Why a coronavirus vaccine ‘October Surprise’ could be an October disaster

There is widespread anticipation of the availability of vaccines to prevent COVID-19 infections so that Americans can get their lives back to some semblance of normal. Some four dozen vaccines, made with a variety of technology platforms, are now in clinical trials; nine are in large-scale safety/efficacy testing. Several of the more promising development programs have been accelerated by a White House crash program, “Operation Warp Speed,” which was launched in May.

It was no secret that there would be intense pressure on the FDA from a White House desperate for good news to provide an “October Surprise” in the form of a vaccine approval before the November 3rd election, even if that approval was premature. When I wrote about this subject only last month, I described the wall that the head of the FDA, Dr. Stephen Hahn, and his colleagues had constructed in order to resist that pressure. Well, watch out for falling debris, because the wall is crumbling.

The first brick in the wall was an FDA policy statement, “Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry,” published on June 30th. It specifies in great detail the criteria for FDA approval of coronavirus vaccines, but the overarching principle is simple: “the goal of development programs should be to pursue traditional approval via direct evidence of vaccine efficacy” in protecting humans from COVID-19—through clinical trials—and a vaccine must be at least 50% more effective than a placebo in preventing the disease. The clinical trials would also need to demonstrate that the vaccine is safe, of course.

Those criteria are extremely important because they emphasize that regulators do not intend to cut corners via “accelerated approval” based on “surrogate endpoints”—such as a vaccine’s ability to elicit antibodies to the virus—but short of actual prevention of infection. The guidance enables FDA Commissioner Hahn to fall back on that policy if he is pressured by his bosses to adopt a lower standard. He went out of his way to emphasize the FDA’s independence and integrity on July 21st, tweeting, “Americans should know that we are steadfast in maintaining our regulatory independence & ensuring our decisions for treatments & vaccines for #COVID19 are based on science & data. This is a commitment that the American public can have confidence that I will continue to uphold.”

And, in a podcast interview with the editor of *JAMA*, Dr. Hahn repeated that theme: “Americans’ and the world’s public trust in the FDA is really important … People depend upon us every day of their lives, and we cannot do anything that would break that trust. That’s a solemn promise.” Part of that promise was that the Agency’s vaccines advisory committee, which is comprised of outside experts, would review vaccine candidates prior to approval.

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> — Dr. Stephen M. Hahn (@SteveFDA) July 21, 2020

In an August 7th article in *JAMA*, Dr. Hahn and two senior colleagues beat the drum yet again, promising "unequivocally" that "candidate COVID-19 vaccines will be reviewed according to the established legal and regulatory standards for medical products."

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They added:

> While Operation Warp Speed is an important initiative and FDA has lent technical expertise around end point selection and safety considerations to this public-private partnership for vaccine development, there is a line separating the government's efforts to focus resources and funding to scale vaccine development from FDA's review processes, which are rooted in federal statute and established FDA regulations.

Dr. Peter Marks, a senior civil servant who heads the FDA organization that evaluates vaccines, has also made his feelings on the subject known. In August, Marks told Reuters that the FDA's evaluations would be guided by science alone and that if he were subjected to political pressure for a premature approval, "I could not stand by and see something that was unsafe or ineffective that was being put through." He added, "You have to decide where your red line is, and that's my red line. I would feel obligated [to resign] because in doing so, I would indicate to the American public that there's something wrong."

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In sum, the message from Drs. Hahn and Marks to several audiences—their bosses at the Department of Health and Human Services and the White House, the public, and the vaccine industry—seemed to be clear: although regulators will streamline regulation and facilitate the development of COVID-19 vaccines, they won't be stampeded into exposing Americans to inadequately tested, potentially dangerous products.

One might think that that would put the matter to rest, and that the American public need not worry about undue political influence on what are essentially scientific and medical decisions. However, recent actions by the FDA and its sister agency, the Centers for Disease Control and Prevention (CDC) have raised widespread concerns:

- the FDA's issuance of an Emergency Use Authorization (EUA) for convalescent plasma, an antibody-rich blood product obtained from patients who have recovered from COVID-19. In theory, infusing a sick patient with the antibodies would neutralize the virus that's present and spur recovery, but many in the medical community – including senior NIH and FDA scientists — felt the EUA was predicated on insufficient evidence (and which has made the completion of rigorous clinical trials difficult or impossible). Notably, the EUA came a on a Sunday, a day after President Trump accused some "deep state" bureaucrats at the FDA of trying to delay a COVID-19 vaccine until after the fall election.
- the CDC's new guidance on testing for the SARS-CoV-2 virus, released on Monday, August 24th, amended the agency's guidance to recommend that people who have been exposed to the virus, typically defined as being within six feet of an infected person for at least 15 minutes, "do not necessarily need a test" if they do not have symptoms. This flies in the face of evidence that the time of highest virus shedding and infectivity is in the days shortly before symptoms emerge and would seem to represent an abandonment of any attempt at contact tracing and isolation of infected persons.

The New York Times reported that, according to two government officials, the CDC changed its guidelines on instructions from higher up the food chain: "One official said the directive came from the top down.

Another said the guidelines were not written by the CDC but were imposed." The change sounds suspiciously like, "If we do less testing, we have fewer cases."

These are, at best, dubious decisions, especially the completely inexplicable CDC *volte-face* on testing, which, if implemented, could significantly set back efforts to suppress the COVID-19 infections.

I am usually suspicious of slippery slope arguments, but I do believe in precedents, and the above two examples are credible precedents for a possible, much worse, far more damaging action – a premature Emergency Use Authorization for a COVID-19 vaccine that had not been adequately tested for safety. There is a suggestion that FDA Commissioner Hahn may be moving toward that: In an interview published by the Financial Times on August 30, he said his agency was prepared to authorize a vaccine before Phase 3 clinical trials were complete, if regulators become convinced that the benefits outweigh the risks.

Another indication of pressure to issue such an authorization(s) is that in a move that is unprecedented, four pharmaceutical companies – Moderna, Pfizer, Johnson & Johnson, and Sanofi – that are developing COVID-19 vaccines are about to issue a statement describing their commitment to prioritize safety before speed by waiting to seek authorization for their vaccine until human trials show "substantial evidence of safety and efficacy," and to adhere to the highest standards in clinical trials and manufacturing. The logic is so unassailable and obvious that one wonders why it even needs to be publicly articulated – unless the companies are being pressured to submit applications to FDA prematurely.

9 Drug Companies Pledge to 'Stand With Science' on Coronavirus Vaccines

The joint statement by competitors was seen as an effort to restore public trust as President Trump has pushed for a vaccine before the presidential election.

But far more worrisome is the existence of a loophole, or workaround, in federal law (U.S. Code, Title 21, Chapter 9), that could be used unilaterally by Hahn's boss, the Secretary of Health and Human Services – Alex Azar, a political appointee and lawyer who has hardly been a paragon of independence or competence over the course of the pandemic.

The relevant section of the law, "Authorization for medical products for use in emergencies," specifies that

> The Secretary may issue an authorization under this section with respect to the emergency use of a product only if, after consultation with the Assistant Secretary for Preparedness and Response, the Director of the National Institutes of Health, and the Director of the Centers for Disease Control and Prevention… the Secretary concludes (1) that an agent referred to in a

> declaration under subsection (b) can cause a serious or life-threatening disease or condition; (2) that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that (A) the product may be effective in diagnosing, treating, or preventing (i) such disease or condition."

Note that the Secretary is only required to consult with, *but not obtain agreement from*, the three subordinates specified in the law. Moreover, none of the officials entrusted with making the decision appear to have any experience with the non-clinical aspects of vaccine production. Ongoing controls on and consistency in manufacturing are essential to ensuring safety and efficacy going forward. For example, can the manufacturer ensure that every batch meets the standards for purity, potency, and sterility? Are there Standard Operating Procedures (SOPs) for those involved in production of the vaccine? Has the facility passed inspection?

It would surprise me not at all if Secretary Azar was already having and documenting conversations with the three, specified subordinates, and staffers in the White House and the Department of HHS were already preparing the necessary decision documents for an emergency authorization for one or more of the COVID-19 vaccine candidates.

Lending credence to that scenario are reports that top administration officials told congressional leaders in July that they were likely to issue emergency authorization for a vaccine before the end of Phase 3 clinical trials in the United States.

For several reasons, that would be unwise. The perception that the authorization was rushed and issued via an unorthodox pathway would fan the passions of the anti-vaccine movement and undermine public confidence in COVID-19 vaccines; but, more important, the short-circuiting of the usual evaluation mechanisms could endanger the vaccine recipients.

There is a reason that vaccines intended to be administered to hundreds of millions of healthy people are extensively tested and the results carefully evaluated. This is a time that science, meticulously applied, and experience with vaccine evaluation must prevail.

The last word goes to Professor and physician Joel Tepper, of the University of North Carolina Lineberger Comprehensive Cancer Center:

> If a substandard vaccine is released, it will hinder, in a major way, efforts to develop a vaccine that is actually safe and effective. The short- and long-term implications of a poor decision will be enormous.

Henry I. Miller, a physician and molecular biologist, was a research associate at the National Institute of Child Health and Human Development, the founding director of the FDA's Office of Biotechnology, and the co-discoverer of a critical enzyme in the influenza virus. Find Henry on Twitter @henryimiller