THE COMMITTEE ON ENERGY AND COMMERCE

MEMORANDUM

February 1, 2015

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing on "Examining the U.S. Public Health Response to Seasonal Influenza"

The Subcommittee on Oversight and Investigations will hold a hearing on Tuesday, February 3, 2015, at 10:00 p.m. in 2123 Rayburn House Office Building, entitled "Examining the U.S. Public Health Response to Seasonal Influenza." This hearing will focus on the role of U.S. public health agencies in protecting the U.S. population from the spread of seasonal influenza. The Subcommittee will examine the strain selection decision-making process, how U.S. public health agencies are improving the effectiveness of response to seasonal flu, and the progress of Federal efforts into developing a universal flu vaccine, advanced diagnostics, new flu vaccine manufacturing technologies, and new anti-viral drugs for treatment of influenza.

I. WITNESSES

- Dr. Anne Schuchat, Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC);
- Dr. Karen Midthun, Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA);
- Dr. Robin Robinson, Director, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response; and,
- Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH).

II. BACKGROUND

A. About Seasonal Influenza

Influenza is a contagious respiratory illness caused by varying virus strains and can range in severity from mild to lethal. In both its seasonal and pandemic forms, influenza is an ongoing

public health concern. In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. An average of 62 million Americans – about 20 percent of the U.S. population – get the flu each year.

Influenza is considered one of the leading causes of death in the U.S., especially in a severe season. Based on 2010 data, CDC has posted the following listing: [1]

Number of deaths for leading causes of death:

- Heart disease: 596,577
- Cancer: 576,691
- Chronic lower respiratory diseases: 142,943
- Stroke (cerebrovascular diseases): 128,932
- Accidents (unintentional injuries): 126,438
- Alzheimer's disease: 84,974
- Diabetes: 73,831
- **Influenza and Pneumonia: 53,826**
- Nephritis, nephrotic syndrome, and nephrosis: 45,591
- Intentional self-harm (suicide): 39,518

(Bolded to add emphasis).

According to CDC estimates for the 1976-2006 time period, seasonal influenza has been associated with as few as 3,000 and up to almost 50,000 deaths each year in the U.S. On average each year, more than 36,000 individuals die and more than 200,000 are hospitalized from influenza and related complications.[2] A study published in 2007 estimated that more than $10 billion is spent annually in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications.[3]

Detailed published estimates of influenza-attributable deaths by age, type, and subtype have not been updated by the CDC for seasons beyond the 2006-2007 influenza season.[4] CDC does not know exactly how many people die from seasonal flu each year. The reasons for this include: States are not required to report individual seasonal flu cases or deaths of people older than 18 years of age to CDC; many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; many patients (especially the elderly) may die from pneumonia unrelated to influenza, so figuring out which cases to include in an analysis can be difficult; most people who die from seasonal flu-related complications are not tested for flu or they seek medical care when flu can no longer be detected.

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[1] CDC FastStats, Death and Mortality, *available at* http://www.cdc.gov/nchs/fastats/deaths.htm.
[2] In a January 28, 2015 phone briefing with staff, the Acting Director of the CDC's Influenza Division stated the estimates for hospitalizations could be as high as 400,000.
[3] CDC Congressional Justification FY 2015, *available at* http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf.
[4] Gonçalo Matias, Robert Taylor, François Haguinet, Cynthia Schuck-Paim, Roger Lustig and Vivek Shinde, "Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status," Influenza Journal 507 (June 27, 2014), *available at* http://onlinelibrary.wiley.com/doi/10.1111/irv.12258/full. However, CDC has indicated to staff that there is an update that covers the 2005-2014 period that will be released shortly.

Given the difficulties on getting the exact number of flu-related deaths, researchers have turned to a variety of modeling techniques to estimate deaths. One retrospective database analysis, which estimated influenza deaths in the U.S. by analyzing data for 12 influenza seasons (1997-2009), found that influenza deaths were highest in older and high-risk individuals. In terms of deaths from influenza and pneumonia, CDC statistics[5] show that, between 1999 and 2011, there were on average some 20 deaths each year (high of 23 and low of 17) per 100,000 of the U.S. population.

Other recent data and CDC statements indicate there is no reason to think that there has been any major change between 2011 and 2014. Over the 1999-2011 period, the death rate per 100,000 was 35 for the group aged 65-74; 140 for the group aged 75-84, and 600 for the 85+ group. There was also a higher than average death rate for infants of less than one year. Adults between 20 and 50 obviously had much lower rates. The figures do not distinguish between those who had received a vaccine shot in a particular year and those who had not; nor any who had a history of previous flu shots.

When the influenza (H3N2) viruses are predominant, they tend to cause more severe illness and hospitalization among the elderly. According to one study, the H3N2 A strain accounted for a seasonal average of 71 percent influenza-attributable deaths compared to the other strains.[6]

The primary method for preventing influenza is an annual vaccination. CDC recommends annual vaccinations for everyone aged 6 months or older. For the 2011-2012 season, about 42 percent of Americans aged 6 months and over were vaccinated.[7] Data from the 2012-2013 season showed that 45 percent of Americans 6 months or older got vaccinated.[8] For 2013-2014 season, the overall vaccination rate was 46 percent.[9] The estimate for this season as of November 2014 was 46.2 percent. According to the CDC fiscal year (FY) 2015 Congressional Justification, the CDC set a performance measure for the long term objective to increase the proportion of adults (18 and older) who are vaccinated annually against influenza. In FY 2013, the CDC set the target at 42 percent, but that target was not met. The FY 2014 target was 50 percent, and the goal for FY 2015 was 53 percent.

HHS has set a goal for States to vaccinate 70 percent of their population as part of the Healthy People 2020 initiative. According to experts, vaccination rates need to be generally above 70 percent for "herd immunity" effects – which limit the spread and protect those without

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[5] www.cdc.gov/nchs/faststats/deaths.htm
[6] Matias, *supra*, note 4.
[7] Written testimony of Dr. Thomas Frieden, CDC Director, before the House Energy and Commerce Subcommittee on Oversight and Investigations, February 13, 2013 at 8 (indicating that the rate was 52 percent but that was for the subgroup of Americans aged 6 months to 17).
[8] Flu Vaccination Coverage, United States, 2012-13 Influenza Season, http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm.
[9] 2010-11 through 2013-14 State, Regional, and National Vaccination Trend Report, http://www.cdc.gov/flu/fluvaxview/reports/reporti1314/trends/index.htm.

immunity – to become apparent. If all seniors received a newly available high-dose version of the flu shot, flu cases among this high-risk population could drop 25 percent.[10]

B. Developing the Seasonal Influenza Vaccine

Because circulating influenza virus strains change, a new vaccine is produced and administered each year to protect against strains expected to be most prevalent that year. As FDA noted in testimony before the Subcommittee on Oversight and Investigations in 2013:

> Influenza is a very challenging virus in that its surface proteins change constantly to evade both our immune systems and vaccines. As a result of these changes, in most years, at least one of the strains in the vaccine must be changed to keep up with changes in the circulating virus.[11]

Each year, public health experts, including those from FDA, the World Health Organization (WHO), and CDC study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC), FDA selects the strains for inclusion in the annual influenza virus – two strains of influenza type A and one strain of influenza type B – to include in the annual influenza vaccine.[12] Because of the lead time needed for manufacturing flu vaccine, the decisions on strain selection need to be made usually by the end of February for the vaccine to be available for the next flu season in the U.S.

There are about 150 million doses of flu vaccine available annually in the U.S., with about 140 million doses from egg-based manufacturing and 10 million doses from cell- and recombinant-based. The estimated lead times to first dose for each type of manufacturing are as follows: egg-based, 22-24 weeks; cell-based, 16-17 weeks; and recombinant, 12-15 weeks.

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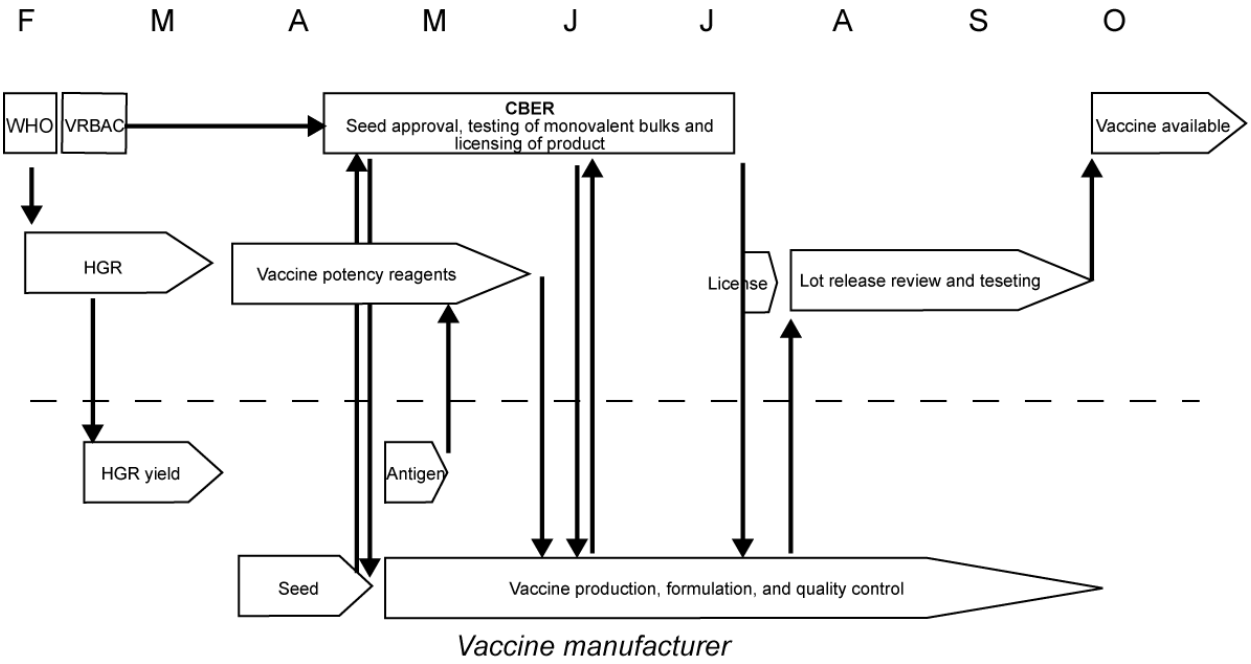
[10] R. Roos, "Large trials finds high-dose flu shot beneficial for seniors," CIDRAP, August 13, 2014, http://www.cidrap.umn.edu/news-perspective/2014/08/large-trial-finds-high-dose-flu-shot-beneficial-seniors.

[11] Statement of Jesse Goodman, M.D., MPH, Chief Scientist, FDA, Hearing before the House Energy and Commerce Subcommittee on Oversight and Investigations, "Influenza: Perspective on Current Season and Update on Preparedness, February 13, 2013.

[12] This is the trivalent vaccine. Since 2013, there has also been a quadrivalent vaccine available that includes an additional B strain.

Below is a graphic illustration[13] of the annual timeline for the U.S. vaccine production process.



C. The 2014-2015 Seasonal Influenza Vaccine

CDC is reporting that flu activity remains high in the U.S. and is widespread in 46 states, D.C., and Guam. Flu activity is likely to continue nationally for several weeks. A key reason that the U.S. is experiencing a severe flu season is because this year's vaccine does not protect well against the dominant strain of influenza, which mutated after the vaccine-production process began for the 2014-15 and does not match well with the H3N2 A strain in the vaccine. Given the lead time needed for manufacturing and regulatory compliance, there was not enough time to modify the vaccine and restart the manufacturing.

Seasonal flu vaccination typically has an effectiveness[14] rate in the range of 50-60 percent.[15] Seasonal flu vaccine effectiveness studies show a low effectiveness rate of 10 percent

[13] Slide 8 from Novartis briefing to Members of the Subcommittee, January 27, 2015 (on file with Committee). HGR refers to high-growth reassortants. The viruses that are made by WHO (in eggs) as the foundation for the year's vaccine. They have surface proteins of the recommended flu strain, but the viral core of strains that are easy to grow.

[14] By effectiveness, CDC means the rate at which the vaccine prevents a person from going to the doctor to seek treatment. Thus, in a population of 100 unvaccinated people exposed to the flu virus, the CDC would expect about 10 to seek treatment. In a population of 100 vaccinated people exposed to the flu virus, the CDC would expect 4 people to seek treatment, but would prevent 6 from going to the doctor.

[15] By way of comparison, effectiveness rates for other vaccines such as for measles are about 95 percent. The comparison highlights the unique challenge posed by the constantly changing flu viruses.

(in high-risk populations) for the 2004-2005 season and a high rate of 60 percent (general population) in the 2010-2011 season. Vaccination, even with effectiveness of about 60 percent, has been shown to reduce flu-related illness, antibiotic use, time lost from work, hospitalizations, and deaths.

An interim analysis of this year's seasonal flu vaccine showed only a 23 percent rate of effectiveness for the overall U.S. population – much less so for most American adults, demonstrating only 12 percent effectiveness for those 18-49 years old and 14 percent for those 50 years or older. This is the lowest rate since CDC has collected standardized, more accurate data of effectiveness rates in the last four to five years.

The lower effectiveness is due to significant mutations in a key flu strain (the dominant H3N2 A strain) that occurred sometime after the strain selection decision for the U.S. vaccine was made in February and before the onset of this year's flu season in the U.S. This occasionally occurs. For example, CDC stated during a staff briefing that the 1999 seasonal flu vaccine had near zero effectiveness because of drift in the strain from mutations. Even with the lower effectiveness, CDC is urging influenza vaccination for any persons who have not been vaccinated yet this season, as the vaccine may still offer benefits. Antiviral drugs are a second line of defense to treat flu illness, and CDC is urging greater use of antiviral medications for the treatment of influenza.

On February 28, 2014, the FDA Advisory Committee voted to retain all 3 current strains for the 2014-2015 trivalent influenza vaccines. At the time of the February 2014 FDA recommendation, the evidence showed a 90 percent match and a 10 percent mismatch between the current H3N2 virus strain and the circulating H3N2 viruses. It is unusual to retain all current strains into another flu season. According to information on FDA's website, since 2002, only in 2003 and 2011 had the FDA Advisory Committee voted to retain all three strains. There also have been two instances, in 2003 and 2004, when the Advisory Committee deferred votes on one of the three strains.

CDC told staff that the agency first detected the drift of the H3N2 A strain in March 2014, but the drift was at an insignificant level, and not yet considered evidence of a distinctive and meaningful drift. Sometime in May, CDC found that the drift resulted in a 17 percent mismatch, representing a level of concern, but not unambiguous evidence of a significant drift.[16] CDC indicated to staff that a drift in the range of 20 to 30 percent would be considered significant, but staff did not get a clear response from CDC as to when CDC knew the drift was

[16] Whether there was enough drift seen in May 2014 to change the strain selection decision is in dispute. Dr. Andrew T. Pavia, M.D., Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah School of Medicine and who has served on federal and state advisory committees on vaccine policy and pandemic influenza preparedness, stated: "If we had picked the vaccine strain in May instead of February 2014, we would have picked the correct one. By April or May, there was good evidence of the drifted A/Switzerland strain; it wasn't clear that it was going to be the dominant strain, but there was a pretty good hint and we probably would have chosen differently." Another flu expert, Dr. Gregory A. Poland, M.D., Professor of Medicine and director of the Vaccine Research Group, Mayo Clinic said the current way of predicting the dominant virus of the coming influenza season is outdated and should be improved. L. Brookes, A. Pavia, and G. Poland, "Why Is Influenza So Difficult to Prevent and Treat? Will We See Improvement Any Time Soon?" www.medscape.com (January 23, 2015). http://www.medscape.com/viewarticle/838459_print

in this range. By September 2014, the mismatch was about 50 percent, and a vaccine candidate for the new strain was identified. As a result, the WHO recommended replacing the H3N2 A strain in the seasonal flu vaccine for the Southern hemisphere. The drift is currently at about a 65 percent mismatch level.

D. The U.S. Government's Roles Related to Seasonal Influenza

Within the Federal government, HHS has primary responsibility for coordinating the nation's response to public health emergencies, such as an influenza pandemic. HHS also is the primary department funding the research and development of influenza vaccines. Within HHS, CDC makes recommendations on who should be vaccinated, tracks the spread of influenza and vaccination rates, and disseminates public health messages encouraging vaccination and other protective measures, such as hand-washing. FDA is responsible for selecting the influenza strains to include in the annual influenza vaccines and for licensing vaccines.

1. U.S. Centers for Disease Control and Prevention

CDC had an enacted level of about $174,558,000 for influenza planning and response in FY 2014.[17]

For effective strategies for increasing flu vaccination, the CDC has advised Committee staff that there are different barriers and strategies depending on the population, but the key elements of an effective strategy are confidence in the recommendation, strong provider recommendation, and access (payment, scheduling, etc.).[18]

CDC focuses on increasing demand with healthcare providers for influenza vaccination each season through investments in health communication with providers and the general public, targeted outreach to high-risk populations, and partnerships with pharmacists as a means to extend the reach of influenza vaccination.

CDC also detects and monitors influenza through a network of laboratories at the State and international levels that are routinely testing samples to: determine the severity of the influenza season; identify viruses that are causing disease and may pose a pandemic threat; and determine the effectiveness of the influenza vaccine and other interventions.

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[17] CDC FY 2015 Congressional Justification, 53 (CDC FY 2015 request of $187,558,000 for influenza planning and response is $15 million above the FY 2014 enacted level), *available at* http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf.

[18] CDC provided strategies to staff for the following groups: Health Care Personnel http://www.cdc.gov/flu/toolkit/long-term-care/strategies.htm; Adults: http://www.cdc.gov/vaccines/hcp/patient-ed/adults/for-practice/increasing-vacc-rates.html; Pregnant women: http://www2.aap.org/immunization/pediatricians/NFIDFamilyVaccinesCalltoAction.pdf.

2. U.S. National Institutes of Health & Biomedical Advanced Research and Development Authority

Below are the most current figures on influenza research.[19] NIH has not released actual figures for FY 2014 and 2015. The influenza figures include all categories of influenza research (vaccines – including universal flu vaccine research, therapeutics, diagnostics, and basic.)

NIH Influenza Funding:
- FY 2013 actual: $304 M
- FY 2014 Estimated: $312 M
- FY 2015 Estimated: $312 M

BARDA is charged with the advanced development and procurement of medical and non-pharmaceutical countermeasures for pandemic influenza preparedness and response. Thus, BARDA supports development of vaccines (including for seasonal influenza), antiviral and therapeutic agents for U.S. licensure. BARDA also supports influenza vaccine stockpiles, securing supplies of raw materials (including eggs for domestic manufacturing of seasonal and novel influenza vaccines, and the manufacturing of novel influenza vaccine candidates for clinical trials). BARDA also supports non-pharmaceutical countermeasure development, such as next-generation ventilators and procurement of masks and respirators. For FY 2014, BARDA spent about $295 million on advanced development investments and about $71 million for stockpile and infrastructure investments to support the influenza program.

3. U.S. Food and Drug Administration

In response to the Committee staff's inquiry about efforts to make improvements in strain selection decisions, FDA has pointed out global improvement efforts and the FDA's role. Improving the influenza strain-selection process and identifying scientific gaps that impact strain-selection decisions is a high priority for the WHO, regulators to improve the FDA, and vaccine manufacturers. All agree that identifying ways and approaches to improving influenza vaccine virus selection is critical. The WHO has held three meetings over the last several years (2010, 2011, and 2014), all with the explicit goal of strengthening the influenza vaccine virus selection and development process. These consultations brought together a diverse group of influenza experts, including the representatives from scores of National Influenza Centers involved in virus surveillance, representatives from the WHO Collaborating Centers for Influenza (e.g., CDC) and the four WHO Essential Regulatory Laboratories including FDA/CBER, manufacturers, and other stakeholders such as influenza modeling experts. Influenza experts from CBER participated in all three of these consultations and made presentations on variety of topics, including development of new assays and regulatory issues related to influenza vaccines. Other topics in the discussion of improvements include: expanding geographic surveillance coverage by significant increases in trained laboratory personnel and equipment; accelerating the understanding of the genetic changes in virus evolution and helping

[19] *See* Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), http://www.report.nih.gov/categorical_spending.aspx.

predict the influence of amino acid changes on virus antigenicity from advances in high-throughput genetic sequencing; and improving assays to allow for a more accurate assessment of the quality of a protective immune response. In 2011, a WHO Conference report acknowledged an assay developed in the 1940s and still used for strain selection decisions has had performance issues in recognizing emerging changes in the H3N2 viruses.[20]

According to its Congressional justification for its FY 2015 budget request, FDA has approved 15 seasonal influenza vaccines for the United States, including Flucelvax and Flublok, two vaccines that do not use egg-based technology in their manufacturing, which offer the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic. Three new quadrivalent vaccines were approved, bringing the total licensed to four that increase the likelihood of adequate protection against circulating influenza B strains. In December 2014, FDA approved Rapivab (peramivir) to treat influenza infection in adults.

In August 2010, the President's Council of Advisors on Science and Technology (PCAST) issued a report on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. Some of the report's recommendations have pertinence to issues with seasonal flu. For example, the report recommended that the FDA should develop and issue a guidance document that defines a clear regulatory pathway for the approval of adjuvants (substances or mixtures of substances added to a vaccine to enhance the immune response) for use in human vaccines, including those for seasonal and pandemic influenza.[21] The PCAST report also recommended that FDA should develop a well-defined regulatory process for introducing alternative assays for seasonal influenza vaccines, and that FDA should define a regulatory process to guide development and implementation for sterility testing of influenza vaccines.[22]

III. ISSUES

The following issues will be examined at the hearing:

- What steps are being taken to improve the influenza vaccine virus selection?
- Could the low level of effectiveness of this season's flu vaccine been increased from 23 percent to 40-50 percent if the vaccine had been adjuvanted?[23]

[20] WHO Conference Report, Strengthening the influenza vaccine virus selection and development process, Outcome of the 2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at the Centre International de Conferences (CICG) Geneva, Switzerland, 7 to 9 December 2011, 31 Vaccine 3209, 3213 (2013).
[21] PCAST report at 47, *available at* http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.
[22] Id. at 27.
[23] No adjuvanted influenza vaccine has ever been licensed in the U.S. to date. Dr. Andrew Pavia stated that with an adjuvanted vaccine "we probably could have made the mistake we made this year and instead of efficacy declining from 65 percent to 23 percent, it might have only declined to 40-50 percent." Brookes, et al., supra note 16.

- What actions could be taken by Federal public health agencies to help mitigate the impact of a seasonal flu vaccine that has significantly lower effectiveness?

- How can advances such as genetic characterization and rapid assessment tools improve flu surveillance and the ability to predict seasonal flu strains?

- What is the status of efforts to shorten the time and increase reliability for preparation of reagents for potency?

- Have BARDA and FDA funded applied research, as recommended by PCAST, which will develop rapid methods for assessing the concentration of antigenic materials, circumventing the need for production of new antibodies and/or traditional immunological tests?

- Has FDA developed a guidance document for developing adjuvants (a substance or mixture of substances added to a vaccine to enhance the immune response to the vaccine)? What is the importance of adjuvants in supporting the flu vaccine response?

- What is the status of the development of a universal flu vaccine?

- What is the path forward for developing a monovalent vaccine to target a significant change in a strain in the seasonal vaccine that occurs too late to modify the seasonal vaccine?

IV. STAFF CONTACTS

If you have any questions regarding the hearing, please contact Alan Slobodin, Emily Newman, or Charles Ingebretson at (202) 225-2927.