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Dr Peter Marks MD, PhD, director of the Center for Biologics Evaluation and Research (CBER) at the US Food and Drug Administration (FDA), highlights the Centerâ??s contributions related to the regulatory science behind vaccine development, including vaccines to prevent COVID-19; the Centerâ??s efforts to facilitate the advancement of the field of gene therapy; as well as his commitment to following the science and remaining steadfast to the truth.

Peter, could you start by clarifying the mission of CBER under the US FDA?

CBER is one of the smaller FDA centers. Its mission is to facilitate and consolidate the review of complex biological products, including blood and blood products, allergenic products, tissues, cellular and gene therapies, and vaccines. In terms of protein therapeutics, most are handled by the Center for Drug Evaluation and Research (CDER) but we do handle those in the area of blood products.

Due to COVID-19, we have our hands full right now, since we have to deal with many therapeutics like COVID-19 Convalescent Plasma and polyclonal immunoglobulins, as well as COVID-19 vaccines, in addition to work on our existing products such as cell and gene therapies. We have an outsized importance presently, with the products we regulate featured routinely in papers every day, so these are certainly interesting times for us.

What interactions does CBER have with Operation Warp Speed in the US?

I am quite familiar with Operation Warp Speed because I played a role in setting it up in April â?? but I have since stepped away from the Operation and I have nothing to do with running it. The FDA recognizes the urgent need to develop vaccines to prevent COVID-19, and we are working collaboratively with industry, federal, domestic, and international partners to accelerate this work.

The interactions we have with these partners are much like those we would have with any sponsor. Our regulatory decision-making is entirely separate. Operation Warp Speed is working to efficiently advance the development of safe and effective COVID-19 therapeutics and vaccines as quickly as they can, but they will be held to the same high standards to which we will hold every other sponsor. It is a level playing field.

I have taken a pretty strong stance, as supported by FDA Commissioner Stephen Hahn, to follow the science for these products as they are developed. This is one of the reasons we issued a guidance entitled, *Development and Licensure of Vaccines to Prevent COVID-19,* and also why we have, in our guidance, addressed the issue of using the Emergency Use Authorization (EUA) process that we have here in the US for COVID-19 vaccines, and also why we have promised to take every COVID-19 vaccine that comes in with an EUA request or a Biologics License Application (BLA) request to a public advisory committee meeting.

It is important to note here that it is the FDA Chief Scientist that signs off on EUAs. We make a recommendation based on our evaluation, which goes to the Chief Scientist, who then makes the final decision.

We need to try and make sure that we are following the science here very closely, and refrain from getting lost in all the noise that is out there in the current environment at this point.

Could you outline the key message from that COVID-19 vaccine development guidance?

Our guidance was intended to place some boundaries on what is acceptable for a COVID-19 vaccine. We wanted to make sure that people had an idea of what we are looking for so that when we receive EUA or BLA submissions they are consistent with our expectations.

Essentially, we have set a floor for efficacy. A COVID-19 vaccine needs to be at least 50 percent effective in a placebo-controlled trial, with the lower bound of the 95 percent confidence interval being no lower than 30 percent. This means that at least 19 out of 20 times the efficacy of the vaccine will be better than 30% greater than placebo.

We are not saying that people should be aiming for 50 percent, of course we want to see a vaccine as close to 100 percent efficacy as possible. That is just the floor we have set because we want to make sure that there is a reasonably good chance that we will see a vaccine with good efficacy.

We are asking for clinical COVID-19 endpoints, so large studies are needed to get there in a timely manner. So far, we have seen that all the manufacturers currently conducting Phase III COVID-19 trials are doing studies randomizing a large number â?? roughly 30,000 or more â?? patients, which would provide a nicely-sized safety dataset. These are also events-driven trials so once a number of endpoints are reached, the sponsors will do interim or final analyses.

The world needs good vaccines here and that is what we would like to facilitate.

Looking beyond just COVID-19, during your time at CBER, what have been some of your learnings when it comes to regulatory science for vaccines?

First, and particularly as a result of COVID-19, we clearly see the fundamental importance of quality manufacturing for vaccines. There is essentially a new interest in vaccine manufacturing â?? and

more efficient vaccine manufacturing. People have once again realized that if we are having a problem like this today and we lack ways to manufacturing vaccines quickly and in large quantities currently, we are likely to run into the same problem again in the future. Vaccine manufacturing has typically been dominated by batch manufacturing but this pandemic might ultimately advance vaccine manufacturing technologies to include components of continuous and semi-continuous manufacturing in the future.

Secondly, we can use immune correlates of protection in areas to speed clinical trials. Once we have immune correlates of protection for COVID-19, that would facilitate new trials. We are using clinical endpoints as a starting point right now since we lack those.

Thirdly, especially with COVID-19, we can see novel vaccine technology, which had previously been used only in smaller trials, coming to the forefront. There are two mRNA vaccines in large Phase III trials, for instance. There are some interesting configurations that could advance the field.

One of the things that is hard for the public to understand is that infectious diseases are each somewhat unique. Our bodies have learnt to generate immune responses to certain pathogens better than others. It so happens that for respiratory viruses like COVID-19, the body does seem to ultimately generate a good immune response, so we are lucky in some ways. It may even be that the immune response is exuberant in elderly people, which is why they become more severely ill, or perhaps the immune response is not quite right. But in contrast, there are pathogens like HIV that directly harm the cells involved in the immune response, in which case it has proven much harder to find vaccine targets. Personally, I do have more hope that we will get there much more quickly with a COVID-19 vaccine than with vaccines for other diseases like HIV, which, as you know, has been a target for the vaccine sector for over a decade now.

Moving on to another hot topic, the Regenerative Medicine Advanced Therapy (RMAT) designation was introduced in 2016? How successful has it been?

The RMAT designation is very much like the Breakthrough Therapy designation but with certain features targeted for regenerative medicine products. The first is that, as opposed to the criterion for Breakthrough Therapy designation that requires the product be better than an existing standard of care, for the RMAT designation, the company simply has to show evidence of activity against the disease in question, instead of showing that the therapy is better than a standard of care. The second is that, should a therapy with RMAT designation be approved under an accelerated approval pathway, which would then require a confirmatory trial, there is an extended array of ways of fulfilling that post-approval commitment. Under standard rules, one cannot simply follow the same patients in the registrational trial for a longer period of time. But for RMAT designated therapies, that is an option. To illustrate, imagine a hypothetical therapy in which replacement bladders are made by seeding cells on scaffolds. If the therapy receives RMAT designation and a clinical trial is performed, after six months of appropriate replacement bladder functioning, we could grant it accelerated approval but we might want to see how the bladders would continue to function after a year or two, so we would be able to simply ask the sponsor to return in six months or another year with more data on that same group of patients.

We have received a large number of applications, especially in the area of cell-based regenerative medicine, but many were requested early on in the development process. It takes time for these products to work their way through, and it is a young field as well, which tends to have more products that do not make it through the entire product development process. We know the statistics of product development: only about 10 percent of the therapies that make it into Phase 1 trials will

ever see the light of day. Cell therapies are not all that different at this point. I am sure we will see some in the near future but it is taking a little longer than might have been thought.

At the same time, we are trying to take a fair amount of leadership in gene therapies. We are very interested in helping to move the field forward by looking at how one can develop gene therapies for small patient populations and also how to do that in what would ultimately be a commercially viable manner. Right now, gene therapy populations that include fewer than 100 patients treated per year are important targets for development. However, due to the expenditures involved in R&D, approval and commercialization, these therapies are not seen as commercially viable targets for companies. On the other hand, if regulatory frameworks and science could be developed for the manufacture of gene therapies, such as reusing certain vectors and changing out inserts, or the use of common manufacturing protocols and techniques, manufacturing costs could be reduced sufficiently to interest more companies into working on gene therapies for patient populations of 50 or 100 people. That could make a big difference in peopleâ??s lives.

The reason to get it right now is because we are going to need to use this type of approach more and more for therapies based on genome editing. Since genome editing targets the correction of very specific mutations, we may start to see lots of different products, and from a regulatory perspective, we will have to figure out a way to approve these individually. Instead of a single entity that treats many patients, we will have lots of small products treating just a small handful of patients â?? but to those patients that are treated, those products will be very important.

There are some challenges but we are going to work through them. It is what patients need. We are also working with other government agencies in the US as well as global regulators on this topic.

Speaking of which, the regulatory landscape globally is not very well-aligned currently, especially for regenerative medicine therapies. How much dialogue does CBER have with global regulators, particularly those in Asia that are also very active in the area of regenerative medicine?

We probably have the most dialogue with our international partners including the European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency (PDMA) in Japan. Through our work with the World Health Organization (WHO) and other avenues, we aim to bring global harmony to the cell and gene therapy space. This is something that we are really very interested in.

That said, such efforts have been adversely affected by COVID-19. In early-January 2020, we were very much on the way to working with global regulatory partners, including representatives from South Korea, India, Singapore and others, to advance global harmonization in cell and gene therapy. But with everyone being so busy with COVID-19, we hope to return to this in the near future.

On a final note, in these uncertain times where we see trust in institutions deteriorating, what message would you like to send to our global audience on behalf of CBER?

There is a lot of noise coming out of the US but when it comes to the FDA, it is patently clear that we are here to follow science to bring benefit to this country and, when possible, to bring benefit to the entire globe. That is only going to happen if we continue to dedicate ourselves to objectively working through the evidence, to follow the science, and to come to independent conclusions. This is what we have done and it is what we will continue to do during this time. We have to remain steadfast to the science. There is no substitute for that. Science is based on truth and, ultimately, truth cannot be

hidden.

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