	Written Testimony **Committee on Science, Space, and Technology** **United States House of Representatives**

"*Fighting Flu, Saving Lives: Vaccine Science and Innovation*"

Statement of

Robin A. Robinson, Ph.D.

Vice President, Scientific Affairs, RenovaCare, Inc.
Former Deputy Assistant Secretary and BARDA Director
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

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Introduction

Good morning Chairwoman Johnson, Ranking Member Lucas, and distinguished Members of the Committee. Thank you for the invitation to opine on medical countermeasure (MCM) preparedness and response efforts for seasonal and pandemic influenza. I am Dr. Robin Robinson, current Vice President of Scientific Affairs at RenovaCare, Inc. and former Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS). I look forward to talking with you about our technological advancements, prospects, and challenges with influenza vaccines and their effects on seasonal and pandemic influenza preparedness.

Over the past 27 years I have devoted my professional career to the development, improvement, innovation, and production of vaccines for existing and emerging infectious diseases. Much of that effort spent in the private sector and federal government service was devoted to inventing new influenza vaccines; stimulating vaccine innovations; providing resources for the development and commercialization of new cell-and recombinant-based seasonal and pandemic influenza vaccines and new seasonal and pandemic influenza vaccines containing adjuvants; building national stockpiles of pre-pandemic influenza vaccines ensuring national and public health security; and expanding domestic and international influenza vaccine manufacturing capacity for pandemics.

Vaccines are one on man's greatest achievements and a cornerstone to today's public health preparedness and response. Without vaccines and public health programs, catastrophic diseases

such as smallpox would continue to wipe out large populations upon introduction to the virus; childhood diseases such as diphtheria, pertussis, tetanus, measles, mumps, rubella, Hemophilus influenza, and others would decimate our youngest and most vulnerable populations; and our elderly population would suffer and decline more rapidly without vaccines for pneumococcal, zoster, and influenza vaccines. However, there are still glaring gaps in our vaccine armory against existing major diseases such as human immunodeficiency virus, hepatitis C virus, malaria, and respiratory syncytial virus. Additionally, more effective vaccines delivering longer lasting immunity for influenza remain elusive. Lastly vaccines for newly emerging pathogens such as Zika virus and other pathogens are only reaching clinical development.

Seasonal influenza epidemics occur every year. However, periodically a novel influenza virus strain, for which there is little human immunity, will emerge and cause a global pandemic like the 2009 H1N1 pandemic, or worse, the pandemic of 1918. Because influenza viruses mutate as they spread and reassort primarily among birds, swine, and humans, achieving protection against seasonal influenza viruses is a significant challenge. Means to control and address the medical and public health consequences of influenza include social distancing, proper hygiene practices, vaccination, antiviral drugs, and diagnostics. In the last decade, we have been repeatedly reminded about the complexity of managing seasonal and pandemic influenza both globally and nationally. The most recent examples include the seasonal influenza vaccine mismatch to the antigenically drifted H3N2 virus during the 2014-2015 influenza season and the avian influenza H5 viruses that killed millions of domestic birds in the Midwest in 2015.

The evolution of influenza vaccines over the past 50 years has witnessed many vaccines starting with inactivated whole virion influenza virus vaccines produced in eggs in the 1970s to a less reactogenic and more purified inactivated egg-based split, subunit influenza vaccines in the 1980s that enriched for the major immunodominant viral hemagglutinin protein. By the end of the millennium, the influenza vaccine industry had compressed from as many as 12 manufacturers to less than four in the U.S. The emergence of highly lethal H5N1 avian influenza viruses from Asia in 1999-2004 for man and birds, including chickens used for vaccine manufacturing highlighted the vulnerability of the influenza vaccine infrastructure and public health preparedness to address potential influenza pandemics. The potential devastation was brought into better focus y 2005 as we understood the catastrophic socio-economic and medical effects of the 1918 influenza pandemic and our the poor immunogenicity of candidate H5N1 vaccine candidates produced by the usual means. These results informed the *National Strategy for Pandemic Influenza* (2005) that laid the game plan to stimulate the development new influenza vaccines using modern technologies; establishment of pre-pandemic influenza vaccine stockpiles for high risk individuals; and expansion of domestic influenza vaccine manufacturing capacity. Through the enactment of $5.6 billion appropriated (2005) to carry out the *HHS Pandemic Influenza Plan* and All Hazards Preparedness Act (2006), this strategic plan became operational with the necessary funding and authorizations, including the creation of the BARDA within HHS to carry out these programs.

Before results of these new influenza vaccine programs could even be realized, the H1N1 influenza pandemic emerged (2009). Dependence on egg-based influenza vaccines, their associated manufacturing infrastructure, and newly implemented pandemic preparedness

capabilities were tested and received mixed marks. Lessons learned from the H1N1 pandemic resulted in the President's Council of Advisors on Science and Technology's (PCAST) *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (2010), which recommended improvements in virus surveillance, in vaccine research and development, and in influenza vaccine manufacturing. As a call to action, HHS reviewed and revised existing plans to develop new influenza vaccines, antiviral drugs, and diagnostics; to assess the size, composition, and usage of influenza vaccine and antiviral drug stockpiles; and to expand our domestic influenza vaccine manufacturing infrastructure and capacity. The common thread throughout these revised preparedness and response plans was that seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly affects what we do in the other.

Following the release of the Department's 2010 *PHEMCE Review* and the PCAST report (2010), HHS adjusted and took steps to execute the pandemic influenza preparedness priorities enumerated in the review and report. Significant progress improving vaccines and manufacturing technologies occurred in the first half of this decade. Specifically, the federal government has partnered with industry to achieve the following:

- Modernization of influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines as well as antigen-sparing vaccines using adjuvants.
    - Flucelvax (2012), the first cell-based seasonal influenza vaccine in the U.S.

    - FluBlok (2013), the first recombinant-based seasonal influenza vaccine in the U.S.,
    - Q-Pan H5N1 vaccine (2013), the first adjuvanted pandemic influenza vaccine in the U.S.
    - Fluad seasonal influenza vaccine (2015), an adjuvanted seasonal influenza vaccine for seniors in the U.S.;
- With NIH, CDC, and FDA, BARDA launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, as recommended by PCAST to optimize the generation of high yielding vaccine seed strains and alternative potency and sterility assays, to expedite influenza vaccine availability. The IVMI initiative improvements cut weeks off the vaccine manufacturing process and increased production yields;
- Establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses with pandemic potential to rapidly immunize the critical workforce at the onset of an influenza pandemic. Clinical trials showed that vaccine stockpiles remained highly immunogenic even those stored for ten years. In parallel, BARDA and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in these stockpiles;
- Multi-fold expansion of domestic influenza vaccine production for pandemic preparedness was afforded by retrofitting older egg-based vaccine manufacturing plants (2007-2011 and 2017) and the building new state-of-the art, award-winning cell-based vaccine manufacturing facilities (2009-2012) through public-private partnerships with industry leading to a domestic vaccine manufacturing capacity able to produce enough pandemic influenza vaccine for the U.S. in six months;

- Establishment of a national infrastructure including the Centers for Innovation and Advanced Development and Manufacturing (CIADM) to rapidly develop, manufacture, and test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 and 2018 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015; and
- Establishment of a global vaccine manufacturing infrastructure with the World Health Organization (WHO) in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases. This initiative has resulted in the establishment of manufacturing facilities making more than four licensed influenza vaccines with a current capacity to produce more than billion doses of pandemic influenza vaccine.

On the seasonal influenza front, HHS responded to the H3N2 antigenic drift and seasonal influenza vaccine mismatch in 2014-2015 by tasking the Department's senior influenza leaders and experts to provide a comprehensive set of recommendations to the former HHS Secretary on how to address the issue of vaccine mismatch in the near and long term. HHS convened numerous meetings from December 2014 through May 2015 with internal and external influenza and vaccine experts from government, industry, and academia to understand the complexities of virus antigenic drift, vaccine mismatch, and influenza vaccine manufacturing and how seasonal vaccines and their manufacturing may be changed to accommodate this type of virus variance. In May 2015, senior HHS influenza leaders provided a set of twenty (20) recommendations to

HHS leadership that may improve virus surveillance and characterization, vaccine design, vaccine manufacturing, vaccine availability and distribution, and ultimately vaccine effectiveness. In June 2015, BARDA hosted a meeting with the influenza vaccine manufacturers constituting the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and with representatives from the WHO, the government of the United Kingdom, HHS agencies, and others to review current influenza epidemiology. This review recommended improving responses to seasonal influenza vaccine mismatches, exercises simulating the 2014-2015 seasonal influenza antigenic drift and vaccine mismatch, and ways to reduce timelines for production of a new seasonal influenza vaccine. Many of these recommendations were adopted, implemented, and assimilated into the way influenza vaccine manufacturers and federal agencies deal with the late emergence of seasonal influenza viruses mismatched to newly produced influenza vaccines.

While the recent introduction of quadrivalent, high-dose, and novel seasonal influenza vaccines by vaccine manufacturers represents incremental progress towards more effective influenza vaccines, the efficacy of seasonal influenza vaccines remains much lower than our expectations and needs. Significant technical challenges before a substantially more effective influenza vaccine is available. Despite the best efforts of the influenza scientists, the vaccine industry and the government, especially at NIH, CDC, and BARDA, the "holy grail" of influenza vaccines – a universal influenza vaccine- remains elusive.

The discovery of antibodies in 2011 to conserved epitopes on the stem region of the influenza hemagglutinin protein, the major immunodominant viral protein responsible for virus attachment

and the major component of influenza vaccines, has led to the development of many chimeric and headless influenza vaccine candidates using different platform expression technologies and their clinical evaluation presently. The discovery of antibodies this year to the influenza neuraminidase protein, which enables virus budding from infected cells and serves as a major target for influenza antiviral drugs, showed neutralization against a broad spectrum of different influenza subtypes; the inclusion of both HA and NA that include these special conserved epitopes will likely serve as a new source of influenza vaccine candidates that may be more effective and provide longer immunity.

BARDA and NIH are working together to foster collaborations with academia and industry in pursuit of more effective influenza vaccines. New evolutionary biology methods such as antigen cartography may be able to predict influenza virus evolution better and understand immune responses to the influenza viral hemagglutinin (HA) proteins from genetically distinct viruses better. By generating specific and random influenza virus mutants to seasonal and pandemic influenza viruses, the evolutionary trend for new virus strains may be understood better and thus may inform vaccine strain selection. With these results, future vaccine candidates may be designed using this forward-looking information and may provide more effective vaccines through what is called “back-boost” vaccine immunity.

Other waves of innovations and technologies since the start of the millennium have provided already started to fill some vaccine gaps. Contemporary vaccine innovations over the past 20 years have included the usage of new adjuvants in vaccines for human papillomavirus and

influenza to enhance and expand protective immunity; making new influenza vaccines in tissue culture cells and by recombinant technologies rather than in embryonated hen's eggs; bacterial glycoprotein conjugation delivering new vaccines to meningococcal and pneumococcal infections; and usage of new viral-vector technologies to produce Ebola and dengue vaccines.

On the horizon are new vaccine innovations that are being evaluated in clinical trials today. These include expansion of viral vector-based and adjuvants for development of vaccines against emerging and re-emerging pathogens including Lassa Fever, Zika virus, Human Immunodeficiency virus, and influenza. Utilization of synthetic mRNA technologies and development of liposome and nanoparticle carriers as carriers for these vaccines into the body are at the forefront of vaccine development against viral diseases and cancer. Structural examination of antigenic epitopes at the atomic level using new imaging technologies are helping to understand the physical properties of antibody and cell receptor binding to antigenic epitopes and to determine which epitopes may be best to target for greater vaccine efficacy, broader vaccine specificity, and longer duration. Innovations in drug delivery technologies may allow transdermal vaccine administration, obviate the need for syringes and needles, and afford rapid distribution and administration of vaccines.

The recent Executive Order (2019) provides a revised plan to modernize influenza vaccine manufacturing and pandemic preparedness. In addition to the continuation of on-going programs on seasonal and pandemic influenza vaccines recommended by previous pandemic plans and the convening a new Task Force to prepare a new pandemic plan, an emphasis was placed on the development of technologies that enable faster production and availability of seasonal and

pandemic influenza vaccines and the development of universal influenza vaccines to coincide with expanded domestic influenza vaccine manufacturing capacity. Potential recommendations will require funding at the multi-billion level through the 2020 decade for NIH, CDC, FDA, and BARDA to successfully implement and achieve these proposed seasonal and seasonal and pandemic influenza vaccine goals.

Even with these advances in vaccines and proposals to reinvigorate influenza vaccine development and preparedness, major challenges still await our efforts going forward into 2020. These include the resurgence of vaccine hesitancy by anti-vaccine advocacy groups with new cyberterrorist-like tactics that contributed to the recent unprecedented outbreaks of measles; competition for resources at large multi-national pharmaceutical companies between vaccines and other drugs products that have smaller cost of goods to manufacture and larger returns on investments; rapidity and availability of vaccines to quell the severity and even spread of catastrophic pathogens such as pandemic influenza viruses and others; the sheer difficulty in translating our basic understanding of immunity into successful vaccines; and last but most importantly, our continued inability to follow through in the many lessons learned reports over the past 50 years on pandemics that have cited the same deficiencies and recommendations with only incremental progress and questioned sustainability.

Conclusion

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing significant threats to global public health and to the United States. Together federal and industry partners have made great strides towards

pandemic influenza preparedness. While we have made progress in leveraging the improvements achieved for pandemic influenza vaccine manufacturing to benefit our seasonal vaccine needs, overall success in improving influenza vaccine effectiveness and duration have not been achieved. Success is dependent on the introduction and implementation of new innovations and technologies into new vaccines as public-private partners. Private industry partnered with U.S. government agencies and NGOs are poised to renew efforts to address seasonal and pandemic influenza challenges and provide the necessary resources, expertise, and technical assistance to attack pandemics with the wisdom and generosity of the U.S. Congress.

Biosketch

ROBIN ROBINSON, Ph.D.

Dr. Robin Robinson currently serves as Vice President of Scientific Affairs for RenovaCare, Inc. directing development of cellular therapies for wound healing. Concurrently he is a Fellow for Regenerative Medicine and Biomedical Research at the Thought Leadership and Innovation (TLI) Foundation on regenerative medicines and independent consultant on vaccines and biodefense matters.

He reentered the biopharmaceutical business sector after retiring in 2016 from federal public service at the U.S. Department of Health and Human Services, where he served from 2008 - 2016 as the first director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary for Preparedness and Response and as BARDA's Influenza and Emerging Disease program director (2004-2008). Dr. Robinson brought BARDA into prominence as one of the top 10 fully integrated R&D organizations worldwide supporting advanced development and acquisition of drugs, vaccines, diagnostics, and medical devices to address the deleterious outcomes of man-made biodefense threats, pandemic influenza, and emerging infectious diseases including Ebola and Zika viruses. 32 of its 250+ medical countermeasure products that BARDA supported since 2008 were fully approved and licensed by the FDA during his tenure; today that total is 52. Dr. Robinson established a pandemic influenza program with scientific and technical experts to implement the national and global strategic plans and policies for the development of new influenza antiviral drugs, vaccines, and diagnostics outlined in the *National Strategy for Pandemic Influenza*. For his leadership in this role, Dr. Robinson was the recipient of the Department of Defense's Clay Dalrymple Award in 2008, the HHS Distinguished Service Award three times, and a finalist for the Service to America Medal in 2009. In 2013-2015 Dr. Robinson was recognized as one of the top 50 most influential persons worldwide in vaccines by Vaccine Nation. In 2018 Dr. Robinson was recognized by Medicine Maker as one of the top 100 innovators in medicine.

Dr. Robinson received a Bachelor of Sciences degree in Biology from Millsaps College in 1976, a Doctoral degree in 1981 from the University of Mississippi Medical School in medical microbiology under Dr. Dennis O'Callaghan on herpesvirus oncogenesis, and completed in 1983 a NIH postdoctoral fellowship at the State University of New York at Stony Brook under Dr. Arnold Levine on molecular mechanisms in oncology. Dr. Robinson pursued his own research as a faculty member in the Department of Microbiology and Immunology at the University of Texas Southwestern Medical School from 1983-1992 on the molecular pathogenesis of herpesviruses and HIV. Prior to federal public service, Dr. Robinson served as the Director of Vaccines at Novavax, Inc. (Rockville, MD) from 1995-2004, where he led the development of 20+ vaccines to hepatitis B and E, influenza, HIV, noroviruses, and human papilloma viruses from early development, clinical trials, manufacturing scale-up, and commercialization through FDA licensure. While at Novavax, he developed patented platform vaccine technologies including virus-like particles and subunit protein vaccines for human pathogens including malaria, human papilloma, hepatitis, and influenza and for prostate, melanoma, and cervical cancers.

Dr. Robinson also served on the Senior Advisory Group for the World Health Organization (WHO) on emerging infectious diseases and pandemic influenza. Additionally, he continues to serve as an editorial board member and reviewer for several professional scientific and technical journals on virology, vaccines, public health, and biotechnology.