of 2011. HHS expects the new facility to provide at least 25 percent of the needed domestic production capacity for pandemic vaccine. This facility also has the capacity to produce seasonal and adjuvanted influenza vaccine as well as other biological products that use this technology for other infectious diseases.

HHS and DOD Have Funded the Research and Development of Recombinant Technology, and One Manufacturer Has Submitted a Licensing Application to FDA

In fiscal year 2009, HHS awarded contracts to manufacturers for the research and development of recombinant technology. Recombinant technology has the potential to increase the overall amount of vaccine available at the end of the production process and speed up the production process itself, in part, because unlike egg-based and cell-based technologies, it does not depend on the replication of the influenza virus for production. In fiscal year 2009, HHS entered into a \$34.5 million contract with Protein Sciences Corporation (Protein Sciences) for the continued development of recombinant technology for use in producing an influenza vaccine. According to HHS, if Protein Sciences' recombinant, seasonal influenza vaccine is shown to be safe and effective through clinical trials, the contract requires the company to establish enough domestic manufacturing capacity to provide finished vaccine within 12 weeks of the beginning of a pandemic and to produce at least 50 million doses of pandemic vaccine within 6 months of the beginning of a pandemic.³⁵ In May 2011, HHS extended its contract with Protein Sciences for 2 years with \$46.8 million of additional funding.

³⁴According to HHS, HHS and Novartis Vaccines shared the cost of the construction of the new production facility, with HHS funding approximately 40 percent of the total cost and Novartis Vaccines funding the remaining 60 percent.

³⁵In April 2008, prior to entering into this contract with HHS, Protein Sciences submitted a licensing application to FDA for its seasonal recombinant influenza vaccine which, as of March 2011, was still under review. According to a Protein Sciences official, FDA is expected to complete its review this year.

In February 2011, HHS awarded two additional contracts for the research and development of pandemic influenza vaccines using recombinant technology. HHS awarded contracts to Novavax, Inc. (Novavax) for \$97.3 million and VaxInnate, Inc. (VaxInnate) for \$117.9 million each for a 3-year period. According to HHS, if the manufacturer and department mutually agree, each respective contract may be extended for an additional 2-year period, resulting in contract amounts totaling \$179.1 million for Novavax and \$196.6 million for VaxInnate (see table 4).

Table 4: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of Recombinant Influenza Vaccine, Fiscal Year 2009 through March 2011

Manufacturer	Fiscal year of award	Total obligations (in millions) ^a	Development status as of March 2011
Protein Sciences	2009, 2011	\$81.3	According to HHS, the contract requires Protein Sciences to establish enough domestic manufacturing capacity to provide finished vaccine within 12 weeks of the beginning of a pandemic and to produce at least 50 million doses of pandemic vaccine within 6 months of the beginning of a pandemic.
Novavax	2011	97.3	According to HHS, the manufacturer is currently designing the clinical trials for its recombinant pandemic influenza vaccine.
VaxInnate	2011	117.9	According to HHS, the manufacturer is currently designing the clinical trials for its recombinant, pandemic influenza vaccine.
Total		\$296.5	

Source: GAO analysis of HHS data.

^aObligations are definite commitments that establish the legal liability of a federal agency to make payments for goods or services ordered or received, immediately or in the future. Because payments are typically made as goods or services are received, the funds listed may not have been expended. Upon termination of a contract, unexpended funds may be deobligated and, depending on the terms of their appropriation, may remain available to the agency.

In contrast to HHS's contract awards specifically designated for influenza vaccine described above, DOD's funding efforts have been more generally targeted toward the research and development of technologies that could be used in producing these vaccines. For example, in fiscal year 2010, DOD entered into technology investment agreements with manufacturers and research institutes—totaling approximately \$86.9 million—for the research and development of recombinant technology through a DOD initiative called Blue Angel. The Blue Angel initiative is intended to accelerate ongoing programs that would potentially assist the federal government in providing a governmentwide response to an influenza pandemic.³⁶ Under the Blue Angel initiative, DOD supported the initial

³⁶DOD also provides funding through its Blue Angel initiative to other entities, such as universities and other federal agencies.

testing of a production process using recombinant technology to produce antigen—the active substance in a vaccine that stimulates the production of protective antibodies—using the 2009 H1N1 pandemic strain.³⁷

According to DOD, although the initiative did not result in a finished vaccine, the first batch of antigen was produced within 30 days of receiving information on the pandemic-causing strain.

HHS and DOD Have Also Funded the Research and Development of Adjuvanted Influenza Vaccines, and Two Manufacturers Are Demonstrating Progress toward Licensure

Since fiscal year 2007, HHS has also awarded contracts for the research and development of an adjuvanted influenza vaccine. Adjuvants have the potential to increase the overall amount of vaccine available at the end of the production process by enhancing the immune response, thereby reducing the amount of antigen needed per vaccine dose. Two manufacturers have demonstrated progress toward licensure of their vaccines by completing clinical trials. HHS awarded three contracts totaling \$152 million to GlaxoSmithKline, Novartis Vaccines, and Intercell AG for the research and development of an adjuvanted influenza vaccine (see table 5).³⁸ Of the three manufacturers awarded contracts, GlaxoSmithKline anticipates submitting a licensing application for its adjuvanted egg-based pandemic influenza vaccine to FDA for review in 2011, while Novartis Vaccines anticipates submitting a licensing application for its adjuvanted egg-based seasonal influenza vaccine to FDA for review in 2012. According to HHS, Intercell AG's clinical trials did not achieve the desired result and were ended.

³⁷This testing was done through DOD's Accelerated Manufacture of Pharmaceuticals program, one of the programs included in DOD's Blue Angel initiative. This program focuses on the creation of a production process capable of making 3 million doses of any vaccine, including influenza vaccine, within 12 weeks of identifying a particular microbe. Under this program, DOD entered into contracts with manufacturers totaling approximately \$51.6 million. Because the Accelerated Manufacture of Pharmaceuticals program is not specific to influenza, we did not include it when determining the amount of federal investments made for the research and development of alternative technologies for use in producing influenza vaccines.

³⁸HHS awarded the contract for adjuvant research and development to IOMAI Corporation. Because Intercell AG acquired IOMAI Corporation in August 2008, we refer to Intercell AG.

Table 5: Department of Health and Human Services (HHS) Contracts Awarded to Manufacturers for the Research and Development of an Adjuvanted Influenza Vaccine, Fiscal Year 2007 through March 2011

Manufacturer	Fiscal year of award	Total obligations (in millions) ^a	Development Status as of March 2011
GlaxoSmithKline ^b	2007, 2011	\$70.2	The manufacturer completed clinical trials and anticipates submitting a licensing application to the Food and Drug Administration (FDA) for its adjuvanted egg-based pandemic influenza vaccine in 2011.
Novartis Vaccines ^b	2007	54.8	The manufacturer completed clinical trials and anticipates submitting a licensing application to FDA for its adjuvanted egg-based seasonal influenza vaccine in 2012.
Intercell AG ^c	2007	27	According to HHS, the manufacturer's clinical trials did not achieve the desired result and were ended.
Total		\$152	

Source: GAO analysis of HHS and manufacturer data.

^aObligations are definite commitments that establish the legal liability of a federal agency to make payments for goods or services ordered or received, immediately or in the future. Because payments are typically made as goods or services are received, the funds listed may not have been expended. Upon termination of a contract, unexpended funds may be deobligated and, depending on the terms of their appropriation, may remain available to the agency.

^bThese manufacturers also have an adjuvanted cell-based pandemic influenza vaccine under development.

^cHHS originally awarded the contract for adjuvant research and development to IOMAI Corporation. Because Intercell AG acquired IOMAI Corporation in August 2008, we refer to Intercell AG.

In addition to its awards through contracts with manufacturers, HHS also provided \$4 million in funding to the National Institutes of Health (NIH)—an agency within HHS—for H5N1 “mix-and-match” studies starting in March 2008.³⁹ According to HHS, these studies are designed to determine whether the adjuvant from one manufacturer can be safely and effectively combined with the antigen from another manufacturer in the case of a public health emergency, such as an influenza pandemic.⁴⁰ The ability to combine the antigen from one manufacturer with the adjuvant from

³⁹The Biomedical Advanced Research and Development Authority within HHS’s Office of the Assistant Secretary for Preparedness and Response provided this funding through an interagency agreement with NIH for the mix-and-match studies. The Biomedical Advanced Research and Development Authority coordinates the development and procurement of medical countermeasures for public health emergencies. The National Institute of Allergy and Infectious Diseases, within NIH, is conducting this research. This institute also supports other research related to influenza, including providing research resources to help develop influenza vaccine candidates and supporting projects focusing on routes of vaccine administration.

⁴⁰Typically, the same manufacturer produces both the antigen and the adjuvant to be used together in the vaccine.

another manufacturer could increase the overall vaccine supply during a pandemic. The preliminary preclinical studies in animals with a H5N1 vaccine were completed in early 2009 in preparation for clinical testing by NIH. However, NIH delayed its work on the H5N1 vaccine to conduct clinical trials testing the unadjuvanted and mix-and-match 2009 H1N1 pandemic vaccine as part of HHS's response to the pandemic. According to NIH officials we spoke with, NIH resumed work on the H5N1 mix-and-match studies in May 2011; officials anticipate completing clinical trials for these studies in 2012.

DOD has also funded the development of adjuvants for use with influenza vaccine. In fiscal year 2009, DOD entered into a technology investment agreement for \$3.3 million with the Infectious Disease Research Institute. According to DOD, the department is currently awaiting the results of completed animal studies using an adjuvanted vaccine.

Some Stakeholders Identified Challenges to the Development and Licensure of Influenza Vaccines Using Alternative Technologies

Some stakeholders and federal reports identified three primary challenges to the development and licensure of influenza vaccines using alternative technologies: low demand, high research and development costs, and regulatory challenges.

Some Stakeholders Said Low Demand Hinders the Development of Influenza Vaccines Using Alternative Technologies

Some stakeholders told us that low demand because of low vaccination rates hinders manufacturers' willingness to develop seasonal influenza vaccines using alternative technologies.⁴¹ According to CDC, during the 2009–10 influenza season, national vaccination rates reached an estimated 41 percent of the population aged 6 months or older for the seasonal vaccine, and an estimated 27 percent for the separate 2009 H1N1 pandemic

⁴¹The challenge of low demand and subsequent discussions of challenges associated with high research and development costs and regulatory challenges do not refer to times when there is an ongoing pandemic, during which demand may increase because of increased risk of disease and death.

vaccine.⁴² Each influenza season more vaccine is produced than is actually used, even in years where there has been a perceived shortage of influenza vaccine because of challenges in the production process. Data from CDC, FDA, and the American Medical Association confirm that—despite an increase in the total amount of influenza vaccine produced and distributed since at least 2001—more doses of seasonal vaccine are produced than distributed each year, including in years when there were few licensed manufacturers or a perceived vaccine shortage (see table 6). This excess vaccine expires and is destroyed at the season’s end as it will not be useful for the next influenza season, when a new vaccine will need to be formulated using the three influenza strains expected to be most prevalent that year. Additionally, despite the increase in influenza vaccine production and distribution and the United States using more seasonal vaccine than any other country, 5 of 12 manufacturer representatives, 1 of 3 industry association representatives, and 2 of 12 other experts we interviewed said that this low demand decreases incentives for manufacturers to develop new seasonal influenza vaccines using alternative technologies.

⁴²CDC, *Final Estimates for 2009–10 Seasonal Influenza and Influenza A (H1N1) 2009 Monovalent Vaccination Coverage – United States, August 2009 through May 2010* (Atlanta, Ga.: 2010). CDC acknowledges that its survey-based estimates of seasonal vaccination rates for the 2009–10 season are overestimates since the projected number of persons receiving seasonal influenza vaccination exceeds the number of doses distributed in the United States. However, CDC notes that these estimates are consistent with previously published interim estimates.

Table 6: Number of U.S.-Licensed Manufacturers of Seasonal Influenza Vaccine and Number of Doses Produced and Distributed for the 2000–01 through 2010–11 Influenza Seasons

Influenza season	Number of licensed manufacturers	Total number of doses produced (in millions)	Total number of doses distributed (in millions)
2000–01	3	78	70
2001–02	3	88	78
2002–03	3	95	83
2003–04	3	87	83
2004–05	3 ^a	61	57
2005–06	4	92	82
2006–07	5	121	104
2007–08	6	141	113
2008–09	6	143–146	111
2009–10 ^b	6	114–115	114
2010–11 (est.)	6 ^c	160–165	163

Source: GAO analysis of Centers for Disease Control and Prevention, Food and Drug Administration, and American Medical Association data.

Note: Table includes the number of doses produced by manufacturers and distributed to customers, such as medical supply distributors, physicians, or other types of providers.

^aOf the three manufacturers of seasonal influenza vaccine for the 2004–05 influenza season, two produced and distributed vaccine and one ceased production and did not distribute any vaccine for the U.S. market after its license was suspended by the United Kingdom in October 2004. In addition to these three manufacturers, two foreign manufacturers' vaccines were purchased by the Department of Health and Human Services for potential use in the United States under an investigational new drug protocol; however, none of these doses were distributed.

^bIn the 2009–10 season, U.S.-licensed manufacturers also produced the 2009 H1N1 pandemic vaccine, which was purchased exclusively by the federal government for distribution in the United States. According to the Centers for Disease Control Prevention, approximately 147 million doses were available for states to order, and about 119 million were shipped to state-designated locations.

^cThe manufacturers of vaccine licensed for the 2010–11 season and their vaccines (in parentheses) were CSL Biotherapies (Afluria), GlaxoSmithKline plc (Fluarix), ID Biomedical Corporation (FluLaval), MedImmune, LLC (FluMist), Novartis Vaccines and Diagnostics, Inc. (Fluvirin and Agriflu), and sanofi pasteur (Fluzone and Fluzone High-Dose).

Stakeholders told us that there are a number of reasons why demand for seasonal influenza vaccine is low. For example, two experts stated that patients commonly do not view seasonal influenza as a serious disease, and another expert and an industry association representative stated there is a need for more patient education on the safety of influenza vaccine to overcome patient and provider hesitancy. Researchers have also found

that patients and providers have concerns about influenza vaccine.⁴³ One manufacturer representative also noted that the current influenza vaccine is less effective for certain populations, such as the elderly, which also decreases demand. We have previously reported that according to CDC, a recommendation from a physician or other health care provider is the most important factor in an individual's decision to get vaccinated.⁴⁴ Additionally, a recent review of survey data found that health care professionals were cited as one of three most important sources of information in making decisions about children's vaccines by 85 percent of parents surveyed.⁴⁵ CDC has made efforts to encourage providers to recommend vaccination to their patients. However, despite these efforts, available data suggest that getting providers to recommend vaccination for their patients has been difficult.⁴⁶ CDC told us that it is working closely with numerous partners to implement an influenza vaccine communication plan utilizing multiple forms of media to reach the general public as well as specific target populations.

HHS officials acknowledged the challenge of low demand for seasonal influenza vaccine; however, they said manufacturers remain interested in pursuing the development of new influenza vaccines using alternative technologies. For example, according to department officials, manufacturers have more than two dozen influenza vaccines in development, and many of these manufacturers have received funds from HHS.

⁴³For example, see Pritish K. Tosh, Thomas G. Boyce, and Gregory A. Poland, "Flu Myths: Dispelling the Myths Associated with Live Attenuated Influenza Vaccine," *Mayo Clinic Proceedings*, no. 83 (2008): 77-84. Also, see Deborah A. Gust, Natalie Darling, Allison Kennedy, and Ben Schwartz, "Parents with Doubts About Vaccines: Which Vaccines and Why," *Pediatrics*, no. 122 (2008): 718-725.

⁴⁴GAO, *Influenza Vaccine: Issues Related to Production, Distribution, and Public Health Messages*, [GAO-08-27](#) (Washington, D.C.: Oct. 31, 2007), 40.

⁴⁵The other two most important sources for parents cited by respondents were family members (46 percent) and friends (22 percent). Allison Kennedy, Katherine LaVail, Glen Nowak, Michelle Basket, and Sarah Landry, "Confidence about Vaccines in the United States: Understanding Parents' Perceptions," *Health Affairs*, vol. 30, no. 6 (2011): 1151-59.

⁴⁶For example, a 2008 phone survey of adults conducted by the National Foundation for Infectious Diseases found that almost 40 percent of respondents reported that they had never discussed influenza vaccination with their physician or other health care worker. National Foundation for Infectious Diseases, *National Consumer Survey: Doctors and Patients Not Talking Enough About Influenza Vaccination* (Bethesda, Md., September 2008).

Some Stakeholders Said High Research and Development Costs Decrease Incentives for Developing Influenza Vaccines Using Alternative Technologies

Some stakeholders said that high research and development costs required for the development of influenza vaccines can decrease manufacturers' incentives to pursue new influenza vaccines using alternative technologies. Six of the manufacturer representatives we spoke with said that research and development costs are high. Furthermore, five manufacturer representatives we spoke with noted that clinical trials in particular contributed to high research and development costs. For example, a representative for one manufacturer we spoke with noted the significant costs associated with the research and development of its currently licensed egg-based influenza vaccine, estimating that his company has spent \$400 million alone on clinical trials. One small-scale manufacturer conducting clinical trials for a new influenza vaccine using an alternative technology estimated that it spends \$150,000 per day on these trials and other expenses as it moves toward applying for licensure. In addition, PCAST—a presidential advisory council—found in a recent report on influenza vaccine research and development that constructing a cell-based influenza vaccine production facility could cost more than \$1 billion and it could take over 30 years to recover the investment.⁴⁷

Access to capital is important to manufacturers because of these high research and development costs. A manufacturer representative and an industry association representative that we spoke with told us that manufacturers' difficulties in raising capital to finance research and development costs deterred or slowed the development of new influenza vaccines produced using alternative technologies. One manufacturer representative told us that in the current economic market it has been challenging for his firm to find investors. Three other manufacturer representatives noted that their decision making is also influenced by perceptions of whether the benefits of a new influenza vaccine will offset these high research and development costs by increasing production efficiency or supporting higher prices for the new product compared to the current vaccine.⁴⁸ HHS told us that it has worked to address this issue through its funding for influenza vaccines using alternative technologies

⁴⁷PCAST, *Report to the President on Reengineering the Influenza Vaccine Production Enterprise*.

⁴⁸Two manufacturer representatives we spoke with noted that the current egg-based influenza vaccine is a low-profit product. According to one report we reviewed, the profit margin of the seasonal influenza vaccine is estimated to be about 20 percent, compared with the 50 percent to 95 percent profit margins that are typical in the pharmaceutical market, with highest margins for novel, proprietary drugs. PCAST, *Report to the President on Reengineering the Influenza Vaccine Production Enterprise*.

and that its support of manufacturers' efforts has helped to change the return on investment such that manufacturers have more incentive to pursue the development of new influenza vaccines using alternative technologies. Additionally, HHS noted that increased investments in this area have generated a significant interest in this type of research and development.

Some Stakeholders Identified Regulatory Challenges That Hinder the Development of Influenza Vaccines Using Alternative Technologies

Some stakeholders identified two regulatory challenges to the development of influenza vaccines using alternative technologies. First, some stakeholders and recent federal reports identified weaknesses in FDA's "regulatory science" capacity—that is, its ability to utilize resources, such as staff expertise, to develop new tests and measures to assess the safety, efficacy, quality, and performance of FDA-regulated products, such as influenza vaccines.^{49,50} Three manufacturer representatives, one industry association representative, and three experts told us that regulatory science weaknesses at FDA create challenges in the review of new product licensing applications, including those for new influenza vaccines. In particular, stakeholders told us that FDA's staff expertise in alternative technologies affects its ability to work with manufacturers developing new influenza vaccines using these technologies, and that limited staff expertise is a challenge to efficient communication. A manufacturer representative told us that FDA's ability to conduct its own research is important in understanding the science manufacturers present in licensing applications, but noted that some of FDA's research programs have been cut in recent years thereby hindering its ability to gain needed experience. An industry association representative told us that manufacturers pursuing the development of some influenza vaccines using alternative technologies sometimes find it difficult to find FDA staff who can answer their questions. One expert said that many experienced senior leaders in FDA's biologics division—where licensing applications for new vaccines are reviewed—have left the agency in recent years; therefore, reviewers are

⁴⁹Regulatory science is a term used by FDA and others to refer to the tests and measures that are used to assess the safety, efficacy, quality, and performance of FDA-regulated products.

⁵⁰FDA Science Board, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology*, a special report prepared at the request of FDA (Washington, D.C., 2007); HHS, *Medical Countermeasures Enterprise Review*; PCAST, *Report to the President on Reengineering the Influenza Vaccine Production Enterprise*; and the Institute of Medicine, *Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary* (Washington, D.C., 2010).

less familiar with these alternative technologies. This expert said this lack of familiarity can make it more difficult for manufacturers to work with reviewers to explain the technology to them.

Some recent federal reports have echoed stakeholders' concerns about FDA's regulatory science capacity. According to a recent HHS report, FDA needs to be able to conduct applied research in order to better incorporate advances in life sciences research and knowledge into the regulatory process. In order to make that possible, the report states that FDA needs greater staff expertise and infrastructure.⁵¹ In addition, a 2007 report prepared for the FDA Science Board—an FDA advisory group—found that the development of products based on new science cannot be adequately regulated by FDA because of a lack of capacity to review new technologies.⁵² However, FDA officials told us that they are not aware of actual examples of lack of expertise within the agency and that their staff consists of highly qualified scientists. Furthermore, FDA officials noted the continuing education that staff members engage in to maintain their proficiency in technological advances as well as the quality of FDA's research programs. The agency said it has the scientific and regulatory experience to adequately assess the safety and effectiveness of vaccines for use in the United States, but as noted later in this report, it continues to fund improvements in regulatory science capacity and staff expertise.

Some stakeholders also identified a second challenge, namely that FDA's written guidance and consultation with manufacturers on some of the requirements for licensure of new influenza vaccines using alternative technologies is not sufficiently comprehensive.⁵³ They noted that FDA's guidance documents do not include all of the various scenarios manufacturers may encounter. Additionally, one manufacturer representative said it can take months to arrange a formal meeting with FDA officials. Another manufacturer representative noted that FDA often conducts its discussions with manufacturers in stages, which can limit

⁵¹HHS, *Medical Countermeasures Enterprise Review*.

⁵²FDA Science Board, *FDA Science and Mission at Risk*.

⁵³According to FDA, officials consult with manufacturers through meetings, which can include technical and regulatory meetings on the pathway to licensure for their specific products. FDA officials said they also provide feedback to manufacturers during advisory committee meetings. Advisory committees, composed of outside experts, provide scientific and medical advice to FDA on the safety, effectiveness, and appropriate use of certain products. In this context, they provide a forum for public discussion of issues that may benefit manufacturers in developing new products.

their ability to plan for long-term issues. According to stakeholders, this lack of detail and incremental approach can hinder manufacturers' abilities to plan their research and development efforts, including those for new influenza vaccines, because they are uncertain as to what requirements they must meet in order to obtain licensure. For example, two manufacturer representatives said that it is unclear what size clinical trials will be required for influenza vaccines using alternative technologies because the guidance documents available are not specific enough in laying out these requirements. In addition, PCAST found in a recent report on influenza vaccine research and development that there is currently uncertainty about the regulatory pathway for recombinant influenza vaccines and recommended that guidance be developed on areas including criteria for formulation, safety, immunogenicity, and efficacy.⁵⁴ Also, one manufacturer representative told us that his company was repeating clinical trials for an adjuvanted vaccine that had already been performed in Europe because the company had been unaware of certain FDA requirements for data that are not typically required for similar vaccines or by regulatory authorities in other countries. The manufacturer representative noted that this situation could have been avoided if FDA had provided a more complete explanation of the requirements in this regard.

FDA officials acknowledged that its guidance documents are high level, explaining that specific instructions are unique to the product as guidance documents cannot cover all possible scenarios. In its comments, HHS officials noted that FDA's guidance is intended to provide a regulatory framework, adding that guidance cannot be specific to individual manufacturing processes because these processes are trade secrets. Because of their inability to be very specific in guidance documents, FDA officials told us that they regularly meet with manufacturers developing vaccines using alternative technologies to discuss various issues and provide advice. They also noted that the agency has a good record of achieving its goals on meeting with manufacturers within a specific time frame, adding that officials often consult with manufacturers in other ways, such as participating in teleconferences. Additionally, FDA officials said that it is necessary to consult with manufacturers in stages because their review is an iterative process. They explained that it is not always apparent what requirements may be necessary for a late phase of clinical

⁵⁴PCAST, *Report to the President on Reengineering the Influenza Vaccine Production Enterprise*.

trials because such decisions are based, in part, on results from earlier trials the manufacturer has completed. Furthermore, FDA noted that it has approved many vaccines for other diseases that used alternative technologies, such as adjuvants, and these manufacturers were able to successfully develop and license their products using FDA's guidance. Finally, FDA has published guidance on criteria for the formulation, safety, immunogenicity, and efficacy for vaccines using recombinant technology, and one manufacturer has submitted a licensing application for its influenza vaccine using this technology.⁵⁵ According to HHS, part of this guidance, which is available on FDA's Web site, is related to clinical trials and is specific to clinical data needed to support the licensure of pandemic influenza vaccines.

HHS Is Addressing Challenges in the Development and Licensure of Influenza Vaccines Using Alternative Technologies

HHS has expanded its recommendations for seasonal vaccination to a larger population and has released a 10-year strategic plan to address national immunizations. HHS also plans to assist manufacturers with high research and development costs by funding the establishment of specialized facilities. In addition, HHS plans to fund the enhancement of regulatory science capacity and FDA's staff expertise to address challenges that may hinder the licensure of new influenza vaccines using alternative technologies.

⁵⁵FDA, *Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines* (Rockville, Md., May 2007), and *Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines* (Rockville, Md., May 2007).

HHS Has Expanded Its Vaccination Recommendations for Seasonal Influenza to a Larger Population and Has Released Its Strategy for National Immunization, Which It Expects Could Eventually Increase Demand for Vaccine

HHS has expanded its recommendations for seasonal influenza vaccination to a larger population and has released its 10-year strategy to enhance immunization rates in the United States, which it expects could eventually increase demand for influenza vaccine. In August 2010, HHS announced that it was expanding its vaccination recommendations for the 2010–11 influenza season from specific target groups based on personal risk from the disease to all persons aged 6 months and older. According to HHS, its expanded recommendations simplify the public health message to providers and to the public on who should be vaccinated against seasonal influenza. Because the 2010–11 influenza season is the first for which the recommendations are in place and the first influenza season after the 2009 H1N1 pandemic, HHS is also evaluating vaccination rates from this season for changes from previous years. For example, preliminary data from CDC suggest an increase in vaccination rates against seasonal influenza among children aged 6 months to 17 years. According to CDC, vaccination rates for this population increased by 6.7 percentage points, or from 42.3 percent during the 2009–10 influenza season to 49 percent, as of February 2011.⁵⁶ Officials noted that currently, only about 40 percent of Americans are vaccinated against seasonal influenza. HHS added that eventually demand for seasonal vaccine could increase by approximately 32 percent—or 100 million people—as a result of the expanded recommendations. Additionally, a rise in immunization rates for seasonal influenza vaccine could result in an increase in the market for this vaccine of approximately \$3 billion annually, according to HHS.

In February 2011, HHS released its updated national immunization strategy, which outlines, in part, the department’s efforts to address low vaccination rates for influenza.⁵⁷ This strategy, called the National Vaccine Plan, lays out HHS’s efforts to enhance aspects of vaccines and vaccination rates against infectious diseases and provides a comprehensive plan for U.S. vaccine and immunization efforts from childhood to adulthood.⁵⁸ As we have noted above, several stakeholders

⁵⁶ CDC, “Interim Results: State-Specific Influenza Vaccination Coverage – United States, August 2010–February 2011,” *Morbidity and Mortality Weekly Report*, vol. 60, no. 22 (2011): 737–43.

⁵⁷ The National Vaccine Program Office is specifically leading this effort. The National Vaccine Program Office is the office within HHS’s Office of the Assistant Secretary for Health that coordinates the federal government’s vaccine- and immunization-related activities.

⁵⁸ HHS, *2010 National Vaccine Plan: Protecting the Nation’s Health through Immunization*, (Washington, D.C., 2010).

we spoke with cited a lack of provider and public education and concerns regarding the safety of vaccines as factors affecting the demand for influenza vaccine. The National Vaccine Plan has been updated to reflect experiences from the 2009 H1N1 pandemic and describes various goals, such as enhancing provider and public education on vaccines and vaccine safety and assisting providers and the public with making informed decisions regarding vaccination. HHS also plans to develop a corresponding implementation plan that will include measurable indicators so the department can assess its progress in achieving the goals of the National Vaccine Plan; HHS anticipates releasing this implementation plan later in 2011. Additionally, HHS launched a new Web site, www.vaccines.gov in the spring of 2011 as another way of educating providers and the public on vaccines and vaccine safety.

HHS Plans to Assist Manufacturers with High Research and Development Costs by Funding the Establishment of Specialized Facilities to Provide Support and Expertise

HHS plans to assist manufacturers with high research and development costs by supporting the establishment of two or three privately owned facilities called Centers for Innovation in Advanced Development and Manufacturing that will provide support and expertise to manufacturers. HHS indicated that it intends to enter into contracts to partially fund the construction of new facilities or the retrofitting of existing facilities using approximately \$478 million available from various appropriations.^{59,60} Although not the primary purpose of these facilities, according to HHS, one benefit of these specialized facilities is that they could reduce smaller, less-experienced manufacturers' research and development costs by providing needed resources and knowledge about manufacturing, and reduce the technical risks of researching and developing medical countermeasures, such as influenza vaccine produced using alternative technologies. These facilities are primarily intended to provide, on a routine basis, core services that include the advanced development and manufacturing of chemical, biological, radiological, and nuclear medical countermeasures. These specialized facilities may also be used in an emergency to make pandemic influenza vaccine produced using

⁵⁹See Pub. L. No. 109-148, 119 Stat. 2786; Pub. L. No. 109-234, 119 Stat. 479; Pub. L. No. 111-32, 123 Stat. 1884; Pub. L. No. 111-8, 123 Stat. 779; Pub. L. No. 111-17, 123 Stat. 3255. Many of these appropriations are available without fiscal year limitation.

⁶⁰Contracts entered into for this purpose will limit the government contribution for the construction of new facilities to 49 percent, with private entities contributing the remaining 51 percent. For the retrofitting of existing facilities, HHS's maximum contribution would be 75 percent, with private entities contributing the remaining 25 percent.

alternative technologies, such as recombinant technology.⁶¹ HHS noted that smaller, less-experienced manufacturers often lack the staff and other resources to address technical issues—such as those related to production, quality control, and licensure—resulting in delays and higher costs, which could cause an effort to fail. These specialized facilities would have the resources to provide manufacturers with the necessary staff, technical resources, and expertise to address these delays that can result in higher costs or effort failures.

According to HHS, these facilities might also reduce the total cost of the federal government’s contracts with manufacturers. By using these specialized facilities for vaccine production, the costs associated with producing these initial vaccine doses, such as those for use in clinical trials, could be included in the facilities’ operating budgets rather than in manufacturers’ research and development contracts, thereby reducing the total amount of these contracts. According to HHS, the enhanced production capacity from these facilities could also help manufacturers with which HHS has contracts avoid production delays. These specialized facilities could also allow smaller, less-experienced manufacturers to focus more on developing new influenza vaccines using alternative technologies rather than on production and licensure issues. HHS anticipates awarding competitive contracts to establish these facilities in 2011 or 2012.

HHS Intends to Enhance Regulatory Science at FDA to Facilitate the Review of Licensing Applications for Influenza Vaccines Produced Using Alternative Technologies

HHS has announced plans to spend \$170 million available from its fiscal year 2009 and fiscal year 2010 annual appropriations, in part, to facilitate FDA’s review of licensing applications for influenza vaccines produced using alternative technologies and for other medical countermeasures.⁶² Specifically, HHS intends to enhance regulatory science at FDA, that is, the development of new tests and methods to assess the safety, efficacy, quality, and performance of FDA-regulated products, such as influenza vaccines. According to HHS’s report, *The Public Health Emergency Medical Countermeasures Enterprise Review*, improvements in

⁶¹A mandatory criterion for eligibility under the HHS contract solicitation (solicitation #11-100-SOL-00011) is that an offeror provide evidence of a commitment to supply plans for producing finished pandemic influenza vaccine within 12 weeks of receipt of a virus strain and 50 million doses within 4 months of strain receipt.

⁶²See The Department of Defense and Full-Year Continuing Appropriations Act, 2011, Pub. L. No. 112-10, § 1835, 125 Stat. 38, 162.

regulatory science at FDA will help strengthen the agency's review of licensing applications.⁶³ In October 2010, FDA released a report outlining a proposed framework for advancing regulatory science using the funding intended by HHS for this purpose. According to FDA, improvements in regulatory science would focus on transitioning products more efficiently through review from initial concepts to licensed products. In its report, FDA identified areas in which it would focus that would potentially assist it in reviewing licensing applications for products more quickly, including during an influenza pandemic or other public health emergency.⁶⁴

In its October 2010 report, FDA proposes additional efforts that could enhance staff expertise in reviewing licensing applications for new vaccines using alternative technologies.⁶⁵ For example, FDA intends to initiate a program to help recruit experts in emerging technologies to work as researchers and reviewers throughout the agency. FDA is also initiating the creation and support of Centers of Excellence in Regulatory Science to conduct applied regulatory science research both independently and in collaboration with the agency. According to FDA, this additional research will enhance staff expertise with emerging technologies.

FDA has issued guidance to the industry on various aspects of vaccine production, such as on the selection of cells as a medium for producing vaccines and the clinical data needed for licensure of pandemic influenza vaccines.⁶⁶ FDA officials noted that developing guidance relies on experience, which takes time to acquire, adding that they plan to continue to make themselves available to manufacturers to consult with and advise them on various aspects of the vaccine development process, including on conducting clinical trials and safety assessments.

⁶³HHS, *Medical Countermeasures Enterprise Review*.

⁶⁴FDA, *Regulatory Science Initiative Framework*.

⁶⁵FDA, *Regulatory Science Initiative Framework*.

⁶⁶FDA, *Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications* (Rockville, Md., February 2010), and *Guidance: Clinical Data of Pandemic Influenza Vaccines*.

Agency Comments

HHS, DOD, and the Department of State reviewed a draft of this report. HHS and DOD provided written comments, which we have reprinted in appendixes IV and V, respectively. The Department of State did not provide comments. HHS also provided technical comments, which we have incorporated as appropriate.

In its comments, HHS stated that it agreed on the importance of expertise and research to the development of influenza vaccines produced using alternative technologies—cell-based and recombinant technologies and adjuvants. HHS also noted that the department has made significant contributions to advancing such expertise and research, as reflected in the collaboration within the department as well as with influenza vaccine manufacturers during the 2009 H1N1 pandemic. For example, HHS described how the Biomedical Advanced Research and Development Authority, FDA, and NIH worked with manufacturers producing both the seasonal and pandemic influenza vaccine. After approving seasonal vaccines from six manufacturers during the summer of 2009, FDA approved pandemic vaccines from four manufacturers in September 2009, and a pandemic vaccine from a fifth manufacturer in November 2009. HHS also described work done that allowed for influenza vaccine to be produced more rapidly. For example, FDA developed a technique to assess the sterility of vaccine, reducing the time for testing from 14 days to 5 days.

HHS's written comments also noted the department's concern that our description of challenges identified by stakeholders could be construed as an endorsement of them. However, as stated in our objectives, scope, and methodology, we examined challenges identified by stakeholders to the development and licensure of influenza vaccines produced using alternative technologies, and we believe our report clearly attributes these statements to the stakeholders. In response to industry concerns, HHS stated that FDA has an excellent record of responding to industry within agreed-upon time frames under applicable law and that FDA's guidance documents cannot be specific to individual manufacturing processes because these processes are trade secrets. HHS also stated that FDA provides clear guidance to manufacturers regarding the size of clinical trials and meets with sponsors of new vaccines at key stages of the product development process to provide further guidance that is informed by earlier trials.

In its comments, DOD agreed with the contents of the draft and noted that it had no substantive or administrative issues with the draft report.

We are sending copies of this report to the Secretaries of HHS, DOD, and State and to interested congressional committees. The report also is available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix VI.

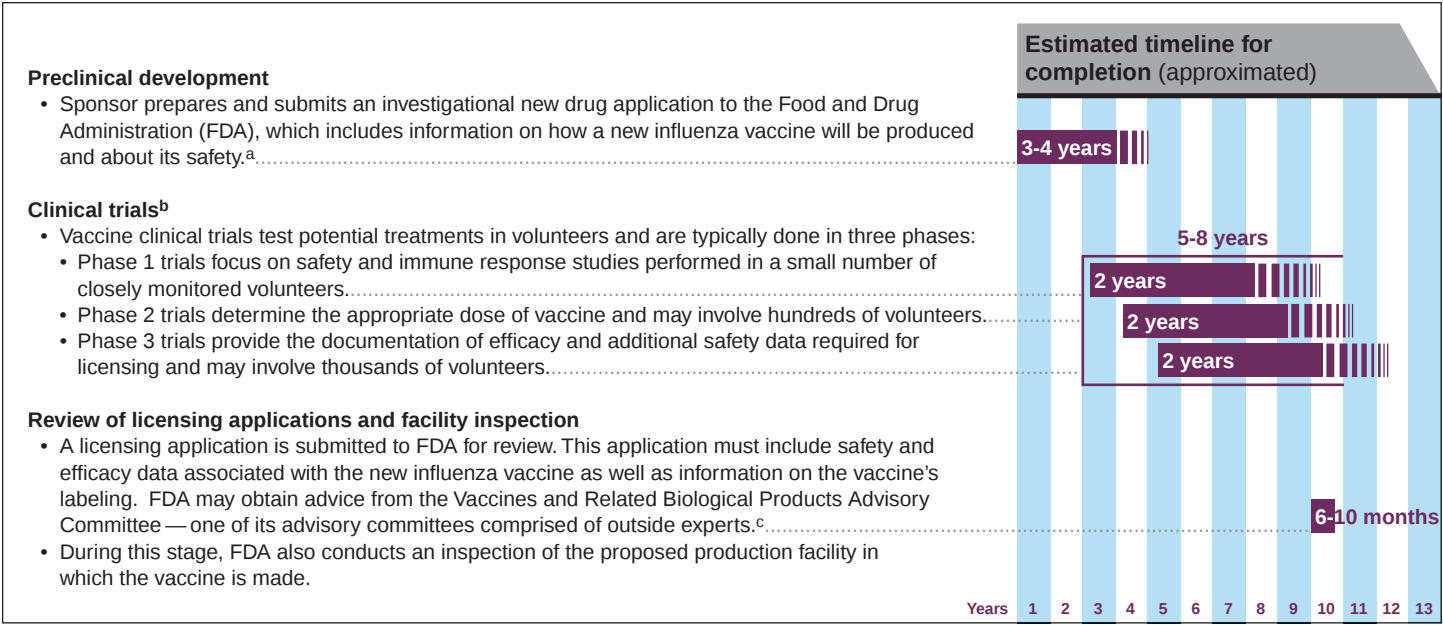
A handwritten signature in black ink, appearing to read "Marcia Crosse", with a long horizontal flourish extending to the right.

Marcia Crosse
Director, Health Care

Appendix I: The Research, Development, and Review of Licensing Applications for New Influenza Vaccine in the United States

The research, development, and review of licensing applications for new influenza vaccine for the U.S. market involve several stages. Manufacturers producing a biological product, of which influenza vaccines are one type, must submit a licensing application for review by the Food and Drug Administration (FDA) in order to market their vaccine in the United States. If FDA approves the application, the vaccine will be licensed for use in the United States. As shown in figure 1, this process can take, on average, a little over 10 years to complete.

Figure 1: Estimated Timeline for the Research, Development, and Review of Licensing Applications for New Influenza Vaccine for the United States



Source: GAO analysis of FDA data.

^aA sponsor may only begin clinical trials in humans after FDA has reviewed and approved its investigational new drug application.

^bAt any time during a clinical trial, if data raise significant concerns about either safety or efficacy, FDA may request additional information or studies or may halt ongoing clinical trials.

^cFDA’s review of a licensing application generally occurs at either 6 months or 10 months after submission of a priority or a standard application, respectively.

Appendix II: Influenza Vaccine Production Process Using Egg-Based Technology

Both seasonal and pandemic influenza vaccines for the U.S. market are produced using egg-based technology—a complex process that involves growing seed strains in millions of fertilized chicken eggs. As shown in table 7, this process involves a sequence of steps that can take approximately 4 to 5 months to complete.

Table 7: Influenza Vaccine Production Process Using Egg-Based Technology

Step of production process	Description
Identification and selection of most prevalent strain(s) ^a	- Entities such as the United Nations' World Health Organization, the Centers for Disease Control and Prevention, and the Department of Defense conduct surveillance to identify the circulating influenza virus strain(s) expected to be most prevalent. - The Food and Drug Administration (FDA) decides which strain(s) U.S. manufacturers must include in the influenza vaccine.^b
Development of modified strain	- One of three laboratories develops a modified strain that has the characteristics of the circulating strain(s) and grows well in eggs.^c This step takes approximately 3 weeks to complete. - The modified strain undergoes additional testing in one of the collaborating centers associated with the United Nations' World Health Organization before being distributed to manufacturers.^d This testing also takes approximately 3 weeks to complete.
Development, growth, and purification of seed strain	- After receiving the modified strain, manufacturers inject it into batches of fertilized chicken eggs to produce a seed strain that can be used for large-scale vaccine production. The modified strain is now called a seed strain. This process takes approximately 3 weeks to complete. - The virus seed strain is injected into millions of fertilized eggs and incubated so the strain can grow. Incubation takes approximately 2 to 3 days. - The virus is collected from the eggs and then inactivated so it is no longer infectious and is unable to cause disease.^e - The virus is then purified and used to produce a concentrated batch of antigen—the active substance of the vaccine that stimulates the protective immune response. - Producing one batch of antigen takes approximately 2 weeks; a new batch can be started every few days.
Testing, filling, and packaging of influenza vaccine	- Manufacturers and FDA test the vaccine using reagents produced and supplied by FDA to determine the potency, purity, and yield of the vaccine and that the potency of the antigen is sufficient to produce protective antibodies—molecules produced by a person's immune system that help fight infection.^f This testing takes approximately 2 weeks. - Manufacturers then fill vaccine doses into vials or syringes. Labels are applied to include information such as the expiration date. This step takes approximately 2 weeks. - FDA releases all lots of influenza vaccine and may conduct additional testing of the vaccine before officially releasing it for distribution. This additional testing occurs concurrently with the manufacturer's testing of the bulk vaccine. This testing can take up to 1 week.

Source: GAO analysis of FDA and United Nations' World Health Organization documents.

Appendix II: Influenza Vaccine Production Process Using Egg-Based Technology

Notes: The seasonal influenza vaccine is called a trivalent vaccine because it contains three strains of the influenza virus. A pandemic vaccine, which follows the same basic production process as a seasonal vaccine, is called a monovalent vaccine because it includes only the one pandemic-causing strain.

^aThe number of influenza strains used varies depending on the type of influenza vaccine being developed. Because multiple influenza strains are in constant circulation, seasonal vaccine is produced annually to protect against the three influenza strains expected to be most prevalent that year (i.e., a trivalent vaccine). In contrast, the 2009 H1N1 pandemic vaccine was formulated to match the single pandemic-causing strain (i.e., a monovalent vaccine).

^bFDA conducts this strain selection process in consultation with its Vaccines and Related Biological Products Advisory Committee.

^cThese three laboratories are located at CSL Biotherapies in Australia, the National Institute for Biological Standards and Control in the United Kingdom, and New York Medical College in the United States. Also, for a seasonal vaccine a modified strain is developed for each of the three influenza strains selected.

^dThis network of laboratories includes five collaborating centers associated with the United Nations' World Health Organization located in Australia, China, Japan, the United Kingdom, and the United States. The Centers for Disease Control and Prevention is the collaborating center in the United States.

^eAt this stage in the process, the virus seed strain is referred to as a virus. Additionally, unlike the injectable influenza vaccine, the live attenuated vaccine is administered as a nasal spray and does not require inactivation because of the weakened nature of the virus in the vaccine.

^fFDA is one of the four United Nations' World Health Organization essential regulatory laboratories responsible for producing and distributing referencing agents for vaccine testing. Reagents are substances used to, for example, measure or detect components during product development. Potency tests are a measure of the vaccine's ability to stimulate an immune response. Sterility tests are intended to determine purity by detecting and identifying vaccine contaminants. Also, antibodies are molecules produced by the immune system that help fight infections.

Appendix III: Egg-Based and Alternative Technologies for Use with Influenza Vaccines

Both seasonal and pandemic influenza vaccines for the U.S. market are produced using egg-based technology—a complex process that involves growing seed strains in millions of fertilized chicken eggs.¹ The antigen for an egg-based influenza vaccine—the active substance in a vaccine that provides immunity by causing the body to produce protective antibodies to fight off a particular influenza strain—is derived from strains well matched to the strains in wide circulation. In order for a vaccine to be most effective, it needs to contain enough antigen to stimulate a protective immune response.²

Egg-Based Technology

Egg-based technology has been used to produce influenza vaccine for several decades. Department of Health and Human Services (HHS) officials we spoke with described it as a “tried and true” production technology with which regulators and manufacturers are familiar. This technology utilizes fertilized eggs as the medium for producing the vaccine.³ Additionally, several decades of safety and efficacy data on the influenza vaccine produced using egg-based technology are available.

However, the timeliness of vaccine production is hindered, in part, by egg-based technology’s reliance on seed strain development and growth. Another factor affecting the production timeline is the amount of antigen produced per egg. For example, during the 2009 H1N1 pandemic, vaccine delivery was delayed, in part, because of poorer yields of antigen per egg than expected. Also, the amount of influenza vaccine that can be produced depends on the manufacturer’s egg supply. It generally takes 12 to 18 months to establish an egg supply large enough to meet the demands of either seasonal or pandemic influenza. Some experts we spoke with

¹There are two types of influenza vaccine approved for use in the United States: (1) an inactivated virus vaccine injected into muscle and (2) a live attenuated vaccine, which contains weakened influenza viruses and is administered as a nasal spray. Also, a modified viral strain is developed from the circulating virus strain. Influenza vaccine manufacturers optimize the growth of this modified strain, which is called a seed strain. This seed strain is used to produce antigen—the active substance of the vaccine that stimulates a protective immune response—and is then collected and purified.

²The vaccine’s antigen needs to be derived from a strain that is well matched to a specific influenza strain—in wide circulation in humans—so that the antibodies formed in response to the vaccine protect against infection. Antibodies are molecules produced by the immune system that help fight infections.

³Producing these fertilized eggs is more difficult than producing eggs for human consumption. The fertilized eggs are typically 9 to 12 days old, and FDA requires that these eggs meet particular sanitation and other requirements.

expressed concern that despite keeping chicken flocks producing the eggs in secure conditions to prevent contamination, these flocks are at risk of infection by, for example, the H5N1 avian influenza virus (also known as “bird flu”).

Alternative Technologies for Use with Influenza Vaccines

Alternative technologies that can be used in producing influenza vaccines include alternative production technologies—such as cell-based and recombinant technologies—as well as the use of adjuvants.⁴ While various alternative technologies are in development, in this report we focus on these three because these are the alternative technologies the federal government has primarily funded.

These three technologies have the potential to expand the supply or accelerate the availability of both seasonal and pandemic influenza vaccines. Expanding the supply or accelerating the availability of influenza vaccine is particularly important during times of a perceived seasonal vaccine shortage—when vaccine is not available and demand is highest—or during a pandemic when demand increases because of increased risk of disease and death. Expanding the supply or accelerating the availability of influenza vaccine can be done in two ways. The first is to increase the overall amount of vaccine available at the end of the production process; the second is to speed up the production process itself by, for example, reducing or eliminating step(s) in the process.

Cell-Based Technology

The key potential benefit to cell-based technology is the ability to increase the overall amount of vaccine available at the end of the production process. This technology for influenza vaccines typically relies on the use of well-established cell lines, such as those originally derived from the kidney cells of monkeys or canines. These cells can exponentially increase in number, allowing for the rapid expansion of the medium used for influenza vaccine production. Additionally, cells can be stored in freezers and prepared for use within days or weeks for large-scale production

⁴HHS refers to this technology as recombinant/molecular technology. According to HHS, this technology is also used for researching and developing a universal influenza vaccine. The National Institutes of Health, which is conducting research on a universal vaccine, defines it as a vaccine that would theoretically provide protection against any strain of influenza without needing to be updated or administered every year to protect against newly emerging annual or pandemic strains. Also, in this report, we are referring to adjuvants made using a combination of oil and water; there are different types of adjuvants that can be used with vaccines.

demands. Vaccines using cell-based technology are licensed for use in the United States for use against other infectious diseases, such as polio. Both seasonal and pandemic vaccines using such technology are also licensed in other countries, such as those in the European Union, including Germany and Spain. Cell-based seasonal and pandemic vaccines are also licensed for use in Iceland and Norway.

Despite the potential benefits of cell-based technology, there are challenges associated with its use. Similar to egg-based technology, cell-based technology relies on seed strain development and growth to obtain the influenza vaccine's antigen. For example, during the 2009 H1N1 pandemic, manufacturers had low production yields in both eggs and cells when they started vaccine production, which resulted in limited supplies for delivery to the public. Also, cell-based technology has not yet been licensed for use with influenza vaccine for the U.S. market. Additionally, few manufacturers have established domestic production capacity for influenza vaccine using this technology, and construction costs for cell-based facilities are high. For example, the construction costs for Novartis Vaccine and Diagnostics Inc.'s cell-based facility in Holly Springs, North Carolina, were over \$1 billion, of which HHS funded approximately 40 percent and the manufacturer funded the remaining 60 percent.

Recombinant Technology

Recombinant technology potentially increases the overall amount of vaccine available at the end of the production process and speeds up the production process itself. First, this technology can also utilize specialized cells—from mammals or from other sources, such as from bacteria, yeast, insects, or plants—that can exponentially increase in number as the medium for influenza vaccine production, allowing for the rapid expansion of the medium used for influenza vaccine production. Recombinant technology also has the potential to speed up the production process because it does not rely on the development and growth of a seed strain to obtain the influenza vaccine's antigen. Instead, antigen is derived from the protein(s) on the surface of the influenza virus or from the virus's genes. Recombinant technology is currently used in U.S.-marketed vaccines against other diseases, such as hepatitis B and the human papillomavirus, so FDA has experience reviewing licensing applications for vaccines produced using this technology.

However, influenza vaccine using recombinant technology has not yet been licensed for use in the United States. Although some influenza vaccine has been produced for use and is currently being used in clinical trials, influenza vaccine has not yet been produced on a large scale using

this production technology. One manufacturer, Protein Sciences Corporation, has submitted a licensing application to FDA for a recombinant seasonal influenza vaccine, but some experts we spoke with said it is unlikely we will know the benefits of this technology in producing influenza vaccine for several years.

Adjuvants

Adjuvants’ antigen-sparing capability has the potential to increase the amount of vaccine available at the end of the production process. Adjuvants—which can be used with influenza vaccines produced using egg-based, cell-based, or recombinant technologies—can enhance the immune response, thereby reducing the amount of antigen needed per vaccine dose. By reducing the amount of antigen needed per vaccine dose, adjuvants could increase the overall influenza vaccine supply. Adjuvants have other benefits beyond potentially accelerating the delivery of influenza vaccine (see table 8).

Table 8: Additional Potential Benefits of Adjuvants

Potential benefit	Description
Enhance immune response in certain populations	Adjuvants can help enhance the immune response in certain populations that tend to respond poorly to vaccination, such as the elderly or those with underlying health conditions.
Enhance immune response	Adjuvants have the potential to enhance the immune response to protect against influenza for multiple years.
Cross protection against multiple influenza viral strains	Adjuvants, in some cases, have been found to elicit an antibody response that may be protective against similar strains of influenza viruses, thereby enhancing the potential efficacy of influenza vaccine. ^a For example, some research has shown that an adjuvanted influenza vaccine against the H5N3 strain provides protection against the H5N1 strain. ^b

Source: GAO summary of President’s Council of Advisors on Science and Technology data and peer-reviewed data.
^aAn antibody is a molecule produced by the immune system that helps fight infections.
^bSee Iain Stephenson, Roberto Bugarini, Karl G. Nicholson, Audino Podda, John M. Wood, Maria C. Zambon, and Jacqueline M. Katz, “Cross-reactivity to Highly Pathogenic Avian Influenza H5N1 Viruses after Vaccination with Non-Adjuvanted and MF-59-Adjuvanted Influenza A/Duck/Singapore97 (H5N3) Vaccine: A Potential Priming Strategy,” *Journal of Infectious Diseases*, no. 191 (2005): 1210-5.

Seasonal influenza vaccines administered with adjuvants are licensed for use in other countries for targeted populations, such as the elderly. Adjuvants are licensed for use with seasonal influenza vaccine in other countries, such as those in the European Union, including Belgium and Italy. Adjuvanted seasonal influenza vaccines are also licensed for use in Argentina, Columbia, Hong Kong, Mexico, the Republic of South Africa, New Zealand, and Thailand. Adjuvants were also used with the 2009 H1N1

pandemic vaccine in other countries. These other countries include Canada and Malaysia.

Although adjuvants have been used in other vaccines licensed for the U.S. market—such as in vaccine against tetanus—FDA has not approved a licensing application for a seasonal influenza vaccine using this technology in the United States; adjuvants were also not used in the U.S. supply of 2009 H1N1 pandemic vaccine. Some experts have noted potential concerns regarding the safety of repeated, annual administration of adjuvants in healthy populations—such as young adults—in a seasonal influenza vaccine.

Appendix IV: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

JUN 06 2011

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street N.W.
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "INFLUENZA VACCINE: Federal Investments in Alternative Technologies and Challenges to Development and Licensure" (GAO-11-435).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in cursive script, reading "Jim R. Esquea", is positioned above the typed name.

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "INFLUENZA VACCINE: FEDERAL INVESTMENTS IN ALTERNATIVE TECHNOLOGIES AND CHALLENGES TO DEVELOPMENT AND LICENSURE" (GAO-11-435)

The Department appreciates the opportunity to review and comment on this draft report.

Regulatory Capacity and Expertise

The Department agrees with GAO that expertise and in-house state-of-the-art research is important and critical, and we believe that we have made significant contributions to advancing such expertise and research, as described below.

The 2009-2010 influenza season was very unusual. A new and very different viral strain of influenza (2009 H1N1), was not identified as being in circulation until production of the seasonal influenza vaccines had already been initiated, and therefore, was not included in the seasonal vaccine. In response to the need, components of HHS, including the Food and Drug Administration (FDA) the Biomedical Advanced Research and Development Authority (BARDA), and the National Institutes of Health (NIH) worked collaboratively with industry, which produced both the pandemic influenza vaccine and the seasonal vaccine, to protect the public from influenza. After approving six seasonal vaccines during the summer of 2009, FDA was able to approve pandemic influenza vaccines from four manufacturers on September 15, 2009 and from a fifth manufacturer on November 10, 2009. The pandemic vaccine was a good match to the circulating pandemic virus. These outcomes reflected extensive communication and cooperation between the influenza vaccine industry and the Department.

In 2009-2011, we conducted cutting-edge scientific work that significantly improved the ability to produce influenza vaccine more rapidly. First, FDA developed a technique to assess vaccine sterility that cut the duration of the test from 14 to 5 days. Second, FDA scientists developed a more rapid way to make one of the key materials needed to test the potency of influenza vaccine. Scientists throughout HHS are currently working to develop new potency tests that would make both seasonal and pandemic influenza vaccines available more quickly. Additionally, multiple HHS agencies are advancing research on universal influenza vaccines. For example, researchers at FDA and the Centers for Disease Control and Prevention (CDC) developed and tested in mice a candidate "universal," off-the-shelf vaccine designed to reduce illness and slow the spread of disease caused by new influenza A viruses that emerge suddenly, spread quickly, and for which there is no specific vaccine available. A single dose of the vaccine reduced illness and virus levels in mice later infected with highly virulent H1N1 and H3N2 (seasonal influenza), and H5N1 (bird flu).¹ In addition, scientists at the NIH Vaccine Research Center used DNA vaccine technology in a two-step immunization approach that was effective against a diverse array of influenza virus strains in mice, ferrets, and monkeys.² These types of vaccine approaches, if effective in humans, could be stockpiled and then used to reduce deaths and severe illness in the event of delayed production of traditional vaccine against a newly emergent influenza virus.

¹ "Single-dose Mucosal Immunization with a Candidate Universal influenza Vaccine Provides Rapid Protection from Virulent H5N1, H3N2 and H1N1 Viruses," PLoS 2010; 5(10) October 4; <http://dx.plos.org/10.1371/journal.pone.0013162>.

² C-J Wei, et al. Induction of broadly neutralizing H1N1 influenza antibodies by vaccination. *Science* DOI: 10.1126/science.1192517 (2010)

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "INFLUENZA VACCINE: FEDERAL INVESTMENTS IN ALTERNATIVE TECHNOLOGIES AND CHALLENGES TO DEVELOPMENT AND LICENSURE" (GAO-11-435)

All of these activities required working very closely with industry, foreign regulators, and other domestic public health agencies. FDA consistently provided one-on-one detailed guidance specific to issues related to each manufacturer, and to industry in general during this process. In addition, HHS increased active surveillance to monitor the safety of these vaccines as they were deployed to the public.

Responsiveness to Industry

We note that GAO includes a finding that that stakeholders GAO interviewed identified regulatory challenges that hinder the development of influenza vaccines using alternative technologies. GAO cites as the sources of this finding meetings attended, journal articles reviewed, and various stakeholders interviewed, including manufacturers pursuing alternative technologies.

Although HHS understands that GAO is simply describing the views that the stakeholders provided, with no intention of endorsing such views, restating such claims may be construed as an endorsement of them. HHS believes that it is important that GAO clarify that their intent is not to substantiate nor endorse the stakeholder views.

Some of the challenges associated with the development of influenza vaccine technologies are documented on FDA's website, including transcripts of Vaccine and Related Biological Products Advisory Committee Meetings (VRBPAC), where topics included in the GAO draft report were discussed.

- <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129568.htm>,
- <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM197912.pdf>
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- <http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4384T-add.htm>
- <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/default.htm>

FDA has actively used these meetings to explore many of the challenges and issues associated with developing these new technologies.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "INFLUENZA VACCINE: FEDERAL INVESTMENTS IN ALTERNATIVE TECHNOLOGIES AND CHALLENGES TO DEVELOPMENT AND LICENSURE" (GAO-11-435)

In response to comments by representatives of regulated industry regarding the timeliness of agency responsiveness, the Department would also like to note that FDA adheres to timelines agreed upon with industry during the Prescription Drug User Fee Act (PDUFA) negotiations for scheduling meetings and responding to submissions. FDA regulations describe key meetings that are helpful in resolving questions and issues raised during the course of clinical development.³ FDA has an excellent record of responding to such meeting requests.

To assist industry and when appropriate, FDA develops guidance to clarify the requirements under a given regulation. The intent of FDA's guidance documents is to provide a regulatory framework. Guidance cannot be specific to individual manufacturing processes, as these very processes are trade secrets. Therefore, FDA strongly encourages manufacturers, especially vaccine manufacturers, to meet with the agency to discuss the scientific options appropriate for their specific needs.

Regarding the clarity of requirements for clinical trials, FDA provides clear guidance to manufacturers regarding the size of clinical trials. FDA meets with the sponsors regularly as they develop their products, starting with the pre-investigational new drug (IND) phase. FDA also strongly encourages sponsors to meet with the agency at the end of phase II, which is a critical milestone in product development. The size of clinical trials will be informed by the efficacy and safety endpoints, which will depend upon the product, the clinical indication, and information gleaned during product development. In addition, FDA has issued two guidance documents that describe endpoints used for clinical trials, including one specific to clinical data needed to support the licensure of pandemic influenza vaccines. They can be found on FDA's website.⁴

³ (1) pre-IND meetings (21 CFR 312.82), (2) certain end of Phase 1 meetings (21 CFR 312.82), (3) end of Phase 2/pre-Phase 3 meetings (21 CFR 312.47), and (4) pre-NDA/BLA meetings (21 CFR 312.47)

⁴ <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm>
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm>

Appendix V: Comments from the Department of Defense



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

June 3, 2011

Ms. Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Crosse:

This is the Department of Defense's (DoD's) response to the Government Accountability Office (GAO) Draft Report, GAO-11-435, "INFLUENZA VACCINE: Federal Investments in Alternative Technologies and Challenges to Development and Licensure," dated May 19, 2011, (GAO Code 290847). Thank you for the opportunity to review and comment.

Though the draft report does not contain any recommendations for our action, the report does contain information that adds to the DoD's knowledge base on influenza. We found no substantive or administrative issues with the draft report. If you require additional information, the points of contact on this issue are COL James Boles (Functional) and Mr. Gunther Zimmerman (Audit Liaison). COL Boles may be reached at (703) 578-8444, or James.Boles@ha.osd.mil. Mr. Zimmerman may be reached at (703) 681-4360, or Gunther.Zimmerman@tma.osd.mil.

Sincerely,

A handwritten signature in black ink, appearing to read "Jonathan Woodson", is written over a horizontal line.

Jonathan Woodson, M.D.

Appendix VI: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crosssem@gao.gov

Staff Acknowledgments

In addition to the contact named above, Thomas Conahan, Assistant Director; George Bogart; Cathleen Hamann; Mariel Lifshitz; Gay Hee Lee; John Rancourt; and Kristal Vardaman made key contributions to this report.

Related GAO Products

Influenza Pandemic: Monitoring and Assessing the Status of the National Pandemic Implementation Plan Needs Improvement. [GAO-10-73](#). Washington, D.C.: November 24, 2009.

Influenza Pandemic: Gaps in Pandemic Planning and Preparedness Need to Be Addressed. [GAO-09-909T](#). Washington, D.C.: July 29, 2009.

Influenza Pandemic: Continued Focus on the Nation's Planning and Preparedness Efforts Remains Essential. [GAO-09-760T](#). Washington, D.C.: June 3, 2009.

Influenza Pandemic: Sustaining Focus on the Nation's Planning and Preparedness Efforts. [GAO-09-334](#). Washington, D.C.: February 26, 2009.

Influenza Pandemic: HHS Needs to Continue Its Actions and Finalize Guidance for Pharmaceutical Interventions. [GAO-08-671](#). Washington, D.C.: September 30, 2008.

Influenza Pandemic: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic. [GAO-08-92](#). Washington, D.C.: December 21, 2007.

Influenza Vaccine: Issues Related to Production, Distribution, and Public Health Messages. [GAO-08-27](#). Washington, D.C.: October 31, 2007.

Influenza Pandemic: Further Efforts Are Needed to Ensure Clearer Federal Leadership Roles and an Effective National Strategy. [GAO-07-781](#). Washington, D.C.: August 14, 2007.

Influenza Pandemic: Efforts to Forestall Onset Are Under Way; Identifying Countries at Greatest Risk Entails Challenges. [GAO-07-604](#). Washington, D.C.: June 20, 2007.

Influenza Pandemic: DOD Combatant Commands' Preparedness Efforts Could Benefit from More Clearly Defined Roles, Resources, and Risk Mitigation. [GAO-07-696](#). Washington, D.C.: June 20, 2007.

Avian Influenza: USDA Has Taken Important Steps to Prepare for Outbreaks, but Better Planning Could Improve Response. [GAO-07-652](#). Washington, D.C.: June 11, 2007.

Influenza Pandemic: Applying Lessons Learned from the 2004–05 Influenza Vaccine Shortage. [GAO-06-221T](#). Washington, D.C.: November 4, 2005.

Influenza Vaccine: Shortages in 2004–05 Season Underscore Need for Better Preparation. [GAO-05-984](#). Washington, D.C.: September 30, 2005.

Influenza Pandemic: Challenges in Preparedness and Response. [GAO-05-863T](#). Washington, D.C.: June 30, 2005.

Influenza Pandemic: Challenges Remain in Preparedness. [GAO-05-760T](#). Washington, D.C.: May 26, 2005.

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