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COVID-19 Vaccines Blaze New Path In the History Of Vaccine Development

by Brenda Sandburg

Vaccine experts, including R&D leaders at Pfizer and Sanofi, describe what has been unique in developing a vaccine for the novel coronavirus, lessons learned from previous vaccines, and challenges that lie ahead.

There have been astounding moments in the history of vaccine development: the first time someone was inoculated with a vaccine for smallpox, which led to the elimination of this most deadly disease from the planet two centuries later; the radio announcement that Jonas Salk's polio vaccine was up to 90% effective in preventing poliomyelitis; and now the development of vaccines to prevent infection with the novel coronavirus, which has killed more than one million people worldwide.

As the first COVID-19 vaccine application nears submission to the US Food and Drug Administration, *The Pink Sheet* talked to experts to get their take on what has been different in the development of this vaccine, the lessons learned from previous vaccines, and questions yet to be answered.

There are numerous challenges that lay ahead after a vaccine is authorized or licensed by FDA, from distribution to assessment of its long-term safety and durability. But the trajectory in the development of vaccines to prevent infection with SARS-CoV-2 is unprecedented.

The most extraordinary aspect of COVID-19 vaccine research has been the speed at which candidates have been created and advanced into clinical trials. It took less than one year from the time the virus was identified in January to move several vaccine candidates into Phase III trials.

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Kenneth Kaitin, a professor at Tufts University School of Medicine and director of the Tufts Center for the Study of Drug Development, said the fastest time prior to this was the development of the mumps vaccine in four-and-a-half years. The timeline for COVID-19 vaccines "is absolutely mind-blowing" for anyone who looks at this space, Kaitin said. (*See sidebar with infographic timeline of vaccine history*).

Other unprecedented aspects of COVID-19 research have been the billions of dollars of government funding, the extraordinary degree of collaboration between companies and the government, the fact companies are manufacturing millions of doses of candidate vaccines before they are approved, and the application of new technologies that have never been used in a commercial product. These include the mRNA platform technology used in *Moderna, Inc.* and *Pfizer Inc.*'s vaccines, the DNA vaccine being developed by *Inovio Pharmaceuticals, Inc.*, and the replication-defective adenovirus-based vaccines being developed by *Johnson & Johnson* and *AstraZeneca PLC*.

What Came Before COVID-19: Two Centuries Of Vaccine Development

By Brenda Sandburg

19 Oct 2020

Infographic timeline looks at key moments in the history of vaccine development, from the first vaccine against smallpox to the polio field trial involving 1.8 million children to the flurry of vaccines created by 'the scientist who saved more lives than all other scientists combined.'

Read the full article here

John Shiver, senior VP, vaccines global R&D at *Sanofi*, said the availability of new technologies has enabled companies to find a candidate and make clinical material faster than they might with more established vaccine platforms. Sanofi is working with novel and established platforms. It has a messenger RNA based candidate in partnership with *Translate Bio*, which is to start clinical trials by December, and an adjuvanted recombinant protein-based vaccine candidate that uses the same technology as Sanofi's Flublok influenza vaccine. That vaccine, being developed in collaboration with *GlaxoSmithKline plc*, entered a Phase I/II trial in September.

All-In-One Protocols

Vaccine makers have also changed their clinical trial protocols to speed up the development process. Shiver said the most impressive thing about working on COVID-19 vaccines has been conducting all the steps of development at the same time rather than in sequence.

"As we're starting Phase I, Phase III is already being planned" and we're making preparations to start commercial production, he said. "Our goal is to have about 100 million doses ready around the time of the start of our Phase III. That has never happened."

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William Gruber, senior VP of vaccine clinical research and development at Pfizer, also cited the collapsed timeframe for developing a COVID-19 vaccine. Typically, Pfizer interacts with FDA after completion of each trial phase before moving onto the next. But its COVID-19 vaccine protocol is an all-in-one Phase 1-2-3 protocol, in which the company has real time interactions with FDA, Gruber said.

“We didn’t cut any corners as far as establishing safety. But we got rid of the white space in terms of the typical times that it takes to go from stage to stage,” he stated. He noted that these review periods can sometimes take 30 to 60 days, which is time the company can’t afford now.

In an unusual move Pfizer and Moderna released the protocols for their pivotal Phase III trials last month. (Also see "*Pfizer Appears Slightly Ahead Of Moderna In COVID-19 Vaccine Race*" - Pink Sheet, 17 Sep, 2020.) AstraZeneca and Johnson & Johnson followed with publication of their Phase III study protocols.

FDA requires companies to provide two months of safety data on half of trial participants following final dose of a vaccine before they can seek emergency use authorization. Pfizer CEO Albert Bourla issued an open letter on 16 October saying the company estimates it will reach this milestone for its BNT162b2 candidate in the third week of November. (Also see "*Pfizer’s COVID-19 Vaccine Will Miss US Election, Bourla Clarifies*" - Pink Sheet, 16 Oct, 2020.)

In addition to demonstrating safety and effectiveness, Bourla said the company must also submit manufacturing data that demonstrate the quality and consistency of the vaccine that will be produced. He expects to have that data ready for submission before the safety milestone is reached.

Clinical Trial Recruitment Hurdles

One issue of concern has been that COVID-19 vaccine trials include participants from minority populations in order to show the vaccine is effective in diverse groups.

Vaccine makers have had difficulty recruiting people of color into their clinical trials. Moderna slowed down its COVID-19 vaccine trial to ensure participants were diverse and Pfizer and its partner *BioNTech SE* expanded the target enrollment for their COVID-19 vaccine trial from 30,000 to 44,000 to increase diversity.

> *“We're about to beat [SARS-CoV-2] with a series of vaccine strategies with which we have no commercial experience. So I*

> *think that over the next two years there will be a learning curve." – Paul Offit, Children's Hospital of Philadelphia and FDA advisory committee member*

Underrepresentation of minorities has been a problem across all clinical trials. A recent study by the Tufts Center for the Study of Drug Development found that of 341 new drug applications and biologics license applications approved between 2007 and 2017, participants who were Black or of African descent were the most highly underrepresented. (Also see "*Expanding The Tent: Improving Trial Participation Among Under-Represented Patient Populations*" - In Vivo, 8 Apr, 2020.)

But there has been a concerted effort to overcome this disparity for COVID-19 vaccine trials. Michelle McMurry-Heath, president and CEO of the Biotechnology Innovation Organization, noted BIO's efforts to help companies diversify their trial ranks. Speaking at the Food and Drug Law Institute's annual conference, she said BIO was matching companies with organizations like the National Medical Association and the National Urban League. (Also see "*BIO Is Helping Companies Boost Minority Participation In Clinical Trials*" - Pink Sheet, 9 Oct, 2020.)

The Johns Hopkins Center for American Indian Health is also seeking to enroll members of the Navajo Nation into Pfizer and BioNTech's mRNA vaccine trial. The Navajo Nation Human Research Review Board reviewed the study and gave its okay for the center to recruit those interested in participating.

On 21 September, the Navajo Nation held an online Town Hall meeting with National Institute of Allergy and Infectious Diseases Director Anthony Fauci, who noted the significance of including Native Americans in a vaccine trial.

"We have the same difficulty getting enrollment in other minority populations, African Americans, Latinx and then others, including Native Americans, Alaskan Natives and Pacific Islanders, so the fact that you are able to do a scientifically sound, ethically sound vaccine trial in this demographic group is really very important," he stated.

NIAID is working with Moderna on its mRNA vaccine candidate, mRNA-1273, which is just behind Pfizer's candidate.

FDA Adaptations

On the regulatory side, FDA has adapted its practices to the urgent quest for a vaccine, rapidly

issuing guidances and revising clinical trial practices to allow telemedicine in lieu of onsite visits at clinical trial sites.

The agency took an unprecedented action in specifying that a COVID-19 vaccine should have an efficacy rate of at least 50%. The recommendation, included in guidance issued in June, is the first time the agency has specified a clinical efficacy rate for a product approval. Pfizer and other frontrunners are aiming to achieve vaccine effectiveness in the 70% range.

Norman Baylor, former director of the Office of Vaccines Research and Review in the FDA's Center for Biologics Evaluation and Research, said there have not been any changes in the agency's review process other than putting more resources into the review and "pulling out all the stops" to analyze the data as quickly as humanly possible.

But FDA has had to deal with political pressure from President Donald Trump, who pushed for a vaccine to be available before Election Day. This has created public doubts about whether the agency will clear a vaccine before it has been proven to be safe and effective and led FDA officials to declare publicly that they would not do so.

Vaccine makers have also sought to quell public concerns. On 8 September, the CEOs of nine companies developing COVID-19 vaccines announced they would not submit a vaccine for approval or an emergency use authorization (EUA) until they had demonstrated safety and effectiveness through a Phase III trial. (Also see "*COVID-19 Vaccine Sponsors' Pledge To Wait For Phase III Helps US FDA*" - Pink Sheet, 9 Sep, 2020.)

Assessing Vaccine Durability, Effectiveness In Special Populations

FDA's Vaccines and Related Biological Products Advisory Committee will discuss the evidence needed to make that determination at its 22 October meeting.

According to the agency's briefing documents for the meeting, the panel will discuss studies that should be conducted pre- and post-licensure to evaluate the safety and effectiveness of COVID-19 vaccine candidates, including in special populations, and to further evaluate the immunogenicity and duration of vaccine effectiveness. They will also talk about the need for postmarketing safety studies following approval of a biologics license application and what will be needed to assess vaccine benefits and risks following issuance of an EUA. No specific vaccine is to be considered. (Also see "*Transparency, And A Mirror: US FDA Advice On COVID-19 Vaccine EUAs Finally Published – Twice*" - Pink Sheet, 6 Oct, 2020.)

Michael Kinch, director of the Center for Drug Discovery at Washington University in St. Louis, said there is not enough information at this point to know if a vaccine is going to be safe, effective, and durable.

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“Durability is something that I think we’re all holding our breath on,” Kinch said. We know from natural infections with other coronaviruses that “you can get the same infection year after year. So that suggests there is not a durable response to natural infection. We don’t know if that’s true of COVID or not, but the data is out there with other coronaviruses that this is an issue.”

In addition, he said clinical trials are being rushed, and if their evaluation is rushed we will end up moving forward with a vaccine even though it may not have a durable response.

“I think the assumption right now is that the first vaccine is going to be mediocre as compared to what will come later,” Kinch stated. “There is a possibility that there will be no vaccine, that we will not have a vaccine that is safe, effective and durable.”

Pfizer’s Gruber noted that the durability of a vaccine remains to be seen. “We’ll continue to try to solve for both the pandemic use as well as routine annual use, if in fact that proves necessary," he said. “It could be that immune response is durable and protection is durable. If it is durable for a number of years, that would be ideal. But we need data to determine that.”

Much remains to be learned about the virus and the activity of the vaccines once they become available.

Paul Offit, director of the Vaccine Education Center at Children’s Hospital of Philadelphia and a member of FDA’s Vaccines and Related Biologicals Advisory Committee, noted that SARS-CoV-2 has already caused a number of clinical and pathological surprises that would never have been predicted based on what we know about human coronavirus.

“It causes inflammation of blood vessels. It causes an unusual multisystem inflammatory disease in children. It rages during the summer, which is not true, really, of any virus that's similar to it,” Offit said. “And we're about to beat it with a series of vaccine strategies with which we have no commercial experience. So I think that over the next two years there will be a learning curve.”