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The Case For Covaxin: Ocugen CEO Shankar Musunuri

by Ben Comer

A potential decline in mRNA vaccine protection against the Delta variant is raising questions about the need for booster shots in the US. Ocugen Inc. and partner Bharat Biotech hope the changing dynamic of COVID-19 in the US will induce the FDA to reconsider additional clinical trial requirements for Covaxin, an inactivated whole virus vaccine authorized for emergency use in 16 countries.

For a brief moment of time at the beginning of July, it seemed as though the COVID-19 pandemic was finally winding down in the US. By August, those hopes were dashed by the emergence of the Delta lineage of variants, later compounded by the return of unvaccinated children to schools across the country.

The three vaccines authorized for use in the US – produced by Pfizer/BioNTech, Moderna and Janssen (a Johnson & Johnson company) – were made widely available to the public for free. And yet, lingering pockets of unvaccinated individuals, particularly in the South and Midwest, helped the virus mount a comeback. Some of those communities expressed fears about new mRNA vaccine technology.

Ocugen Inc, a Malvern, Pennsylvania-based gene therapy company focused on rare ophthalmology diseases, announced in December 2020 that it would partner with India-based Bharat Biotech to commercialize the latter's inactivated, whole virus COVID-19 vaccine, called Covaxin, in the US and Canada. In a surprise to some of Ocugen's investors, the company announced in June that it would pursue a standard Biologics License Application pathway in the US, as opposed to the faster-to-market Emergency Use Authorization pathway, based on feedback from the FDA. (Also see "*Can Delta Variant Effectiveness Fill Brazil-Sized Hole In Bharat Biotech's Prospects?*" - Scrip, 5 Aug, 2021.)

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In an interview with *In Vivo*, Shankar Musunuri, Ocugen's CEO, co-founder and board chairman, made the case for quick approval of Covaxin, on the basis of strong efficacy against the Delta variant, a known technology platform that could put mRNA skeptics at ease, and convenient vaccine temperature storage compared with the deeper freeze required by the three vaccines currently available in the US, among other attributes. Musunuri was guardedly hopeful that the FDA, in light of pending emergency use authorizations by the World Health Organization (WHO) and Health Canada, might still change its mind about an EUA. But even if it does not, Musunuri sees a long-term opportunity for Covaxin in the US.

Q **Ocugen is primarily an ophthalmology company, focused on rare eye disorders. How did your partnership with Bharat Biotech and Covaxin come about?**

SHANKAR MUSUNURI, CHAIRMAN AND CEO, OCUGEN INC.

A We are an innovative company focused on unmet medical needs. Our team has a deep expertise in vaccine development and commercialization. Many of us came from Wyeth, where we helped develop many products, including Prevnar 13 and FluMist. And when we looked at the landscape of vaccines available in the second half of last year, we realized there was something missing. The three vaccines, which are now approved – one with a Biologics License Application (BLA) and two with Emergency Use Authorizations (EUA) – are all based on the spike protein. We know scientifically that if you focus on one part of the virus, eventually mutations will escape. So we asked ourselves, with our expertise and knowledge and network, is there anything we can do? We can't sit on the sidelines. It's like a war, and we want to contribute to the public health initiative and save lives. We had worked with Bharat Biotech when I was at Wyeth many years ago, and Bharat grew very big over the last 20 years, and was involved with innovative vaccine projects, working the Gates Foundation, for example. And today they manufacture 16 vaccines and supply close to four billion doses to address global needs. They are almost like the crown jewels of Indian vaccines and have a

strong reputation. They are working in collaboration with the Indian Council of Medical Research, the equivalent of the NIH in India, with an inactivated whole virus vaccine, similar to how the polio or hepatitis or rabies vaccines, and others, were developed. We looked at Bharat's vaccine, and it offered broad protection, and other vaccine makers in the US were not developing anything similar. And this vaccine also had an additional adjuvant, which was developed in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), which actually stimulates a T cell response. That is a very important factor for the long-term immunological memory of any vaccine. Our scientific advisory board took a deep dive and decided that the vaccine could really support public health needs and save lives in the US. And we'd had a relationship with them in the past: we did a project with them at Wyeth, they did a great job, and I kept in touch. We got in because we wanted to help out with the pandemic and we felt a moral obligation to do it.

Q **Covaxin as you've said is a whole virion inactivated vaccine. If it is eventually approved by the FDA, how will you position Covaxin versus the other vaccines approved for use in the US?**

A I think we rightly predicted, last year, that viral escape would occur and that we would see mutations. Today, the Delta variant is a great example. We have seen large surveillance data, including public data out of Israel, showing that efficacy associated with vaccines targeting the spike protein is going down. If you look at our Phase III data with Covaxin, we are the only company with efficacy data on the Delta variant from a controlled clinical trial. The majority of cases belong to the Delta lineage. With the specific Delta variant itself, which represents the vast majority of cases in the US today, Covaxin showed 65.2% efficacy, which is remarkable. Because of the Delta variant, Covaxin becomes more valuable for the North American population and globally.

Q **Are you actively studying Covaxin as a universal booster shot, which could be administered regardless of an individual's initial vaccine type?**

A Based on how the vaccine works, we believe it would be a great booster, because it

delivers a broad immune response. We are considering all options and working with the FDA. There are predictions now that this pandemic is going to continue for the next few years. And if some of the efficacy is waning with the existing vaccines, a booster with broad protection is ideal. You could also potentially reduce the frequency, so we are considering all of those options in the US when we are talking to regulators. As soon as we have a clear agreement with the FDA, and what needs to be done, we will update the markets.

Q **Last June, Ocugen announced that it would pursue the BLA regulatory pathway, as opposed to an EUA, for Covaxin. Is there any possibility, given the magnitude of Delta variant transmission and death in the US, that the FDA would consider allowing an EUA for Covaxin?**

A We have been working with the FDA on the regulatory pathway for a BLA, because of the potential for this pandemic to continue for several years. We decided to focus on the long-term strategy and make sure we get the vaccine eventually approved in the US. We will continue on that path. However, EUAs are based on unmet medical need and FDA does have a lot of flexibility to grant them. While we are working on the BLA path, there may opportunities, given the Delta variant or other things that could happen in the future, to update the FDA and see what happens. All three vaccines that received authorizations or approvals in the US conducted trials in the US, that is the precedent. But we are in the middle of a pandemic, and regulators need to be flexible. We got that flexibility from Health Canada, and our partners are going through the WHO approval processes, so hopefully those things may help in the future. We would like to bring this to the US market as soon as possible for the benefit of the patients. Our partners at Bharat have also completed a pediatric trial in a two-plus age group. The study was conducted in India, and they are in the final stages of analyzing the data. I think it should come out shortly, in the fall. We're closely watching that and will see what opportunities arise when that data becomes available.

Q **Is there a ballpark timeframe for when you expect clarification from the FDA on clinical requirements for Covaxin, as needed for the BLA?**

A We are hoping the FDA will give us a response quickly: we would like to get started in the fourth quarter. But then two senior people left the agency, one of whom we were interacting with. (Also see "*US FDA's Top Two Vaccine Officials Announce Surprise Retirements*" - Pink Sheet, 31 Aug, 2021.) We are asking for the FDA's help. What bridges do they need? We do have a large data set coming out of India, it is not a small trial, almost 26,000 patients. In India, I think Bharat has administered 50 to 75 million doses. And the numbers are increasing every week, so there is a lot of human experience with Covaxin. Of course, certain agencies have certain regulations, and they want you to do certain things. But again, it's a pandemic, and there could be some flexibility. That's why we are waiting. As soon as we know how to utilize the data, and see what bridges and other things they need, we are ready. The departure of two senior leaders may have some impact on the timeline, but I'm hoping it won't be too long. It is tough when senior people leave, everything goes into the doldrums.

Q **Do you think the departure of Marion Gruber and Phil Krauss from the FDA will have a substantial impact on the timeline for Covaxin's BLA?**

A Probably not, because our communication with the FDA right now is pretty good. They keep the whole review team in the loop, we didn't lose the complete link. They are paying attention to vaccines and they are bringing several people from FDA when they interact with companies. It's not like we're dealing with one person, and if the person leaves, you have to recreate the relationship. The FDA has been very supportive in that respect, keeping multiple groups involved.

Q **Ocugen is pursuing an interim order with Health Canada, the equivalent of an FDA EUA. How do you explain the discrepancy between these two regulators, and why Health Canada, but not FDA, is willing to consider an accelerated, emergency use approval?**

A Based on our interactions, Canada is also looking outward, in the sense of what is going on globally, because remember, these are extraordinary times. And regulators have to make extraordinary decisions. Unfortunately, there is no global regulatory consensus. In times like this, the WHO, FDA, EMA and other large health agencies,

including the Indian boards of health, should all be working together. India has a lot of vaccine companies that supply a lot of vaccines, billions of doses every year. Ideally, they would have some consistency, and a treaty would be really helpful for pandemics, and I hope they will do that in the future. But this is the problem, and not just for Ocugen. Every company is going through multiple countries, multiple approvals. It is duplicating all the work, why do companies have to go through that? Unfortunately, that is the system. We updated the FDA and Health Canada, and in the case of Health Canada, they were more open to the global experience; they are watching the WHO and they agreed to accept a full filing with the data we have. And that was very beneficial. I wish the FDA had the same philosophy, but it does not.

Q **The WHO is expected to grant an Emergency Use Listing (EUL) for Covaxin in the coming weeks. Do you think that could have any bearing on Covaxin's regulatory pathway in the US?**

A That would definitely help, highlighting an EUL from WHO, and the fact that Health Canada is considering an interim order. The scientific community hopefully will catch up on that. If you step back, how do you control the pandemic? Is it practical to go to the global population and vaccinate everybody with just a spike-based vaccine and then every six months, administer booster shots? You will have a nightmare controlling the pandemic. A broad-spectrum vaccine, such as Covaxin, created on a known technology platform – like the polio vaccine platform – offers a lot of benefit. It is not a new technology, and the vaccine hesitancy folks can relate to it. My kids got it, my grandkids got it. I can take this. Plus there is the end to end element, which boosts the T cell response; nobody's talking about it. If you have a good vaccine, you'll get a good T cell response. Our partners have published extensively, in Cell, in Lancet, all the top journals, because they are collaborating with the Indian equivalent of the NIH to produce this vaccine. I'm hoping the scientific community will make some noise, based on the publications. We will continue to push this with the FDA. I wish it was available to protect lives today.

Q **Novavax announced its Phase III COVID-19 vaccine trial data around the same as Ocugen, in June and July. Novavax, however, is pursuing an EUA, despite**

FDA's signaling in May that it would stop offering EUAs for COVID-19 vaccines. What is different about Ocugen's clinical program compared with Novavax?

A The difference with the Novavax vaccine is that they recruited patients in the US for their clinical trials, that's the only missing piece. Novavax is also a spike-based vaccine, so that is not going to solve the problem. Tomorrow, there could be a multivariant emerging. That is why having a differentiated vaccine with broad protection in the toolkit is essential.

Q **Recognizing that the regulatory situation is in flux, what is your best guess for when Covaxin might be available to patients in the US, outside of clinical trials?**

A If we had to do trials, it will take time. It won't be before 2022. But if something changes because of the emergency need, and a lot of emerging variants and people are dying, there could be an avenue. In Canada we plan to launch in our fourth quarter of this year, so whatever FDA decides, we'll be ready. We announced our manufacturing technology transfer to Jubilant HollisterStier in Washington State for US production, all of that work is ongoing. We're preparing for the Canada launch because it is an active review of our file. If we get a new opportunity with the FDA, we will be ready.

Q **How optimistic or pessimistic are you about the FDA changing its mind, and allowing Ocugen to apply for an EUA as opposed to a BLA pathway?**

A I am not overly optimistic. Typically, you would need a clinical study with a US demographic. However, if you take a step back scientifically, and look at what changes from a US clinical study before launching in other countries, the answer is not much. Are you changing any formulation, are you changing any dosage across the globe? It is important to collect the data from a safety perspective, because different groups may have different reactions. It is always good to collect data. But in the middle of the pandemic, when history tells you a lot of these inactivated virus

vaccines are the same vaccine, including the hepatitis vaccine, that are given to every population across the country, is a US study critical? Canada and others are saying, it doesn't matter in the middle of the pandemic. So is there a path when you have two-plus pediatric data available? If our partner provides that data before the mRNA vaccines? Will that help? That is another hope, if we get the data ahead of others, then we'll have these serious discussions with agency. There is an unmet need, and kids are going to school, and parents are really worried about the kids. Is there anything we can do with this? So those are all avenues we're trying to pursue. In fact, we conducted a Harris poll which showed the majority of the vaccine hesitancy people are looking for other options. We believe, based on our poll, that a majority of the vaccine hesitant crowd would take our vaccine, which could be very important for controlling the pandemic. The opportunities are there, but sitting here today, it is tough to read the FDA. But our job is to educate as innovators.

Q **Aside from what we've already discussed about positioning Covaxin against other COVID-19 vaccinations, have you thought about price? Will you try to compete with other vaccines on that basis?**

A Currently the prices have been set by government procurement. They are getting a similar price range, about $20 per dose. In Canada it may be a little different. Even though we could say that we have broad protection, we want more, we are not expecting to do that, we will go with the procurement price. Once the pandemic is somewhat under control, and we move into booster studies and annualization from 2021 on, then the private market will open up. At that time, we will have to gauge what others are doing, and how we position ourselves. The US is buying vaccines for domestic distribution, but it is also purchasing a large amount of vaccines for the stockpile, as well as global distribution, because if you don't vaccinate global population, you can't control the pandemic. One feature of Covaxin that I haven’t mentioned is about storage. We are expecting two or three years of shelf life at 2 to 8 degrees Celsius [35 to 48 degrees Fahrenheit], and six months at 23 degrees Celsius [73 degrees Fahrenheit]. Think about that. Let’s say the pandemic is brought under control and becomes endemic – you will still have breakthrough infections. How do you control that? This is the perfect vaccine for the CDC to stockpile and store,

> because it can be distributed quickly. Many of the pediatricians in this country only have a simple refrigerator. So if you have a product that can be stored just like they store other vaccines, it will be a lot easier for them. This is the perfect vaccine, too, for global vaccine diplomacy. We will continue to work with the government while we are working with the FDA, and want to help out wherever we can.