Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Flu Season: U.S. Public Health Preparedness and Response""

December 4, 2019

The Honorable Dr. Robert Kadlec, M.D. M.T.M&H, M.S., Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services

The Honorable Brett Guthrie (R-KY)

1. One division within the U.S. Department of Health and Human Services (HHS) that did not testify at the December 4, 2019 hearing was the Centers for Medicare and Medicaid Services (CMS). CMS, however, can impact flu vaccination through its reimbursement policies.

   In order to improve both seasonal and pandemic influenza preparedness, should CMS consider preferential reimbursements—reimbursing certain products at a higher rate—to incentivize a greater domestic manufacturing footprint for different types of flu vaccines, such as the cell-based and recombinant vaccines?

   This question would be best addressed by the Centers for Medicare & Medicaid.

2. What steps is the Administration taking to address the pipeline of antibiotic drugs that are so critical for our pandemic response and national security?

Antibacterials are of specific concern as they relate to national security; if civilians are saved from an initial threat only to die from a subsequent hospital or community acquired bacterial infection, efforts to protect persons from public health threats have ultimately failed. Within the U.S. Department of Health and Human Services (HHS), the Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA) is using an integrated strategy to provide support across the medical countermeasure (MCM) development pipeline to support preparedness and response efforts focused on novel antibiotics.

BARDA seeks to revitalize the antibacterial pipeline through three primary efforts:

- **Combatting Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X): In partnership with the Wellcome Trust, the National Institutes of Health, the Bill and Melinda Gates Foundation, and the governments of the United Kingdom and Germany, BARDA supports the CARB-X program through a cooperative agreement awarded to Boston University since 2016 to support antibacterial innovation and early-stage research and development. The world's largest public-private partnership devoted to early-stage antibacterial development, CARB-X has**

provided over $174 million to support 54 projects. CARB-X's portfolio contains 33 active projects, including novel classes of antibiotics, new diagnostics, and nontraditional approaches. Six projects have advanced into the clinical trial phase, including a diagnostic program that recently transitioned into BARDA's advanced development portfolio.

- **Advanced Research & Development Portfolio: BARDA's advanced research and development portfolio currently supports 15 antibacterial candidates spanning 11 public-private partnerships. The candidates in the portfolio collectively address all five priority biothreats (Plague, Tularemia, Melioidosis, Glanders and Anthrax) and a majority of CDC's priority antibiotic threats. Seven of these candidates are currently being evaluated in Phase 3 clinical trials. BARDA supported research and development that provided part of the predicate for FDA approvals of Melinta's VABOMERE® (2017), Achaogen's (now, Cipla's) ZEMDRI™ (2018), and Tetraphase's XERAVA™ (2018). BARDA also supports a complementary next generation diagnostics development program. Future priorities focus on expanding the portfolio to include nontraditional approaches (e.g., bacteriophage, host-directed therapies, etc.) and vaccines.**

- **Project BioShield: Recognizing the importance of making next-generation antibiotics that overcome antibiotic resistance available in the SNS, BARDA entered into a partnership with Paratek Pharmaceuticals to support the continued advanced development, potential approval, and potential procurement of Nuzyra® (omadacycline) for the treatment of anthrax. Antibiotics like Nuzyra® that could address specific biothreat indications as well as multidrug resistance while at the same time broaden the SNS's current stockpile of antibiotics will dramatically enhance the nation's preparedness.**

The Honorable Jeff Duncan (R-SC)

1. In your March 14, 2019 testimony to the Senate Appropriations Committee, you stated "I think if you ever had a chance to look at the curves of, not necessarily what happened in 1918, but if we projected what would happen today in terms of the speed of the transmission of a flu-like illness in a population that's vulnerable, it would be explosive. And in some ways, the faster you can get vaccines, literally, saves thousands of lives. And again, the economic benefits are also derived from that." You stated that "One of the challenges we have now quite frankly with our flu vaccine supply is the predominance of that is from eggs."

    a. Given the issues associated with derivation of vaccines from eggs, both in time and efficacy, do you support investment in late-stage non-egg-based technologies?

In an influenza pandemic, the best protection is a vaccine that 'matches' the circulating pandemic virus. Production of vaccine in chicken eggs requires adaptation that can result in divergence of the vaccine from the circulating virus infecting humans, potentially reducing its effectiveness. Influenza vaccine produced with more modern technologies,

including cell-based and recombinant vaccines that do not require egg adaptation could result in a better "match" between the seasonal flu vaccine and the strains that are actually circulating. Further, egg-based production capacity cannot be readily increased in an emergency, because of the highly specialized facilities involved (and the requirement for hundreds of thousands of chicken eggs moving into the factory every single day). Vaccine produced by cell- and recombinant-based technologies utilize facilities that are more generic and common, potentially allowing expansion of production capacity and producing more vaccine faster, thereby enabling vaccination of more individuals sooner.

ASPR/BARDA has supported and continues to support investment in late-stage development and licensure of non-egg based seasonal and pre-pandemic influenza vaccine technologies.

Utilizing supplemental funds appropriated by Congress, ASPR/BARDA supported the development and production of 23 new or improved influenza vaccines, antiviral drugs, and diagnostics. Specifically, ASPR/BARDA began supporting the development of different cell-based manufacturing technologies in 2006. As a result of these investments, a cell-based influenza vaccine (Flucelvax®) was developed that can now be administered to individuals four years and older. Additionally, the first recombinant influenza vaccine (Flublok®) was developed for people over 18 years of age.

In addition to product development, ASPR/BARDA continues to support domestic manufacturing capacity for non-egg based influenza vaccines. Both of the new licensures noted above were accompanied by new U.S. manufacturing facilities/ capacity, adding to the single U.S. facility (for egg-based vaccine) that had operated previously and substantially increasing overall U.S.-based influenza vaccine manufacturing capacity. Most recently, in December of 2019, BARDA awarded a contract to Sanofi Pasteur to expand domestic manufacturing capacity for the recombinant influenza vaccine. This is in direct support of the 2019 Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health and will increase domestic capacity for both seasonal and pre-pandemic vaccine.

The overall capacity for influenza vaccine production in the U.S. is still predominantly egg-based; therefore, it is important to continue investments in the further optimization and expansion of non-egg based technologies to reduce overall reliance on egg-based products. Such efforts include the need to explore additional vaccine production platforms like fully synthetic production methods to further improve domestic vaccine response capabilities.

b. Do you believe HHS, specifically BARDA, should ensure novel, multi-modal technologies are being supported to better respond to influenza?

Yes; ASPR/BARDA has supported and continues to support development of new technologies that can be used to improve the response to influenza. Incorporation and development of new technologies to improve influenza response is done across all aspects of the response – from production, delivery and administration of vaccines, to improved diagnostics, personal protective devices, and therapeutics. Some specific examples include:

- **Cellular and Recombinant Vaccine Technologies**
- **Platforms that allow even faster vaccine production**
- **Adjuvants that can improve efficacy**
- **Alternative approaches to vaccine delivery that can increase coverage, effectiveness, and ease of administration**
- **Development of improved influenza antivirals and immunotherapeutics**
- **In-home, and eventually wearable, diagnostics**

c. Is there a benefit to our population to invest in platform technology that cannot only respond rapidly to influenza, but Ebola and other emerging threats?

Yes, there is significant benefit to national preparedness to support platform technologies that are adaptable and versatile to support an enhanced response. The availability of such platform-based approaches would transform national preparedness against currently known threats as well as newly emerging threats in the future. ASPR/BARDA is investing in multi-purpose, flexible manufacturing platforms to support multiple production requirements. While many of these approaches, particularly those that will be useful for an influenza response, are early in development, ASPR/BARDA has made and continues to make investments to accelerate development of platform-based vaccine technologies. For example, as part of the investment with the Zika supplemental funding, ASPR/BARDA funded development of a Zika vaccine made using mRNA technology. This technology has promise as a rapid platform for a number of infectious diseases, including influenza and novel diseases that may emerge in the future. This technology is already showing dividends, having progressed a candidate into clinical trials, providing data that will inform development of other vaccines, and identifying areas for process improvement that will benefit manufacturing of any vaccine utilizing this platform.

The Honorable Susan Brooks (R-IN)

1. Pandemic influenza and emerging infectious diseases are one of the greatest biological threats we are facing – but one thing I am aware of are the significant funding pressures on the entire Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), especially the strategic national stockpile (SNS).

   The PHEMCE Multi-Year Budget outlined $1.2 billion in funds needed for the SNS in FY20. These funds are needed for replenishment of existing countermeasures and procurement of new products. And last year, I believe the FDA approved 28 new medical countermeasures & more were approved this year. The House Labor-HHS bill got as close to the needed number as possible - $920 million.

a. Could you explain how important adequate funding for the SNS is for ensuring we are prepared for the threats of pandemic influenza, emerging infectious diseases like Zika and Ebola, and intentional biological threats like smallpox or anthrax?

The Strategic National Stockpile (SNS) manages and delivers life-saving MCMs during public health emergencies. It is the largest federally owned repository of pharmaceuticals, critical medical supplies, Federal Medical Stations, and medical equipment that is available for rapid delivery to support federal, state, and local response. SNS's MCMs are intended to help state and local health agencies replenish depleted supplies or support a response requiring specific products not readily available (e.g. an antidote to a specific biological or chemical agent). Ultimately, if a biological, chemical, radiological, or nuclear event occurred in the U.S. today, the SNS is the *only* Federal resource readily available to respond once state and local MCM supplies are depleted. In addition, some SNS MCMs are not commercially available because of small supplies and limited use (e.g. anthrax). U.S. pharmaceutical supply chains run on a just-in-time model, often containing no more than a 30-day supply of pharmaceuticals under normal conditions. As a result, commercially available products may not exist in necessary quantities or be positioned in ways that allow rapid distribution and use during public health emergencies. If/when shortages occur, assets in the SNS support the initial response. The SNS is critical to enhancing national preparedness and ensuring MCMs are available if and when needed during public health emergencies.

The funding in the Fiscal Year (FY) 2020 appropriation will allow the SNS to make additional investments in key Public Health Emergency Medical Countermeasures (PHEMCE) priorities. The SNS requires funding to maintain the current inventory as well as replenishing products originally purchased under Project BioShield (PBS).

b. And, could you explain what happens if the SNS does not receive funding? My understanding is that inadequate funding places stress on the larger PHEMCE – and especially other priority areas like the Special Reserve Fund, or funding to combat Pandemic Influenza, EIDs like Ebola or Zika, or antimicrobial resistance.

PBS funding is used for initial MCM procurement and rarely supports ongoing maintenance and replacement of the product after it is approved by the Food and Drug Administration (FDA). The PHEMCE SNS Annual Review process recommends the most risk-balanced and sustainable portfolio of holdings for the SNS and supports more effective decision making to both maintain current capabilities and absorb additional products.

2. As you know, in October the White House issued an Executive Order titled "Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health." The Executive Order looks at four critical areas: (1) the health and economic impact of a flu pandemic; (2) ensuring an "all of government approach" to preparedness; (3) improving existing vaccines and developing new technologies; and (4) manufacturing more effective vaccines faster.

The EO referenced a recent Council of Economic Advisors (CEA) report which found a severe pandemic could have $3.7 trillion in economic costs and would lead to the hospitalization of 4.3 million people. The EO recommended a range of government actions to improve the 80-year old egg-based technology used in today's vaccines and speed the vaccine manufacturing process.

We know that HHS lacks sufficient Congressional funding to achieve these goals. Last year, BARDA received just $270 million for pandemic flu preparedness, while the most recent PHEMCE multi-year budget outlined $775 million in funding needed this year alone to achieve basic preparedness.

Dr. Kadlec, we know that once a pandemic is identified, the U.S. government will immediately need $10-12 billion just to provide vaccines to protect the American people. That doesn't take into account all of the funding now to prepare and implement the Executive Order.

a. Do you agree we need to devote substantially more funding to pandemic preparedness?

As you are aware, influenza poses one of the greatest, fastest spreading and most costly (in terms of lives and economic costs) threats we face as a nation. As noted in the White House Council of Economic Advisers Study on Influenza, "in a pandemic year, depending on the transmission efficiency and virulence of the particular pandemic virus, the economic damage would range from $413 billion to $3.79 trillion. Fatalities in the most serious scenario would exceed half a million people in the United States. Millions more would be sick, with between approximately 670,000 to 4.3 million requiring hospitalization."[1] The more prepared the nation is for the next pandemic, the more lives saved and less economic impact.

ASPR/BARDA has made significant progress in supporting innovation and domestic preparedness over the last decade, supporting advanced research and development leading to FDA licensure of the first non-egg based influenza vaccines, cell-based Flucelvax®, and recombinant-based Flublok®. Equally as important are ASPR/BARDA's substantial investments in establishing, maintaining, and expanding domestic manufacturing of these vaccines, increasing overall pandemic influenza vaccine manufacturing capacity from approximately 60 million antigen doses to over 600 million within six months of the start of production.

Significant gaps in response capabilities still exist, including the time and person-to-person interactions needed to diagnose infection (delaying treatment and increasing the likelihood of person-to-person virus transmission), lack of FDA-approved therapeutics for individuals with severe influenza disease, domestic manufacturing capacity and supply chain control

[1] The Council of Economic Advisers. (2019), Mitigating the Impact of Pandemic Influenza through Vaccine Innovation, October 30, 2019, https://www.whitehouse.gov/wp-content/uploads/2019/09/Mitigating-the-Impact-of-Pandemic-Influenza-through-Vaccine-Innovation.pdf

(for vaccine, adjuvant, therapeutics, and ancillary supplies), and time to availability and subsequent administration of first vaccine dose. ASPR/BARDA will continue to make progress in addressing these existing gaps to ensure technologies are available to address both seasonal and pandemic influenza, as well as for sustaining the successes achieved to date. Currently existing domestic manufacturing facility capacity, critical to the Nation's response capabilities, will be maintained.

b. What are you doing to ensure BARDA, CDC and other HHS agencies have the resources they need to be prepared?

ASPR is working with other components of HHS and with OMB to explain our needs through the FY 2021 President's Budget.

c. Will we see additional funding requests to support the EO in the President's Budget in February?

ASPR is working with HHS and the White House Office of Management and Budget (OMB) to finalize the FY 2021 President's Budget. We anticipate the Budget will be released in early February. ASPR looks forward to providing more details on our FY 2021 request at that time.

3. We know that influenza viruses change over time, creating serious challenges for public health. As a New York Times article described earlier this year, flu viruses evolve constantly – they are "ruthless masters of disguise" when it comes to tricking our immune systems.

   The egg-based manufacturing process has been a mainstay of influenza vaccine production for more than 80 years. This process is well established and has made a significant contribution to public health. However, dependence on egg-based technology has significant limitations, including long supply times and the potential for virus mutations during the production process as the virus adapts to grow in the eggs.

   Cell- based vaccine manufacturing can address limitations of the egg-based process. This technology provides the ability to scale flu vaccine manufacturing with greater efficiency and avoids egg-adaptation, thereby providing a better "antigenic" match to circulating strains.

   a. What is ASPR and BARDA doing to optimize the use of cell-based manufacturing processes for flu vaccines?

Investments in modern influenza vaccine technologies have led to the licensure of new cell- and recombinant-based influenza vaccines by the FDA. Through this advancement we can expedite manufacturing, including influenza vaccines with adjuvants that can provide more vaccine with less vaccine antigen (antigen-sparing) and greater cross-protection against antigenically-different virus strains. For cell-based manufacturing, ASPR/BARDA supported efforts by the cell-based influenza vaccine manufacturer to improve the manufacturing process, resulting in a doubling of domestic vaccine production capacity for that vaccine.

b. How can the growth and expansion of cell-based vaccines technologies improve our ability to respond to a flu pandemic and protect the American people?

In an influenza pandemic, the best protection is a vaccine that 'matches' the circulating pandemic virus. Production of vaccine in chicken eggs requires adaptation that can result in divergence of the vaccine from the circulating virus infecting humans, potentially reducing its effectiveness. Influenza vaccine produced with more modern technologies, including cell-based and recombinant vaccines that do not require egg adaptation could result in a better "match" between the seasonal flu vaccine and the strains that are actually circulating. Further, egg-based production capacity cannot be readily increased in an emergency, because of the highly specialized facilities involved (and the requirement for hundreds of thousands of chicken eggs moving into the factory every single day). Vaccine produced by cell- and recombinant-based technologies utilize facilities that are more generic and common, potentially allowing expansion of production capacity and producing more vaccine faster, thereby enabling vaccination of more individuals sooner. ASPR will continue to invest in next-generation technologies, platforms, and manufacturing processes to further improve the scale, flexibility, efficiency, and speed of influenza vaccines, as well as in clinical studies to better understand potential benefits of existing vaccines. In addition, utilizing these flexible manufacturing technologies domestically improves our capability to rapidly produce other critical MCMs for other threats.

c. Does the government have plans to procure additional doses of cell-based vaccines through agencies such as the VA and the Department of Defense to support the growth and usage of these innovative technologies, especially as I understand there is some evidence that these vaccines could provide better protection for vulnerable veterans and the military that stands on the frontline of America's defense.

HHS is unaware of plans for procurement at VA and DoD. This question would be best addressed directly by those Departments. ASPR does work in close collaboration with partners, including VA and DoD, to share information on current MCM development and discuss potential stockpiling of products. Thus, VA and DoD have information on the availability of potential product and where product is currently in the developmental pipeline.

4. During FDA's vaccine approval process, randomized clinical trials (RCTs) are essential to determining the safety and efficacy of a vaccine. However, after a vaccine becomes licensed, a tremendous amount of real-world evidence (RWE) is generated from the millions of Americans being vaccinated each season.

   Given the changing nature of the influenza virus, this data can show how vaccines behave and protect diverse and critical populations, such as children and the elderly, in "real" and across multiple influenza seasons. It allows researchers to better measure clinical outcomes and could be useful in guiding policies for FDA and CDC and improving vaccine technology in the future

In practice, RWE provides a living, breathing, pool of data to help the U.S. government and the global influenza community gain a practical perspective on how to predict and prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

a. What is FDA doing to capture more RWE during each flu season?

This question would be best addressed by FDA.

b. What public health lessons could be learned from examining RWE every year?

Please refer to FDA's response.

c. Do you believe it would be useful to incorporate RWE into your decision making processes during each flu season?

Please refer to FDA's response.

d. Could RWE be included in the future in FDA product labels?

Please refer to FDA's response.

5. The President's September Executive Order (EO) on flu vaccines directs agencies, including ASPR and BARDA, to 'advance the development of new, broadly protective vaccine candidates that provide more effective and longer lasting immunities.' However, the recent BARDA RFI posted on October 30 only requests information on manufacturing capacity for vaccines and adjuvants. Will there be additional BARDA opportunities that are intended to help with research and development for new, broadly protective vaccine candidates – particularly for technologies that may be in Phase I?

Yes, there are and will be other opportunities to support advanced research and development of vaccine candidates for influenza. ASPR/BARDA utilizes a number of different approaches to obtain information, as well as solicit proposals, for advanced development of vaccines, therapeutics, and diagnostics to detect, prevent, and treat influenza. In fact, ASPR/BARDA currently has an open Broad Agency Announcement soliciting proposals for products to develop and improve influenza response capabilities, including improved vaccines.