COVID-19 vaccine update from FDA Director Peter Marks, MD, PhD

On Dec. 3, 2020, the AMA hosted the fourth webinar in the "COVID-19: What physicians need to know" series.

About the event

Hosted by AMA physician leaders, each installment of this webinar series aims to gain fact-based insights from the nation’s highest-ranking subject matter experts working to protect the health of the public, particularly during the COVID-19 pandemic.

Host

- Susan R. Bailey, MD, AMA President

Guest

- Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA)

Dr. Marks joins Dr. Bailey once again to discuss the latest developments on the road to effective COVID-19 vaccines. Dr. Marks will do a deep dive into the Emergency Use Authorization (EUA) process, specifically explaining how the timeline has been shortened from a matter of years to a matter of months.

Physicians will learn the similarities and differences between routine vaccine development and the EUA process and understand how accelerated approval is being arrived at safely.
Transcript

Dr. Bailey: Hello, and thank you for joining us today for the latest in our "What Physicians Need to Know" series about COVID-19 and other important issues in health care. I'm Dr. Susan Bailey, president of the American Medical Association. And the purpose of today's webinar is to help you gain a better understanding of the vaccine review process and the path ahead. Our previous webinars featured representatives from the Food and Drug Administration and the CDC to explore aspects of COVID-19 vaccine development, allocation and distribution. If you weren't able to join us for those sessions, I encourage you to watch replays of the videos which are available for free on our website. You can find them at ama-assn.org\covid-19-webinars. Or you can simply visit our homepage and search for COVID-19 webinars.

Ten months into our collective response to COVID-19 and the pandemic is more deadly and widespread than ever before with record high surges occurring across the upper Midwest and really all over the country. More than a quarter of a million of our fellow citizens have been lost, including physicians, nurses and other health care personnel on the front lines. Despite the surges and the heightened risks, physicians and care providers continue to work tirelessly in hospitals and ICUs around the country. They are truly the heroes of this moment. And so are the scientists and researchers who have been working around the clock and under intense pressure to develop a safe and effective vaccine or vaccines in record time.

All of us remain hopeful and encouraged by what we’re hearing about vaccines in the late trial stages. But we're not quite there yet. We must remain focused and continue to encourage our patients to do their part in limiting the spread of this virus. That means continuing to wear masks, washing our hands frequently, physically distancing as much as possible. With two prominent vaccines now under review by the FDA, we asked Dr. Peter Marks back to talk to us about the review process and answer questions you may have. Dr. Marks, whom we featured in our initial webinar back in October is director of the Food and Drug Administration Center for Biologics Evaluation and Research. He's board certified in internal medicine, hematology and medical oncology. He led the Adult Leukemia Service at Yale University and served as chief clinical officer of Smilow Cancer Hospital in New Haven before joining the FDA in 2012 as the center’s deputy director.

In his current role as director, he and his team are tasked with ensuring that the COVID-19 vaccine that is ultimately produced is both safe and effective, and that it has gone through a rigorous evidence-based and transparent process. Today, Dr. Marks will talk about the process the FDA is going through to get these vaccines authorized, and we hope this information not only provides you with a greater understanding of the steps the FDA is taking to ensure safety and efficacy, but also gives you the information you need to assure your patients about the reliability of the vaccines once they're authorized or approved. We also hope that you can understand that Dr. Marks might not be able to
talk about any specific vaccines that are now under review as FDA officials are limited in what they can discuss while in the middle of the review process.

However, he can explain the rigorous process underway and what steps lay ahead. And we're planning for additional webinar events with the FDA once we have authorized vaccines so that we can go more in depth on the specifics of each one. Now please join me in welcoming Dr. Peter Marks.

**Dr. Marks:** Thanks very much, Dr. Bailey. Let me try to get up my slides here. Okay. Thanks very much. So what I'm going to do is I'll try to spend the first 20 or so minutes here just taking you through some basic aspects of our vaccine review process here, particularly focusing on the process that will culminate in emergency use authorization, because that is what is probably most relevant for the first few vaccines that we're going to see. So FDA's role in vaccine development is quite wide ranging. We've been regulating vaccines back since 1903 following the passage of the Biologics Control Act of 1902. And actually a vaccine was one of the first two biologics ever licensed, that was smallpox vaccine. So we've been doing this for a while. And actually, the agency actually was part of National Institutes of Health up through 1972.

So we've done so with a research bent, an applied scientific research bent to understand the basic aspects of these and the basic nature of the products that we regulate. So we not only deal with the evaluation of safety effectiveness making regulatory policy, but we also do a variety of other things for vaccines, such as we're involved in strain selection, reference standard production. We are involved with release, which is making sure that when the vaccine is finished being produced, it is what it says it is. It's got the correct identity and the correct potency. And we're also involved in making sure that after the vaccine is given to people in large numbers, that we make sure that it continues to be safe, our post-marketing surveillance programs. And more recently, particularly with the various user fee programs that have come up, we've been tasked with helping to advance vaccine manufacturing technologies, such as by trying to start to apply newer manufacturing technologies like continuous or semi-continuous manufacturing to vaccines.

But of all of those things, what has become really clear during the past year is that all of these things really feed into what is most important for us, which is helping to ensure public confidence in any vaccine that FDA puts its in perimeter of approval on. And that's because the public has so much issues right now with vaccine confidence that people who might never have been considered vaccine hesitant seem to be such. And we could spend a whole webinar on whether that's due to political climate or whether that's due to social media and the disruption of some of how we all have the same narrative, but whatever the case, we have to do a very good job making sure that people can feel like they're getting the information they need and that we've done our jobs so that they feel comfortable taking these vaccines.

So we're all aware that most of the vaccines coming up now, in fact, all of the lead candidate vaccines in the United States are targeting the spike protein or S protein. There are some candidates in very
early stages that are looking at both spike and N proteins. And obviously outside of the United States, there are some whole killed virus vaccines being studied. The most advanced candidates as of December now are the two mRNA candidates that we have currently in-house under consideration for emergency use authorization. That's the one from Pfizer BioNTech and one from Moderna. But there were a few other vaccines that are moving along into more advanced stages of development. There is a phase three trial ongoing in the United States for a chimpanzee adenoviral vector vaccine by AstraZeneca, Oxford, and an adenoviral 26 vector vaccine by Janssen.

Both of those are in phase three trials in the United States now that are enrolling. And somewhat behind those are protein subunit vaccines from Novavax and Sanofi-Translate Bio, which are, they're somewhat behind, but also moving ahead in development. And obviously this is not to slight the other 186 plus vaccines that are in various stages of development, but these are the ones that are most relevant. And I think most of us on this webinar right now probably are concentrating right now on the top two of these on the list, the two mRNA ones because that's what we see closest to authorization.

So how did we get to a place where we're getting vaccine development in less than a year when normally this is a process that takes several years? Well, traditional vaccine development is a highly de-risk activity. It's a highly de-risk activity because vaccines don't make companies a lot of money generally. And so they're going to try to reduce the cost of research and development by spreading out the risk over time and only advancing from one stage to a next after they know that it's likely that the product is going to work. And so manufacturing is often advanced in a similar manner. And one often doesn't see scale up of manufacturing till very late in the game. What that means is that one can be close to an approval and one still doesn't have lots of vaccine available for distribution.

So normally you can see here kind of after first in human studies, you have the more definitive safety and efficacy studies, and large efficacy studies, and commercial scale manufacturing starts towards the very end. But what has been done as part of operation work speed and also by other manufacturers that are not part of operation work speed is by collapsing some of the steps. You can't eliminate things necessarily, but what you can do is work at risk. And so the scale up of manufacturing started very early on in development, really in phase one, two, and at risk to scale up to commercial scale manufacturing to start manufacturing millions of doses without actually knowing that the vaccine would ever be given an authorization or approval. And that actually saves a significant amount of time.

Additionally, eliminating dead space between phase one, two, and phase three was another thing that saves some time here. Now, obviously we can't work time and make follow up any faster than it is. So at the end of the day, when we authorize a vaccine, we're only going to have a few months of follow-up data for safety and efficacy, but we do have the ability to do post-marketing surveillance. And we do have the ability to follow people in clinical trials for a longer period of time. And we'll say more about that. So in order to make sure that everyone understood what the kind of ground rules for vaccine development were, we put out two guidance documents, one on kind of the general
development of COVID-19 vaccines, and one that was more specific to how things would need to be done for an emergency use authorization.

Because by August to October of this year, it became clearer to us that the first vaccines that would come through would indeed likely be granted emergency use authorization because of the incredibly pressing nature of this crisis. And we'll talk more about the difference between a biologic splice since application and emergency use authorization and why one might use an emergency use authorization even if one had very similar data in this situation.

Now, when we think about vaccine development, some of the things that we really have to think about is step back and realize that I'm not going to talk a lot today about manufacturing quality. We as physicians often don't think a lot about that, but for biologics, that manufacturing quality is so critical. When you look at some of the catastrophes that have occurred in biologics, the one that led to the passage of the Biologics Control Act of 1902, actually there were two of them which were manufacture and quality issues. And probably the other most notable one in our history was the Cutter incident was also a manufacturing quality issue. We obviously spent a lot of time there because you can't even start to think about safety and efficacy until you have a quality vaccine. Biologics, you can't engineer in quality after the fact. They have to be quality by design upfront.

We obviously look at our safety and efficacy. And then for these particular vaccines, post-market surveillance plan are going to be very important. So our guidance noted that particularly for these vaccines where underserved minorities are being disproportionately affected by COVID-19, we really needed to encourage clinical trial sponsors to enroll minority populations, older populations, populations that are traditionally underrepresented in clinical trials. And although we can't mandate that they do this, we don't have a regulation that says you must, we do have a bully pulpit. And that bully pulpit has been relatively effective because the trials have enrolled a good cross-section of individuals, including a good number of older individuals. So the trial populations we wanted to make sure about were obviously ethnic and minorities and others, older individuals.

Ultimately, we know that we're going to have to have data on pregnant women and pediatric populations, that obviously is going to come a little bit later than the initial trials data in adults. We also did something for these vaccines that we have not done before. But when you have a once in a century, hopefully pandemic, you get to do things a little differently. And that is, instead of just saying in general, we wanted efficacy of some level. We actually put a specific number and we said that the vaccine should be at least about 50% effective. And we put a lower bound on the 95% confidence interval of 30%. Why did we do that? It's because we understand that in this particular situation, there is a crisis with an opportunity cost when you manufacture a vaccine and you really don't want to put something out there that's not highly effective because we know that when people are vaccinated, they will tend to change their behavior.
And you would hate to have a vaccine that paradoxically leads to more spread because people change their behavior to do less mat squaring or less social distancing. We also, as part of this guidance put forward the fact that we wanted to see a minimum median of two months of follow up for both safety and to ensure that the vaccine had some durable effectiveness. Now, the issue of two month follow up has been talked about a lot, but the rationale here is that most, that is about 95% of the serious adverse events with vaccines become apparent within about six weeks and certainly within two months of the administration of the vaccine. So this at least helps us feel comfortable that when we deploy these vaccines, that there's anything that's in a significant way of a serious adverse event, we will have seen it. Because the trials ultimately are trials that are involving tens of thousands of individuals ranging right now from 30,000 or so for the Moderna, to 44,000 for the Pfizer vaccine.

In terms of post licensure, we're talking about making sure that there is a robust post licensure safety follow-up program and that will include continuing to follow the clinical trial participants for up to two years after they've initially been enrolled and also having both a passive and an active safety surveillance program in place once a vaccine is authorized or licensed. You might say, well, why couldn't we use an immune correlative protection? That is, why couldn't we just look at the antibodies that were made in response to these vaccines rather than using a clinical endpoint? Well, there's two reasons. One is kind of, well, let's say they're both practical. One is that we don't know yet whether the immune correlative protection and the antibodies truly correlates to a clinical prevention of disease. We hope that's the case, perhaps, but we'll know once we have the data.

But from a more practical purpose, it turns out that when you have the incredibly large number of cases that we're having right now, you get there actually faster with clinical end points, unfortunately. And we also talked about in our guidance, the ability to use the emergency use authorization procedures. Now, to describe emergency use authorization to you, I'd like to back up and just explain what a normal biologics license application requires. Biologics are licensed in the United States under the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. The Public Health Service Act includes the successor to that original Biologics Control Act of 1902, which says that we have to have safe, pure, and potent biologics. And the Federal Food, Drug, and Cosmetic Act, when grafted on top of that says that those also have to be effective.

The effectiveness standard that we use is that a product to be licensed has to have substantial evidence of efficacy from adequate and well controlled trials. And for vaccines, those are generally clinical trials that are randomized involving tens of thousands of individuals. And we have several different types of BLA approvals, including our traditional one, where you're able to use an immune correlative protection, you can potentially get an accelerated approval. And for vaccines that we can't actually study in humans, which isn't the case for COVID-19 but is the case for smallpox, anthrax and other bio-terrorism agents, we have a way of doing an approval for a vaccine or other products where we use animal models that are validated look at efficacy. And we use humans administration for safety.
Now Emergency Use Authorization came about after the terrorist attacks of 9/11, because at that time, it became clear that we were potentially subject to threats such as chemical, biologic or radio nuclear events where we might not have approved medical products to treat people who have disease, yet we might have things in development that could potentially benefit them. And in that kind of a public health emergency, once a public health emergency is declared, and there's a method for doing that in which the secretary of health and human services can declare a public health emergency, which is what we are in now. These products can be used without informed consent by just providing people with information about them even though they are investigational products.

Now, the standard that's used for these emergency use authorization products, for therapeutic products, and for that matter would apply to any product, the minimum standard is that they may be effective and the known and potential benefits outweigh the known and potential risks. Obviously, there can't be an available alternative product if you're using this, because if there was an available approved alternative product, you'd use that. Now, this standard of may be effective doesn't necessarily breed the kind of confidence that people might want to have for a vaccine given to healthy people. And we recognize that. It's the floor. But for what we've decided is rather than be at the floor, or just sitting on the floor, we need to be closer to the ceiling, more like a light fixture off the ceiling. And that's why in an emergency use authorization for COVID-19 vaccine, we've articulated in our guidance that it has to have clear and compelling efficacy from a large, well-designed phase three clinical trial.

It might not be exactly the same as the standard we use for biologics license application, but it's going to be close. And when we bring these in, though we might not go through every last line listing of the 44,000 patients the way we would for a biologics license application, we're going to do a fair amount of that. And we're going to look extremely carefully at the manufacturing information, the safety data, and the efficacy data that we receive so that we feel confident that what comes out of this process is the kind of vaccine that all of us would want to take in our own arms and have our families take. We talked about doing this in a transparent manner by bringing the vaccine to a public advisory committee meeting so that providers and the general public could see a discussion of the data that is being used, to come up with an authorization if an authorization is ultimately granted.

And we also noted that there would have to be this enhanced post-deployment surveillance. And just to give you an idea of what this enhanced surveillance looks like, it turns out the government actually works pretty well with each other at lower levels. And we have a good collaboration with the Centers For Disease Control and Prevention and have worked very nicely with them to come up with what is really an interdigitating safety surveillance program where we collaborate on monitoring of adverse events that are reported to the Vaccine Adverse Event Reporting System, which is a passive system. People fill out forms, be they patients or providers. It's the traditional adverse event reporting system. CDC happens to have an active surveillance program where they actually can get near real time information on more than 12 million people through the vaccine safety data link and the clinical


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immunization safety assessment.

And CDC also designed an app to be used by those who elect to do so, which will allow them to get reminders on their cell phones to report adverse events. And if certain adverse events are screened out by computer, they will get calls from CDC for follow-up to check on them. Now, the FDA will collaborate with CDC on passive monitoring through the Vaccine Adverse Event Reporting System. But we also have a safety system which involves using very large databases, the Sentinel System, you may have heard of that, which is able to gather data from claims-based databases covering hundreds of millions of lives. And we also have our little unique piece of that for biologics is because it's variable important to be able to take a signal and either confirm or refute it. We have of millions of lives that we can be able to look at through to the electronic health record level.

Obviously we don't get the patient's data, we get results of the queries, it's a distributed database model. But this will allow us to keep good surveillance for about 20 safety outcomes of interest, things like Guillain-Barre syndrome transfers myelitis, vasculitis, things that can be seen very rarely with vaccines at a higher rate than unvaccinated. So we want to be looking for those. Want to be looking for things that could be evidenced for instance of enhanced antibody dependent enhancement given what we know about corona viruses, although we don't have any evidence for that yet. In terms of the Vaccine and Related Biologics Product Advisory Committee meeting, this is again, something being done for transparency. Our committee will have a variety of external experts. Their recommendations are non-binding, but we generally like to try to follow them.

We have experts in this case, including vaccinologists, several individuals with coronavirus experience, and statisticians and both industry and patient representatives. Obviously we've committed to going to this committee before any emergency use authorization is granted. And we’re going to be doing that both on December 10th and December 11th, on the 10th for the Pfizer BioNTech candidate, and on the 17th ... I think I might've said the wrong, I might've said 11th. Then December 10th and December 17th, sorry, to discuss the Moderna candidate. So two weeks in a row. One question that will come up is how fast will we see a vaccine authorized after that? And it will depend on the discussion at the advisory committee, but we’re hoping that within about a week afterwards, we'll see an authorization if everything goes well for each of those.

So just to finish up here and I look forward to taking questions, we've shortened vaccine timelines here without compromising vaccine safety and efficacy. We cannot compromise that standard. We're going to use an approval process or authorization process that is as transparent and open to the public as possible. And we're hoping that this focus on transparency and this concern about safety and effectiveness, and our commitment to making sure that any vaccine that we authorize is going to be one that we ourselves are very comfortable taking, having our families take, and thereby having the entire population take. That has to be really clear because we hope that we can bring back enough people into the fold for believing in this amazing thing we have of vaccines. So I look forward to
answering questions. Thanks for your attention.

**Dr. Bailey:** Thank you, Dr. Marks. That was a great, great overview. We received well over 100 questions in advance of this event. Obviously we can’t address all of them, but we’ll do the best that we can. Many of the questions were about vaccine distribution, such as when physician offices will be able to administer vaccines to their patients. And so since the FDA is not managing the distribution portion of this, we will save those questions for another time. And as we noted earlier, we won’t be able to get way down into the weeds about specific vaccines under review, but we will be able to do that on our next webinars after we have authorized vaccines. So speaking of getting down into the weeds, we had a lot of questions about the nature and the safety of mRNA vaccines of, are they safe? What should we know about them? Do they affect our genetic makeup? Help us go back to freshman biochemistry and understand that.

**Dr. Marks:** Right. So these mRNA vaccines are basically using a snippet of genetic material to allow production of the protein and expression of these proteins for a transient period in cells. And the presence of that protein on the surface of the cell, probably combined with some of the adjuvant effect, the irritant effect of the mRNA on the immune system seems to make a very good immune response to the protein. And that’s why we believe we’re seeing these really nice responses to these vaccines. Now, mRNA vaccines, this is the first time we will have a widely distributed mRNA vaccines, but they have been around and used for vaccines in clinical trials for a number of years. In previous infectious disease outbreaks, for instance with Zika Virus, an mRNA vaccine was in development then, and there have been mRNA vaccines studied for influenza as well.

So we do have some experience giving these to humans, albeit not to this tremendously large group. One of the concerns that’s commonly asked about these is, is there a chance somehow that a retrovirus will get the mRNA and get it into our genome somehow? And what we can tell from everything we know from animal experiments and from previous human experience is although it is theoretically possible, practically, it hasn’t been observed. Now, obviously we’ll have a lot more data soon, but it’s simply not, it’s not something that at this point we are concerned enough about to prevent us from moving forward.

**Dr. Bailey:** What is the half-life of the mRNA in the vaccine? How long does it actually last in your system?

**Dr. Marks:** Good question, and it’s probably a matter of weeks.

**Dr. Bailey:** Okay. So not very long at all. Okay. There were a lot of questions about, and you touched on this, use of the vaccines in pregnant women and children. We know that there weren’t pediatric patients in these initial clinical trials for a number of reasons, what do you think the future of coronavirus vaccines in children will be? Are there plans to study that?
Dr. Marks: Well, let me just back, that's all great. Let me just back up to one thing. The trials, because the definition of pediatrics in the United States and outside of the United States is slightly different, we're lucky in the United States because they were studied in individuals 16 and up. So we will probably get down to the 16-year-olds. Now, that's maybe not a lot of solace. Also, additionally, in the Pfizer trial, there were about 50 children ages 12 to 17 that were studied. They were studied actually earlier on, but you're right, we're going to need to study a larger contingent of children. And the way this will happen, and I know it's already been publicly announced by Moderna, and I suspect other manufacturers will follow suit shortly. They are going to start trials shortly where they do typical age de-escalation, where they'll start in 12 to 15-year-olds, then move to seven to 12-year-olds and then down the line.

And the nice thing about this, I think will be that by the time we get to those trials, they'll be able to use immune correlates of protection. So they won't have to wait to do a large trial in lots of kids to make sure that they have clinical end points. They'll probably just use immune correlates. So we get an answer in a faster manner because obviously it will be a good thing to get these deployed in children to help bring an end to this pandemic. And the same thing goes with pregnant women. Pregnant women, there are... a few dozen women have become pregnant during clinical trials, excuse me, sorry. A few dozen women have become pregnant during clinical trial, so we'll have data on those, but there will be additional studies that will be conducted during various stages of pregnancy under written informed consent so we get more data on these vaccines in pregnancy.

Dr. Bailey: Great. Thank you. Lots of questions about talking to patients about the vaccines. How can we best address the safety of these vaccines that have been under the EUA authorization process? Patients know that this has gone really rapidly. I have some patients that are skeptical of this vaccine given the fast that everything has proceeded so quickly. What's the best way to discuss this with patients?

Dr. Marks: Well, I think obviously there's no one right way. But for my way of thinking about this, we do have the fact that these were very large trial programs. And even though the trial follow up, we might have a median of two months of follow up on 44,000 or well, it's actually 38,000 patients or so, and one of them, and this'll be, we'll have a median follow up of a certain number of tens of thousands of patients. It means some of those patients will have been followed for a longer period of time, right? Because some will be followed for four or five months because these trials began in late July. And given their size, that means we'll have several thousand individuals that will have been followed for that longer period of time.

Now that's not totally reassuring perhaps. But when you think about it, for many vaccines that we approve, we don't have these very large trials quite as large. And so I think I would reassure patients that the trials, although they were done in a kind of compressed manner, they were done in a way that's giving us much of the same data that we would have for the kind of vaccines that we get every
day. And that the safety and efficacy has been very well vetted. And that there's also going to be continued monitoring going on and that the public will be informed if there are any concerns. But make no mistake about it, we would not let any of these out of the FDA if we really had any concern that there was any hint that was going to be of concern to patients. And unfortunately, there's a cost to this of being careful, right?

There's the cost right now that another regulator happens to have made this vaccine available sooner than we did, or we will. And that's because we're really taking care to make sure that when people get this vaccine, we will have really vetted it for safety. And if there is something there, we'll know about it and we'll know what we're looking at so we can have a conversation about it. So due care is being taken. And I think this is a balance, we're getting there as fast as we can because we understand people are losing their lives to this virus. But we also understand that the only way that we're going to save more lives is if we can get a large fraction of the population to take the vaccine.

**Dr. Bailey:** When we met earlier this fall, we talked a little bit about the Reagan-Udall Foundation and its role with the FDA in doing vaccine public education. Are there plans to roll out a public education plan along with approval of the vaccines?

**Dr. Marks:** The Centers for Disease Control deals with that more than we do, but we will probably take part in that as well. And I can just tell you some late breaking news which is very relevant to providers listening, it's you who people will believe more than anyone else about taking a vaccine. They're going to be looking to say, if you say that you're comfortable taking the vaccine, they're going to be willing to take the vaccine. FDA, we're down a little bit. I was actually impressed we weren't... I was worried we would be in the basement. We weren't in the basement. We were actually not too far down from providers, but it really is head and shoulders, providers head and shoulders above the rest really are trusted. And to the extent that we can help educate and that you're learning about these, and that you have questions, we to answer them because if you're comfortable with these vaccines, that's going to rub off on your patients.

That's going to rub off more. As a leukemia doctor, you go through these long conversations often about different chemotherapy options and this and that. And you could see people's eyes were glazing over and at the end they'd ask you the key question. "So, doc, what would you do? Would you take this one if it were you, or would you give it to your family?" And that's the place where we need to get providers to the sense of comfort that they would answer yes to that.

**Dr. Bailey:** There is nothing like that one-on-one relationship between a patient and a physician. So I agree with you wholeheartedly on that. Looking longer term, how are we going to learn how long these vaccines are effective? We get lots of questions like, "Well, am I going to have to take one every year or every five years? Is once enough?" How are we going to find that out?
**Dr. Marks:** We're going to find that out through several ways. The first is that the people who are enrolled in the clinical trials will be followed. Most of them are following people for two years and they will be checking on their immunity during that time, because we can measure, now that we are getting a sense of what the immune correlates of protection are, we'll be able to monitor those over time. So we'll see how people are doing over time. We'll also have our larger surveillance of the population of vaccinated individuals to see if we're starting to get breakthrough infections. So those two things will really help us. That is the part, there's no denying that we don't... that's not something that we can tell people how long they'll benefit from this. But I would say the following, we know that we're going to get at least months of protection out of this, and it's months of protection that will help us all climb out of this COVID-19 crisis.

**Dr. Bailey:** One question that I've gotten personally from patients, and we got questions from our listeners, should someone who's had COVID-19 get the vaccine?

**Dr. Marks:** That is a discussion to have with your physician. I think that it's going to be a really interesting one. It would potentially depend on your risk group and would also depend on the severity of COVID-19 that you've had. Now I'm speaking more as a physician than as an FDA official because there is going to be a little bit of art to this. The good news is the way the vaccines were studied, even though there were people enrolled independent, when they were enrolled into the trials, even though they were tested at the beginning to find out whether they had had COVID-19, they were randomized without knowledge of whether they had COVID-19 or not. So people were vaccinated who had had COVID-19. So at least we do not believe from looking at the clinical trial data that there is any adverse effect of being vaccinated if you've had COVID-19.

But the question will be, if you've had a severe case of COVID-19 recently, which tends to produce very good antibody levels, should you also get vaccinated? It doesn't really help you a whole lot. And I think that's going to be a provider decision more than one that we may have a recommendation from FDA. That might come from CDC. We'll see.

**Susan Bailey:** Okay. As far as the EUA process, the Pfizer vaccine will be looked at by the advisory committee on the 10th, the Moderna vaccine on the 17th. My understanding is that a minimum of two days prior to the meeting that the data will be made available for public view. We discussed that last time that we would be able to have access to all of the data that the FDA has access to.

**Dr. Marks:** Well, it'll be access to the company briefing book, which I can tell you the companies put together pretty extensive information on the vaccine, enough that it will be plenty of a good read for most providers. And we'll put together a briefing book from FDA. People won't have access at that time to the primary data. That's tens of thousands of pages of data and it includes protected health information. So we can't make that available. But the company documents will contain many summary tables that will be of interest. And I think the ones, at least I'm pretty sure they'll satisfy most providers' curiosity for the major end points.
Dr. Bailey: Assuming that these meetings go well and we get authorization for these first two vaccines, what does the timeline look like going forward into January, February for some of the other vaccines that are currently in phase three trials?

Dr. Marks: It's very hard to tell you what's going to happen there. What I can just give you is a general outlook. The trials are enrolling reasonably quickly. It's public knowledge, actually, they've been making public the number of people enrolled in these trials. And so they're enrolling reasonably quickly. Will they finish enrollment? They may finish enrollment by, for at least for the two large phase three trials that are ongoing right now in the United States, they may reach their enrollment goals before the end of the year or by January. And then given the number of end points we've been seeing, it may not take that long to have a readout after that. So I can't tell you exactly when, but the fact that we have so many cases of COVID-19 right now, it's so unfortunate for us as a country.

And the only upside to it is that when you're doing a clinical trial with an endpoint that's a clinical infectious disease endpoint, it's been easy to get to those end points because there are just so many cases.

Dr. Bailey: Assuming that we have a multitude of vaccines to choose from next summer, a year from now, how will we choose? Will patients get to choose which vaccine they have? Will that be their physician's choice? It's a luxury to think about, but how do you think that'll turn out?

Dr. Marks: Well, it's a really good question. It may be that the advisory committee on immunization practices may make some recommendations. It may turn out that by looking at the different characteristics of the vaccines, there might be some that are more effective in one population than the other and some that have lower side effects initially. It may be that for instance, I'm just making up a hypothetical that the mRNA vaccines are associated with... They're not infrequent development of mild side effects such as fatigue, achiness, or low grade fever for a day or two after administration. It may be that in children, if you had a vaccine, completely hypothetically, if you had a vaccine that had similar or somewhat lower efficacy but had fewer side effects, you might decide that that was more reasonable to use there because children just... It's the same reason why people never liked the old wholesale pertussis vaccine.

You don't like unhappy children. But that would probably be the types of things we'd look at. It is a high bar though that we're going to be dealing with, because it's a matter of, again, now I'm not giving you any stock tips. It's a matter of, Pfizer released in their press release, and as Moderna did, they had 95% effectiveness across a wide range of individuals. So we're lucky that these first vaccines out of the gate, if everything checks out on our review seemed to be very good vaccines.

Dr. Bailey: Looking at the patients in the trials, those that hadn't got the placebo, at what point in time will they be unblinded? And if they do choose to get an active ingredient vaccine, how's that going to affect the long-term safety monitoring?
Dr. Marks: It's a great question. And I'm not going to be able to give you a definitive answer today because I think the advisory committee may discuss this some more. But the way things have been heading has been towards the idea of either allowing participants in the trial to ask after a certain date, whether they received active or placebo, or just to tell all the placebo patients that they received placebo and then give them the option of switching over at the time that would be appropriate for their risk group. Because what would happen then naturally is the older individuals would get vaccinated a little earlier on with their risk group and we'd then have some more followup time as younger, healthier individuals got vaccinated later on by the couple of months probably with their risk group. But that's just tentative right now. I'm just giving you, it's like we say in guidance, that's the current thinking, but it could change after our advisory committee meeting.

Dr. Bailey: I understand. The Pfizer vaccine was approved for use in the UK yesterday. And we discussed last time about the FDA reviewing international data. Will any of that data be used to inform the EUA process on December 10th when the committee meets or after that?

Dr. Marks: The Pfizer vaccine data that was used by the UK is the same data that we'll be using. And it's just a matter of differences in how regulators review products. We take, and I can't speak to the political or the regulatory status of the United Kingdom and how they came to their decision, but I can speak to ours, which is that we know that we're moving... Our folks, they feel the responsibility to move as fast as they possibly can. They were eating turkey sandwiches on Thanksgiving while they were reviewing documents. Okay? People were moving as fast as they can, but they know that we in the United States have a unique position, which is that among all global regulators, we are the ones that actually don't just look at the company's tables. We actually get down and dirty and we look at the actual adverse event reports, the bad spelling errors that are made by physicians sometimes, et cetera.

We catch those, the copy paste errors that are made. We look down at those data. We look at the actual line listings submitted. And by the way, nobody has to feel like... I'm not being judgmental because I made enough of those copy paste errors in my day. So I'm not going to cast anyone. So just so you know, but what I'm saying here is that we do a dive here so that at the end of the day, we're going to feel really confident that this... We have been known globally as kind of the gold standard regulator. And I can tell you that other regulators trust us because even today I've answered, I can't tell you from whom, but other global regulators, I've answered emails from three other continents already today wanting to know what we're doing because people trust us because they know we're going to do a good job. They're going to know we're going to do... the FDA approval is a stamp that is going to be one where when we say that we're comfortable with it, people should be able to trust this.

Dr. Bailey: That's wonderful. At what point do we go from the EUA process for approving COVID-19 vaccines to the typical biologics license process?
Dr. Marks: Great question, Dr. Bailey. So we’ve already made it clear to all of the sponsors that if they submit in any way, they have to be ready to then get on with submitting a biologics license application in the not too distant future. So we would expect that within a few months, once things calm down and with getting their vaccine out, we will receive their biologics license application or have it completed. In some cases, they’ve already started, what’s called a rolling submission where they’ve already submitted parts of that biologics license application. And they will simply complete that in the next few months. And then once that’s completed, there will be a period where we will then review that completed version and then issue a license.

The EUA here, if one had a magic wand, the company would have used their magic wand and overnight created a biologics license application. And if we had some magic wand for reviewing, we would’ve been able to go poof, and have a BLA review. That’s the nature of the data that’s being contained in these. The clinical trials, again, that’s an important thing to stress with patients. The clinical trials, because I’m getting a lot of writing campaigns right now. Like, “These are untested...” No, these are very well tested, 30,000, 40,000 people randomized trials. That means 15 to 22,000 people getting these vaccines. That’s a good size trial. That’s actually above the median for the size of trial programs for vaccines that we receive at FDA for prophylactic vaccines. If you look at some of the previous vaccines like HPV vaccine, Pneumovax, those are the kinds of size trial programs that we’re looking at.

Dr. Bailey: Right. Well, we’ve pretty much covered all of the questions. Of course, we could go on and on, this is such an interesting discussion. But Dr. Marks, I want to thank you so much for sharing your knowledge and wisdom with us. Thanks to everyone for joining us today. This is just such a critical discussion. It’s just amazing how quickly everything has progressed and the prospect of, especially frontline health care providers and those in long-term care facilities as has been recommended by the ACIP. Actually starting the immunization process by the time the holidays roll around just gives me goosebumps. It’s just absolutely miraculous. And we have additional webinars in the works. So we will, of course, keep you apprised of future dates, topics, and events. We so appreciate your participation and we’ll see you again soon. Stay safe.

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