DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

April 27, 2015

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Chairman Murphy and Representative DeGette:

Thank you for your March 9, 2015, letter regarding the U.S. public health response to seasonal influenza. I am pleased to respond to your questions on behalf of Secretary Burwell.

1. **Please list the authorities that are available to HHS to respond to seasonal influenza drifted strains. What criteria would be used by HHS in using such authorities?**

   Answer: The statutory authorities for research and development, licensing, administration and use of vaccines are the same regardless of the influenza strain and whether or not there are drifted strains. The Department of Health and Human Services (HHS) has authorities under the Public Health Service Act (PHS) to conduct research, development, testing, and distribution of seasonal influenza vaccines and to coordinate with State and local quarantine and communicable disease control activities. See, for example, research and development authorities under sections 301 and 319L of the PHS Act (42 U.S.C. 241 and 247d-7e); coordination of vaccine research, development, testing, licensing, production, distribution and evaluation under title XXI of the PHS Act (42 U.S.C. 300aa-1 – 300aa-6); and control of communicable disease authorities under sections 311, 361, and 362 of the PHS Act (42 U.S.C. 243, 264, 265). These and other authorities under the PHS Act support seasonal influenza vaccine programs and communicable disease control activities of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response, and the National Vaccine Program. HHS also has authorities, delegated to the Food and Drug Administration (FDA), to license vaccines or approve them for investigational use under section 351 of the PHS Act (42 U.S.C. 262) or

authorize them for emergency use under section 564 of the Federal Food, Drug, and Cosmetic (FFD &C) Act. (21 U.S.C. 360bbb-3).

2. **Would using an adjuvant in a seasonal flu vaccine to boost effectiveness against a drifted strain require emergency use authority? If not, what authority would be needed?**

   Answer: If FDA receives a license application for a seasonal influenza vaccine containing an adjuvant that is shown to be safe and effective, then FDA can license the vaccine. In addition, as described further below, FDA can use its expanded access and emergency use authorization authorities to allow use of an unlicensed vaccine.

   Adjuvants are an ingredient in a number of vaccines against other bacterial and viral pathogens, and are being investigated for use in seasonal influenza vaccines. The purpose of formulating vaccines with adjuvants is to increase the immune response to the vaccine. This may allow a decrease in antigen dose, the provision of broader efficacy, or both.

   No U.S.-licensed seasonal influenza vaccine includes an adjuvant. Studies of investigational seasonal and pandemic influenza vaccines containing various adjuvants have been conducted. Studies include, but are not limited to, whether use of adjuvanted seasonal influenza vaccine induces a higher immune response to influenza strains included in the vaccine as well as a response to circulating influenza strains that are not included in the vaccine. FDA has approved an adjuvanted H5N1 vaccine for pandemic use, and is always willing to work with sponsors who are developing adjuvanted seasonal influenza vaccines for potential licensure.

   While the use of adjuvants in seasonal influenza vaccines is promising, the use of an unlicensed vaccine for the prevention of infection by a drifted strain of influenza under Emergency Use Authorization would require a declaration that circumstances justify such an authorization, while use under Expanded Access would require a determination that there is no comparable or satisfactory alternative therapy. In each case, to support such use, FDA would need to determine that the potential benefits outweigh the potential risks based on the available data.

3. **Does HHS believe that a legislative clarification of public health emergency authority would be helpful?**

   Answer: The Department believes that its current authorities are adequate for managing the public health response to the seasonal flu in the U.S.

4. **What databases does HHS have that could be used to track the effectiveness of influenza vaccines?**

   Answer: CDC conducts studies to measure the benefits of seasonal flu vaccination each flu season to help determine how well flu vaccines are working. These vaccine effectiveness (VE) studies regularly assess and confirm the value of flu vaccination as a public health intervention. Study results of VE can vary based on study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied.

   Through the U.S. Flu VE Network, CDC has been working with researchers at universities and hospitals since the 2003-2004 flu season to estimate how well flu vaccine works through observational studies using laboratory-confirmed flu as the outcome. The U.S. Flu VE Network currently consists of five study sites across the U.S. that measure the flu vaccine's effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. CDC's observational studies at U.S. Flu VE Network sites measure outpatient visits for laboratory-confirmed influenza infections using a highly-accurate lab test called rRT-PCR to verify the outcome. These studies compare the odds of vaccination among outpatients with acute respiratory illness and laboratory-confirmed influenza infection to the odds of vaccination among outpatients with acute respiratory illness who test negative for influenza infection. More information on the VE Network visit this link: http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.

5. **What steps is HHS taking to obtain effectiveness information on the influenza vaccines that HHS purchases?**

   Answer: Currently, HHS/CDC purchases and distributes approximately 10-15% of the total seasonal flu vaccines available in the United States each year through CDC's Vaccines for Children and Section 317 Immunization Programs. CDC solicits contracts for all products licensed for use in the United States each flu season and awards contracts to multiple vendors. The products purchased by HHS/CDC are generally the same as those available to the private sector, and therefore the findings from the U.S. Flu VE Network are relevant to the vaccines purchased by HHS as well as those purchased by the private sector.

   In the event of pandemic influenza emergency, we expect that the U.S. government would purchase and distribute pandemic influenza vaccines. We are prepared to estimate pandemic vaccine effectiveness with the Pandemic VE Network (consisting of the current network supplemented by several additional sites to increase sample size). HHS/BARDA also supports field effectiveness studies with industry partners for pandemic influenza vaccines as a FDA-licensure commitment.

I hope that this information is helpful to you. Thank you for your continued commitment to public health preparedness.

Cc: ASPR

FDA Commissioner

CDC Director

Sincerely,

Jim R. Esquea
Assistant Secretary
for Legislation

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

April 9, 2015

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
House Energy and Commerce Committee
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Murphy:

Thank you for your letter of March 9, 2015, concerning the House Energy and Commerce Committee's interest in additional information on the public health response to seasonal influenza.

I appreciate the opportunity to provide responses to your recent questions in the enclosed document. We also welcome this chance to share a recent Centers for Disease Control and Prevention (CDC) study, published in the journal *Vaccine*, that shows the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States during a nine-year period, from 2005-2006 through 2013-2014. This estimate represents an almost one-quarter (22%) reduction in the deaths that would have occurred in the absence of flu vaccination during that time. CDC has estimated previously that seasonal flu-associated deaths in the United States range between 3,000 and 49,000 people each year.

To conduct the study, researchers applied statistical modeling with U.S. age-group specific estimates of flu-associated excess deaths, monthly flu vaccination coverage estimates, and summary seasonal flu vaccine effectiveness estimates. Overall, the findings from the study continue to support the benefits of flu vaccination. They suggest that increased flu vaccination coverage and increased flu vaccine effectiveness would help to prevent more flu-associated deaths. The article is available on the *Vaccine* journal website at www.sciencedirect.com/science/article/pii/S0264410X15002315.

Again, thank you for your interest and support of public health-related issues. Should you have additional questions, please contact Randy Katsoyannis in the CDC Washington Office at mkatsoyannis@cdc.gov.

Sincerely,

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosure

cc: The Honorable Fred Upton
The Honorable Frank Pallone

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
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Sincerely,

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosure

Dr. Thomas Frieden Questions for the Record
Committee on Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

1. **If in the future there is another drift of influenza strain and/or a significant risk of a seasonal influenza vaccine mismatch or low effectiveness, under what circumstances would CDC support the production of an off-cycle monovalent seasonal influenza vaccine? What are the criteria for such a decision? Will CDC apply the same rigor used for deciding on a monovalent vaccine to respond to a pandemic as that used for deciding on a monovalent vaccine to respond to a seasonal influenza drifted strain?**

   Answer: The decision to produce an off-season monovalent influenza vaccine may not be the only way to address mismatched seasonal influenza vaccines. A more preferred approach by FDA and others is a strain change that could be accommodated into the standard seasonal influenza vaccine, if feasible based on manufacturing timelines.

   The decision to produce an off-cycle monovalent seasonal influenza vaccine would be made following a recommendation by the FDA's Vaccines and Related Biological Products Advisory Committee and would be based on several factors, including:

   1) Anticipated public health impact of the drifted strain, as determined by the magnitude of antigenic differences, subtype, and antiviral drug susceptibility, among other factors, and the ability of a monovalent vaccine to mitigate that impact;
   2) Probability that drifted strain will become predominant in the coming flu season; and
   3) Stakeholder consensus (including the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Advisory Committee on Immunization Practices (ACIP), health care providers, and vaccine manufacturers) on the feasibility of an effective deployment, including capacity to produce enough vaccine in time to achieve high coverage before flu season.

   It is important to understand that the decision to make a monovalent vaccine against a pandemic strain of influenza (antigenic shift) versus to make a supplemental vaccine for the seasonal vaccine in the case of antigenic drift of influenza is based on the risk factors inherently associated with the two different circumstances by which these two types of influenza viruses emerge:

   - "Antigenic drift" refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates. These small genetic changes

usually produce viruses that are closely related to one another. But these small genetic changes can accumulate over time. This can lead to viruses that look different to a person's immune system; the antibodies created against older viruses no longer recognize the "newer" virus, and the person can get sick again. In this scenario, we would expect the seasonal influenza vaccine to retain some effectiveness against a drifted strain of influenza viruses. In addition, during a drifted season we would expect some level of population immunity due to prior exposures to seasonal influenza viruses. This type of change in the H3N2s circulating in humans was detected in 2014.

- The other type of change is called "antigenic shift." Antigenic shift is an abrupt, major change in the influenza A viruses that emerge from an animal population. This results in new influenza virus proteins that are very different from viruses currently circulating in humans. Because of this, the majority of the population would have no serological immunity to the new (e.g. novel) virus, and we would expect to see a much higher population attack rate. In a pandemic or "shift" scenario, the existing seasonal influenza vaccine would likely have little to no effectiveness at all. Such a "shift" occurred in the spring of 2009, when an H1N1 virus with a new combination of genes emerged to infect people and quickly spread, causing a pandemic.

Pandemic influenza has the potential to be considerably more detrimental to the human population than would a drifted, seasonal influenza virus. In the case of the emergence of a pandemic strain, the decision to produce a monovalent vaccine is clear-cut. In the face of the emergence of a drifted strain an evaluation of risk combined with the logistical considerations regarding how quickly an additional monovalent vaccine could be made available and at what cost become important decision-making considerations. In each scenario ACIP/CDC would use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process to derive recommendations (more information about this process can be found here: http://www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html).

2. **Did CDC staff between May 1, 2014 and November 1, 2014 ever examine possible responses for the U.S. to the drifted influenza A H3N2 strain? If so, when, and what staff were involved? What were the potential responses considered, and what was the basis for the decision on each of the proposed responses?**

Answer: CDC's work on the identification and response to the drifted H3N2 strain began prior to May 2014 and involved leadership and staff from CDC's Influenza Division and across the agency. The ability to make vaccine production decisions depends on the development of a suitable candidate vaccine virus. CDC began the process of creating a vaccine candidate virus that was more antigenically similar to the drifted strain in May 2014 (detail below). Prior to that several other events had already taken place:

- In March 2014, CDC detected 5 viruses showing reduced titers with antiserum made against A/Texas/50/2012 (the 2014/15 N. Hemisphere vaccine H3N2 component). On March 28th, then CDC Influenza Division Director and WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza Director Dr. Nancy Cox contacted fellow WHO Collaborating Center directors alerting them to CDC's suspicion of a potential antigenic drift. The purpose was to ask if any countries had detected the same antigenic variants in their surveillance, investigating the presence of geographic spread. This communication facilitated the identification of variant viruses in other regions, **including a virus that was used for generation of candidate vaccine viruses used in vaccine production.**
- In April 2014, CDC expanded genetic analysis of H3N2s to characterize more viruses and gather more data for analysis; at the same time, other WHO collaborating centers began looking specifically for this specific variation in their circulating H3N2 viruses.

In May 2014, CDC began growing a potential candidate vaccine virus strain (A/Palau/6759/2014) that would be more antigenically similar to the drifted virus strain. In June 2014, CDC isolated that candidate vaccine virus strain, and submitted it to New York Medical College (NYMC) for the generation of a high-yield reassortant vaccine virus candidate strain. In July 2014, CDC received a new, egg-grown drifted H3N2 variant A/Switzerland/9715293/2013, and immediately forwarded it to the influenza reassorting lab at NYMC for creating another potential vaccine candidate virus. In August 2014, CDC performed the preliminary test on A/Palau/6759/2014 to determine if it could qualify as a candidate vaccine virus. Unfortunately, testing indicated that this strain did not have the characteristics to qualify as a vaccine candidate virus. In September 2014, CDC received back a high yielding vaccine candidate virus (A/Switzerland/9715293/2013) from NYMC. CDC then performed its testing on the candidate virus and determined that it qualified as a candidate vaccine virus. On September 26, the WHO recommended the new H3N2 vaccine strain (A/Switzerland/9715293/2013) for inclusion in the Southern Hemisphere vaccine (for 2015).

On October 3rd, CDC published a Morbidity and Mortality Weekly Report (MMWR) entitled "Update: Influenza Activity — United States and Worldwide, May 18–September 20, 2014." It reported that a new H3N2 vaccine strain was selected for inclusion in the Southern Hemisphere vaccine. It also reported that "of the 141 influenza A (H3N2) viruses characterized (78 international and 63 U.S.), 69 (49%) were antigenically similar to A/Texas/50/2012, the influenza A (H3N2) component of the 2014–15 influenza vaccine for the Northern Hemisphere." The influenza season, defined as increased activity above a predetermined threshold, began the end of November 2014. On December 3rd and 4th, after CDC had enough evidence about the viruses that were actually circulating in the United States during the 2014-15 season to determine that the drifted viruses would be

of clinical importance, it released a Health Advisory regarding the potential for circulation of drifted influenza A (H3N2) viruses, and held a press briefing.

3. **What criteria does CDC use to determine that an influenza strain targeted in a current vaccine has significantly drifted and may significantly lower the effectiveness of the current vaccine (i.e. degree of mismatch, trends, locations of mismatch)?**

Answer: There is a difference between vaccine match and vaccine effectiveness. At least two factors play an important role in determining the likelihood that flu vaccine will protect a person from flu illness: the characteristics of the person being vaccinated (such as their age and health); and, the similarity or "match" between the flu viruses the flu vaccine is designed to protect against and the flu viruses spreading in the community. CDC uses multiple laboratory methods in determining if circulating viruses match the vaccine viruses:

1) Antigenic Characterization (analyzing properties of the viruses' surface proteins): Determines how similar the vaccine virus is compared with the circulating viruses using animal sera containing antibodies raised to vaccine virus and representative circulating viruses. More information can be found here: http://www.cdc.gov/flu/professionals/laboratory/antigenic.htm . Using similar methods, human sera from individuals in different age groups vaccinated with the current seasons' vaccine are tested for their ability to react with circulating viruses. In either case, the detection of low reactions with currently circulating viruses characterizes them as antigenically drifted viruses.

2) Genetic Characterization (analyzing the sequence of the viral genes): Genetic analysis of the major surface protein of the virus, the hemagglutinin (HA), which is the target of neutralizing (protective) antibodies, identifies signature amino acid changes are associated with antigenic drift variants.

The relationship between antigenic *match* as determined by these laboratory methods and vaccine *effectiveness* is not straightforward. Even when we identify a drifted strain via the methods above, we cannot predict how well the vaccine will work until the proper epidemiologic field studies are conducted once the influenza season has begun. We have accelerated the pace of these studies so that we get interim results as quickly as possible during the season.

4. **There have been significantly drifted influenza viruses before, four times over the last 20 years according to CDC's testimony. Did the CDC have a contingency plan in case the influenza vaccine was mismatched to a drifted H3N2 A strain? What was the plan, and how was it implemented? Will CDC make any changes in the contingency plan? If so, please identify and explain the changes.**

Answer: In general there are HHS-wide plans for a variety of influenza scenarios. CDC's contingency plan in the event that a drifted strain emerges late (well after the vaccine production and distribution process has begun) is to emphasize the use of other tools in the arsenal to fight the flu. CDC emphasized the use of antiviral medications as a "second line of defense" (to be used in concert with vaccination) and the importance of everyday preventive actions like covering coughs, social distancing and frequent hand washing. CDC feels this is a solid, evidence-based approach and would expect to implement a similar strategy if faced with the same situation. During a "drift" season, CDC continues to recommend influenza vaccination because the vaccine will likely still offer some protection, and it is likely that other influenza subtypes that the vaccine is well matched to will continue to circulate. For example, this year we are seeing a late season predominance of influenza B strains, which are covered by this year's seasonal vaccine. CDC is also increasing contingency plans related to strengthening antiviral treatment practices since these are not yet well implemented but can be of greater importance during years with substantial drift.

5. **Does CDC have a specific public communication strategy when there is a mismatched influenza vaccine in a severe flu season? If so, what is it?**

   Answer: To reduce the substantial burden of influenza on the United States, CDC recommends a three-pronged approach: increasing the number of people vaccinated against influenza, appropriate use of influenza antiviral agents, and promoting respiratory hygiene and cough etiquette.

   Getting a flu vaccine is the best way to prevent influenza illness and protect against its potentially deadly consequences. When a person is sick with flu, however, antiviral flu drugs are a treatment option. During seasons when the availability or effectiveness of one of these interventions is compromised (for example, scenarios where there is insufficient vaccine supply or low vaccine effectiveness), CDC places additional emphasis on the remaining interventions. Thus, while CDC continues to recommend vaccination as an important and still useful preventive measure during a season where there may be or there is reduced vaccine effectiveness, extra emphasis is placed on the use of influenza antiviral drugs for treatment of high risk persons and everyday preventive actions to reduce the transmission of influenza and other respiratory viruses.

   This includes a large communications component, with expanded outreach to clinicians, public health partners, and the public, across multiple channels. While communications efforts are broad-based, as well as targeted, the goal of these efforts is to protect the people who are most vulnerable to serious complications from flu during that given season. For the 2014-2015 season, since surveillance data indicated that H3N2 viruses were predominating and these seasons have been associated with added burden of severe illness among people 65 and older and young children, targeted efforts

emphasized outreach to people in those groups and professionals who care for people in those groups.

This includes:

1. Direct outreach to clinicians (e.g., health alert network messages, clinician outreach and communication activity calls (COCA)).
2. Outreach to clinicians through professional organizations representing those patients at greatest risk (e.g., geriatricians, pediatricians, Infectious Disease Society of America, American Academy of Pediatrics)
3. Outreach to clinicians through mass media (e.g., traditional news media, specialized media like Medscape)
4. Outreach to public health partners (e.g., weekly situation and recommendation updates)
5. Outreach to the public through mass media (e.g., press releases, weekly web updates)

The decision about when to implement this shift in messaging is data driven (e.g., when the data are sufficient to conclude that drifted viruses are predominating and vaccine effectiveness may be reduced). Communications during seasons when vaccine effectiveness may be reduced must find the right balance between openly disclosing a possible sub-optimal match in one vaccine component, and not discouraging vaccination uptake; vaccination may still provide benefit, especially against other viruses that may circulate in the season. Early data regarding vaccine effectiveness are not available when key messages need to be given regarding vaccination and antiviral use. Communications must be timely, repeated and transparent. The goal of communications is that public should understand that the flu vaccine may offer only partial, reduced protection, but that vaccination can continue to offer protection from illness and hospitalizations. At the same time, greater emphasis is placed on including antiviral medications as a "second line of defense" (to be used in concert with vaccination) and the importance of everyday preventive actions like covering coughs and frequent hand washing.

6. **Since the hearing another study on the high-dose influenza vaccine was published in The Lancet Infectious Diseases. The study funded by FDA, and co-authored by Centers of Medicare and Medicaid Services (CMS) and CDC personnel, found the high-dose vaccine was 22 percent more effective than standard vaccines in older populations. This finding was similar to a previous study that showed 24 percent more effectiveness. When will CDC include the high-dose vaccine on the agenda for CDC's Advisory Committee on Immunization Practices (ACIP) meeting to see if the advisory committee would be willing to express a preference for the high-dose vaccine indicated for people 65 years of age and older?**

   Answer: The Advisory Committee on Immunization Practices (ACIP) has recommended high-dose inactivated vaccine (Fluzone HD, Sanofi Pasteur) since its

licensure by the Food and Drug Administration (FDA) in 2009, and included the vaccine in the 2010-11 recommendations for use in persons ≥65 years-old. Adopting ACIP's recommendation, the Centers for Disease Control and Prevention (CDC) has included Fluzone HD , along with other flu vaccines, in the U.S. influenza vaccine recommendations each season since its approval.

ACIP is reviewing the evidence for Fluzone HD and could consider preferential language. Note that ACIP recommendations already state that Fluzone HD has been found to be more effective than standard dose vaccine in one study. More information available here:
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm and
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5916a2.htm.

7. **In a future influenza season with a drifted strain and/or vaccine mismatch like this season, will the CDC defer until after the influenza season starts from issuing a health advisory that aims to raise more awareness among doctors and patients about antiviral drugs and recommends the use of these drugs as soon as possible for high risk groups? Or will CDC issue such a health advisory as soon as there is a new WHO recommendation, even if it is several weeks before the start of the U.S. influenza season?**

Answer: CDC believes that broad public communications about influenza should be data-driven and include actionable information. Consumer research indicates that the public and physicians are widely aware of the fact that how well the flu vaccine works can vary. Premature communications suggesting possible vaccine failures could have unintended public health consequences including decreased vaccine uptake which could result in greater morbidity and mortality. Needless additional unintended economic and industry consequences could result from premature communications about reduced vaccine effectiveness.

CDC believes that influenza communications this season were appropriate in their timing. Information about the appearance of drifted viruses was made public regularly. Information about the changing Southern Hemisphere vaccine formulation also was made available. CDC continues to recommend vaccination during drifted seasons for a number of reasons, including:

- We cannot know which viruses will circulate over the season. The influenza vaccine protects against three or four different influenza viruses, depending on which vaccine is administered (trivalent or quadrivalent). Vaccination can thus protect against circulating "vaccine-like" viruses. Sufficient data on which strains are actually circulating during a given season after it begins are needed to know if the predominating strains are a poor match to the vaccine.

- Antigenic characterization data is not the same as vaccine effectiveness. In the past, substantial vaccine effectiveness has been measured during drifted seasons. Antibodies created through vaccination with one influenza virus can

sometimes offer protection against drifted influenza viruses (this is called cross-protection). Thus, flu vaccination may still reduce flu illnesses, doctors' visits, and missed work and school due to flu, as well as prevent flu-related hospitalizations and deaths.

As long as vaccine may provide benefit, CDC will recommend that vaccination efforts continue and communication efforts to promote vaccination will continue. It is important to note that CDC also regularly communicates about the fact that how well the influenza vaccine works is variable.

Additionally, communicating about antiviral drugs is a core component of CDC's annual messaging and guidance. Research suggests that antiviral drugs are underutilized, thus the agency places heavy emphasis on these communication efforts routinely. Core efforts are reinforced and expanded during seasons when drifted viruses are predominating and vaccine effectiveness may be reduced. Decisions to expand communications efforts have human resource implications thus these decisions are data-driven and are made after the data supports additional intervention is warranted.

8. **What actions is CDC taking to assess the use of adjuvants to boost the effectiveness of seasonal influenza vaccine that is viewed as having substantially lower than typical effectiveness rate for a seasonal influenza vaccine? What does the current data show, and what additional data (if any) would CDC need to make such an assessment?**

Answer: DC does not have a lead role in assessing the use of adjuvants in boosting effectiveness of influenza vaccine – BARDA does have a number of activities taking place in this area. BARDA has improved influenza vaccine effectiveness by supporting the advanced development of antigen-sparing vaccines using new adjuvants for pandemic influenza vaccines towards FDA licensure. Some studies have shown that these adjuvants can provide a 6-24 fold antigen-sparing effect and greater immunogenicity for H1N1, H5N1 and H7N9 candidate vaccines, wide cross-reactivity among influenza virus A subtypes, longer duration of immunity, and priming effect for stronger booster vaccinations, Other studies in infants and elderly populations with H1N1 vaccines formulated with these adjuvants showed a greater immune response for these adjuvanted vaccines than their antigen-alone vaccine counterparts in clinical trials. Since 1997 millions of young children and elderly persons in 35 countries including Canada and many in Europe have received Novartis' Fluad®, an inactivated seasonal trivalent influenza vaccine formulated with MF-59 adjuvant, resulting in responses to many circulating seasonal influenza viruses as compared to non-adjuvanted seasonal influenza vaccine counterparts in these populations. In 2013, FDA licensed GlaxoSmithKline's adjuvanted Q-PAN H5N1 pandemic influenza vaccine.

9. **Are vaccination rates the best performance metric for evaluation of CDC's performance related to influenza? Are there other performance metrics that could be used to evaluate CDC's performance?**

Answer: CDC measures performance related to influenza through several metrics, of which vaccination rates are only one. Vaccination coverage rates are one important metric for performance related to influenza. There are four Healthy People 2020 targets for influenza vaccination coverage reported annually by age (children 6 months through 17 years, adults 18 years and older) and special populations (health care workers, pregnant women). Most recently, CDC has also reported interim coverage rates; these are preliminary estimates through November, which provide a useful tool to focus attention to the importance of vaccination during December and beyond and to help target attention to those groups that appear to be lagging in coverage. Following each influenza season, CDC reports final influenza coverage rates for the August through May period. Seasonal influenza vaccination coverage rates have improved over the past several years, although they are still below the Healthy People 2020 targets.

In addition to reporting vaccination coverage rates, CDC also estimates the burden of disease averted by influenza vaccination. Using a model CDC published in 2013 to estimate the number of influenza-associated illnesses and hospitalizations averted by influenza vaccination during the 2005-2013 influenza seasons, CDC provides updated estimates for each influenza season. While this estimate is a result of CDC's program, it could be a considered to be metric of the healthcare and influenza control system as a whole. In the December 12, 2014, Morbidity and Mortality Weekly Report (MMWR), CDC reported that during the 2013-2014 flu season, flu vaccination prevented an estimated 7.2 million influenza-associated illnesses, 3.1 million medically-attended illnesses, and 90,000 hospitalizations. Influenza vaccination during the 2013-2014 season thus resulted in an estimated 17% fewer adverse health outcomes associated with influenza. These outcomes are a result of the circulating strain and its severity, the influenza vaccine production, distribution and delivery system, healthcare prevention practices, and consumer behavior. These also reflect the effectiveness of currently available vaccines that season.

There are additional performance metrics that are important in assessing CDC performance related to influenza. CDC is the focal point for the gathering and analysis of data – both virologic and epidemiologic – to guide recommendations for vaccine composition and the formation of clinical guidelines for prevention and treatment of influenza. As a WHO Collaborating Center for Influenza Surveillance, the Agency serves as the lead for gathering virologic data year-round. CDC also plays an important role in the development and qualification of candidate vaccine viruses for use in the manufacture of influenza vaccines. The more global surveillance data that CDC is able to gather and analyze, the faster and more

effectively it can use these data to inform influenza vaccine development. CDC also builds capacity around the globe for other nations to create and sustain their own influenza surveillance systems. This in turn provides additional viruses or genetic information available for global surveillance.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for
Preparedness & Response
Washington, D.C. 20201

April 13, 2015

Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Chairman Upton:

As requested in the March 9th letter from your Subcommittee on Oversight and Investigations, enclosed are the responses to the six (6) questions for me in my capacity as the Director of the Biomedical Advanced Research and Development Authority (BARDA).

Do not hesitate to let me know if you have any additional questions.

Respectfully,

Robin Robinson
BARDA Director
Deputy Assistant Secretary for Preparedness and Response

Dr. Robinson Questions for the Record
House Committee on Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

1. **How is BARDA's work improving the effectiveness of influenza vaccines?**

Answer: The Biomedical Advanced Research and Development Authority (BARDA) has supported, primarily for pandemic preparedness and response purposes, the development of more effective influenza vaccines, which have added by-product benefits for seasonal influenza. BARDA has improved the effectiveness of influenza vaccines by modernizing influenza vaccine manufacturing. This has been done through support for advanced development of cell- and recombinant-based seasonal and pandemic influenza vaccine candidates towards Food and Drug Administration (FDA) licensure and by building greater domestic vaccine manufacturing capacity. These investments have led to FDA licensure of two, first-in-class, seasonal influenza vaccines in the U.S. This includes Novartis' Flucelvax®, cell-based vaccine, in 2012 and Protein Sciences' FluBlØk®, recombinant-based vaccine, in 2013. The underlying technologies supporting these modernized vaccines have the potential to make influenza vaccines available sooner.

BARDA has also improved influenza vaccine effectiveness by supporting the advanced development of antigen-sparing vaccines towards FDA licensure using new adjuvants for pandemic influenza vaccines. Some studies have shown that these adjuvants can provide a 6-24 fold antigen-sparing effect and greater immunogenicity for H5N1 and H7N9 vaccines. In addition, adjuvanted vaccines induced an immune response that had broader cross-reactivity within the influenza virus A subtypes, suggesting that they may provide broader protection. Clinical trial studies for infants and elderly populations who received H1N1 vaccines with these adjuvants showed a greater immune response to the adjuvanted vaccines than their antigen-alone vaccine counterparts. FDA licensed GlaxoSmithKline's Q-PAN H5N1 pandemic influenza vaccine in 2013.

BARDA, along with the National Institute of Allergy and Infectious Diseases (NIAID) and industry and academic partners, has supported the development of novel types of influenza vaccine candidates (e.g., chimeric HA stem vaccine) for seasonal and pandemic influenza. Early pre-clinical studies suggest that these candidates have potential as possible universal influenza vaccines. BARDA led the development and manufacturing of the chimeric HA stem vaccine candidates in 2014, while NIAID will conduct more clinical trials with these vaccine candidates. Additionally, BARDA launched its "More Effective –Universal Influenza Vaccines" initiative on March 16, 2015 by issuing a

Request for Proposals (RFP). More specifically, the RFP will solicit proposals for the advanced development of more effective influenza vaccine candidates.

2. **How is BARDA's work improving strain selection decisions?**

Answer: Since 2010, BARDA and the Centers for Disease Control and Prevention (CDC) have developed and utilized a vaccine strain selection process designated as the Influenza Risk Assessment Tool (IRAT). IRAT identifies novel circulating strains of influenza viruses with pandemic potential (e.g., avian H5N1, avian H7N9, swine H3N2v) based on virus pathogenicity and transmissibility. Each year, IRAT informs decision-makers regarding what vaccines should be in the national pre-pandemic influenza vaccine stockpile that BARDA manages. BARDA utilized the IRAT in 2013 to develop, manufacture, test, and stockpile H7N9 vaccines in record time.

In pilot projects with academic investigators, BARDA is supporting, through NIAID contracts and solicitations, the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines. The antigen cartography work was also supported by NIH and NIAID funding.

3. **How is BARDA's work improving influenza vaccine manufacturing, accelerating the production process, accelerating the production process, and increasing the manufacturing capacity?**

BARDA has supported the development of 18 influenza medical countermeasures since 2007. These countermeasures were used during the 2009 H1N1 pandemic and have been stockpiled for avian influenza H5N1 and H7N9 outbreaks. Since December 2005, the Department of Health and Human Services (HHS) has been supporting fundamental medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department's *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Review* (2010) and the President's Council of Advisors on Science and Technology (PCAST) report (2010), HHS made a mid-course adjustment and took steps to efficiently execute the pandemic influenza preparedness priorities enumerated in the review and report. For influenza vaccines, HHS set a goal of "more and better influenza vaccines sooner" meaning that we need more effective vaccines available at a faster rate and in larger quantities for both seasonal and pandemic influenza.

BARDA is directly responsible for working with industry and federal partners to: (i) support advanced development of new influenza vaccines, antiviral drugs, and diagnostic devices leading to FDA approval for the U.S. market; (ii) improve influenza vaccine

manufacturing resulting in greater vaccine production yields and availability sooner; (iii) build and maintain stockpiles of pre-pandemic influenza vaccines for the critical workforce and antiviral drugs at the federal and State levels; and (iv) expand domestic and global pandemic influenza vaccine manufacturing infrastructure and capacity multifold.

HHS has made significant progress improving vaccines and manufacturing technologies. Specifically, BARDA has partnered with industry to achieve the following:

- Modernized influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines, as well as antigen-sparing vaccines including:
    - Flucelvax® (licensed 2012), the first cell-based seasonal influenza vaccine in the U.S.
    - FluBlØk® (licensed 2013), the first recombinant-based seasonal influenza vaccine in the U.S., and
    - Q-Pan H5N1 vaccine (licensed 2013), the first adjuvanted pandemic influenza vaccine in the U.S.

- Launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative with the National Institutes of Health (NIH), CDC, and FDA, as recommended by the PCAST. This was done to optimize a generation of high yielding vaccine seed strains and develop alternative potency and sterility assays to expedite influenza vaccine availability. The IVMI initiative improvements cut significant time off the vaccine manufacturing process and increased production yields as seen in the vaccine response to the H7N9 virus outbreaks in China in 2013. Vaccine manufacturers are testing these improvements in beta tests with H5N1, H1N1, and other influenza vaccine strains to determine their feasibility and applicability for commercial manufacturing.

- Established and maintained pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses that have pandemic potential in order to immunize the critical workforce and other high risk populations rapidly at the onset of an influenza pandemic. Together, BARDA and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in this stockpile.

- Provided multi-fold expansion of domestic influenza vaccine production for pandemic preparedness by retrofitting older manufacturing plants (2007-2011) and

building new manufacturing facilities (2009-2012) through BARDA's public-private partnerships with industry. Today, the U.S. vaccine manufacturing capacity for pandemic influenza vaccines is ~ 500 million doses within six (6) months of pandemic onset.

- Established a national medical countermeasure (MCM) response infrastructure to develop, manufacture, and rapidly test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015. BARDA's national response infrastructure is comprised of the following programs:
    - Nonclinical Studies Network (2011) comprises of 17 laboratories able to perform animal testing;
    - Centers for Innovation in Advanced Development and Manufacturing (CIADM) (2012) comprised of three (3) government-industrial-academic consortia to develop and manufacture MCMs for chemical, biological, radiological, and nuclear (CBRN) threats routinely and during emergencies for pandemic influenza and emerging infectious diseases such as Ebola;
    - Fill Finish Manufacturing Network (FFMN) (2013) comprised of four (4) Contract Manufacturing Organizations to provide aseptic filling of medical countermeasures for CBRN threats, pandemic influenza, emerging infectious diseases, and possibly U.S. drug shortages (pilot program between FDA and BARDA);
    - Clinical Studies Network (2014) comprised of five (5) Clinical Research Organizations to provide clinical evaluation of medical countermeasures, as needed, for man-made and natural threats including Ebola.

The CIADMs and FFMN fulfilled the PCAST Report recommendation to expand and improve vaccine manufacturing capacity. This was done to meet the national goal of making the first dose of pandemic influenza vaccine available within 12 weeks of pandemic onset and to ensure that sufficient quantities are available to meet national demand in less than six (6) months.

- Established 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 has resulted in the licensure by these partner countries of four licensed influenza vaccines and a current capacity to produce more than 300 million doses of pandemic influenza vaccine.

The HHS response to the H7N9 avian influenza outbreaks was exemplified by federal agency cooperation and public-private partnerships with industry. This was made possible by building upon lessons learned from the 2009 H1N1 pandemic and investments made in pandemic vaccine strain selection, innovations in vaccine strain development, vaccine manufacturing modernization, IVMI improvements in the vaccine manufacturing process, and the usage of new adjuvants. The HHS interagency IRAT process determined that the risk from H7N9 was significant and that it would be prudent to stockpile vaccine. BARDA played a key role in these HHS efforts including utilization of new cell- and recombinant-based flu vaccines developed with BARDA support. Secondly, to provide vaccines faster, H7N9 vaccine seeds using biosynthetic methods were developed by Novartis with BARDA support as a result of the technology derived from the HHS IVMI initiative. Finally, the Novartis CIADM in Holly Springs, North Carolina played a major role in the development, manufacturing, clinical testing, and stockpiling of H7N9 vaccines in record time.

4. **How is BARDA's work helping to improve overall recognition of influenza virus mutations?**

Since 2010, BARDA and CDC have developed and utilized IRAT to identify novel circulating strains of influenza viruses with pandemic potential (e.g., avian H5N1, avian H7N9, swine H3N2v) based on virus pathogenicity and transmissibility. IRAT informs decision-makers each year on what vaccines are needed in the national, pre-pandemic influenza vaccine stockpile that BARDA manages. BARDA utilized the IRAT in 2013 to develop, manufacture, test, and stockpile H7N9 vaccines in record time. Mutations in the viral genomes of these viruses with pandemic potential are tracked by CDC, NIH, and BARDA, as well as WHO influenza collaborating laboratories. This is done to determine whether they affect virus pathogenicity, transmissibility from animals to humans, and in some cases immunogenicity and whether they impact the viral neuraminidase gene to cause antiviral drug resistance.

BARDA is supporting the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines in pilot projects. These techniques are used to identify natural influenza virus mutations, through experimental selection, using pooled human sera from different influenza seasons. This is done to determine if these mutations confer properties to virus mutants that out compete other circulating influenza virus strains.

5. **Has BARDA's work identified any areas that could improve the speed and/or accuracy of the decision-making process for the U.S. public health response to seasonal influenza? If so, please explain.**

   In pilot projects and with academic investigators, BARDA is supporting the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines.

6. **Does any of BARDA's work relate to improving the tracking of influenza vaccine effectiveness? If so, please explain.**

   BARDA's support of pandemic influenza vaccine development includes effectiveness studies. sometimes required and regularly supported Since the licensure of GlaxoSmithKline's (GSK) Q-PAN H5N1 pandemic vaccine with AS03 adjuvant in 2013, BARDA and GSK have worked together to prepare clinical study protocols for vaccine effectiveness studies and pharmacovigilance measures to monitor adverse safety events for submission to FDA. After FDA review, BARDA and GSK will establish the necessary clinical research infrastructure for clinical investigators to conduct studies and safety registries in the event of an H5N1 pandemic. Also, these protocols and registries will serve as templates for similar clinical vaccine effectiveness and pharmacovigilance studies for other pandemic influenza vaccines.

   Additionally, BARDA has developed an interactive SAP-based computer-modeled tracking tool to determine the flow of pandemic influenza vaccine from the vaccine manufacturers to the distributors. From there, a tracking tool which interfaces with CDC's SAP-based system can monitor the flow of influenza vaccine from the distributors to the actual healthcare providers administering the vaccine. Pandemic influenza exercises are planned for 2015. These exercises will test the information flow, reliability, and limits of these coordinated tracking tool systems.

   BARDA, along with influenza vaccine manufacturers, is developing two-dimensional bar codes on vaccine vials and packaging. This is being done to ensure that more comprehensive information can be readily disseminated, collected, analyzed rapidly, and utilized to track the flow of vaccine supply from manufacturers to distributors, and to retailers and healthcare providers.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

APR 0 8 2015

Dear Mr. Chairman:

Thank you for giving the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the February 3, 2015, hearing before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, entitled "Examining the U.S. Public Health Response to Seasonal Influenza." This is a response to your letter of March 9, 2015.

We have restated the questions below in bold, followed by our responses.

1. **Has FDA ever approved a monovalent influenza vaccine to target a drifted seasonal influenza strain? If so, when? What were the circumstances? What legal authorities were required for the approval?**

Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. Minor changes in the protein structure in influenza viruses, known as "antigenic drift," occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition.

In 1986, FDA approved a monovalent influenza vaccine to supplement the trivalent influenza vaccine to address a drift of the H1N1 strain. The summary minutes from the July 1986 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting demonstrate that the meeting was not devoted to influenza, but included several agenda items, and it was during this meeting that the advisory committee received an update on outbreaks of influenza that were occurring. The outbreaks were attributed to an H1N1 strain not previously selected for inclusion in the vaccine. At the time of strain selection, there was very little information available on the H1N1 strains circulating globally, but at the time of this particular meeting, some limited laboratory and epidemiological data had become available. Taking into consideration the manufacturing timelines, the committee recommended a monovalent H1N1 vaccine, but acknowledged that it was uncertain whether such a vaccine was needed or should be produced. Approximately 7 million doses of the 1986 monovalent vaccine were manufactured and distributed late in 1986.[1]

Below is the relevant text, copied from the July 1986 VRBPAC summary minutes:

[1] CDC Morbidity and Mortality Weekly Report (MMWR() 37 (31) p. 469.

4. The committee was briefed on recent outbreaks of influenza involving H1 strains with significant antigenic variation from the H1 strain (A Chile/83) which was recommended for inclusion in the trivalent vaccine formulation for the 1986-87 influenza season. At the time that decision was made, there was very little information available on H1N1 strains circulating in the world. Very recently, outbreaks with the new H1 variant have been laboratory confirmed in Singapore, Hong Kong, Taiwan and Japan. Other outbreaks have been reported but are not yet laboratory confirmed. The limited laboratory and epidemiological data which were available were reviewed. The issue before the committee was whether an additional monovalent H1N1 vaccine based on the new variants should be produced to supplement the trivalent vaccine which has already been prepared.

The committee noted that it did not have sufficient epidemiological data - attack rates, identification of at risk target populations, severity of disease, etc. - to resolve the scientific issue of whether the H1N1 monovalent vaccine is needed or should be produced. However, it was also noted that the committee is constrained by a more pragmatic factor: the manufacturers informed the committee that they believed a delay of 3 to 4 weeks (i.e. to mid August) in making a decision about whether to produce the vaccine would mean that the vaccine could not be available until January or February, when it might be too late for effective use for the flu season. To delay making the decision until September would, in the manufacturers' judgments make it virtually impossible to have the vaccine available for any part of the upcoming influenza season. The manufacturers believe that an immediate decision is required. The committee noted that if the manufacturers are correct, waiting for adequate epidemiological data would preclude the possibility of producing the monovalent H1N1 variant vaccine for the upcoming flu season. Under these circumstances, the committee recommended that if the manufacturer's are correct in their assumptions, the 1986 H1N1 variant strains, represented by A/Taiwan/1986 should be included in a supplemental vaccine for the 1986-87 flu season.

In addition to "antigenic drift" major changes, known as "antigenic shift," can also occur and have the potential to lead to a pandemic, as the world experienced in 2009, for which a monovalent influenza vaccine was approved and utilized to respond to the influenza pandemic.

We note that vaccines are approved under section 351 of the Public Health Service Act.

2. **Has there ever been a delay in the production of an influenza vaccine because a vaccine manufacturer was waiting for FDA to provide the reagents? If so, when? What were the circumstances?**

To our knowledge, the United States has never experienced an untimely delay in the production or availability of influenza vaccine because a manufacturer was waiting on FDA to provide the reagents needed for manufacture.

3. **In August 2010, the President's Council of Advisors on Science and Technology (PCAST) issued a report on reengineering the influenza vaccine production enterprise. The report recommended that the FDA should develop and issue a guidance document**

that defines a clear regulatory pathway for the approval of adjuvants. What actions, if any, has FDA taken to implement this recommendation?

This question refers to PCAST recommendation 6-2: DEVELOP ADJUVANT GUIDANCE DOCUMENT:

"Adjuvants can be an important mid-term solution to vaccine supply and will be an essential component to a long-term solution of developing recombinant protein-based influenza vaccines. The FDA should develop and issue a guidance document that defines a clear regulatory pathway for the approval of adjuvants for use in human vaccines, including those for seasonal and pandemic influenza. This guidance document should define the goals for adjuvant use (i.e., dose sparing, boosting efficacy in the elderly), specify rational endpoints for clinical trials, and stipulate safety criteria. Because the safety and efficacy of adjuvants can only be evaluated in the context of the final vaccine product, the current practice of approving final products, as opposed to adjuvants alone, is a rational one."

FDA has taken the following recent actions, with respect to adjuvants:

- Worked with other national regulatory authorities (NRAs) through the World Health Organization (WHO) on a document entitled "Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines." This guideline document was published by WHO in 2013 and constitutes guidance for NRAs and for manufacturers of biological products on the nonclinical evaluation of adjuvants and adjuvanted vaccines, the type of data needed to justify the inclusion of adjuvant in the vaccine as well as considerations for early clinical trials. FDA does not plan to write a separate guidance document on adjuvanted seasonal influenza vaccines, as the WHO guidelines document on adjuvants and adjuvanted vaccines that FDA and other NRAs developed reflects an international consensus. The current FDA guidance documents on influenza vaccines also apply to adjuvanted influenza vaccines. In 2013, FDA licensed an adjuvanted H5N1 influenza vaccine, manufactured by GlaxoSmithKline Biologicals.

4. **The PCAST report also recommended that FDA should develop a well-defined regulatory process for introducing alternative assays for seasonal influenza vaccines. What action, if any, has FDA taken to implement this recommendation? Have any alternative assays for flu vaccines been approved in the last three years?**

This question refers to PCAST recommendation 3-3: POTENCY TESTING

"FDA and BARDA should fund applied research to develop rapid methods for making potency assays for testing inactivated influenza vaccines. This should be a high-priority effort carried out through a combination of in-house programs at FDA and contracts to companies, aimed at creating and implementing such methods within a 2-3 year time frame. Possible methods include mass spectroscopy coupled with molecular biological techniques for making affinity reagents. Such methods will need to be carefully validated by comparison with the standard radial immunodiffusion assay. In addition, FDA should develop a well-defined regulatory process for introducing alternative assays for HA potency for seasonal influenza vaccines, initially alongside existing assays."

FDA has taken the following recent actions, with respect to developing alternative assays:

- The Agency has been working closely with the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC) in supporting development of new, faster, and better potency assays to measure the amount of active viral hemagglutinin (HA) protein in inactivated influenza vaccine lot release samples as part of the HHS Influenza Vaccine Manufacturing Improvement (IVMI) initiative recommended by the PCAST report (2010).

- Promising alternative potency assays being developed at FDA include an Enzyme-Linked Immunosorbent assay (ELISA) and a Surface Plasmon Resonance (SPR) assay. Both of these approaches are being designed to replace the Single Radial Immunodiffusion (SRID) assay for both multivalent seasonal and monovalent pandemic vaccine potency determination and are ready for comparison studies. They are being evaluated for feasibility to accurately measure HA in influenza vaccines in comparison to the SRID assay, as well as their suitability to monitor vaccine stability.

5. **The PCAST report recommended that FDA should define a regulatory process to guide development and implementation for sterility testing of influenza vaccines. Has FDA implemented this recommendation?**

This question refers to PCAST recommendation 3-4: DEVELOP PLATFORM TECHNOLOGY FOR STERILITY TESTING:

"The FDA and BARDA should support the development of rapid methods to test the sterility of influenza vaccines, through such molecular biological techniques as PCR and shotgun DNA sequencing. This should be carried out through private sector contracts and in collaboration with manufacturers. The methods should be performed in parallel with existing sterility testing of seasonal influenza vaccines, to demonstrate the sensitivity and validity of the methods. The FDA should define a regulatory process to guide development and implementation."

FDA has taken the following recent actions with respect to sterility testing:

- Effective June 2012, FDA amended the sterility test requirements for biological products to acknowledge the advancement in new sterility test methods that yield accurate and reliable test results in less time. The final rule provided manufacturers of biological products greater flexibility and encouraged use of the most appropriate and state-of-the-art methods for ensuring the safety of biological products.

- FDA and BARDA are working with the vaccine manufacturers and several sterility assay companies to evaluate, optimize, and validate new rapid sterility methods as part of the IVMI initiative recommended by the PCAST report (2010). For example, one sterility method supported under this initiative by BARDA takes only five days, rather the usual 14 days, to obtain results and is under evaluation not only by influenza vaccine manufacturers but by manufacturers of other pharmaceutical products as a time- and cost-saving measure throughout their aseptic manufacturing processes. The goal is to develop a new platform for automated rapid sterility testing that will reduce the time it takes to

perform sterility testing from the current 14-day method prescribed by the U.S. Pharmacopeial Convention (USP). For example, there is published literature describing rapid sterility testing. In 2011, FDA published a paper that concluded that the Rapid Milliflex Detection System, utilizing Schaedler blood agar (SBA) medium, appears to be a promising rapid alternate method to the compendial sterility method, having the advantage of taking only five days for sterility testing of biological products, including inactivated influenza vaccines.[2]

Thank you, again, for contacting us concerning this matter. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines.

If you have additional questions, please let us know.

Sincerely,

Meghan Scott

for Thomas A. Kraus
Associate Commissioner for Legislation

cc: The Honorable Fred Upton
Chairman
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce

[2] Parveen S, Kaur S, Wilson David SA, Kenney JL, McCormick WM, Gupta RK. Evaluation of growth-based rapid microbiological methods for sterility testing of vaccines and other biological products. *Vaccine* 2011 Oct 19; 29 (45):8012-23.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

April 2, 2015

The Honorable Tim Murphy
Chairman, Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your March 9, 2015, letter about the U.S. public health response to seasonal influenza. I am pleased to respond to your questions.

1. How is NIAID's work improving the effectiveness of influenza vaccines?

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute of the National Institutes of Health (NIH) for research on infectious diseases, including influenza. NIAID's long-standing influenza research program supports research to improve the effectiveness of influenza vaccines. These efforts include studies to develop new vaccine technologies, to boost the immune response to vaccines, and to develop "universal" influenza vaccine candidates that could provide lasting protection against multiple strains of influenza.

NIAID research has contributed to the development of innovative influenza vaccine technologies that have improved effectiveness of influenza vaccines for specific populations. For example, NIAID supported the first clinical trials of a high-dose influenza vaccine developed by Sanofi Pasteur and approved for use among the elderly by the U.S. Food and Drug Administration (FDA) in 2009. NIAID also supported early-stage development of Flublok, the first vaccine using recombinant influenza vaccine technology instead of the more time-intensive egg-based culture for virus growth. Flublok was approved by FDA for use in adults; because it does not contain egg proteins, Flublok provides a potential alternative to egg-based vaccines for individuals with egg allergies. Recombinant influenza vaccine technology also could facilitate rapid startup of vaccine manufacturing and may be useful in the event of a pandemic or vaccine shortage.

In addition, NIAID-supported researchers are investigating ways to enhance the immune response to current licensed seasonal influenza vaccines, including through the use of adjuvants. For example, NIAID Vaccine Research Center (VRC) researchers are conducting clinical trials on various DNA prime-boost vaccine combinations with the goal of improving the potency and durability of current licensed seasonal influenza vaccines. NIAID also funded a large clinical

trial to evaluate an intradermal influenza vaccine, approved for use by the FDA in 2012, which requires less antigen to achieve the same effectiveness as previously licensed seasonal influenza vaccines. This vaccine formulation and similar technologies could help to extend available vaccine supplies.

NIAID's Vaccine Treatment and Evaluation Units (VTEUs), part of the Institute's long-standing clinical research infrastructure, have allowed NIAID to rapidly test new influenza vaccines and vaccination strategies and to respond to emerging public health concerns, such as the 2009 H1N1 pandemic. NIAID also participates in the Influenza Vaccine Manufacturing Improvement Initiative in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), and FDA. Under this initiative, NIAID is supporting efforts to develop higher-yield influenza virus vaccine strains, improve influenza strain selection, and develop novel assays to accelerate vaccine production. NIAID research also is helping to improve the effectiveness of vaccines to protect against influenza strains with pandemic potential. NIAID intramural researchers, in collaboration with the biotechnology company MedImmune, are generating candidate live, attenuated influenza virus vaccines against such strains. These vaccines are being evaluated in preclinical and clinical studies and could be an important tool in a rapid response to emerging pandemic strains.

NIAID has intensified efforts to develop an effective universal influenza vaccine candidate capable of eliciting a broad and potent immune response against a wide range of distinct influenza viruses. NIAID is collaborating with BARDA and CDC to investigate the human immune response to universal influenza vaccines in a planned Phase I clinical trial in the VTEU network. In addition, the NIAID VRC is developing a promising universal influenza vaccine strategy based on the use of self-assembling ferritin nanoparticle technology to increase the breadth and magnitude of the immune response. A successful universal influenza vaccine could address the problem of variable vaccine efficacy by reducing or eliminating the need for yearly seasonal influenza vaccines.

2. How is NIAID's work improving strain selection decisions?

NIAID has a long-standing commitment to basic and clinical research on influenza to better understand how influenza strains emerge, evolve, and infect animals and humans. Although NIAID has no role in the selection of strains for seasonal influenza vaccines, NIAID has developed new technologies and surveillance networks to help understand the evolution of influenza virus strains and inform influenza vaccine strain selection.

NIAID is supporting cutting-edge research on influenza genomics to gather critical data about influenza viral evolution and circulating strains that will help inform strain selection. NIAID has promoted the use of next-generation sequencing through the Influenza Genome Sequencing Project (IGSP) and the Influenza Research Database (IRD). The IGSP has sequenced the complete genetic blueprint of more than 16,000 influenza viruses and made this information publicly available through databases such as IRD and GenBank at the National Center for Biotechnology Information. NIAID also has supported the development of novel

bioinformatics and data analysis platforms, such as Antigenic Cartography and Antibody Landscaping, which could one day help predict which viral strains may emerge in the future.

In addition, NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program is supporting researchers around the world to study the factors that control the emergence and transmission of influenza viruses among animal reservoirs, and the immunological determinants of whether an influenza virus causes only mild illness or results in severe disease or death. The CEIRS Program continually monitors cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential, such as the avian influenza strains H5N1 and H7N9. CEIRS Program research augments surveillance efforts by the CDC, the World Health Organization, and others, helping to create a more comprehensive picture of the incidence and characteristics of influenza virus strains worldwide to better inform influenza vaccine strain selection decisions.

3. How is NIAID's work helping to improve overall recognition of influenza virus mutations?

NIAID recognizes the critical need to develop a more comprehensive understanding of seasonal and pandemic influenza viruses and plays a leading role in efforts to characterize their evolution and pathogenesis. NIAID supports essential research and surveillance efforts to identify and track the appearance and spread of established and mutated influenza virus strains to shed light on the emergence, evolution, and severity of influenza pandemics as well as seasonal influenza.

The NIAID-supported Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program brings together multidisciplinary teams of researchers that are collecting thousands of influenza viruses from humans and animals in the United States and throughout the world. The CEIRS investigators rapidly characterize these viruses to evaluate their pandemic potential and to determine if they have specific mutations associated with enhanced disease or resistance to antiviral drugs. In conjunction with these efforts, the NIAID intramural research program aims to map viral virulence factors that determine the occurrence and severity of infection in different animal hosts. NIAID researchers are investigating the dynamics of viral mutations associated with different hosts and characterizing the host response to infection.

NIAID-supported researchers also are investigating how influenza viruses mutate and how these mutations influence transmission and disease severity. As discussed in the response to question 2, NIAID supports the sequencing and cataloging of full influenza genomes in public databases, providing additional information to researchers about changes in the influenza virus. Taken together, these efforts provide public health officials with essential information that can be used to identify the emergence and spread of specific strains, as well as strengthen the development of public health strategies crucial to lessening the impact of seasonal influenza and responding to a potential pandemic.

Thank you for your continuing commitment to public health preparedness. I hope that this information is helpful to you. I will provide a copy of this letter to Representative Diana DeGette, the co-signer of your letter. Best personal regards.

Sincerely,

Anthony S. Fauci, M.D.
Director
National Institute of Allergy
and Infectious Diseases

cc: Representative Diana DeGette