Encouraging Vaccine Innovation: Promoting the Development of Vaccines that Minimize the Burden of Infectious Diseases in the 21st Century

Report to Congress

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U.S. Department of Health and Human Services

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I. Introduction

On December 13, 2016 the 21st Century Cures Act was signed into law (P.L. 114-255). The law was intended to accelerate the process of discovery, development, and delivery of health care innovation. In compliance with Section 3093 of the 21st Century Cures Act, the Secretary of Health and Human Services (HHS) is required to prepare and submit, within one year of enactment, a report to Congress on encouraging vaccine innovation. The Secretary, "in collaboration with appropriate agencies or offices within the Department of Health and Human Services, including the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Biomedical Advanced Research and Development Authority, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives, and post publicly on the Internet website of the Department of Health and Human Services, a report on ways to promote innovation in the development of vaccines that minimize the burden of infectious disease."[1]

Specifically, the report "shall review the current status of vaccine development and, as appropriate—

A. Consider the optimal process to determine which vaccines would be beneficial to public health and how information on such vaccines is disseminated to key stakeholders;
B. Examine and identify whether obstacles exist that inhibit the development of beneficial vaccines; and
C. Make recommendations about how best to remove any obstacles identified under subparagraph (B) in order to promote and incentivize vaccine innovation and development." [1]

Summary

The U.S. vaccine enterprise is well established and has been successful at bringing innovative and new and improved vaccines to the market. However, the vaccine enterprise is at a turning point as challenges to innovation have increased for remaining infectious disease targets. Currently, HHS leads concerted and targeted efforts to address many of these challenges, spur continued innovation, and improve public health. This report examines the current state of U.S. vaccine development and innovation, highlights existing challenges, and offers potential opportunities and levers that could foster innovation.

II. Development of the Report

On behalf of the HHS Secretary, the National Vaccine Program Office (NVPO), in the Office of the Assistant Secretary for Health (OASH), coordinated the development of this report. NVPO,

[1] Encouraging Vaccine Innovation, § 3093 of the 21st Century Cures Act (Dec. 13, 2016). Retrieved from https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf

in collaboration with the Office of the Assistant Secretary for Policy and Evaluation (ASPE), the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), created an interagency Vaccine Innovation Steering Committee (VISC).

The VISC examined the vaccine enterprise and the relative contributions of key stakeholders involved in the development, licensure, and use of vaccines. The VISC explored issues facing key stakeholders in the current environment and opportunities for the U.S. government (USG), within its existing authorities, to address some of these challenges. Additionally, HHS convened a panel of non-federal experts on June 27, 2017. The participants on the panel provided their individual views, not a group consensus, on these issues; they represented a wide range of stakeholder perspectives including science, medicine, public health, regulatory, vaccine safety, patient policy, consumer advocacy, and private sector industry.

III. Background

Vaccines have an inherent societal benefit. They protect individuals and communities against serious infectious diseases and dramatically reduce the burden associated with such infectious diseases including hospitalizations, deaths, and health care costs in the United States. With further innovation and continued development, new and improved vaccines may have an even greater benefit to society.

The USG is one of many key stakeholders involved in the U.S. vaccine enterprise, a network of industrial, government, academic, non-profit, and private partners engaged in infectious disease surveillance, basic and applied research, product development, regulatory evaluation and licensure, recommendations for introduction and use, and vaccine uptake. **Table 1** provides a brief description of the components of the U.S. vaccine enterprise, which generally characterizes the lifecycle of a vaccine. The USG works with diverse partners to shepherd potential vaccine candidates through the staged development process. Once a vaccine is licensed by FDA for use, many stakeholders — such as patients, providers, payers, and public health officials — become involved in the immunization delivery system.

Pursuing the development of vaccines is a long, expensive, and high risk endeavor. It begins with initial product interest, informed by existing and available information on disease burden and technical feasibility. Once the decision to pursue vaccine development is made, at least a decade of investment is typically needed to advance potential candidates from basic and applied research to licensure, production, and delivery into the immunization delivery system.

Numerous candidates are tested in pre-clinical and early stage clinical trials, but not all have the technical feasibility and potential product interest to move forward through the pipeline **(Figure 1)**. As candidates move forward through the various stages of clinical trials, time and resource investments increase significantly. Data from clinical studies serve as the basis for licensure; it

can take several years for a sponsor [i.e., the company, organization, or individual that sponsors the investigational new drug application (IND) for the conduct of clinical trials or biologics license application (BLA) for licensure] to demonstrate that the vaccine candidate meets the necessary FDA standards for vaccine safety and effectiveness. As a vaccine candidate progresses toward licensure, further investments are needed to demonstrate the ability to make the vaccine candidate at large scale and in the intended commercial production facility. Overall, the time and financial investments necessary to develop a single safe, effective, FDA-licensed vaccine are high. These costs are even greater when considering the high-risk environment for investment, where most vaccine candidates do not make it to FDA-licensure and the costs of failed products must also be absorbed. The riskiness of the decision to invest in vaccine development takes into account the generally smaller markets for vaccines, which are usually administered once. This is in contrast to therapeutic products, which may be given several times or for a long duration throughout a patient's lifetime. The success of currently licensed vaccines in the immunization delivery system and the anticipated markets for potential new vaccines also contribute to the risk of development. Factors that decrease the cost or risk of development, such as USG policies or actions, may help foster innovation and development.

IV. Scope of the Report

This report focuses on the U.S. network of industry, non-profit, foundation, government and academic partners engaged in vaccine research and development (R&D). This network is responsible for developing the majority of new vaccines available worldwide since World War II, a reflection of the current network's success in innovation. Cooperation and collaboration among these major partners are necessary to advance vaccine candidates through the development pipeline.

Industry plays a central role in this collaboration. The number of companies involved in the vaccine enterprise has evolved over the years with a significant decrease in the number of large manufacturers that produce vaccines. Currently, the vaccine industry is comprised of numerous small biotechnology companies and four large manufacturers: GlaxoSmithKline, Merck and Co., Inc., Pfizer, and Sanofi Pasteur. In addition to industry, organizations such as non-profits and foundations support efforts to decrease costs and accelerate the pace of vaccine R&D and optimization (e.g., Global Health Vaccine Center of Innovation, Hillemen Laboratories, Coalition for Epidemic Preparedness Innovations).

Academic partners play a key role in the generation of new ideas and technologies. Both large and small companies bridge academic research and commercial development by supporting basic laboratory research for vaccine candidates and by conducting Phase 1, 2, 3, and 4 clinical trials. Phase 1 clinical trials evaluate early safety and immune responses to the vaccine candidate. Phase 2 clinical trials involve dose-ranging and more comprehensive safety and immunogenicity studies. Phase 3 clinical trials are pivotal and require large-scale studies of safety and effectiveness. Phase 4 clinical trials are conducted post-licensure and may be performed to fulfill post-marketing requirements and to provide additional assessments of less

common rare adverse events or information on the duration of vaccine-induced immunity. During Phase 1 and 2 studies, the vaccine manufacturing process is also developed and refined to ensure consistency and high-quality. Due to limitations in capacity and funding, small companies often stop development at Phase 2 and large companies shepherd promising vaccine candidates through the later, costlier stages of clinical trials, licensure, and commercial production.

Vaccine development is also a global enterprise. Depending on the specific vaccine candidate in development, a manufacturer may seek licensure in multiple countries, and face varying regulatory requirements. Extensive resources are required to engage in a global market, which can be a key factor in deciding which vaccine candidates to support in development programs. Efforts to expand regulatory convergence across countries are ongoing.

The success of the vaccine industry in bringing new, FDA-licensed vaccines to the public is dependent on an environment shaped, in part, by government actions and policies. The USG has a general interest in supporting the development, licensure, and introduction and use of vaccines that protect the public against infectious disease threats. More broadly, the USG has an interest in innovation — bringing new ideas and technologies to fruition — that may further improve public health and address and/or prevent emerging infectious diseases. Innovation can occur across the vaccine development spectrum, including with manufacturing processes (e.g., cell-based and recombinant influenza vaccines)[2] and new delivery systems (e.g., a patch instead of a needle), as well as novel candidates and improvements to existing vaccines (e.g., use of new and improved platforms or adjuvants).

V. Current Status of Vaccine Development

Currently, more than 120 vaccine candidates are under development for the prevention of more than 40 infectious disease targets as reported on the Pharmaceutical Research and Manufacturers Association of America (PhRMA) website **(Table 2)**.[3] Additional sources that track vaccine development programs are the World Health Organization (WHO) and the U.S. government. The WHO Vaccine Pipeline Tracker lists vaccine candidates currently under clinical development.[4] The USG's ClinicalTrials.gov is the largest U.S. clinical trials database. While not an exhaustive list, these sources represent the vast majority of active development programs.

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[2] Two new alternatives to egg-based influenza vaccine manufacturing – cell-based and recombinant vaccines – are examples of new methods to produce influenza vaccines. Both FDA-licensed vaccines were funded by HHS through BARDA in support of alternatives to domestic and egg-independent vaccine production capacity to respond to future pandemics.

[3] Table 2 lists only vaccines for infectious diseases; however, the full report (Medicines for Vaccines in Development 2017 Update) is broader and includes cancer therapeutic drugs.

[4] World Health Organization. WHO vaccine pipeline tracker. Retrieved from http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/

Vaccine development is at a turning point for three primary reasons: (1) the prevailing business model prioritizes vaccine candidates with large markets, yet market sizes are likely smaller for many remaining targets which focus on subsets of the population; (2) substantial investment is needed to address the scientific complexity of remaining targets, which may also require further investment in novel approaches to demonstrate safety and effectiveiness; and (3) uncertainty of the public health priority and demand for some targets may be unclear, which increases the uncertainty of the potential return on investment (ROI) and, therefore, investment risk of development.

Some vaccines currently under development are expected to receive a recommendation for administration to a subset of the population rather than a universal recommendation for a broad cohort of individuals. For example, vaccines that most benefit subpopulations – such as pregnant women or persons undergoing elective surgery – may only receive recommendations for use among those populations. This presents several challenges, especially for small companies. The market for these products may be smaller and more difficult to estimate because of uncertainty about the population for whom the vaccine might be recommended and the expected level of utilization.

Additionally, new vaccine targets are more scientifically complex and challenging. The challenges presented may require substantial investment in new tools, standards, analysis methods, and other novel approaches to demonstrate safety and effectiveness. Public health priorities have historically been evident to stakeholders due to the clear disease burden of many infectious agents (e.g., measles, polio) and the public health demand for vaccines. The development of certain vaccines — for example, universal influenza vaccines and respiratory syncytial virus (RSV) vaccines for infants — is considered a high priority as reflected in the number of companies working on these vaccine targets. However, the public health priority for some vaccine targets is less clear. In order to support an enabling environment for continued innovation the following factors are important: having a shared understanding of market size; making investments in science and development programs; and knowing which vaccines are public health priorities within the vaccine enterprise.

Small and Large Companies

While the USG provides the majority of support for basic and applied research in the academic setting, most vaccine candidates are developed by small companies that drive innovation in early stage development. Many of these companies rely on funding from multiple sources including USG and venture capital, until late stage development when products with a potential ROI attract large companies for investment.

The handful of large companies with the resources and expertise to support manufacturing, licensure, and commercial production may face vaccine development constraints in several ways. First, there are only a few companies to potentially shepard a vaccine through to licensure. Second, vaccine manufacturers are generally part of large pharmaceutical parent companies. Therefore, vaccines often compete with other pharmaceutical products — that can

have a higher ROI and lower risks — for limited development resources. Third, vaccine manufacturers typically have capacity constraints, in that manufacturers plan for the global market. This requires navigating multiple regulatory authorities and immunization policies, which may vary from country to country. Reaching regulatory convergence across countries is a continued opportunity to improve efficient use of limited resources. Often, only products anticipated to have a global market provide sufficient incentive for large and risky investments. Investments in emerging priorities may also have opportunity costs. For example, supporting development of an Ebola virus vaccine (with an uncertain market) may require a company to shift resources from other development programs. Essentially, R&D investment in new or improved vaccines depends on projected costs and ROI.

Role of Federal Agencies

HHS has a far-reaching mission to protect and promote public health and respond to urgent and emerging disease threats. Within HHS, the major federal agencies and offices in the vaccine enterprise working on vaccine development include: NIH, FDA, CDC, BARDA (within ASPR), and NVPO. Outside of HHS, the Department of Defense (DoD) and the U.S. Agency for International Development (USAID) also make investments in vaccine development.

Federal agencies and offices work in tandem with a broad range of stakeholders to optimize vaccine development. For example, HHS plays a key role in ensuring timely development and production of well-matched seasonal influenza vaccines, and is leading and coordinating efforts to improve these vaccines. Because influenza viruses are constantly changing, seasonal influenza vaccines must be updated annually in order to match the vaccine with currently circulating virus strains. The yearly influenza vaccine strain selection, vaccine production, and licensure is a highly coordinated process that is based on global influenza data collected from health partners around the world, particularly the World Health Organization. For more than 10 years, the Pandemic and Seasonal Influenza Risk Management Meeting has served as a senior-level forum for decision-makers from stakeholder agencies. Leadership from BARDA, CDC, FDA, NIH, NVPO, and others regularly meet to identify and address risk management issues related to the development, acquisition, deployment, and utilization of medical and public health countermeasures for pandemic and seasonal influenza. Additionally, HHS agencies and offices actively partner with the scientific community through workshops or other means to determine how to close the gap between vaccine discovery and delivery. The role of HHS agencies and offices is described below.

National Institutes of Health (NIH)

NIH supports and conducts basic and applied research, translational research, and clinical evaluation focused on identifying vaccine targets and advancing novel candidates through the vaccine development pipeline for a broad array of infectious diseases. NIH works closely and collaboratively with partners in academia, industry, and other federal agencies to facilitate vaccine innovation and development. It also supports the training of research investigators and fosters communication of medical and health sciences information. In addition, NIH directly

supports vaccine development through its intramural program. For example, the NIH Vaccine Research Center (VRC), is dedicated to improving global human health through the rigorous pursuit of effective vaccines, and is developing and evaluating vaccines for HIV/AIDS, influenza, Zika, and Respiratory Syncytial Virus, among other diseases. NIH collaborates with multiple partners to facilitate the development of vaccine platform technologies that will enhance the USG's ability to respond to emerging disease threats and accelerate vaccine development during public health emergencies.

Basic research: An initial critical component for vaccine development is the advancement of basic research aimed at understanding how pathogens cause disease and, in turn, how the immune system responds to infection. NIH supports basic research on more than 300 pathogens to elucidate pathogen biology; examine interactions among pathogens, hosts, and the environment; and determine the ways that microbes survive and multiply. Historically, NIH researchers have laid the groundwork for development of numerous vaccines by developing reliable animal models, identifying and characterizing multiple vaccine targets, defining the mode of transmission for such targets, and identifying critical components that trigger an immune response. In addition, NIH supports programs to more fully understand the mechanisms involved in the immune responses to infection and vaccination, such as the Human Immunology Project Consortium (HIPC). HIPC is a large, collaborative research effort that focuses on studying vaccine responses of well-characterized human cohorts to better understand the immune system, its regulation, and the differences between immune systems that do and do not respond to vaccination. Data from this effort will be used to develop and evaluate new vaccines and immunization strategies that work in a greater diversity of individuals and help identify those potentially at risk for an adverse event.

Translational research: Advances in basic research lead to targets and strategies for the development of new and improved vaccines. NIH supports translational research to turn concepts into products and provides services to researchers to facilitate vaccine development. The NIH Partnerships Program for Translational Research is a long-standing initiative that encourages new research collaborations among experts from different disciplines of academia and industry and ensures that basic research findings and technologies are translated into new product development approaches. Recent Partnerships initiatives have focused on structure-based design of novel immunogens for vaccine development and the development of vaccines targeting antimicrobial-resistant bacteria. In addition, NIH offers comprehensive pre-clinical services to industry partners and academic researchers that seek to fill the gap between discoveries made at the basic research stage and the development of clinical products, including evaluation of vaccine candidates, assay development, safety and toxicity testing, product optimization, and pilot lot manufacturing. Modern vaccines often require the addition of adjuvants, which are molecules that trigger the initial activation of the immune system. NIH adjuvant discovery and development efforts are critical to the development of new and improved vaccines against infectious diseases. NIH conducts pre-clinical evaluation of novel adjuvants in combination with infectious disease vaccine candidates. Together,

these programs provide a tool box for vaccine developers looking to produce novel vaccines, such as vaccines with increased efficacy or vaccines for specific age groups.

Clinical evaluation: To help turn basic research and translational discoveries into products that impact public health, NIH has made a significant investment in establishing state-of-the-art clinical trial networks for vaccine development and evaluation. This includes early clinical trials of novel vaccine candidates to evaluate safety and immunogenicity, efficacy trials, and post-licensure studies of vaccines that can help inform clinical practice. One of the key programs NIH utilizes to evaluate promising vaccine candidates is the Vaccine and Treatment Evaluation Units (VTEUs), a network of sites that provides a ready resource for conducting clinical trials. NIH frequently serves as the Investigational New Drug Application (IND) sponsor for vaccine candidates, and interacts with the FDA throughout the entire product lifecycle, to ensure that all regulatory requirements are being met, and that the vaccine candidate is on the right path for licensure.

Food and Drug Administration (FDA)

FDA has a central role in vaccine development, as it is the federal agency charged with ensuring that vaccines undergo a rigorous and extensive development program to determine and ensure the safety, purity, and potency of these products. After a vaccine is FDA-licensed, FDA continues to monitor its safety, purity, and potency. Vaccine development programs include studies conducted by manufacturers according to FDA standards to evaluate safety and effectiveness in the target population. Clinical trials are conducted according to plans that reflect FDA's expertise in clinical trial design. FDA guides development of vaccines from pre-Phase 1 through Phase 4. Through meetings between medical and scientific experts from the FDA and the manufacturer, often early in the development of a vaccine candidate, and at critical later times, the sponsor (i.e., the company, organization, or individual that sponsors the IND for the conduct of clinical trials) gains valuable advice about planned clinical trials, development milestones, and data requirements.

Vaccine review and licensing: Thanks to staffing increases that are supported by industry user fees, FDA has been able to further optimize its vaccine review and licensing process to encourage the development of new vaccines and make vaccines available for use sooner, without lowering FDA's standard for safety and effectiveness. This is achieved by implementing available innovative, flexible regulatory mechanisms and pathways. Expedited development pathways (e.g., Fast Track Designation, Priority Review, Accelerated Approval) and innovative regulatory mechanisms (e.g., use of the animal rule and adaptive trial designs) applicable to vaccine candidates are outlined in **Tables 3-4**. FDA has worked effectively to implement these flexible regulatory pathways and review practices. This flexibility has translated into a high proportion of vaccine approvals on the first regulatory review cycle, thereby increasing predictability for vaccine developers.

Regulatory science and innovation: Research is fundamental to FDA's ability to provide effective scientific and regulatory evaluation of vaccine candidates. FDA conducts its research activities in conjunction with its regulatory activities, which provides the agency a unique perspective on both fronts. A wide variety of rapidly evolving technical and scientific issues concerning the safety and effectiveness of vaccine candidates requires knowledge of new developments in basic research in the relevant biological disciplines. For this reason, FDA scientists conduct research in a variety of areas including evaluating new techniques and tools for regulatory testing of product safety and effectiveness, as well as developing strategies for new product development.

International collaboration: The development, manufacturing, clinical evaluation, and regulatory review of vaccine candidates are a global enterprise. FDA continually engages with its international regulatory counterparts to work toward harmonizing scientific standards and approaches for developing vaccine candidates, evaluating their safety and effectiveness, and overseeing their manufacturing and quality. For example, FDA has been a Pan American Health Organization (PAHO) and World Health Organization (WHO) Collaborating Center for Biological Standardization since 1998. As such, FDA is a key participant to develop and revise specific recommendations for the production and quality control of vaccine candidates of major international public health importance. In the hope that more vaccine candidates can be licensed and available to multiple regions of the world, FDA also works with the WHO, other National Regulatory Authorities (NRAs), and with industry to encourage international convergence, more efficient product development, and development of the scientific and regulatory standards for safety and effectiveness that will help achieve these goals.

Post-licensure manufacturing and safety monitoring: FDA continues to intensively oversee vaccine production after the vaccine candidate and its manufacturing processes are approved, to ensure continued safety and effectiveness. Furthermore, FDA may also require, at or after the time of approval, manufacturers to conduct additional post-market studies to evaluate known or potential serious risks. FDA evaluates safety signals that may arise, and takes appropriate steps as needed, such as communicating vaccine safety information to the public and health care providers or requiring manufacturers to change the prescribing information (i.e., vaccine labeling).

FDA monitors the Vaccine Adverse Event Reporting System (VAERS), a nationwide, joint effort with the CDC to conduct post-marketing passive surveillance and collect information about adverse events reported to occur after the administration of licensed vaccines. In addition to VAERS, the Sentinel Initiative is FDA’s national electronic surveillance system for the post-market safety monitoring of medical products. The Sentinel System was implemented as an Active Post-Market Risk Identification and Analysis program in response to section 905 of the Food and Drug Administration Amendments Act of 2007. The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, the vaccine safety portion of the Sentinel system, was initiated in 2009 as one of several national vaccine safety surveillance systems deployed during the

H1N1 influenza pandemic. The PRISM database covers more than 190 million individuals in several data partner organizations. PRISM, which has capabilities for broad-based signal detection as well as for evaluating safety signals that may be identified, is used by FDA to evaluate vaccine safety in the post-licensure setting.

Centers for Disease Control and Prevention (CDC)

CDC leads the U.S. immunization program, which defines disease burden and implements and evaluates national immunization policies and programs. CDC identifies, controls, and prevents infectious diseases through public health surveillance, epidemiologic studies, vaccine use recommendations, vaccine purchasing and service delivery, health communications, and post-marketing vaccine safety, vaccine effectiveness, and vaccine impact studies. CDC provides domestic and international leadership in laboratory technologies and techniques to detect and characterize vaccine-preventable and emerging diseases. CDC collaborates with both domestic and global partners to maximize the effectiveness of immunization policies and programs.

Disease surveillance: In the United States, laws and regulations mandate reporting cases of specified infectious and non-infectious conditions to local, state, and territorial health departments. Health departments work with health care providers, laboratories, hospitals, and other partners to obtain the information needed to monitor, control, and prevent the occurrence and spread of these health conditions. Health departments notify CDC about the occurrence of certain conditions, and CDC receives, secures, processes, and disseminates nationally notifiable infectious diseases data. Through networks of state health departments, academic institutions, and other collaborators, CDC is able to address important issues in infectious diseases and identify new problems as they arise.

Infectious disease detection and response: It is critical to detect emergent, new diseases through domestic and international surveillance programs that characterize and track these diseases and identify potential targets for vaccine development. Through epidemiologic studies, diseases patterns are described and at-risk populations are identified. Etiologic agents are isolated and characterized in CDC laboratories, often in collaboration with networks of scientists across the United States and internationally. CDC laboratories may develop vaccine candidates for emerging diseases. Before a vaccine is FDA-licensed, CDC subject matter experts have met with pharmaceutical companies to share insights into the epidemiology and possible effectiveness of vaccines in development. CDC also conducts modeling and analysis to predict the potential impact of vaccines and economic analyses to establish the value proposition of vaccines.

National immunization policy: Once a vaccine is licensed by FDA, CDC sets the U.S. child and adult immunization schedules based on recommendations from the Advisory Committee on Immunization Practices (ACIP). ACIP is a federal advisory committee that provides advice to the CDC Director regarding the most appropriate use of licensed vaccines and related agents for control of vaccine-preventable diseases in the civilian population of the United States. In setting immunization schedules, CDC establishes the

standards of medical practice for immunization for the nation. In addition to inviting input from ACIP, CDC works with nongovernmental professional organizations or other public health service advisory committees. CDC and ACIP work with professional organizations including the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) to harmonize the pediatric immunization schedule, and with the American College of Physicians (ACP), AAFP, and the American College of Obstetricians and Gynecologists (ACOG) to harmonize the adult immunization schedule. Unique to ACIP is its role in determining the vaccines included in the Vaccines for Children (VFC) program. Nongrandfathered private health plans, health plans offered through state and federal health insurance exchanges, and Medicaid expansion programs are required to provide first dollar coverage (i.e., with no cost-sharing to the patient) for the vaccines included in the CDC immunization schedules. CDC immunization recommendations provide an estimated potential market size for the vaccine manufacturer.

National immunization program: CDC supports the nation's public health infrastructure, which includes public health experts and systems critical to the success of our nation's immunization program. This public health infrastructure promotes immunization recommendations across the lifespan; fosters convenient access to recommended vaccinations; provides a safety net for those who cannot otherwise access immunization services; manages vaccine shortages; monitors the safety and effectiveness of vaccines and vaccine policies; prevents disease outbreaks and responds early and rapidly should they occur; and prepares to respond quickly and comprehensively to other urgent vaccine emergencies, such as pandemics.

In collaboration with the Centers for Medicare & Medicaid Services (CMS), CDC implements the federal VFC program. Through this program, CDC provides vaccines at no cost to eligible children from birth through 18 years of age. Through its federal contracts and centralized distribution system, CDC purchases and distributes vaccines to a network of more than 44,000 enrolled provider sites each year. The nationwide VFC program is responsible for vaccinating more than half of U.S. children annually. CDC also provides vaccines to 64 immunization program awardees for vaccinating uninsured, poor adults, and for use in outbreak responses.

CDC conducts communications research and develops evidence-based tools, training, and resources about immunization for the public and health care providers. CDC's health communications work is focused on describing the benefits of vaccines and risks of vaccine-preventable diseases, and responding to frequently asked questions about vaccines. CDC also implements a robust provider education program on topics ranging from how to make a recommendation to answering questions about vaccine safety.

Through the National Immunization Survey, the National Health Information Survey, and the Behavioral Risk Factor Surveillance System, CDC measures childhood, adolescent, and adult immunization coverage. CDC uses these data to inform program decisions and to reduce disparities in immunization coverage.

Post-marketing vaccine safety and effectiveness: Following introduction of a new or improved vaccine recommendation, CDC and FDA collaborate on conducting studies to monitor the impact of the vaccine in the community setting. This work includes monitoring vaccine safety through VAERS in collaboration with FDA, and conducting vaccine safety studies through the Vaccines Safety Datalink (VSD) network and the Clinical Immunization Safety Assessment (CISA) network.

CDC also conducts post-marketing studies to evaluate the effectiveness of vaccines. These studies help characterize the performance of vaccines when used routinely among the recommended population. The findings from these studies are used by vaccine manufacturers and FDA in making decisions to revise the license; and by ACIP and CDC in making decisions on recommendations for the use of vaccines, such as number of doses, time intervals, and recommended populations.

Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response

BARDA's mission is to develop and procure needed medical countermeasures (MCMs) including vaccines against chemical, biological, radiological, and nuclear (CBRN) agents; emerging infectious diseases; and pandemic influenza, whether natural or intentional in origin. BARDA funding bridges the "valley of death," the critical juncture between R&D and late stages of product development where funding requirements significantly increase and many development programs are forced to stop due to lack of funding. BARDA provides non-dilutive funds for the late stage development of new product technologies toward approval, clearance, or licensure of MCMs. Many such MCMs lack meaningful commercial markets and, without USG support, would be unlikely candidates for development.

BARDA fulfills its mission by supporting advanced R&D of needed MCMs; working in collaboration with manufacturers, NIH, CDC, FDA, DoD, and the Department of Homeland Security (DHS); supporting technology innovation through strategic initiatives; and managing acquisitions for stockpiling. Although originally envisioned as a preparedness organization, BARDA is also responsible for developing capabilities to respond to novel and emerging threats such as the recent MERS, Ebola, and Zika outbreaks. The research, development, procurement, stockpiling, and deployment of MCMs needed to protect the public in the event of a public health emergency is the responsibility of multiple departments and agencies in the USG, which constitute the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The PHEMCE is an interagency coordinating body led by the HHS Assistant Secretary for Preparedness and Response. It includes interagency partners from CDC, FDA, NIH, DoD, DHS, Veterans Affairs (VA), and the U.S. Department of Agriculture (USDA). It coordinates the development, acquisition, stockpiling, and recommendations for use of medical products needed to effectively respond to a variety of high-consequence public health emergencies, whether naturally occurring or intentional.

BARDA achieves its mission by establishing public-private partnerships through several approaches:

Direct advanced research and development support: BARDA maintains contracts with commercial parties to carry out a comprehensive set of tasks that comprise the technical, regulatory, clinical, and manufacturing components of MCM development. While the cost of these services is reimbursed by the USG, the FDA license and the right to sell the final product commercially belongs to the commercial partner. This approach has been successful with pandemic influenza vaccines and, thanks to USG support and BARDA and NIH efforts, it has led to the development of cell-based, recombinant, and adjuvanted seasonal influenza formulations.

Core services support: Through several networks, BARDA provides a variety of product development services (e.g., safety and efficacy studies in animal models, manufacturing filling and finishing services, clinical study support from designing clinical protocols to managing clinical trial sites).

Leveraging investments in technologies: BARDA supports platform technologies that streamline development and manufacture of MCMs against novel or emerging microbial pathogens. Investments in platform technologies may play a key role in refining or expediting vaccine development and manufacturing in ways that make it more amenable for biodefense or public health programs.

BARDA is implementing innovative public-private partnerships. Agreements under its "Other Transaction Authority"[5] enable flexible advanced research and development funding to attract non-traditional government contractors and stimulate innovative vaccine development, overcoming contracting constraints under the Federal Acquisition Regulations.

National Vaccine Program Office (NVPO)

Created in 1987 to provide leadership and coordination among federal and non-federal stakeholders on vaccine-related activities, NVPO works to ensure activities are carried out in an efficient, consistent, and timely manner. NVPO's efforts include:

Strategic leadership and coordination: NVPO prepares and issues the National Vaccine Plan which establishes priorities across the vaccine system. This includes providing strategic direction for vaccine research, development, safety and efficacy testing, licensure, production and procurement, and the distribution and use of vaccines. It also involves evaluating the need for further effectiveness or adverse effect studies. The plan, which is developed in collaboration with federal and non-federal partners, is designed to be reviewed and updated annually.

Coordinating the National Vaccine Advisory Committee: NVPO staffs and oversees the National Vaccine Advisory Committee (NVAC), a federal advisory committee

[5] Authority for Other Transactions was established by Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006. Additional information can be found here: http://www.phe.gov/about/amcg/otar/pages/default.aspx

charged to advise and make recommendations to the Assistant Secretary for Health on the means to achieve optimal prevention of human infectious diseases through immunization. Specifically, NVAC studies and recommends ways to encourage the availability of an adequate supply of safe and effective vaccines in the United States; recommends research priorities and other measures to enhance the safety and efficacy of vaccines; advises on the implementation of the national vaccine program responsibilities; and annually identifies the most important areas of federal and non-federal cooperation that should be considered in implementing the national vaccine program responsibilities.

VI. Innovation Challenges and Opportunities

The U.S. vaccine enterprise is well established and has been successful in bringing numerous new and improved products to the market. Federal agencies are central in this role, supporting key components of the vaccine enterprise **(Table 1)**. Government policies can support an enabling environment within the vaccine enterprise. A recent example is a change to the Vaccine Injury Compensation Program (VICP), a federal program that provides compensation to individuals injured by certain vaccines. While the VICP has always covered vaccines recommended by the CDC for routine administration to children, the passage of the 21st Century Cures Act expanded VICP coverage to include vaccines recommended by the CDC for routine administration in pregnant women. This important expansion of VICP coverage encourages innovation and development by expanding liability protections under the National Childhood Vaccine Injury Act of 1986.

Challenges and Opportunities

The remaining targets for vaccine development are challenging the enterprise: they are scientifically complex; may require new tools to evaluate their safety and efficacy; target sub-populations most impacted by disease rather than the general population; and may not be considered high public health priorities. Addressing these new and different challenges by reducing or eliminating potential obstacles may shift the balance of risk and reward to favor investments in innovation**.**

As a participant in the vaccine network, USG actions and policies can act as levers to promote vaccine innovation and address many of the challenges characterized in this report. Four specific challenges are described below; potential opportunities (italicized) to enhance existing activities and implement new efforts are also presented. Such activities are supported by multiple HHS agencies and offices.

- **Limited understanding of the science to develop optimal vaccines.** There is a limited understanding of the pathogenesis and immune responses against some targeted infectious agents, lack of optimal immune response to potential vaccine candidates, and a limited understanding of the mechanism of protection of some vaccine

candidates. Correlates of protection may be required for a vaccine candidate to be measured as effective. These correlates may not exist for some candidates.

Opportunity: Enhancing scientific understanding of mechanisms involved in immune responses to infection and vaccination. *Basic and applied science is the foundation of vaccine development. The USG, through NIH and CDC, provides substantial support for studies to better understand key immunological characteristics of vulnerable populations, such as neonates, infants, and the elderly, that are aimed at developing more effective vaccines to protect these groups. Federal investments in adjuvant discovery and development show promise in exhibiting different immune stimulatory properties. This provides a tool box for developers looking to produce novel vaccine candidates for specific age groups (e.g., the very young and older adults). Additionally, continued support for translational research and clinical vaccine development and evaluation can be critical for innovative products, particularly for small companies that do not have the resources to fully develop a product.*

- **Challenging clinical trial design for specific populations.** Conducting clinical trials to evaluate the safety and efficacy of certain preventive vaccines may be particularly challenging for several reasons, including: relatively low disease incidence (e.g., congenital cytomegalovirus disease; neonatal group B streptococcal disease); limited infrastructure in affected geographic areas (e.g., Ebola virus vaccines), ethical considerations (e.g., assessing novel approaches to pertussis vaccination of pregnant women to prevent neonatal pertussis where vaccination of pregnant women is already recommended); or new settings (e.g., hospital acquired infections).

  Opportunity: Using regulatory flexibility and novel scientific tool development. *FDA's implementation of innovative and flexible regulatory mechanisms and pathways has ensured that approval of vaccine candidates keeps pace with technological and scientific advances. FDA recognizes that novel scientific tools will be necessary to translate scientific discoveries into safe and effective vaccines for infectious diseases that address important health concerns and benefit public health. To this end, FDA has efforts underway regarding the development and use of novel clinical trial designs, including the use of biomarkers, innovative statistical analysis techniques, and real world evidence to facilitate vaccine innovation and development as described in* ***Table 5****.*

- **Converging regulatory requirements across countries.** Regulatory convergence across countries may decrease the resources required to engage in a global market. Increasing opportunities to align regulatory processes and, where possible, regulatory standards could cut redundancies, time, and costs associated with navigating requirements in multiple countries.

  Opportunity: Enhancing global activities. *Using FDA best practices to expand regulatory convergence may decrease the resources required by companies to engage in a global market. Examples include adoption of internationally recognized technical guidance documents, standards and scientific principles, common or similar practices*

and procedures, or adoption of regulatory mechanisms that might be specific to a local legal context, but that align with shared principles to achieve a common public health goal. Improving coordination with other countries such as agreement on clinical endpoints, where feasible, and assay and batch-release testing results, could have an impact on timelines and vaccine availability.

- **Uncertain ROI for new and improved vaccines.** The greater the uncertainty in the technical development, regulatory licensure, and vaccine uptake, the higher the risk to industry. Unclear estimates of disease burden, including mortality and morbidity estimates; future ACIP recommendations; insurance coverage; perception of individual risk; and patient and health care provider belief in the value of the vaccine product all contribute to uncertainty.

Opportunities:

Increasing surveillance and epidemiological studies. *Epidemiological surveillance is critical to (1) assess disease burden that informs which targets are important to public health for development; such data supports clinical trial design and shapes the final target product profile of the vaccine; and (2) identify needs for new vaccines or effectiveness concerns among existing vaccines. CDC gathers reliable epidemiological data to support clinical trial design and shape the final product profile of the vaccine. CDC and NIH also support efforts to enhance global activities in surveillance as well as development of global clinical trial sites. If the epidemiology of a disease shifts, reliable epidemiological data is required to understand the burden of disease and confirm the specific population at risk for the disease to determine whether vaccination is an appropriate strategy and if current development programs are on target.*

Enhancing communication frequency and transparency with the USG and external stakeholders including industry. *Continued communication between FDA and industry can decrease regulatory uncertainty by discussing data needed for a desired indication in the early stages of development. Further, with regard to potential recommendations for use, improved communication between CDC and industry may help reduce uncertainty about the implementation of new vaccine policy and programs. In addition, CDC has standardized ACIP working group guidelines so various working group approaches and timelines for communicating with vaccine developers are more predictable.*

Improving vaccine uptake. *Uptake of existing vaccines in a given population may predict uptake of new vaccines in that population. Ongoing efforts to improve vaccine uptake across the lifespan and among persons at increased risk for vaccine-preventable diseases or their complications should be sustained. Increasing uptake of currently available vaccines supports investments in new vaccines by increasing the projected market for new products.*

Public-private partnerships. *Historically, vaccine innovation has been driven by disease epidemiology, burden, and severity. However, for some high priority vaccine*

targets, public-private partnerships are central to facilitating development. Vaccines for pandemic influenza preparedness or biodefense, such as smallpox and anthrax vaccines, are purchased solely by the government as there is no viable commercial interest or market. In such situations, public-private partnerships are leveraged. For example, BARDA's advanced vaccine development and procurement programs are conducted in partnership with industry as a critical component of public health preparedness against a wide range of threats. Development of vaccines with small markets or a low estimated ROI could benefit from public-private partnerships with federal support. Public-private partnerships are important to facilitate development of high-priority products. USG investment could be leveraged to develop certain vaccines that would not be undertaken without incentives.

VII. Conclusion

Much progress has been made in understanding the complex scientific issues inherent in making a vaccine; adapting regulatory needs to a changing environment; and supporting policies that facilitate progress and innovation. Sustained USG investments in critical areas are needed to translate advances in science and discovery into vaccine innovations that improve health and quality of life in the United States. Catalytic investments in some areas as identified above may further propel innovations toward licensure and delivery. For example, a systematic, evidence-based process to assess and communicate public health needs for new and improved vaccines, including a critical review of disease epidemiology, the merits of individual targets, gaps in information, and efforts to address these gaps could spur innovation. Understanding the issues facing key stakeholders and their respective roles and contributions to the vaccine network could also help unify and focus efforts on several vaccine targets while strengthening the U.S. vaccine enterprise to face future challenges in the decades to come. Innovative and flexible public-private partnerships are essential to incentivize development of vaccines that would not otherwise reach licensure due to unfavorable ROI as compared to other therapeutic products.

As a result of continuous development and innovation, vaccines have had a profound impact, protecting Americans across the lifespan. This report outlines challenges and opportunities facing the vaccine enterprise that, if addressed, could spur continued progress and innovation toward the availability of future vaccines to improve public health in the 21st century.

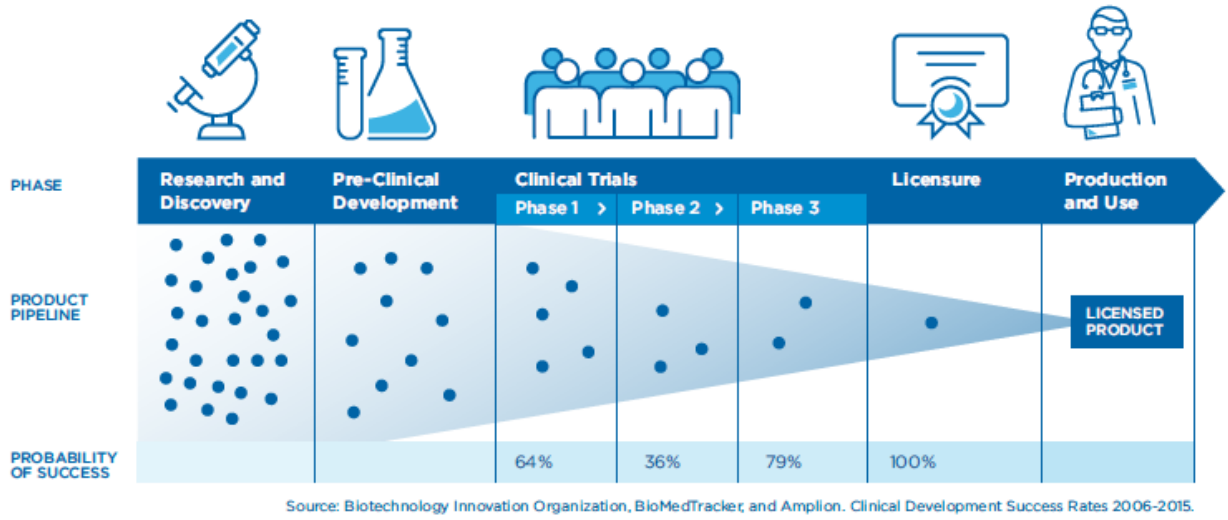
List of Tables and Figures

Table 1: Components of the U.S. Vaccine Enterprise

Components	Description
Basic & Applied Research	Improve the knowledge base regarding the antigenic components of infectious agents, underlying mechanisms of infectious disease, the human immune system, and host-pathogen interactions. Develop applied research tools (e.g. animal models) on host protection, development, and evaluation of vaccine candidates.
Product Development*	Develop the "target product profile", a high level summary of characteristic traits and key features of the product (e.g., number of doses, target population). Conduct proof of concept studies (e.g., use of data from animal models, assay development). Develop a clinical program that involves studies in humans to determine the effects of vaccines for safety, immunogenicity, and efficacy through a staged process. Process development leading to consistent manufacturing of the final vaccine.
Regulatory Evaluation and Licensure	Evaluate vaccine safety and efficacy in proposed target populations (e.g., children, adults) encompassing an assessment of manufacturing data, methodologies and assays to assess safety, purity, and potency, pre-clinical safety and proof-of concept data derived from animal studies as well as data derived from human clinical trials.
Recommendations for Introduction and Use	Provide recommendations for use to indicate which civilian populations should receive a vaccine and under what conditions (e.g., indications and contraindications), including recommendations for the number and timing of doses as well as the route of administration for both adult and pediatric populations. Recommendations take into account the risk-benefit of vaccination.
Vaccine Uptake	Support the immunization delivery system to ensure all individuals across the lifespan have access to the Advisory Committee on Immunization Practice-recommended vaccines and vaccinations and monitor the impact of vaccine uptake, safety, and effectiveness.

*Disease burden and epidemiology inform the development of the vaccine product and the target product profile.

Figure 1: Probability of Success across Phases of Vaccine Development



Source: Biotechnology Innovation Organization, BioMedTracker, and Amplion. Clinical Development Success Rates 2006-2015.

Table 2: Medicines in Development for Vaccines, 2017 Update (as of October 23, 2017)

*The content of this report has been obtained through public, government and industry sources, and the Springer "Adis Insight" database based on the latest information. This report is current as of October 23, 2017. The medicines in this listing include medicines being developed by U.S.-based companies conducting trials in the United States and abroad, PhRMA-member companies conducting trials in the United States and abroad, and foreign companies conducting clinical trials in the United States. Some products may not be in active clinical trials.

This information is not comprehensive. The entire portfolio of vaccines in clinical development in the United States is available at clinicaltrials.gov. The table provided here is reproduced from the source and include only infectious disease vaccine candidates (https://www.phrma.org/report/list-of-medicines-in-development-for-vaccines-2017). Clarifications provided by HHS are noted in the source notes.

Indication	Vaccine Name	Sponsors	Development Phase
Adenovirus infections (prevention)	PXVX0047 (adenovirus type 4 and type 7 vaccine)	PaxVax	Phase 1
Anthrax (pre-exposure prevention) (Fast Track)	**NuThrax**™ anthrax vaccine adsorbed with CPG 7909 adjuvant	Emergent BioSolutions	Phase 2
Anthrax (prevention)	Px563L (recombinant protective antigen vaccine)	Pfenex	Phase 1
Chikungunya infections (prevention)	Chikungunya vaccine (virus-like particle vaccine)	PaxVax	Phase 2
Chikungunya virus infections (prevention)	mRNA-1388 (messenger RNA vaccine)	Moderna Therapeutics	Phase 1
Cholera (prevention) (pediatric)	**Vaxchora**® cholera vaccine, live, oral	PaxVax	Phase 3
Clostridium difficile infections (prevention)	VLA-84; (recombinant fusion protein vaccine)	Valneva	Phase 2
Clostridium difficile infections (prevention) (Fast Track)	Clostridium difficile toxoid vaccine	Sanofi Pasteur	Phase 3
Primary *clostridium difficile* infection (prevention) (Fast Track) (adults, elderly)	PF-06425090 (adjuvant-formulated modified vaccine) vaccine)	Pfizer	Phase 3
CMV infections (prevention)	VBI-1501A	VBI Vaccines	Phase 1

Indication	Vaccine Name	Sponsors	Development Phase
CMV infections in patients under- going stem cell transplantation (prevention)	**Pepvax** cytomegalovirus peptide vaccine	Helocyte	Phase 2
CMV infections in patients under- going stem cell transplantation (prevention)	**Triplex** cytomegalovirus peptide vaccine	Helocyte	Phase 2
Cytomegalovirus (CMV) infections in transplant patients (prevention)	ASP0113 (bivalent plasmid DNA-based vaccine) ORPHAN DRUG	Astellas; Vical	Phase 3
Dengue (prevention)	TAK-003 (dengue vaccine)	Takeda Pharmaceuticals	Phase 3
Dengue (prevention)	TDENV (tetravalent dengue virus vaccine)	GlaxoSmithKline; U.S. Army Medical Research and Materiel Command	Phase 1/2
Dengue (prevention)	V180 (tetravalent subunit vaccine)	Merck	Phase 1 completed
Dengue (prevention) (Fast Track)	**Dengvaxia**® dengue tetravalent vaccine	Sanofi Pasteur	Phase 2
Diphtheria, haemophilus, hepatitis B, pertussis, polio, tetanus (prevention)	**Infanrix Hexa**® combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B (recombinant), inactivated polio-myelitis, and adsorbed conjugated *Haemophilus influenzae* type b vaccine	GlaxoSmithKline	Phase 3
DTP-HepB-polio-Hib infections (prevention) (infants)	PR5i (V419) (pediatric hexavalent combination vaccine)	Merck; Sanofi Pasteur	application submitted
Ebola virus infections (prevention)	Ebola recombinant viral vector vaccine	GlaxoSmithKline	Phase 2
Ebola virus infections (prevention)	Ebola virus vaccine (Ad26 EBOV vaccine)	Janssen Vaccines & Prevention	Phase 3
Ebola virus infections (prevention)	Ebola virus vaccine + Matrix-M™	Novavax	Phase 1
Ebola virus infections (prevention)	INO-4212 (polyvalent DNA based vaccine)	Inovio Pharmaceuticals	Phase 1
Ebola virus infections (prevention)	MVA-BN Filo (monovalent vaccine)	Bavarian Nordic; Janssen Vaccines and Prevention	Phase 3

Indication	Vaccine Name	Sponsors	Development Phase
Ebola virus infections (prevention)	V920 (Ebola vaccine)	Merck	Phase 3
Ebola virus infections (prevention), Marburg virus infections (prevention) (adults, elderly)	MVA-BN Filo (multivalent vaccine)	Bavarian Nordic; Janssen Vaccines and Prevention	Phase 2
Ebola/Marburg virus infections;(prevention)	**VesiculoVax**™; Ebola virus vaccine	Profectus Biosciences	Phase 1
Enterovirus A infections (prevention)	TAK-021 (EV71 enterovirus A vaccine)	Takeda Pharmaceuticals	Phase 1
Escherichia coli infections (prevention)	JNJ-63871860 (multivalent glycoprotein conjugate vaccine)	Janssen Vaccines and Prevention	Phase 2 completed
Falciparum malaria (prevention)	PfSPZ-Cvac (live unattenuated malaria vaccine plus chloroquine)	Sanaria	Phase 1
Falciparum malaria (prevention) (Fast Track)	PfSPZ-GA1 (live attenuated malaria vaccine)	Sanaria	Phase 2
Hemorrhagic fever caused by hantaan virus and puumala virus (prevention)	HTNV/PUUV DNA vaccine	Ichor Medical Enterprises; United States Army Medical Research and Materiel Command	Phase 2
Hepatitis B (prevention)	**HEPLISAV-B** HBsAg-1018 vaccine	Dynavax Technologies	application submitted*
hepatitis B, diphtheria, tetanus, pertussis (DTP), haemophilus infections, poliomyelitis (prevention)	Shan 6 (DTP-HepB-Polio-Hib pediatric hexavalent vaccine)	Sanofi Pasteur	Phase 2
Hepatitis C (prevention)	hepatitis C vaccine (recombinant viral vector vaccine)	GlaxoSmithKline	Phase 2
Herpes zoster (prevention)	V212 (inactivated VZV vaccine)	Merck	Phase 3
HIV infection (prevention)	**PENNVAX®-GP** Clade A, B, C, D HIV DNA vaccine	Inovio Pharmaceuticals	Phase 1
HIV infections (prevention)	GOVX-B11 (clade-B DNA HIV vaccine)	GeoVax Labs	Phase 2
HIV infections (prevention)	HIV recombinant proteins vaccine	GlaxoSmithKline	Phase 2

Indication	Vaccine Name	Sponsors	Development Phase
HIV infections (prevention)	HIV vaccine (Ad26 Mos HIV trivalent vaccine)	Janssen Vaccines and Prevention	Phase 2
HIV infections (prevention)	HIV vaccine (Ad26 Mos HIV vaccine)	Janssen Vaccines and Prevention	Phase 2
HIV infections (prevention)	HIV vaccine (MVA mosaic HIV vaccine)	Janssen Vaccines and Prevention	Phase 1/2
HIV infections (prevention)	HIV vaccine (prime-boost vaccine)	Sanofi Pasteur	Phase 2
HIV infections (prevention)	HIV vaccine Ad4-Clade C	PaxVax	Phase 1
HIV infections (prevention)	HIV vaccine Ad4-mGag	PaxVax	Phase 1
HIV infections (prevention)	IHV001 (subunit HIV vaccine)	Profectus Biosciences	Phase 1
HIV infections (prevention)			Phase 1
HIV infections (prevention) (combination with other HIV vaccines)	DNA-C (DNA HIV vaccine)	EuroVacc; National Institute of Allergy and Infectious Diseases	Phase 1/2
HIV-1 infections (combination therapy)	AGS-004 (autologous dendritic cell vaccine)	Argos Therapeutics	Phase 1
Hookworm infections (prevention)	Na-APR-1(hookworm monovalent vaccine)	Sabin Vaccine Institute	Phase 1 completed
HSV-type 2 infections (prevention)	HSV529 (herpes simplex virus type 2 vaccine)	Sanofi Pasteur	Phase 1
Infections (prevention)	mRNA MRK-1777 (messenger RNA vaccine)	Merck; Moderna Therapeutics	Phase 1
Influenza (prevention)	deltaFLU-LAIV (influenza virus delta NS1 vaccine)	Vivaldi Biosciences	Phase 2
Influenza (prevention)	**FluNhance**™ recombinant influenza vaccine	Protein Sciences	Phase 2
Influenza (prevention)	influenza A virus vaccine H1N1 (Ii-key hybrid cancer vaccine)	Antigen Express	Phase 1
Influenza (prevention)	influenza A virus vaccine H5N1 (Ii-key hybrid cancer vaccine)	Antigen Express	Phase 1
Influenza (prevention)	influenza A virus H5N8 vaccine	Seqirus	Phase 1

Indication	Vaccine Name	Sponsors	Development Phase
Influenza (prevention)	influenza A virus H7N9 vaccine	EpiVax	Phase 1
Influenza (prevention)	influenza H3N2 vaccine (intranasal)	FluGen	Phase 1
Influenza (prevention)	influenza virus vaccine quadrivalent (aQIV-aQIV)	Seqirus	Phase 3
Influenza (prevention)	M-001 (universal influenza vaccine)	BiondVax; National Institute of Allergy and Infectious Diseases	Phase 2
Influenza (prevention)	mRNA-1440 (influenza virus H10N8 messenger RNA vaccine)	Moderna Therapeutics	Phase 1
Influenza (prevention)	mRNA-1851(influenza virus H7N9 messenger RNA vaccine)	Moderna Therapeutics	Phase 1
Influenza (prevention)	VXA-A1.1-H1 (H1N1); (oral influenza vaccine)	Vaxart	Phase 2
Influenza (prevention) (6-<48 months of age)	**Flucelvax**® influenza vaccine	Seqirus	Phase 1/2 completed
Influenza (prevention) (6-35 months of age)	**VaxiGrip® QIV IM** quadrivalent inactivatedinfluenza vaccine	Sanofi Pasteur	Phase 3
Influenza (prevention) (6-59 months of age)	**Afluria Quadrivalent**® influenza vaccine	Seqirus	Phase 3 completed
Influenza (prevention) (adults, elderly)	influenza A virus H5N1 vaccine	Seqirus	Phase 3
Influenza (prevention) (elderly)	**Fluzone® QIV HD** quadrivalent inactivated influenza vaccine - high dose	Sanofi Pasteur	Phase 3
Influenza (prevention) (elderly)	MER4101 (MAS-1-adjuvanted seasonal inactivated influenza vaccine)	Mercia Pharma	Phase 1
Invasive and non-invasive pneumococcal infections	PF-06482077 (pneumococcal vaccine)	Pfizer	Phase 1
Invasive Group B Streptococcus infections (prevention)	PF-06760805(multivalent vaccine)	Pfizer	Phase 1

Indication	Vaccine Name	Sponsors	Development Phase
Invasive *Staphylococcus aureus* infections in surgical populations (prevention) (Fast Track)	PF-06290510 (4-antigen Staphylococcus aureus vaccine)	Pfizer	Phase 2
Lyme disease (prevention) (Fast Track)	VLA15-101; (hexavalent protein subunit vaccine)	Valneva	Phase 1
Malaria (prevention) (plasmodium falciparum)	malaria next generation vaccine (recombinant)	GlaxoSmithKline	Phase 2
Measles, mumps, rubella (prevention) (pediatric)	MMR vaccine	GlaxoSmithKline	Phase 3
Meningococcal A,B,C,W and Y disease (prevention) (adolescents)	Men ABCWY vaccine	GlaxoSmithKline	Phase 2
Meningococcal A,C,W,Y disease	NmVac-4 A/C/Y/W-135 DT (meningococcal conjugate vaccine)	JN-International Medical	Phase 2 completed
Meningococcal A,C,W,Y disease (prevention) (adults, children, elderly)	Men Quad TT (second-generation meningococcal ACYW conjugate vaccine)	Sanofi Pasteur	Phase 3
Middle East respiratory syndrome(MERS) (prevention), coronavirus infections (prevention)	GLS-5300 (DNA vaccine)	GeneOne Life Science; Inovio Pharmaceuticals	Phase 1
Mosquito-transmitted viral infections (prevention)	AGS-v (protein-based vaccine)	Imutex; National Institute of Allergy and Infectious Diseases	Phase 1
Multi-season influenza (prevention)	**CodaVax**® influenza A virus H1N1 vaccine	Codagenix	Phase 1
Norovirus infections (prevention)	VXA-G1.1-NN (oral norovirus vaccine)	Vaxart	Phase 1
Norovirus infections (prevention); (adults, elderly)	TAK-214 (norovirus vaccine)	Takeda Pharmaceuticals	Phase 2
Pandemic influenza (prevention)	**PanBlok** influenza virus vaccine	Protein Sciences	Phase 2
PNAG-expressing bacterial infections (prevention and treatment)	AV0328 (conjugated oligosaccharide vaccine against dPNAG [deacetylated polymeric- N-acetyl glucosamine])	Alopexx Vaccine	Phase 1/2

Indication	Vaccine Name	Sponsors	Development Phase
Pneumococcal infections (prevention) (adults, children, elderly)	V114 (pneumoconjugate 15-valent vaccine)	Merck	Phase 2
Poliomyelitis (prevention)	TAK-195 (sabin-strain inactivated polio vaccine)	Takeda Pharmaceuticals	Phase 1
Rabies (prevention)	Rabies VRVg (purified vero rabies vaccine)	Sanofi Pasteur	Phase 2
Recurrent vulvovaginal candidiasis (prevention)	NDV-3 (alum-adjuvanted recombinant protein vaccine)	NovaDigm Therapeutics	Phase 1/2
Reduction of recurrent urinary tract infections caused by multi-drug resistant bacteria (Fast Track)	UTI vaccine	Sequoia Sciences	Phase 1
Reduction of the frequency of COPD exacerbations associated with non-typeable haemophilus influenza and moreaxella catarrhalis	haemophilus recombinant vaccine	GlaxoSmithKline	Phase 2
Respiratory syncytial virus (RSV) infections (prevention)	JNJ-61187165 (RSV vaccine)	Janssen Vaccines and Prevention	Phase 1 completed
Rotavirus infections (prevention)	rotavirus vaccine	PATH; SK Chemicals	Phase 2
RSV (prevention) (maternal immunization)	RSV recombinant vaccine	GlaxoSmithKline	Phase 2
RSV infections (prevention)	JNJ-61187191 (RSV vaccine)	Janssen Vaccines and Prevention	Phase 1 completed
RSV infections (prevention)	RSV vaccine(replication-defective recombinant vaccine)	GlaxoSmithKline	Phase 2
RSV infections (prevention)	VXA-RSV-f (oral RSV vaccine)	Vaxart	Phase 1
RSV infections (prevention) (6 months-5 years of age) (Fast Track)			Phase 1
RSV infections (prevention) (adults, elderly)	MVA-BN RSV (recombinant RSV vaccine)	Bavarian Nordic	Phase 2

Indication	Vaccine Name	Sponsors	Development Phase
RSV infections (prevention) (elderly)	JNJ-64400141 (RSV vaccine)	Janssen Vaccines and Prevention	Phase 1
RSV infections (prevention) (elderly) (Fast Track)			Phase 2
RSV infections (prevention) (infants)	MEDI8897/SP0232 (monoclonal antibody vaccine)	MedImmune; Sanofi Pasteur	Phase 2/3
RSV infections (prevention) (maternal immunization) (Fast Track)	RSV F protein vaccine	Novavax	Phase 3
RSV infections in infants (prevention)	RSV vaccine	Sanofi Pasteur	Phase 1
Seasonal influenza (prevention)	influenza virus vaccine quadrivalent (plant-based VLP vaccine)	Medicago	Phase 3
Seasonal influenza (prevention)	NB-1008 (influenza intranasal vaccine)	NanoBio	Phase 1
Seasonal influenza (prevention) (elderly)			Phase 2
Seasonal influenza (prevention) (elderly)	**Nanoflu**™ seasonal influenza nanoparticle vaccine	Novavax	Phase 1
Seasonal influenza (prevention), pandemic influenza (prevention)	**NasoVAX**™ recombinant influenza vaccine(intranasal)	Altimmune	Phase 2
Seasonal influenza subtypes A and B (prevention) (6-35 months of age)	**Fluarix® Quadrivalent** influenza vaccine	GlaxoSmithKline	application submitted
Serogroups ABCWY meningococcal infections (prevention)	PF-06886992	Pfizer	Phase 1
Shigella diarrhea (prevention)	Shigella conjugated and outer membrane vaccine	GlaxoSmithKline	Phase 2
Shigella infections (prevention) (Fast Track)	Shigella vaccine (Flexyn2a)	LimmaTech Biologics	Phase 2
Smallpox (prevention) (freeze-dried)			Phase 2
Smallpox (prevention) (liquid-frozen)	**Imvamune®** smallpox vaccine	Bavarian Nordic	Phase 3
Streptococcal B infections (prevention) (maternal immunization)	Streptococcal B conjugated vaccine	GlaxoSmithKline	Phase 2

Indication	Vaccine Name	Sponsors	Development Phase
Streptococcus pneumonia disease(prevention) (infants)	S. pneumococcal next-generation vaccine	GlaxoSmithKline	Phase 2
Tdap booster (prevention)	**Adacel+** tetanus, diphtheria, acellular pertussis (Tdap) booster vaccine	Sanofi Pasteur	Phase 2
Toxic shock syndrome from Staphylococcus enterotoxin B exposure (prevention)	**STEBVax** recombinant detoxified SEB vaccine	Integrated Biotherapeutics	Phase 1
Tuberculosis (prevention)	tuberculosis recombinant subunit vaccine	Sanofi Pasteur	Phase 2
Tuberculosis (prevention)	tuberculosis recombinant vaccine	GlaxoSmithKline	Phase 2
West Nile virus infections (prevention)	HBV-002 (recombinant subunit vaccine)	Hawaii Biotech	Phase 1
Yersinia infections (prevention)	plague injectable vaccine ORPHAN DRUG	DynPort Vaccine	Phase 2
Zika virus infections (prevention)	GLS-5700 (DNA-based synthetic vaccine)	GeneOne Life Science; Inovio Pharmaceuticals	Phase 1
Zika virus infections (prevention)	mRNA-1325 (messenger RNA vaccine)	Moderna Therapeutics	Phase 1/2
Zika virus infections (prevention)	Zika virus vaccine (inactivated Zika vaccine)	Sanofi Pasteur	Phase 1

*Vaccine FDA-approved November 10, 2017

Source Notes:

Fast Track—upon request by a sponsor, the FDA can grant this designation to facilitate the development and expedite the review of a drug or biologic to treat a serious condition and fill an unmet medical need. When considering a biopharmaceutical company's request for Fast Track designation for an investigational drug or biologic, the FDA evaluates whether it will affect factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one, and whether a condition can be adequately addressed by available therapy. With Fast Track designation, early and frequent communication between the FDA and the biopharmaceutical company is encouraged throughout the entire drug development and review process to help to quickly

resolve any questions or issues that arise, potentially leading to an earlier approval and access by patients.

Orphan Designation—Upon request by a sponsor, the FDA can grant special status ("orphan status") to a drug or biologic to treat a rare disease or condition. In order to receive an orphan designation, a qualifying drug or biologic must be intended for the treatment, diagnosis, or prevention of a rare disease or condition that affects usually fewer than 200,000 people in the United States.

Phase 1—Researchers test the investigational drug or biologic in a small group of people, usually between 20 and 100 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Phase 2—The investigational drug or biologic is given to volunteer patients, usually between 100 and 500, to determine whether it is effective, identify an optimal dose, and to further evaluate its short-term safety.

Phase 3—The investigational drug or biologic is given to a larger, more diverse patient population, often involving between 1,000 and 5,000 patients (but sometimes many more), to generate statistically significant evidence to confirm its safety and effectiveness. Phase III studies are the longest studies and usually take place in multiple sites around the world.

Source: https://www.phrma.org/report/list-of-medicines-in-development-for-vaccines-2017

Table 3: Expedited Regulatory Pathways Applicable for Vaccines

Pathway	Description
Breakthrough Therapy Designation	The Food and Drug Administration Safety and Innovation Act established this program in 2012. Breakthrough Therapy designation is based on the following criteria: 1) The product is intended to be used alone or in combination with one or more drugs to treat a serious or life-threatening disease or condition and 2) Preliminary clinical evidence indicates that the product may demonstrate substantial improvement on a clinically significant study endpoint(s) over available therapies. Breakthrough therapy designation provides the manufacturer more intensive FDA guidance on an efficient vaccine development program, thereby facilitating the scientific evaluation during the Investinational New Drug Application (IND) stage; an organizational commitment involving senior managers and experienced review staff. FDA may consider a "rolling review" of the Biologics License Application (BLA); this allows sponsors to submit sections of the BLA to FDA for review as they are completed, as opposed to waiting to submit the complete BLA at one time. *FDA has approved two vaccines that had Breakthrough Therapy designation, both for*

	the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroup B.
Fast Track Designation	The Food and Drug Administration Modernization Act of 1997 mandates the Agency to, at the request of the sponsor, facilitate the development and expedite review of drugs, including biological products, intended to treat serious or life-threatening diseases or conditions and that demonstrate the potential to address unmet medical needs. Fast Track adds to existing programs, such as accelerated approval, the possibility of a "rolling review" for an application. An important feature of fast track is that it emphasizes the critical nature of close and early communication between FDA and the sponsor to improve the efficiency of product development. *Numerous vaccines have been approved that received Fast Track Designation, including vaccines for the prevention of cervical cancer and cholera.*
Priority Review	Vaccines that hold the promise of delivering a significant improvement over existing therapy for serious or life-threatening conditions can be designated for “priority” review, and a shortened six-month FDA review goal. *Numerous vaccines have been approved that had Priority Review status, including vaccines to prevent cervical cancer, invasive meningococcal serogroup B disease, cholera, and pneumococcal conjugate vaccines.*
Accelerated Approval	This program, begun in the early 1990s, allows FDA to approve products for serious or life-threatening conditions based on evidence of a product’s effectiveness that is reasonably likely to predict clinical benefit, reducing the time it takes for needed medical products to become available to the public. Such approval may be subject to verification of clinical benefit through additional studies conducted after approval (Phase 4 studies). *Since its creation, the accelerated approval program has been used to approve numerous vaccines, including those to prevent influenza, Haemophilus influenzae Type b (Hib) and invasive meningococcal disease caused by Neisseria meningitidis serogroup B.*

Table 4: Innovative Regulatory Mechanisms

Mechanism	Description
Animal Rule	In 2002, a rule was promulgated that allows animal efficacy data to be used as a basis for approval, when human efficacy studies are not ethical or feasible to conduct. The relevant regulations permits FDA to license vaccines based on adequate and well controlled animal studies when the results of those animal studies establish that the vaccine is reasonably likely to produce clinical benefit in humans, provided that safety in humans has been established. The use of anthrax vaccine for the prevention of anthrax after suspected or confirmed exposure to Bacillus anthracis when used with recommended antimicrobial therapy was approved using the Animal Rule pathway.
Adaptive Trial Designs	FDA is actively involved in working with sponsors to help develop adaptive trial designs. Using this approach, the FDA is seeking to

	facilitate efficient clinical development and to assure FDA confidence in the results. The goal of these designs is to reduce the size and duration of the trial, demonstrate an effect if one exists or provide broader dose-response information. These adaptations are performed with close attention to statistical rigor.

Table 5: Novel Approaches to Clinical Trials

Approach	Description
Biomarkers	A novel approach to clinical trials is the use of biomarkers to evaluate vaccine efficacy more quickly than traditional clinical endpoints. Although biomarkers are currently used in vaccine development, including as surrogate endpoints to support earlier evidence for regulatory decision-making, identification of novel biomarkers to predict safety and efficacy during early and advanced clinical development and regulatory use is critical to advance important new vaccines into different age bands or populations. Biomarkers that are well validated, help scientists understand the disease process.
Innovative Statistical Analysis Techniques	Novel statistical methods to analyze data from complex novel trials may provide more rapid, potentially less expensive and more reliable answers about vaccines. For example, innovative statistical methods may help predict if interim evidence of a vaccine's safety and efficacy is likely to be borne out by further study, or if subject accrual needs to be adjusted.
Real World Evidence	Real world evidence is defined as data regarding the usage, or the potential benefits or risks, of a drug/vaccine derived from sources other than randomized clinical trials. Real world evidence can be derived from a variety of sources relating to the delivery of health care and its outcomes, including observational studies, electronic health records, claims and billing data, and product and disease registries. Use of such evidence has the potential to allow researchers to answer questions about the effects of a vaccine and outcomes efficiently, saving time and money while yielding answers relevant to broader populations. This could help streamline clinical development and help inform the safe and effective use of vaccines. Of note, FDA already utilizes real world evidence via its Sentinel Initiative, which is one of the largest uses of this type of information in health care and is proving vital for monitoring vaccine safety and analyzing safety signals. However, the science of using evidence from clinical experience to establish vaccine effectiveness, e.g., to evaluate new uses of vaccines, is still in its infancy. Development of methodologies is needed to address the types of data that could be used and how, study design and conduct, and analysis methods.