AMA webinar series: FDA review process for COVID-19 vaccine candidates

On Oct. 7, 2020, the AMA hosted the first 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.

In the first episode, the speakers gave a comprehensive overview of the FDA vaccine review process.

Speakers

- Susan R. Bailey, MD, AMA President
- Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research at the FDA

Dr. Bailey and Dr. Marks also discussed what the process looks like for COVID-19 vaccine candidates and the differences between the Emergency Use Authorization (EUA) and Biologic License Application (BLA) pathways.

Transcript


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Dr. Bailey: Hello and thank you for joining us for this discussion and an inside look at the development and approval process of a vaccine for COVID-19. I'm Dr. Susan Bailey, president of the American Medical Association. The purpose of this call is to help physicians and the public have a better understanding of the vaccine development process. We appreciate everyone taking the time to be a part of today's call.

Dr. Bailey: On behalf of everyone at the AMA, I want to send out my most sincere and heartfelt thank you to physicians everywhere who have responded so heroically in this pandemic. 2020 has tested us in ways that few could have imagined, but time and again, physicians, nurses and our entire health care community have risen to the challenge of this moment. Some have died. Many have fallen ill. All have worked extremely long hours under intense pressure and in sometimes very dangerous conditions. We still have a lot of work ahead of us to defeat COVID-19, but we know that the development of a safe and effective vaccine is a critical step toward a return to normalcy.

Dr. Bailey: The AMA has championed the widespread use of vaccines since the early 1960s when the Sabin oral vaccine was developed to combat polio. Vaccines remain among the safest and most effective ways to prevent illness and protect public health. Now, of course, all of us are eagerly awaiting a vaccine for COVID-19, but we cannot rush the development of a vaccine at the expense of rigorous safety oversight. We can't compound the devastating impact of COVID-19 by rushing an unsafe or ineffective vaccine to market.

Dr. Bailey: Our special guest today has unique insights into the development of a COVID-19 vaccine, and we are so thankful that he is here to walk us through the review, safety and efficacy processes that are in place.

Dr. Bailey: Dr. Peter Marks is director of the Food & Drug Administration Center for Biologics Evaluation and Research. Dr. Marks, who is board-certified in internal medicine, hematology and medical oncology, 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.

Dr. Bailey: In his current role as director, he and his team are tasked with ensuring that the COVID-19 vaccine that's ultimately produced is both safe and effective and that it has gone through a rigorous evidence-based and transparent process despite the accelerated timeline. Now, that's no easy task, but the work of Marks and his team could not be more important than it is right now. So please join me in welcoming Dr. Peter Marks. Thank you.

Dr. Marks: Thank you so much, Dr. Bailey, and thank you all for listening today. What I'd like to do over the next about half an hour is take you through some of the key aspects of the vaccine development process mainly focusing on a distinction at the end of between what a biologics license application is for a vaccine and an emergency use authorization. But to set this up, I just want to
spend a couple minutes on the vaccine development process, how we review vaccine candidates, the various access pathways for vaccines, and I'll probably broaden that out a little bit so you have a little bit of extra bonus material there, and talk about our public advisory committee process.

Dr. Marks: But before I really launch into this, I think Dr. Bailey already alluded to probably one of the most important things that we can do at FDA at this time, which is that for reasons that have to do with a combination of factors, vaccine confidence is at an all-time low, at least in my lifetime, and that's because we no longer, I think at least one of the reasons, we no longer see and feel the incredible benefit of vaccines. Nobody understands quite the fact that none of us really see smallpox. We wouldn't know it unless we saw it in a textbook because it's not around anymore. Polio and measles, many of these infectious diseases we have to study in textbooks because we don't see them except when they come to our shores as imported cases.

Dr. Marks: Really, this issue combined with the fragmentation of society with social media, et cetera, has led to this real crisis in confidence of vaccines. So for us, getting back to vaccine confidence is incredibly important and what we often hear is, "Well, all these vaccines have these incredible side effects, and the side effects are worse than the infectious diseases themselves." And we have to work to combat that myth. It's true that where you have very high vaccination rates, people seem to forget about the fact that for instance, for measles, when you look, this is from an editorial or an editorial piece by Peter Hotez and [Bill] Marsh where measles, mumps, rubella vaccine, incredibly safe vaccine. It's not entirely with zero side-effects, but as you can see from the right side here, you're talking about some fever-related seizures in a couple of individuals out of 10,000 vaccinated. You don't see any deaths on that side.

Dr. Marks: On the other hand, if you look, we know very well that in low and middle income countries that measles is associated with actually a pretty significant number of deaths, and in a high-income country like the United States, if we were to have it return, we would also see deaths of measles encephalitis and possibly measles pneumonia. So, really important to get back to vaccine confidence.

Dr. Marks: I just show you the same issue here for influenza. Influenza vaccine saves lives, and yet we have people that they're very insecure about taking the influenza vaccine because they believe it will give them the flu or it will do something worse. So vaccine confidence is the ultimate goal here of what we do, even though our regulatory remit is a quality, safe and effective vaccine.

Dr. Marks: Just to back up here, for SARS coronavirus 2, the main vaccine target that is being used for the vaccines that are being studied in the United States is the spike protein. This is this trimeric protein, three subunit protein that decorates the surface of the coronavirus and which binds to the angiotensin-converting enzyme 2 receptor to get into cells. There are other surface proteins that could be used as antigens, including the end protein, but this has been where most of the effort has focused on.
Dr. Marks: That's not the only thing you can do in terms of making a vaccine. The vaccine approaches have been used included DNA vaccines, RNA vaccines, in fact the two most advanced candidates in the United States currently are RNA vaccines. There are protein subunit vaccines coming up quickly and development. Outside of the United States in both China and Europe, there are inactivated virus vaccines being developed that's similar to inactivated polio virus vaccine where you grow up the virus and kill it and administer it potentially with an adjuvant. There are non-replicating viral vectors. There are those already that are in large-scale clinical trials in the United States in that category. Replicating viral vectors, which are in development, and then further back in development or virus-like particles, some of which can even be produced in plants. Lots of different approaches. These are just among the types of diversity that we'll be looking at in terms of vaccines that we currently have under investigation, new drug applications, and ones that may wind their way ultimately to our approvals.

Dr. Marks: Just very quickly, all of us probably are familiar with the fact that vaccines tend to be tested initially in animals, then move into the typical phase I, II, III clinical development. The one difference to just note for vaccines is that phase II clinical development for vaccines can be pretty large, actually comprising hundreds of individuals rather than dozens of individuals as it might for, for instance, an oncology drug, and phase III clinical trials for vaccines, the randomized control clinical trials, can get to be very large.

Dr. Marks: How large? Well, if you look, on average, many of these, over the course of the years, have been involving 20,000 individuals. In this particular case for COVID-19, the manufacturers of these vaccines have agreed to do trials of about 30,000 individuals, at least for three of the vaccines, and for a fourth vaccine that's just entered phase III clinical trials in the United States, which is the single-dose regimen that's being used as public knowledge, it's 60,000 patients in that trial. Lots of patients, which gives us large safety datasets and will hopefully get us answers in terms of these event-driven trials towards whether or not they are effective as well as safe.

Dr. Marks: When we think at FDA about vaccine development, it all has to start with manufacturing quality because that is just so fundamental here. If you think about probably the worst event in vaccine history from the standpoint of FDA, it was the Cutter incident in 1955 in which it was ultimately a manufacturing quality issue where, unfortunately, polio, inactivated polio vaccine, was not inactivated adequately, and children got polio from the vaccine that was supposed to prevent it. Can't have anything like that ever happen.

Dr. Marks: We spend a lot of time making sure we do not let history repeat itself, and we care a lot about manufacturing quality. We care about safety and efficacy, and in addition, in this particular case, as we'll come to, post-market surveillance, which is always important for vaccines, will really take on a heightened importance for a COVID-19 vaccine. We at the end of the day June put out a guidance on the development licensure vaccines to prevent COVID-19, which really covered the waterfront here of what we expect for chemistry manufacturing controls; nonclinical data; the clinical trials that we need,
including the kinds of size trials we'd need; what we're expecting from post-licensure safety evaluation; the kinds of diagnostic and serologic assays that would be used in these trials to demonstrate effectiveness as well as some additional considerations. I'll spend a couple minutes now just going through some of the highlights, so you have an idea.

**Dr. Marks:** In terms of nonclinical considerations, we like to see nonclinical studies in animal models that help identify potential vaccine-related safety risks as well as they can provide information helping us to select the dose, dosing regimen and route of administration to be used in clinical studies. Now, what we need in terms of that nonclinical data can vary from vaccine to vaccine because for some vaccines, we have more experience on a given platform than on others.

**Dr. Marks:** In terms of clinical trials, we really have a situation here that is one that makes it a little challenging because, often, we at FDA are able to facilitate rapid vaccine development, for instance, for influenza vaccine because we understand the immune correlates of protection. That is, what marker can we use, be it antibody formation or some other property, be it T-cells or others, that we can see that we know that the immune response that we see in response to the vaccine correlates with the clinical outcomes.

**Dr. Marks:** We don't yet know that for SARS coronavirus 2, and so we're going to, for our first few vaccines, have to rely on what we see in terms of clinical outcomes. And that means that we'll expect these first couple of vaccines that come through to reach clinical end points as opposed to just reaching immunologic end points. Ultimately, we hope to be able to derive the knowledge from these first couple of vaccines that'll come through to be able to understand those immune correlates of protection, and then speed up vaccine development for further vaccines. We're hoping that people will use novel trial designs to help speed up the process, and we've been talking with people about that.

**Dr. Marks:** The other thing that we've been telling people about clinical trials is that the data set we're going to need is going to need to be large enough that we make sure that we don't have problems that could be associated with vaccination in this area. We know from viruses like in the coronavirus-ilk family that this issue of enhanced respiratory disease could be a problem, at least theoretically, and we need to make sure that by giving a vaccine, we're not going to cause more problems than we by giving a vaccine, we're not going to cause more problems than we started off with.

**Dr. Marks:** In terms of the enrollment into clinical trials, FDA doesn't have the power to tell companies, "You have to enroll X number of this type of patient." On the other hand, we do have the ability to strongly recommend things. In this case, in our guidance, we strongly recommended that, as the companies go about enrolling in these trials, they make sure that they enroll the populations that are really in need of a coronavirus vaccine, because otherwise we're not really going to be serving those in need.
Dr. Marks: So, we asked that an adequate number of older individuals and individuals with medical comorbidities get enrolled in these trials, that potentially pregnant women and women of childbearing potential be enrolled in clinical trials. Although pregnant women may come in a second wave, certainly women of childbearing potential are being enrolled. We need to have pediatric population plans, and they may come also kind of as a second wave as we develop more confidence in the adult population that's vaccinated.

Dr. Marks: We talk about in this guidance that early phase studies, Phase 1, 2 studies would be in the healthy individuals, but in the later phase trials, we would want to see those individuals with medical comorbidities enrolled. We talk about how we want people to try to go from different candidates down to a single candidate that they then put into rigorous controlled trials that should be randomized, blinded, and placebo-controlled. Alternatively, if a placebo is not used, a vaccine that's irrelevant should be used for comparison.

Dr. Marks: In terms of clinical end points, we've asked that they be laboratory-confirmed COVID-19 or laboratory-confirmed SARS-coronavirus-2 infection. Same difference, really, and that acute cases of COVID-19 should be virologically confirmed, even if they're diagnosed clinically and, really, that it's okay to monitor here and confirm by either virologic or serologic methods. In many cases, the companies are pursuing both.

Dr. Marks: One of the core pieces of this guidance that went out was what we did, which was unusual for us. Nobody can remember that we've ever put out a point estimate that was recommended in terms of efficacy that should be achieved. But in this case, based on really careful consideration, careful discussion, we felt that an effective vaccine here should be at least 50% more effective than placebo in preventing SARS-coronavirus-2 infection. We also put a lower bound of an appropriately adjusted confidence interval of 30% for the 95% confidence interval. What that does is that that combination ramps up the size of these trials so that they will be robust in terms of giving us hopefully clear and compelling efficacy data at the end of the day.

Dr. Marks: We're obviously allowing people to do interim and final efficacy analyses, and all of the trials that I'm aware of have interim analyses and are being monitored by DSMB. These are all event-driven, so they get to a certain number of events and they will be looked at. And so in terms of the safety that will go with that efficacy, the general safety evaluation, we've asked for these trials to be at least the size of other safety datasets that we've had and that is at least several thousand people. In general, it's a minimum of 3,000 for preventative vaccines, but we usually like many more than that, if we can. We wanted to have enough follow-up for safety, and as the guidance that was issued yesterday on the emergency use authorization articulates, we've asked for a median of two months of safety follow-up after the final vaccination in the population that's enrolled in the trial.

Dr. Marks: Some people would like longer than that. Some people would like shorter than that. But the rationale for that two months is that when you look at events that we see with other vaccines, such
as Guillain-Barre syndrome, transverse myelitis, other immune vasculitis, they tend to occur within a median of two months or before. So that seemed like a reasonable compromise, given what we'll talk about later in terms of safety surveillance.

**Dr. Marks:** When we talk about that post-licensure safety evaluation, it's that in order to have a robust plan, we're asking manufacturers to come in and speak with us early on to plan that pharmacovigilance. Now, the companies will do pharmacovigilance on their studies, and FDA in collaboration with the Centers for Disease Control and Prevention will do safety surveillance and potentially even some efficacy determination in the population in which a vaccine is ultimately deployed under an emergency use authorization or a biologics license application. We'll obviously make sure that if we identify any possible risks that we do additional targeted studies on those.

**Dr. Marks:** Just as an additional consideration as I finish up here, a lot of people have wondered whether we could get to an accelerated approval. An accelerated approval would be done for a vaccine using an immune correlative protection based on the immune response, obviously, but until, as I mentioned earlier on, until we have a better handle on how those immune correlates correspond to clinical outcomes, we're going to need to base things on our traditional clinical end points.

**Dr. Marks:** So I haven't mentioned to you one thing that was mentioned in the guidance was how we would potentially do an emergency use authorization. In order to give you how that would be done, I'd like to just back up and talk about how we provide access to novel therapies. So this is relevant both to vaccines and to general therapeutics, so I'm going to consider this like the bonus prize you get on TV at night when you order that thing that you don't need for that reason that doesn't make sense, but the ads on, anyway… I'll try not to be funny anymore. The expanded access provisions allow us to provide access to novel therapies. Probably would not be used in this case of a coronavirus vaccine, but I'll mention them. We have access to biologics license applications, which have a certain standard that I'll tell you about, and emergency use authorization.

**Dr. Marks:** When we give something out by expanded access, expanded access provisions came into being after the HIV crisis, because they allowed FDA to make investigational products available to those with serious diseases or life-threatening conditions that were not participating in clinical trials if there were certain circumstances met, such as there wasn't a satisfactory alternative to treat their condition, they couldn't be enrolled in a clinical trial, the benefit outweighed the risk and doing so wouldn't impair the development of the medical product that was being used.

**Dr. Marks:** And we have different flavors of expanded access. Individual patient access, in which the physician determines the probable risks from the therapy doesn't exceed that from the disease, and, really, FDA determines that the patient can't obtain access under another protocol. It's generally one course of treatment, and this has become relatively easier for patients, physicians to access through the FDA website. There are forms that one can get. And the main thing here is that FDA doesn't get the drug for people, you have to be able to get the drug from the company, and the company has to be

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willing to give it.

**Dr. Marks:** There’s another flavor of this, which is that we do have an emergency version in which, really, no paperwork is needed, you just contact the emergency number at FDA, and we oftentimes, within hours or sometimes even on the spot, are able to grant requests. Intermediate-sized population access, such as what was used for convalescent plasma, is what is used when there are larger populations and there’s more evidence that exists that the proposed treatment could be a benefit. I’m not going to say a lot more about this, except to say that it’s yet again another access mechanism, and treatment IND, which has been used for vaccines in the past. It was used, for instance, with the meningococcal B vaccines, when there were college outbreaks on campuses in order to vaccinate tens of thousands of individuals, but not hundreds of thousands of individuals or millions of people, is when a vaccine or a medical product has been shown to be safe and effective in clinical studies, but it’s waiting FDA’s approval.

**Dr. Marks:** Now, biologics license applications is how many people would love to see a vaccine become available. But biologics license applications take time to prepare after the completion of clinical trials. They’re highly structured documents that contain, at least in the United States, line listing data for all the patients that are enrolled in the clinical trials. Lots goes into putting these together. We've had biologics license applications that run hundreds of thousands of pages. And we look at those pages, and we do our own analyses. We look at the manufacturing information, all of the different pieces that go into this to make sure that the vaccine is safe, pure, potent and effective. Our standard that we use, that there has to be substantial evidence of efficacy from adequate and well-controlled clinical trials, generally for a vaccine, that means at least one large, well-controlled, randomized Phase 3 trial.

**Dr. Marks:** We have different types of biologics license application approvals. The one that is traditional means that it’s based on a clinical endpoint and is not necessarily subject to needing any further studies. There’s accelerated approval, in which an intermediate or surrogate end point is used. That would be for a vaccine, like using an immune correlative protection, where a subsequent study is needed in order to confirm the benefit using a clinical end point.

**Dr. Marks:** And in some cases, we can approve a biologics license application without efficacy data in humans. That’s called an animal rule approval, and that’s done in rare circumstances where you simply cannot look at efficacy in a human, because there’s just no way to wait long enough to watch enough people get botulism or anthrax, et cetera, and you can’t expose them to it. So, this allows us to look at safety in humans and efficacy in a validated animal model. Then, ultimately, a field study is done for confirmation of clinical benefit. But one doesn’t need to use an animal rule approval when you have a situation like we have now with COVID-19, where we have so much disease circulating.

**Dr. Marks:** The other way of making something available is under emergency use authorization. Emergency use authorization was put in place after the terrorist attacks of 9/11 to ensure that
potentially life-saving medical products could be available to people in medical need when there wasn't an approved and available alternative. And that means that sometimes we have products that may have been developed to a certain point, but they're not needed, no one's going to buy them, and they're on the shelf. Some of them may not even be on the shelf. Some of them may need to be developed. So, because they will not have made it through the entire pathway and yet could potentially bring benefit, the standard that was determined for these emergency use authorization was lower and Congress determined that it could be a standard of may be effective. Notice difference between substantial evidence of effectiveness and may be effective. In this case, its known and potential benefits need to outweigh the known and potential risks.

Dr. Marks: So it's a very different standard, but for a vaccine, we're going to treat things a little differently than for a conventional therapeutic, because for a therapeutic given to a person who is ill, the benefit-risk is probably going to be different and it is different than a vaccine that's going to be used to vaccinate healthy people, and not just a few healthy people, literally hundreds of millions of healthy people.

Dr. Marks: So for a COVID-19 vaccine, what we're going to be looking for is that there has been a careful evaluation of quality, safety, and efficacy. We're going to have to see clear and compelling efficacy in a large, well-designed Phase 3 clinical trial, much the same way as we would need for the determination of a substantial evidence of effectiveness that we would see in a biologics license application. So the standard that we're going to use here is higher, and we'll also be using a public advisory committee meeting to have a very transparent process here so that people can see, when this vaccine comes through, the data are robust and compelling, and they'll have confidence in this, we hope, and as we hope physicians will. And we realize though, that even though we'll have very robust efficacy information, we believe, there will be a weakness here, and that weakness will be that we won't have the length of safety follow-up that we'd normally like to have. But we intend to try to make up for that somewhat by having an enhanced post-appointment surveillance, that is using the large claims based databases and claims based databases that are linked to the electronic health record in some places to be able to, in real time, look to see if there were any problems arising.

Dr. Marks: And so this is how we would anticipate an emergency use authorization would help. Why do we consider using an emergency use authorization? Well, the reason is that the amount of time that could be saved by avoiding the administrative portion of this is significant. Yes, it means we may not have all the formatted tables that we might have, it may mean that we don't have the time to look at every different cut of the data that we normally would over the course of several months, but it is a benefit risk here of trying to get a vaccine out there for a… it's really, we have an infectious disease that's killing close to or above 1,000 people a day right now, and it doesn't look like it's getting any better. That doesn't give us an excuse to be able to put anything that's not safe out there, don't get me wrong. But what it does mean is that, as we think about how we go about our benefit risk calculation, it means that maybe we will put a little bit of the safety monitoring towards the post-market or post-
deployment end of things, as opposed to waiting six months, which could lead to the loss of a lot of lives. So, our hope is that through the vaccine and biologics products related advisory committee meeting people, there'll be transparency here into our benefit risk calculations. The advisory committee meeting will take place in a public venue, it will be streamed and potentially even broadcast.

Dr. Marks: We will take any vaccine that comes to us for COVID-19 for an emergency use authorization or biologics license application to this advisory committee meeting. And the experts there, which have been vetted pretty thoroughly for conflict of interest, will hopefully have a robust discussion and people will see and have insight into what we're thinking. By the way, also what will be out there along with this advisory committee meeting, will be briefing books prepared by the company and prepared by FDA, so they'll have a sense of what the data look like as well in hard copy.

Dr. Marks: Our next needing in this case for COVID-19 vaccines is actually a meeting on October 22nd that we'll discuss in general development authorization in licensure of COVID-19 vaccines. There are some really challenging issues that have to be discussed because aside from, you know, safety and efficacy, one has to think about what are we going to do after the first effective vaccine comes available? What do we do for the second one? How do we try to keep getting safety data in a robust manner? How do we go about the best way of collecting that post deployment safety data? So, all of those things are really important to us.

Dr. Marks: And with that, I think this is going to be a really important time for us for vaccines. We at FDA are very committed to doing whatever we can to gaining back the public's trust in vaccines. And for us, that means doing our job, which is making sure that whatever comes out of this process is safe and effective and has a tremendously high quality. And that there is very good transparency into what we've done so that doctors and the American public can see that we've done our job correctly. So, thanks and I look forward to answering questions.

Dr. Bailey: Thank you so much, Dr. Marks. That was an amazing discussion about the process of vaccine approval, but we may as well go ahead and address the big elephant in the room right up front, we received a lot of questions about this. During the first Presidential debate in September, President Trump said a vaccine would be ready and available in a few weeks, and we've heard in the past that he said, it'll be ready by election day, and of course, this is at odds with what we hear from the scientific community. But it raises questions and concerns for physicians about who was ultimately driving a vaccine approval process and decisions. How can physicians be assured that politics don't impact the approval process and how do we reassure our patients about this?

Dr. Marks: Yeah, so, it's a very good question and I think the best answer I can say is we have done our best to make sure we have our commissioner's commitment, that politics will stay out of this process. The Secretary of Health and Human Services testified last week, before Congress, that politics will stay out of this. And you have my word that, to the extent that anyone will listen to me,
politics is going to stay out of this process. We have an incredible staff of career scientists who are infectious diseases physicians, as long with the statisticians and risk communicators who are all working on this. And they will be the ones who need, by necessity, they need to be the ones who look at this and who make this determination about whether the vaccine is safe and effective. They'll do that in conjunction with our manufacturing experts that come from a variety of different disciplines, who will make sure that this vaccine, whatever it is, is of very high quality.

**Dr. Marks:** And I'm hoping that everyone, if I could ask for anything as like a gift, it would be that everyone would just take a pledge to just stop politicizing vaccines, let's just keep this out of the realm, this is just too important for all of us. We just have to focus on the public health mission here, because really for all of us, when you think about it, if we all want to get back to our lives, as we would like them to be, we're going to have to have a vaccine that probably has somewhere on the order of 70 to 80% efficacy. I'd love it if it had more, but if at least it has 70 or 80% efficacy and we can get 70 to 80% of people to take it, we might be in a place of herd immunity here. But we're not going to get 70 to 80% of people to take it unless we really come together as communities and really stop focusing on the what's wrong here and all of the noise and start focusing on what vaccines can really do.

**Dr. Bailey:** Well, we've had a lot of questions and I want to let the audience know about vaccine distribution, and that is going to be dealt with in a webinar that we're having next week with the CDC on the 13th. And so we're not going to ask any of those questions today, but for those that want answers to that, please tune in with us and I'll give you that information in a bit. It is such a challenge. I have said before that one of the most unfortunate things about this pandemic is that it occurred during an election year. And so in the process of the pandemic and the search for therapeutics and vaccines, unfortunately, the FDA and the CDC have really taken some hits and the public has lost confidence in the credibility of the FDA and the CDC. How do we get this back and how do we convince our colleagues as well as our patients to take a vaccine, which we hope will be very safe and effective in this type of skeptical doubting climate?

**Dr. Marks:** I think one way we get it back is we have people who are career scientists, people like myself, who get out there, and we articulate that we are here for the American public. We don't look from side to side, we look straight ahead at public health, at people, mothers, fathers, sons, daughters, friends, all of them need a safe and effective quality vaccine and that's what we're here for, we're here to make sure that our greater American family gets the same quality, safe, effective vaccine that we want for our own families. I think if we can articulate that, if we can do our job, and we will do this in as public a manner as we can so that people can see that we are not trying to pull any fast ones here, that we are going to make sure that everything is discussed.

**Dr. Marks:** And that is probably going to be challenging because no vaccine is going to have such a clean safety profile that it's going to be... it's not going to be light drinking water, and even water can be dangerous if you drink too much of it. I'm sorry, that's the regulator in me coming out. But it's going
to be nuanced because I'm sure that when we have these discussions, people will say, well, the vaccine caused an achy arm and it caused this and that, we're going to have to deal with that. But that honesty is what I think people are craving now and I think, my hope is that ultimately we'll convince enough people, and I actually think the analogy here may be a little bit like physicians with early adopters and late adopters that there may be areas of the country that are early adopters of the vaccine.

**Dr. Marks:** They will have a good vaccine coverage. They will start to be able to get coronavirus under control, COVID-19 will come under control, because they'll have enough people vaccinated initially that they'll be able to start to actually go back to, wow, contact tracing and vaccinate people in those circles that need vaccination and ultimately they'll have success. And once we have pockets of the country that have success, success will breed success. So that's my crystal ball says that's how it's going to look like. But the first step I think is that we have to be truthful, honest, we can't sugar coat that everything's perfect, but we need to get back that trust. And that's the only way I think we can do that is by being what we are, having people see that they have a team of folks that are absolutely committed to them, not to the various sides.

**Dr. Bailey:** The vaccine and biologics advisory committee that's meeting on October 22nd, you said in your presentation that really, they're just going to be kind of going over parameters and the process of approving a vaccine. So just to make sure that everybody's very clear, it's not anticipated that any vaccine approvals will be considered at that particular meeting.

**Dr. Marks:** No, it's not anticipated that that will happen. And I think that we really, if these are event driven trials, it's anyone's guess when they will reach a sufficient number of events. Is it at the outer realm of possible that before the end of October, one of them could reach a sufficient number of events to have an interim analysis? I suppose it's at the outer realm of possibility, but I think as Dr. Tony Fauci has said, I think I agree with him that probably it's more likely we're going to see something in November, December timeframe.

**Dr. Bailey:** Along those lines. I want to ask you a question. I've seen in a couple of places, looking at the events that are going to be measured, that there would need to be at least five severe cases of COVID-19 diseases in the placebo group, and that seems really small to me. Can you explain the statistics that will inform the decision regarding effectiveness? We've all our careers seen studies that may have shown statistical significance but were not clinically relevant. Can you help me understand this?

**Dr. Marks:** Yeah, that's a floor, okay? We wanted that as a floor because we weren't sure how many we're going to see. But we wanted a floor to at least be able to know that the vaccine is able to prevent some cases of severe coronavirus infection. We'd like to have something that doesn't just take care of mild infection. And although it may not be the most robust data, it's at least better than nothing. And so we chose five as kind of a floor. I know that there are some prominent infectious diseases doctors that
would have liked us to pick a higher number, but there is just a certain challenge here of balancing what we'll have and so we pick that as a floor.

**Dr. Bailey:** Okay, you mentioned briefing documents that the pharmaceutical companies will be presenting. Will those be available for public consumption?

**Dr. Marks:** Absolutely. And so what will happen is we would anticipate, now this is going to be a fast process. So normally, we like to get them up sooner, but my guess is probably within about two days, ideally about two to three days advance of the advisory committee meeting, there will be a document from the sponsor, the company, and a document from FDA that will be on the web that people will be able to pull down, read through and look through the data and see what's going to be presented.

**Dr. Bailey:** So what are FDA's plans for making safety and efficacy data available for review by the scientific and medical communities prior to authorization? Do you have… what types of opportunities will be available for us to give you input? Do you have a plan, like you're going to once a week, every two weeks, do you have a communications plan laid out?

**Dr. Marks:** I mean, we don't have a communications plan quite like that. The advisory committee meeting will have time for an open public hearing. So if people would like to comment on the data that they see from the vaccine manufacturers, they'll be able to do so there. We're always willing to take comments. And my guess is that at least there have been some discussions among manufacturers, and we'll see where they go, about how much of these data may be made available in public or databases or in databases that could be accessed by investigators.

**Dr. Bailey:** Okay. I'm going to get a little nerdy here. We've never had an mRNA vaccine in widespread usage. And two of the leading candidates, at least in the U.S., are on an mRNA platform. So what kind of plans do we have? Have we seen any signal yet that there's an unusual side effect profile to these vaccines and plans for long-term safety and efficacy studies and surveillance for this really unique type of vaccine?

**Dr. Marks:** Yeah, it's great question. One of the things we're lucky about is that even though there's not a licensed mRNA vaccine, mRNA vaccines have been used in clinical investigations for a number of years now. And they were used in the Zika and they've been used in other settings. So we have had enough people treated with them. Granted, those were not COVID-19 or related vaccines, those were other mRNA based vaccines. So at least, though, we feel confident that the platform itself is not necessarily associated with, at least in the hundreds to thousands of people who have been treated in those and aggregate to those trials with anything that's really notable that I could call out to you.

**Dr. Marks:** And as we go through this, though, because we totally recognize with you, we don't know are there possible late effects? We don't see them from the earlier trials, but we'll obviously be looking very closely with pharmacovigilance. The good news, I think, there, from hundreds to thousands
treated previously, we don’t see any signal there, which hopefully means that if there's going to be something, it's not going to be something that's going to be common, it's going to be something that's rare. But still, we want to detect the rare as well. So we will look for it.

**Dr. Bailey:** Okay, great. How will adverse effects be reported? How will physicians be notified if a problem arises in the post-surveillance period after the initial approval?

**Dr. Marks:** Yeah, you'll probably hear about it from multiple sources, but including by postings by FDA if need be. If there’s something that's a real alert, you'll be hearing about it. This is something where we can't take chances here and so if there were something, we'd communicate it rapidly and broadly.

**Dr. Bailey:** Great. Lots of questions about just the general fast-tracked process. One question, will the FDA adopt this fast-tracked process for other vaccine in the future? Or do you think this is going to be COVID specific?

**Dr. Marks:** Oh boy. Oh boy. So yeah, everyone...

**Dr. Bailey:** I know it's real crystal ball stuff.

**Dr. Marks:** No, this is a great question because it's one that keeps me up at night. Some of the things we're doing here during this COVID-19 outbreak is we have folks at FDA, we've gone to being almost a 20, it's not quite a 24/7 shop, but we're about a 20 hour a day shop now, to a 22 hour a day in terms of various shifts that are working. I'm not sure that we could continue this type of breakneck pace after COVID-19. That said, I think there will be elements of what we've come to do during COVID-19 that we will continue on with, some of the ways we've learned to develop policy more effectively, some of the ways that we've gone to have communications with manufacturers and perhaps some of the ways we've tried to take out some of the dead time in reviewing applications. So I think those things will hopefully stick with us.

**Dr. Marks:** Whether or not we could shave down certain other things, for instance, we've managed many times to turn around investigation of new drug applications to give people the okay to proceed within a week or two. Normally it's four weeks. Four weeks is already pretty short and so it's hard to say that we would do that moving forward. So I just want to set reasonable expectations that there are some things that I think we will probably take out of this, but I don't want to over-promise here.

**Dr. Bailey:** Okay. A lot of questions dealt with really wanting to get pinned down on when do you think that a vaccine will be available? Really, when do you think, realistically speaking of crystal balls, will we be able to see approval? When will it be available to frontline workers, which has been the high priority group from the National Academy’s recommendations? And when will it be available broadly?
Dr. Marks: I think this is one of these probability and odds questions. I think the probability starts to increase measurably as we move in through November and into December. And again, I would be, barring some safety concern that we don't know about, I would be hoping that we start to see something, again, I don't know for sure so I'm saying this, don't know for sure, don't say I said it's definitely going to happen, but I would think the probability increases to a reasonable likelihood that we'll have something before the end of the year and that's starting to get deployed into frontline workers in a significant way by the beginning of the new year. And then it'll start to expand into larger populations. Again, speculation and a bit of wishful thinking, but I think it's informed speculation.

Dr. Bailey: Okay. That's good for me. Your informed speculation is a lot better than a lot of other people's informed speculation. There are a lot of vaccines that are being studied around the world, trials going on in Europe, of course, Russia, China. But what is the process for a vaccine whose studies have been done outside of the US being approved for use in the US?

Dr. Marks: Yeah, so we don't have a great problem with foreign data as long as it meets our standards. So we'll look at whatever data someone wants to bring to us, and if it meets our standards and we can verify the data as we need to, we could potentially approve a vaccine on the basis of foreign data. We might ask for some small study to be done in the United States to ensure that the immune response in the US population is similar to whatever population, that would all depend on specifically where the vaccine was studied, so I can't say for sure we'd need that, but that would be the one thing that we might ask for. Nothing wrong with that, we just want to make sure, though, that we can do what we do at FDA.

Dr. Bailey: That's great. It's really encouraging to me that how quickly subjects have enrolled in the various trials. I've got that the Pfizer BioNTech trials have got almost 40,000 participants enrolled, Moderna's got almost 30,000. Moderna's given it's booster shots to about 20,000, and almost 30,000 in the Pfizer trial have gotten their booster shots. So it's just amazing how quickly this has all happened. One last question before we wrap up. You mentioned briefly about not having great immune correlates of protection and needing to go by actual infection to judge the efficacy of the vaccine. What about using... are there any T-cell studies that you think will become available for common use?
**Dr. Marks:** Fantastic, fantastic question. The trials are looking at T-cells, and I think we're going to see, we'll see whether that could be very important here because it may turn out that although antibodies are the first thing we see, it may be that the T-cell response is what's going to let us know whether we have a long lasting response, which is one of the real things that's an unknown here. How many months of immunity or how many years of immunity are we going to get from these vaccines? So really more to come, but T-cell mediated immunity will be something to look at here carefully, and it is being studied, and we'll be looking at those data.

**Dr. Bailey:** Great. Well, I just want to thank everyone for joining us on this very important informational session on the vaccine development process. Thank you, Dr. Marks, for your insights and your candor. And I'd like to thank everyone who asked questions that helped deepen our understanding of this process and the stakes involved. We will be working closely with you to make sure that this information gets disseminated as it comes out because total transparency and honesty is what's going to make the difference between vaccine acceptance and vaccine hesitancy. And there's really a lot to be encouraged about in the vaccine development process. But all that really matters is that when a vaccine becomes available, that it is safe and effective and that the public at large, as well as physicians, have total confidence in the process that got us here.

**Dr. Bailey:** So for questions about vaccine distribution and prioritization, allocation, we will talk about that during our joint webinar with the CDC and staff from the Advisory Committee on Immunization Practices next Tuesday, October the 13th. If you'd like to register for that event, please send us an email at amaeventsatama-assn.org. That's AMA events, A-M-A E-V-E-N-T-S @ama-assn.org. So thanks again to Dr. Marks for your time today and your insights. I hope we're able to talk again soon as this process goes along. And thanks to everyone in our audience for joining us. Well, I wish everybody good health.

**Dr. Marks:** And Dr. Bailey, thank you very much. And thanks to everyone who’s taken the time to listen today. And I just want to bookend what Dr. Bailey said at the beginning, thank you all so much for everything you do every day on the front lines caring for patients in this terrible pandemic. Thank you, and please be safe.

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