The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
Washington, D.C. 20515-6115

Dear Chairman Pallone:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the December 4, 2019, hearing before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, entitled "Flu Season: U.S. Public Health Preparedness and Response." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

Karas Gross

Karas Gross
Associate Commissioner for
Legislative Affairs

cc: The Honorable Greg Walden, Ranking Member, Committee on Energy and Commerce

The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations

The Honorable Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

U.S. Food & Drug Administration
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The Honorable Brett Guthrie (R-KY)

1. **An Executive Order issued by President Trump on September 19, 2019 directs the U.S. Food and Drug Administration (FDA) as well as other agencies to accelerate the adoption of improved influenza vaccine technologies.[1] What actions does FDA plan to take to implement FDA's responsibilities under the Executive Order? Please also include information about the timeline for these actions.**

FDA, in collaboration with the scientific community and influenza vaccine manufacturers, is working to improve influenza vaccine manufacturing. Several efforts related to the Executive Order have been initiated and are ongoing, including the development of:

- alternative methods to prepare the reference reagents needed for determining vaccine potency,
- new methods to expedite the calibration of potency reagents,
- improved assays to determine potency of influenza vaccines, and
- higher yielding vaccine candidates.

Successful development and implementation of these methods and technologies could help compress the timeline for the production process and provide greater predictability.

In terms of timelines, we are currently actively working in these areas, have recently made notable progress regarding improving the yield of a pandemic vaccine candidate, and expect the work on potency reagents to be ready for potential adoption into the commercial manufacturing process within the next three to five years, dependent upon their acceptance by the vaccine manufacturers.

In addition, the following are part of FDA's routine activities:

- FDA has been and is committed to continuing to work with its Federal partners, the scientific community, and vaccine manufacturers to help address the public health threat caused by seasonal and pandemic influenza.
- FDA has utilized in the past, and will continue to utilize, applicable regulatory pathways and programs to expedite development and evaluation of additional influenza vaccines.
- All influenza vaccines approved by FDA have been demonstrated to be safe and effective. It is critical that Americans know that they can rely on the safety and effectiveness of vaccines.
- FDA is facilitating the development and adoption of advanced manufacturing technologies for influenza vaccines, which have the potential to address the need for maximally efficient, agile, and flexible manufacture of both current and next-generation influenza vaccines.

[1] Executive Order, *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health* (Sept. 19, 2019), available at *https://www.whitehouse.gov/presidential-actions/executive-order-modernizing-influenza-vaccines-united-states-promote-national-security-public-health/.*

2. A few years ago, we had a flu season where there was a bad mismatch between the flu vaccine and a flu strain that had drifted. If FDA were confronted with vaccine mismatch again, what would FDA do differently than in the 2014-2015 flu mismatch season to respond to the mismatch?

The process for making recommendations about which vaccine strains to include for each year's influenza season must occur many months in advance of influenza season. This is to accommodate the time that is required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses consisting of antigens derived from three or four different influenza virus strains.

With respect to the 2014-2015 influenza season**,** the drifted H3N2 viruses that were detected in the United States in March 2014 were uncommon. When a drifted virus first emerges, it is difficult to predict whether the virus will die out or circulate widely, or when either of those scenarios would occur. Leading up to the 2014-2015 influenza season, the drifted H3N2 viruses became more common after the WHO convened a meeting in September 2014 to select the seasonal influenza vaccine for the Southern Hemisphere. Because of the time required to manufacture influenza vaccine, it would not have been possible to make adequate amounts of influenza vaccine containing the drifted H3N2 virus in time for our peak influenza season, which usually occurs between December and February.

However, since then, FDA has proactively initiated several efforts to 1) improve communication about antigenically drifted influenza strains by periodic review with CDC of virus surveillance data for potential antigenic drift, 2) improve and expedite candidate vaccine virus availability by generating additional candidate vaccine viruses for drifted strains of concern, 3) expedite vaccine reagent preparation for drifted virus strains, and 4) improve vaccine testing methods by developing alternative potency assays with improved accuracy and sensitivity that could potentially expedite influenza vaccine availability. These efforts will help us to be more prepared to expeditiously respond to flu strain drifts in the future.

3. Under what circumstances would it be appropriate to pursue a monovalent rescue vaccine to respond to a drifted influenza strain?

The decision to pursue a monovalent influenza vaccine as an addition to a seasonal influenza vaccine already produced or in production would depend on a balancing of several factors:

- when during the influenza season the emerging influenza strain was detected,
- the probability that the strain was likely to emerge as a major threat to public health
- its potential public health impact based on its potential to cause morbidity and mortality,
- the ability to rapidly produce a matched vaccine candidate and the needed testing reagents, and
- the availability of adequate manufacturing capacity.

Balancing these factors is critical, because a decision to produce monovalent vaccine while seasonal vaccine production is still in progress could disrupt the production of the latter, potentially negatively impacting the overall influenza vaccine supply.

Discussions pertaining to pursuit of a monovalent rescue vaccine for the United States would include BARDA, CDC, FDA, and vaccine manufacturers. FDA and its Federal partners have already conducted an exercise regarding the potential production and release timelines for such a licensed vaccine.

The Honorable Jeff Duncan (R-SC)

1. **It appears that universal flu vaccines carry tremendous potential, as we do not need to modify the flu vaccine to a different strain each year. I also find it encouraging to hear there is tremendous progress with respect to universal flu vaccine development.**

    a. **How will the FDA treat regulatory approval of these novel vaccines?**

    For the past several years, FDA has been working to anticipate and address challenges associated with using new technologies in the development and approval of vaccines to prevent influenza disease. Evaluation of new influenza vaccine candidates is based on existing knowledge and experience with regard to currently licensed influenza vaccines, as well as state-of-the-art science. FDA has approved novel influenza vaccines, including cell-based and adjuvanted influenza vaccines, utilizing existing regulatory pathways and expedited programs, which would also be applicable to a universal influenza vaccine.

    b. **Is the FDA ready and prepared with an approach to consider these vaccine candidates for regulatory approval?**

    Yes, FDA is prepared. Please see above response. Furthermore, FDA is working with industry and HHS partners to facilitate the testing of candidate universal influenza virus vaccines, and to identify approaches to demonstrate the safety and effectiveness of universal influenza vaccines.

The Honorable Susan Brooks (R-IN)

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

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

    In practice, RWE provides a living, breathing, pool of data to help the U.S. government and the global influenza community gain a practical perspective on how to predict and

prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

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

Please refer to the Centers for Disease Control and Prevention's (CDC) response.

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

Please refer to CDC's response.

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

Please refer to CDC's response.

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

FDA's Center for Biologics Evaluation and Research (CBER) acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided that RWE studies are of adequate design and conduct.

For influenza vaccines, FDA is using large databases in the post-market setting to evaluate vaccine effectiveness. FDA has helped validate this methodology with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database to compare the effectiveness of high dose versus standard dose seasonal influenza vaccines for people 65 years of age and older. This collaboration has provided valuable analysis in support of public health for these specific influenza vaccines.

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

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

For influenza vaccines, FDA is using large databases in the post-market setting to further evaluate the effectiveness of FDA-approved vaccines. FDA has helped validate this methodology with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database to compare the effectiveness of high dose versus standard dose seasonal influenza vaccines for people 65 years of age and older. This collaboration has provided valuable analysis in support of public health for these specific influenza vaccines.

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

At a minimum, FDA can review RWE each year for signs of an increase in certain adverse events or the occurrence of previously unseen events. For example, in the past FDA has used RWE to assess whether there has been any increase in Guillain-Barré syndrome with the seasonal influenza vaccine.

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

CBER acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided the RWE studies are of adequate design and conduct.

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

FDA is willing to consider the submission of RWE by sponsors for inclusion into product labels, and will assess each request upon its own merits. As stated above, CBER acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided the RWE studies are of adequate design and conduct.

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