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Pharmaceutical Industry Caution vs. U.S. Government Push for Accelerated COVID Vaccine Approvals

(Source: An article by Jerry Avorn, M.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H for the New England Journal of Medicine)

On September 8, 2020, nine pharmaceutical company leaders took the unprecedented step of stating that they would refuse to apply for approval of a COVID-19 vaccine until adequate trial data was available. This announcement reflected an unusual role reversal at a time of unexpected regulatory anomalies. For decades, manufacturers have criticized the U.S. Food and Drug Administration (FDA) for being too slow and demanding too much evidence before issuing approval for a product. But in the face of growing public concern that the federal government might push forward release of a COVID vaccine despite inadequate evidence, these roles seem to have reversed.

This week, the FDA imposed a two-month waiting period after clinical trials have concluded to ensure that no immediate adverse effects are reported by those participating in the clinical trials. A careful, data-driven decision would be far better than a few months' more sales after a premature approval in October. The industry is hesitant to put itself in the position experienced as when FDA emergency use authorizations (EUAs) that went wrong for hydroxychloroquine and convalescent plasma.

The manufacturers' pledge stipulated that any application to the FDA for vaccine approval or an EUA would require data "demonstrating safety and efficacy through a Phase III clinical study that is designed and References conducted to meet requirements of expert regulatory authorities such as [the] FDA." FDA guidance issued in June stated that for approval, a vaccine should demonstrate a 50% or greater reduction in the incidence or severity of COVID infection as compared with placebo - a relatively high bar. The necessary combination of person-time and disease incidence is daunting: with case rates plateauing or falling in many places where trials are being conducted, it's plausible that by late October no trial will have accrued enough clinical events to demonstrate a statistically significant difference for this efficacy measure. But the FDA guidance document also allows for an EUA or accelerated approval if efficacy is suggested by changes in a surrogate measure that is "reasonably likely to predict" protection against SARS-CoV-2.

In recent years, under combined pressure from the pharmaceutical industry, Congress, and some patient advocacy groups, the FDA has increasingly accepted changes in laboratory tests or imaging studies as the basis for approval, even if trials have not fully demonstrated clear links to clinical benefits in "how patients feel, function or survive." Thus, under the pledge, a manufacturer could still receive approval for a vaccine, who does not have to follow the recommendations of his staff scientists or advisory committees.

The criteria for an EUA are even less rigorous: the commissioner

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In Brief...

- **Johnson & Johnson** has launched the Phase III trials of its COVID-19 vaccine candidate, and the company believes its single dose formulation could help the pivotal trials proceed much faster than the two-dose vaccines. The trials were launched September 23 and has already shown promising safety and efficacy in animal studies published at the end of July in *Nature*. Phase I/II data is to be published very soon.
- The **Healthcare Distribution Alliance (HDA)** announced the election of *Dr. Robert Mauch*, executive vice president and group president of **AmerisourceBergen** to the position of chairman of HDA's board of directors. He replaces *Greg Drew*, president of Value Drug. *Chad Gielen*, president and CEO of Louisiana Wholesale Drug will serve as vice-chairman.
- A Preliminary survey of 71 member companies of the **Federation of Japan Pharmaceutical Wholesalers Association (JPWA)** revealed 2.54% growth in their sales year-over-year in FY2019. Data also showed a small drop in gross profit margin of 0.02 points to 6.87%. The prior year also showed a slight decrease in gross profit margin.
- **Merck KGaA** has announced that *Belén Garijo* will take over as chief executive, replacing *Stefan Oschmann*. She will also serve as the new chair of the executive board in addition to her CEO role. She assumes her new position on May 1, 2021 and will make her the second female CEO in the big pharma top 20, alongside *Emma Walmsley* of GlaxoSmithKline.

COVID-19 Then and Now…How Far Have Treatments Come Since the Beginning of the Pandemic

(Source: An article by IFPW staff writer, Christina Tucker)

Sometimes it is difficult to remember how the world was when COVID-19 started approximately nine months ago. The first four months ushered in unimaginable fear as the virus surfaced first in Wuhan, China, then quickly spread to Europe, United States and other countries Travel advisories turned into travel shutdowns. Front line healthcare workers struggled to treat patients as they dealt with a severe lack of vital equipment, such as ventilators, and personal protective equipment. Hospitals overflowed with patients while global economic shutdowns permeated the news headlines, along with a stunning worldwide death toll.

Fast forward to today - while COVID-19 is still impacting populations worldwide, the way it is handled and treated has changed. Perhaps the best demonstration of the differences between "then" and "now" is shown in the treatment and recovery of two prominent world leaders, Prime Minister Boris Johnson of the United Kingdom and U.S. President Donald Trump.

Prime minister Johnson tested positive for COVID-19 around March 27, 2020 and self-isolated at his residence at 11 Downing Street, with no immediate spike in concern since his symptoms were mild. Johnson is overweight and over the age of 50 (he

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Pharma Industry (cont.)...

must simply believe, in a public health emergency, that a product's "known and potential benefit…outweigh [its] known and potential risks." The EUAs for *hydroxychloroquine* and convalescent plasma were justified in this way. But if an antibody titer is used as evidence of efficacy for early approval, its clinical meaning could be difficult to assess, given that the medical community has known this infection for less than 10 months. What antibody level could reliably be predicted to confer immunity? Exactly which antibody? For what duration? Achieving levels similar to those seen in recovered patients may not be compelling enough, since we are still learning about the extent to which such natural immunity confers protection from infection and for how long. Linkage of an unvalidated surrogate measure to clinical benefit is challenging at best, but it is particularly so for an emerging disease with limited clinical experience. And beyond efficacy, will a vaccine that increases antibody levels or reduces COVID severity also reduce contagiousness in a vaccinated patient? Not necessarily — an important issue to consider in assessing its public health impact.

Under accelerated-approval regulations, decisions based on such unvalidated surrogate measures must require conformatory clinical trials once a product is in routine use. But in the past, some company-designed follow-up studies have not provided the needed data or were not completed in a timely manner. This challenge would be even greater if widespread availability of a vaccine makes it harder to enroll patients in a placebo-controlled trial. After such an accelerated approval or an EUA, there is no clear policy regarding reassessing such decisions and modifying them if necessary.

Phase clinical trials are generally scaled to demonstrate efficacy but have limited power to assess adverse events. Thus, a pledge to complete a phase trial will not in itself adequately define a vaccine's safety. The adverse event information from a phase trial will depend on what kinds of patients are enrolled, how long the trial lasts, and how adverse events are ascertained. The clearest answers about risks will come only after widespread use by hundreds of thousands of people, followed in systematic post-approval surveillance systems that can detect and quantify side effects.

The American public is already dangerously skeptical of the process of COVID vaccine development. This credibility problem will inevitably diminish vaccine uptake, whatever occurs in October. Fortunately, poll respondents also said they were confident that the agency would only endorse a vaccine that is safe and effective, indicating widespread support for FDA scientists and non-political appointees.

COVID-19 Then and Now (cont.)...

is 55), which put him at higher risk of worsening symptoms. At a news conference on April 2nd, his prognosis began to change drastically and he was admitted to the St. Thomas' Hospital with a persistent fever and significant breathing issues, which had shown to be increasingly prevalent in more severe COVID patients.

Covid-19 can take different forms. Many individuals who contract it may scarcely notice the virus or may be completely asymptomatic. Others grow critically ill and face possible death within a short window. Those with even moderate symptoms can experience chest pains, headaches, cold spasms and extreme fatigue. Clinical experts agree that the most dangerous phase is week two. After that patients generally start to recover. But some precipitously crash, as the virus attacks the lungs. This was the case with Johnson, who was moved to intensive care for more serious treatments (which were few), including oxygen. He was not, however, put on a ventilator, nor was he prescribed Cpap treatment (a less invasive form of oxygen treatment.) After eight days, Prime Minister Johnson was discharged from the hospital to continue his convalescence at home.

Fast-forward to October 2, 2020 when U.S. President Donald Trump tested positive for COVID-19. Initially he insolated at the private residence of the White House, but was transferred to Walter Reed National Military Medical Center for more intense patient oversight after a drop in oxygen levels. Amazingly, three days later, he was discharged from Walter Reed and returned to the White House where he would receive his last drug infusion under his doctor's care. How did Trump, a 74 year-old overweight man, manage to show significant improvement in a such a short amount of time? Clearly, the changes in treatment and additions of COVID-19 therapeutics made all the difference.

President Trump's treatment began with supplemental oxygen the evening of October 3nd. Upon admission to the hospital, he was also treated with the latest therapeutics available, including the antiviral *Remdesivir* by Gilead, which is given intravenously in either a 5- or 10-day course. He was also given Regeneron's *RGN-COV2* cocktail combination of two antibodies which is directed against a key protein of the virus that causes COVID-19, SARS-CoV-2. These antibodies bind to a region on the main surface spike protein that helps the virus attach to a receptor on human cells called *angiotensin-converting enzyme 2*. The targeted region is dubbed the receptor binding domain. One antibody comes from a human who had recovered from a SARS-CoV-2 infection; a B cell that makes the antibody was harvested from the person's blood and the genes for the immune protein isolated and copied. The other antibody is from a mouse, which was engineered to have a human immune system, that had the spike protein injected into it. These antibodies attach to the virus protein and inhibit the proteins from entering human cells, greatly reducing the viral load in the body.

President Trump also received the steriod *dexamethasone*, which has shown promise in severe cases but that doctors warn should not be used early in the course of the illness. Trump's drop in oxygen levels to 93% at one point prompted the decision to initiate the steroid therapy, with it being determined that "the potential benefits early on in the course" outweighed any downside. On the evening of October 5th, President Trump was discharged and returned to the White House. Certainly the options available to the Trump medical team made all the difference. Prime Minister Johnson did not have those options available to him early in the pandemic, thus his diagnosis, treatment and recovery period was much different.

The availability of these innovative therapeutics have completely changed the way physicians are treating COVID patients, and with great success. While virus rates are showing significant increases and "second waves" are emerging in various locations around the world, the death rates from the disease continue to hold steady or drop due to these newly-developed treatment options. Hopefully, this will be sufficient to stave off the previous poor outcomes until a widely available vaccine is on the market, sometime in 2021-22.