WEBINAR TRANSCRIPTION:

CHALLENGES TO EXPAND COVID-19 VACCINE PRODUCTION

Presented by Prashat Yadav; Matthew Downohan; Esteban Corley

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INTRODUCTION

Minute 00:24 Ferdinando Regalia:

Good morning and good afternoon everyone, my name is Ferdinando Regalia head of the social protection and health division at the *Inter-American Development Bank.* Thank you so much to all of you for joining this webinar organized by the *Criteria Network* and the Social Protection and Health Division. Today we will be talking about the challenges and opportunities to expand production of safe and effective Covid-19 vaccines.

The cycle that usually takes years has been compressed in the space of about one year, from the genomic sequence of the virus to the regulatory approval of the growing number of vaccine candidates, to their production and distribution, and even in the middle of the very harsh reality of unequal roll out of the Covid 19 vaccine around the world, we cannot forget about what has been accomplished over the last year.

Producing and distributing all the Covid-19 vaccines that the world needs is a major undertaking. Just to put things in perspective for all diseases, prior to the pandemic, the world produced about 5 billion doses of vaccines a year, and to reach out immunity the world will need around 11.5 billion doses of vaccines with a two doses regime. This truly is a need across all the countries, without taking into consideration the need for future other vaccination and boosters.

So, the challenge is massive, and to talk about these challenges and opportunities to expand Covid-19 vaccine production, I am joined here today by three truly outstanding experts:

Prof. Prashant Yadav is an internationally recognized expert in the area of health supply chains, and a Senior fellow at the *Center for Global Development,* an affiliate Professor at *INSEAD Business School* and a lecturer at the *Harvard Medical School.*

Matthew Downham with over thirty years of experience working in the pharmaceutical industry for companies like *Novartis* and *AstraZeneca*, leads now the Sustainable Manufacturing Group at *CEPI - Coalition for Epidemic Preparedness Innovation,* an organization that everyone knows very well by now, whose mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.

And Esteban Corley who also has over thirty years of experience working with biopharmaceutical companies, who has devoted his career to developing and manufacturing biosimilar products. Esteban is currently the General Director of mAbxience Argentina and was directly involved in the production of Covid-19 vaccine.

We are going to have a conversation of about 45 minutes with these distinguished guests, which will be moderate by myself and by my colleague Marcella and also, we will have the time to discuss questions coming from the public. So, please, I invite all of you to share your questions with everyone through the chat. And now with no further ado, let's begin our session and I'm going to pass the word to Marcella.

PANEL DISCUSSION

Minute 03:40 Marcella Distrutti: Thank you Ferdinando, and thanks to all our panelists and everyone who has joined us today to participate in this discussion, we have an exciting discussion ahead so let's jump right in. So, to begin I would like to ask a question to Prashant. Prashant, thank you again for joining us, ¿could you tell us, in simple terms, how the main Covid vaccines are produced and what are some of the main bottlenecks that we face to scale up their production?

Minute 04:05 Prashant Yavad: Thank you Marcella and thanks for having me and thanks everyone for joining this very interesting and important session. Before answering Marcella's question I want to start by saying one thing which I believe is important, that I think throughout the scale up and the development of Covid vaccines we have not adequately recognized the importance of multiple colleagues, friends, parties, collaborators, who work on the chemistry manufacturing and control function, people who are manufacturing scientists who have been working extremely hard, day and night, in trying to stabilize the processes, get things going, doing scale up, while also working on many of their early process things. So, I think it is important to recognize that it is a complex task, that it is an undertaking that requires a lot of hard work, and we should recognize how much the manufacturing people have worked on this.

So, to answer Marcella's question, I think of it as three separate blocks that have to all come together. The first block is the sourcing of key input materials and these materials would consist of, if it's an adjuvanted vaccine, which we have one, the sourcing of the adjuvant, if it's a nucleic acid vaccine that requires special kinds of enzymes or lipids then sourcing those input materials, also vials and other substances and some vaccine manufacturers use single use equipment of various types.

So sourcing, that is the first part. The second part is what we commonly call as drug substance manufacturing, so think of it as the reactors and the filters that are essentially making the core of what goes into the vaccine, or in the newer nuclear acid vaccines producing the RNA, these are plants which consist of a series of reactors connected to each other with lots of filtration and purification steps in between, that's the first part of drug substance manufacturing.

From there the vaccine goes into formulation fill and finish and the best and easiest way to imagine that is adding some final substances to the bulk vaccine or the core drug substance and then using specialized filing lines where that is being filled into small vials, glass vials in most cases, and that's usually highly automated process, it is something that is similar to what we use in many other injectable drug lines but it is important to keep in mind that it is in a highly aseptic environment, which means anybody who enters that part of the manufacturing facility has to be completely gowned and has to ensure that they are maintaining all of the requirements for what aseptic manufacturing needs.

So, those are three blocks, now, what are the bottlenecks? The bottlenecks keep shifting, there is not a single bottleneck, I think we have gone through a journey in which we started by saying, well, our bottleneck is fill and finish capacity and we resolved some of it through many different things that happened, thankfully we have government capacity, government investments in fill and finish

manufacturing network which we could leverage in some parts of the world, in other parts of the world we could use existing or additional capacity that had recently come up, so then we said is not so much fill and finish sometimes it is the drug substance manufacturing and we saw that in one or two particular cases where if the yield coming out of a process was lower than what we had anticipated, then we didn´t have enough drug substance itself.

And then, in many cases, we found that is not the drug substance or the fill and finish step, but it is actually some input materials that are the bottleneck, the lipids or other specialized chemicals, and so, I think that the bottleneck keeps shifting because we are thinking about these as individual steps versus asking the question: what is our synchronized capacity to deliver the output we are seeking? And, does our system have the capability to deliver this in a synchronized manner?

And I think, if we use that lens we will not be in a situation where we solve one and another bottleneck pops up, and we solve that bottleneck and another one pops up, we will then have an overall system which can deliver the throughput that we are seeking and this is easier said than done because it is not a single network, is not that there is a single company which is doing one part or another, is a very diversified and decentralized network where lots of different companies are involved in different steps, so, managing the synchronous throughput and balancing it is harder and requires a good flow of information and it requires very active collaboration and coordination between these steps.

Minute 09:12 Marcella Distrutti: Thank you so much Prashant, thank you for this overview, I think it sets the state of mind for this discussion and this calls for us to view this in a more integral and comprehensive way. Matthew I would like to turn to you now to follow up on this question, on this matter. Some people suggests that a typical vaccine manufacturing plant can use anywhere between nine thousand (9000) different materials, sourced from about three hundred (300) suppliers who are spread across dozens of countries. In this scenario, can you share with us some thoughts on the challenges that manufacturers are facing in the supply chain of the Covid Vaccine?

Minute 09:49 Matthew Downham: Sure, of course and thank you very much for this opportunity and following on from Prashant's excellent introduction, the numbers you just quoted I am sure are not far from the truth, and especially when you scale that up to think particularly in response to the current Covid pandemic many manufacturers have increased their manufacturing footprints collaborating with contractors, contract development organizations, etcetera.

So, the actual scale to meet the current vaccine manufacturing supplies is astronomical compared to typical numbers, as Ferdinando introduced and said, manufactures this year are looking to producing somewhere in the region of fifteen billion doses of vaccines, while in a typical year, vaccines manufacturers are producing about five billion doses, so you can see instantly the scale of this.

And as Prashant has already articulated is not one company who does this, is many different suppliers of parts, of components, of technology, of essays, of support kind of release essays pre-clinical and post, UC type essays… So, there is all sorts of areas where bottlenecks can and do occur and one of the things, one of the core bottlenecks that we are hearing about at the moment and CEPI has been monitoring this

quite closely, recently especially given the interest in Covid Vaccines and the need to supply the Covax facility.

And we crystalized a global summit on the 8th and 9th of march and there was flagged quite clearly that one of the main bottlenecks in the moment is the supply of raw and/or single use materials so this comes down to things like filters, tubing, chromatography media, single use bio reactors, but the list goes on and on.

And one of the things that has happened is that the manufacturing of the vaccine lacks components of the end to end supply chain that link has accelerated and escalated quite significantly, but it is difficult for the suppliers in the next stage job to track that because of the forecasting, because of the prediction of precisely how much vaccines the manufacturers are going to make and therefore how many filters, how much tubing, how many single use bioreactor bags, we are even hearing upstage from that some Borosilicate for example, people are supplying the Borosilicate to make the glass vials, to be formulated and filled with vaccine, that next stage of the chain is having troubles keeping up with the demand, so it is not just the vaccine manufacture and what happens in the vaccine post manufacture formulation and fill, is what happens upstream from there as well.

To give you some illustration of that, so I worked in AstraZeneca for about eight years and I transitioned to CEPI at the first of January this year so I was with AstraZeneca until the end of 2020, predominantly working in the flu vaccine franchise, and we will typically start ordering single use materials and bags obviously, almost a year in advance of needing them and then that forecast, that planning, that has not been so feasible with Covid because Covid has just accelerated so dramatically and rapidly and so there is that kind of supply bottleneck.

Now, there is a number of people looking out to resolve this, the *World Trade Organization* for example, are looking at ways to expedite cross border transactions and export licenses and the manufacturers of the single use materials are looking at ways to expand that manufacturing to meet the demand, such demand that exists at the moment and there is certain legislation that needs to be addressed, in terms of preventing hoarding or stockpiling of materials and some companies have done that as well.

So, there is a whole series of events now that are being locked out so a whole series of deliverables and solutions being locked out to try and address the current bottleneck but as Prashant articulated, that could be the bottleneck we resolve and then in a month or two there could be another bottleneck, we are making biologicals and they are inherently difficult to make and varied, and as a result, very challenging. That is where we kind of sit at the moment, so I hope it kind of addresses the question and certainly the numbers you quoted would be far off once you use it in a standard vaccine manufacturing platform.

Minute 14:31 Marcella Distrutti: Thank you Matthew, thank you for shedding light on this supply chain challenges and the different components and the channels we need to export and import and trade controls, it does shed a lot of light on the issue. And, to follow up on that I would like to ask a question to Esteban. Esteban, in our region, in Latin America and the Caribbean, there have been efforts and discussions with using repurposing existing plants for vaccine production, so I would like to hear

from you, what are some of the main challenges that countries may face to do so? and taking into consideration what Matthew and Prashant have already mentioned about the inputs that might be needed for this process.

Minute 15:13 Esteban Corley: Thank you Marcella, thank you very much for this invitation and for the honor. The two preceding people who have spoken, have already taken most of the input I had to bring, but I can confirm one of the informations that Matthew brought in, we have placed purchase orders for something like 2000 different components just to be able to manufacture the vaccine, so, I think that there are two or three points that I would like to bring about particular difficulties in Latin America.

I think what we have being seeing in the lasts years but is very patent with Covid is that technology platforms have changed dramatically for vaccine production, what used to be just a production of the pathogen itself, or the virus itself, or the bacteria or the attenuated version of that has really changed to recombinant versions, so, really vaccine production has turned into modern biotechnology essentially and that in a sort of way has left the Latin America's capacities a little bit behind I think all our historical vaccine production was more oriented towards historical vaccines. So, in a crisis such as the Covid vaccine we needed a running start, and that is where, the infrastructure already built into Latin America was essential to kick into the effort and here is where we find all this points that both Prashant and Matthew pointed out so clearly.

First of all, supply chain is worldwide, is international, most of the materials we are using are imported and from not so many suppliers and all this list of things that particularly Matthew mentioned are problems we have had. We have had issues with the single use bioreactor bags, with the single use bags that we use for our mixers, with filters, with tubings...

However, I think the good news about that is that I think that that would be and it is growing at a very fast pace and as a matter of fact it was a concern for us but it has not been a bottleneck really, we have been able [to work it out] and also I think that pertains to the area that we are in the biotech area so most of the suppliers were historical suppliers, and it is also true as Matthew and Prashant were saying usually we put in purchase order for a year or a year and a half, two years... And all of the sudden we came out and we said: No, we want to scale up. And buying bioreactors today is an issue, we have bought additional bioreactors and lead times are about a year.

And this is considering that you already have a facility that can receive those materials, so, again I think that the construction that has to be done for the future is preparedness, we need at least a certain amount of hubs or facilities in the region that have the capability to grow quickly in case of need.

And I will take just one more second, in the particular case of the biotech sector Argentina, Brazil, Mexico, have a certain amount of leadership in the region and there is some infrastructure which is already there, which can be built on, but if it is not there it is very very hard, setting up a facility from scratch is anything from 24 to 36 months, there is buying, commissioning, qualifying, so you really need something in place if you want to handle a crisis.

Minute 19:08 Marcella Distrutti: Thank you Esteban, thank you so much for illustrating these challenges to us, of these global supply chain issues. So now, Ferdinando, I would like to handle this discussion back to you.

Minute 19:19 Ferdinando Regalia: Yeah, actually I am going to pick up exactly where Esteban just left it, looking more into medium perspective, Matthew, we chose the current vaccine platform and I think we all now became acquainted with different platform technology, [which one] has the strongest potential in terms of cost flexibility and technology transfer, etcetera, to scale up manufacturing capacity for Covid-19 vaccine in middle-income countries?

Minute 19:50 Matthew Downham: Thank you very much, indeed and certainly one of the pleasing things with the most newest technology is the mRNA vaccines, and we have seen the escalation in terms of prevalence and capability quite significantly; as many people know now some of the problems with them has been their kind of storage requirements, the super cold storage, minus seventy (-70), minus eighty (-80) [degrees Celsius], but there it lies an opportunity to be innovative and address that issue moving forward.

But certainly, the mRNA vaccines are really proving themselves to be very beneficial in terms of the speed and the quantity which can be produced in a short amount of time and the vaccine effectiveness they are demonstrating. The note of caution, I would say, is though that you shouldn't put all your eggs in one basket and it's important to include a number of different platforms for a whole range of manufacturing supply chain, and also human beings immune response to vaccines, and so the viral backed up vaccines, the viral backing platforms which is AstraZeneca's based on the chimpanzee adenovirus sample and the Gorilla's viral backbones as well, they offer cost-benefit, they offer flexibility and the key thing is speed, so, one of the things that CEPI has been looking at is the cost-benefit of developing the vaccines in the Covid scenario and how to improve that.

If you think about when the Covid virus sequence was known through to when the vaccine had submitted emergency use licensing approval date, it was about a 300 day period and a 50 day period, it went on after that to get clinical trial dates, but in that 300 day period, look at the projection, the cost, just in human lives but also financially, trimming that by 50 days, a 100 days even down to making it a hundred day window which Boris Johnson ahead of the G7 Summit has proposed should be the new target, it is an aspirational target CEPI shares as well. But how tremendous savings in public health, in people's lives, and financially from a business context as well, etcetera.

So, the key thing is the time as well, to be able to produce vaccines, to scale them up, etcetera. And the birth of more novel more recombinant vaccines has really demonstrated the value of this. And these are all things that should be considered as we transition into hopefully facilitating improvements in vaccine manufacturing capability and capacity, particularly in low and middle-income countries which is a key component of how CEPI is moving forward to try and secure and feature that being recognized as a hugely beneficial preparedness and response initiative to facilitate vaccines supply within these geographies moving forward in the future.

So, that kind of addresses some of the core components to address this question but having a number of vaccine technologies is key for multiple reasons, the recombinant ones are really proving themselves of great value and great benefit, more work to be done but certainly very promising.

Minute 23:23 Ferdinando Regalia: Thank you Matthew, and putting this in number of days, I think everyone can really relate to it. Esteban, in your experience, what are the incentives or mandates or public policies, subsidies that are useful in creating and enabling environment for scaling up production in middle-income countries?

Minute 23:49 Esteban Corley: I think that is a very interesting question and I think that most technology-based companies... I come from the research system and we are the typical example of a small start-up thirty years ago that went developing and joining forces finally with the pharma industry and particularly in Argentina is quite strong. I think Latin American countries have a lot of tools that maybe they are not completely using, one, I think, is the purchase power, we always believed in subsidies and grants and things such as those but, at the end of the day we are also the users of those materials, so, I think with an starting line that is common to all of us, there is the possibility that maybe there could be some small preference for local production but within an international tender type of environment in which the same conditions there is a small advantage given that would allow probably the establishment of local capacity.

I think a warning sign was given when we had the flu crisis a few years back, as you might remember and there was a flu scarcity and for example, Argentina had no capacity at all to produce vaccines and the government set out and requested the pharma industry to invest and in exchange for that they would purchase, they will make contracts for purchasing but keeping the same conditions on prices of the revolving fund.

I think that type of incentive would be helpful in the future. As we have been discussing, usually this requires really very big investments, clinical trials are enormous, the costs of production are very high, the materials are expensive, the investment in facilities are very very high, so I don't really see except for this certain capacity of selling to our own governments, I don´t see that other instruments could be really significant to help.

Minute 26:26 Ferdinando Regalia: Thank you Esteban and I want to bring in the discussion Prashant Yadav's opinion, what other tools of public police could be put in place to really think in the medium term, to scale up capacity of production in middle-income countries?

Minute 26:47 Prashant Yavad: So, Ferdinando, I think we have to think about this problem at two levels. The first is we need a global way to think about what would be our total response capacity for vaccines against potential new pathogens and that is not a decision that should be done region wise, because the models that we can use if we were to do this globally can look different and it could include having some nods of the network in the Latin America Region and other regions of the world.

So that's one which is essentially based on the idea that: can we have capacity which can be very very quick to start manufacturing a vaccine that is developed and approved by a regulation in our country?

How quickly can additional sites start manufacturing that vaccine without requiring extensive amounts of alterations in their process parameters, etcetera?

That is one conversation, which is about our fastest response manufacturing capacity network for a future pathogen.

The second is, what can a region do to both be a part of such network and also independently of that create some capacity? And in that respect, I would like to say two things, on one, I slightly disagree with Esteban, so the first is when we think about capacity we are distinguishing between capacity for fill and finish and capacity for drug substance manufacturing, capacity for fill and finish we need more for the medium term than perhaps what governments can guarantee through advanced purchase commitment.

I mean, the fact that we have capacity to do this in some parts of the world and other parts are developing it is a result of government subsidy into creating such somewhat publicly funded fill and finish networks, without them we will have not been at the point that we are in terms of fill and finish capacity, so, we do need some government subsidy, just the ability to fulfill future demand would not get manufacturers or firms of contract manufacturers to develop it.

And that is also, we know, much more changeable, which means in respect of what kind of vaccine, what platform, becomes successful or has a bigger market we will have the need for fill and finish, so in that sense is a no-regrets move for government capacity, it also has a longer shelf life in the sense that things don't change in their technology that quickly.

Then there is drug substance manufacturing, that is where things are tricky, which means that trough government subsidy you create one type of capacity, we may see the repeat of what Esteban was describing which means, you know, fifteen years ago we will say yes there is capacity in Latin America to do inactivated virus manufacturing but that is not what we need today, right? We moved on to recombinant, we are now moving on to nucleic acid, so on drug substance we need capacity which is flexible, which is multi- platform and which can be configured, changed, which has the right kind of start up to be enhanced and it needs to be constantly upgraded, so it is not just static in the sense that yes this is what we are creating, it needs to keep changing as the times and the technologies are changing.

And that is a very difficult thing to start up and made sustainable because whether you do it with advanced contracts or you do it with the government subsidy, those who are the frontiers of biotechnology companies are the ones who will keep changing and figuring out what is the right technology so then it gets into incentives not just for Covid or vaccine manufacturing capacity, then it starts getting into incentives for science and manufacturing science more generally speaking, which then becomes a much bigger debate, and I do not have answers to it but at least that is the framework through which we should be thinking about it Ferdinando, thank you.

Minute 31:10 Ferdinando Regalia: Thank you, thank you to all the speakers is very very clear and this way in which Prashant is putting it is really quite enlightening in terms of the option going forward. I want to remind our audience that you can write your questions in the chat function, English y

lo pueden escribir en español and we are going to translate it for the panelists. I want to give the floor back to Marcella.

Minute 31:38 Marcella Distrutti: Thank you Ferdinando. So, in this next couple of questions, I would like to talk a little bit about technology transfer. Matthew let me start with you, can you help us understand how easy or how difficult it is to transfer vaccine related technology and how [to do it]?

Minute 31:57 Matthew Downham: Sure, I'll try to explain it. I guess if we think of the two extremes, the first extreme is the location where the technology is going to be transferred to, is fully established, has the buildings, the infrastructure the lab space, the resources, supplies, etcetera, and the trained personal, trained workforce, expert trained workforce. That is one extreme, the other extreme is none of that, and between those two extremes there can be all manners of shading, all manners of grey in terms of what is stablished, what is not stablished, etcetera, so the difficulty comes in the worst-case situation when there's nothing and you have to build a building, you have to equip it, you have to build the labs, you have to train people to be working within that facility, etcetera. That's the longest lead time, because you are going to do all the infrastructure build to then have a facility to transfer in the technology question.

If you have all of that in place, the laboratory, the expertise, the facilities are all in place, then it's easier because is a case of transferring the technology in the established facility and training people up, that alone takes some time even with the infrastructure in place, because people have to be trained, they have to prove they can operate independently, there has to be several checks and balances within that scope.

On most cases the site from where the technology is transferred from or the facility where it is transferred from still exist and it is running that technology to back compare with to ensure validation, from a validated perspective, the facility is now accepted and enabled to run the new technology, there is quite a few sorts of checks and balances that are required within that situation.

What it does also assume, in either scenario, is that the technology in question has been developed, has been validated prior to transfer and that is crucial to ensure the comparability in the validation of the technology post-transfer.

It is also important to recognize also that they're both kind of key aspects, you have to have the analytical requirements in place, now that technology is transferred it generates samples, they need to be analyzed, they need to be analyzed against on leveled plain field and appropriate standards, with appropriate comparisons to demonstrating the transfer was done completely successfully and they may need to be legal and contractual or even proprietary agreements, IP agreements in place and especially when you transferring between companies, from one company to another and/or geographies because there might be different legislation, there might be different proprietary requirements depending on the nature of the transfer between the two.

So, the easiest is between companies from one side to another, within the same country or from one company to another site in a different country. So, it's the variances again that create the shades of grey,

to be honest with you, and what is key is that kind of on-sites and then the kind of ultimate licensure, the verification that is been established when the technology is being established and suitable and fit for purpose and validated, etcetera.

I'm coming back to what some of the speakers have said actually and I'm going to take this opportunity to announce that CEPI is about to launch a request for information across Latin America, Africa, Southeast Asia and the Middle East, so I think they will be launching this server later today to get an understanding of the landscape vaccine manufacturing capacity and capability in these four different geographies, to start piecing together and understanding what does exist? But also, and more importantly what doesn't exist? and the idea there is to start building together a road map, maybe a five-year kind of road map to start building manufacturing capacity and capability either from the ground up where it doesn't exist in the country, or where it exists in the country developing it, so that this facility has more autonomy to be able to provide its people and its local region with vaccines, in a more agile readily available way than maybe we do have currently.

I will stop there but I just wanted to share that because it all fits in to this response of tech transfer and having the facilities properly equipped, resources, etcetera to undertake tech transfer to.

Minute 36:40 Marcella Distrutti: Thank you Matthew, and thank you for sharing this amazing information, really, that we are going to be able to access this information quite soon. It is definitely going to help all the efforts.

Esteban, to follow up a little bit from what Matthew has just said, and to sort of like illustrate it to the Covid context, would you tell us more specifically when we talk about technology transfer in the case of Covid vaccines, what exactly is being transferred from country to country or from company to company? We know that this might change depending on the platform that is being used, but in general just so people can understand, what exactly is being transferred and you know, what strategies nowadays are more effective to doing so? because we are in a pandemic so there might be constraints to travelling, visiting different countries, so please tell us a little bit about that.

Minute 37:31 Esteban Corley: Yeah this is a good point you bring up, because this is the first tech transfer that we have done completely by zoom, and webinars, and using our cellphones to show the equipment and the connections and things such as those, and even for audits, something that Matthew brought up when you try to transfer between facilities you usually try to audit the other facility and the receptor to understand and you start by doing what is called a gap fit analysis, you try to understand the differences between equipment, the lay out of the facility, capacity of the people…

I will go into that in a second but I wanted to follow up on Prashant cause I think he said something extremely important and in this we do not disagree, we are actually involved with drug substance manufacturing so I was not paying that much attention to fill and finish, so I am sorry for that, but yes certainly the support of the scientific and innovation system in our countries is essential and to the education because one thing that we always point out that for example in Argentina we had to hire 60 additional people in 4 months and we have them in Buenos Aires because we have a strong scientific education in our universities which are public, so that is something I did not considered it within the

subsidies but it really is a subsidy because the education is free and in this sense Latin American education and universities are essential to have the people, which takes me back to tech transfer, it is essential to have people, people who understand who are familiar with the technologies, or at least with a similar technology.

In the particular case of... our case I'm just talking about concrete cases, we produced monoclonal antibodies but of course it shares a lot of the technological things with the vaccine production in the sense that we produce cells in a big scale, than we have a downstream process, and that we can do seeds and our people are prepared, and we have a strong analytic capacity and this is something that I think Matthew pointed out that cannot be emphasized enough: The analytic capacity is essential, also in the particular case of the technology transfer between countries, a third party analysis, an independent analysis of how the facilities or all the different parts of the transfer are performing are very important and that I have to say is a little scarce in Latin America not so much because of scientific capacity is not there but I think the formal discipline is not there, the good laboratory practice, the good documentation practice, the certifications, the systematic approach, so you can send things to the university and then you will probably get a result back in time but that will not really work in the regulatory environment.

I think there... yes, there is a slight disconnection we really need to work on. And to finish, what is being transferred here? And I think this is an epic moment in history, I think really, everything is being transferred, everything, the cell lines, the virus, all the knowledge, we have received everything to be able to produce the drug substance, the analytics, the training, the fill and finish, the formulation, so, it is also an incredible time to learn and also to be able to check against a completely external source your preparedness.

And I think, again, what we're building here the infrastructure that is being built during this Covid pandemic will remain, the contacts, the agreements, the mutual knowledge, the trust and that we will be much better prepared for the next wave if there is a next wave, hope it isn't. But if it will come, I think the whole infrastructure is much stronger now than it was eleven months ago it seems crazy, but it is eleven or twelve months ago there were really things that were not articulated and now there is a strong network working worldwide. So, I will leave it here to let Prashant also comment.

Minute 42:19 Marcella Distrutti: Thank you Esteban, it is remarkable indeed how far we have come, and it is the second item you mention the topic of preparedness and I think is a very important message for us, one of the lessons of what we are going through right now is how can we invest more in preparedness especially for and if there is a next one.

Prashant, to finalize this section on technology transfer I have one more question for you, in a typical licensing agreement, the licensor grants the licensee the right to use its patented technology, so the question is: how can governments help facilitate technology transfers and how can governments help firms enter into licensing agreements?

Minute 43:10 Prashant Yavad: Yeah, a very important and pertinent question Marcella asks, there are a couple things I want to highlight. So first, I think we have to keep in mind that if you are a big vaccine or even a biologics company like the kinds Matthew has led or work within the past, then you

know who are likely external manufacturing partners, you have at some point interacted with them you have some idea about their asset configuration and you know their team capabilities. But if you are a small biotech which has never developed a vaccine and ends up being the first to develop, they have never done that transfer, their team does not know the landscape of who could be external tech manufacturing partners with the exception of maybe they have a staff member who leads their tech-ops function, who used to work with Matthew in the past and therefore knows him from his previous job, but they don't.

So, in the future we might continue to see this dynamic that a small biotech is the one that first develops a vaccine candidate, and they don't have the tech transfer function internally which means just firms acting on themselves to do tech transfer will not always work, it can work sometimes, if that firm happens to be a big one which has done multiple tech transfer with their so many manufacturing partners.

So we need to think about what can be a public role, so there are two parts that stand out in this: the first is what Matthew and CEPI are doing, which means if we know the assets configuration and the team capabilities of different manufacturers around the world then we can help, whoever doesn't know this by saying here is a global public goal you are a small or not small anymore, you are a large biotech which has succeeded in developing a vaccine and you want to know where else can you transfer, what are the asset configurations? Here is the information and that funding, that global public good is a public role is a government role.

The second is there will be instances where we can fix the assets with money but we will not be able to fix people with money that quickly and in order to have the people who understand chemistry manufacturing and controls in every region of the world whether it is in Latin America or South Asia or Africa, it may be a ten years journey before we will have the people, so in that interim can we create an on-demand pool of CMC Tech transfers people? Quality CMC specialists without borders.

This would be people where if Esteban says: We are trying this new team we have done maps in the past but maps didn´t allow us to do this plasmid things, do you have somebody who can come and help our team with plasmids? Well yes, we will pull this person from the CMC experts without borders and send it to work with Esteban. Or if another company in Brazil wants to try to switch from inactivated to recombinant and are struggling with some of this, we send a few people there.

So, funding this pool of CMC experts is a core government function it is an important part of our short and medium term need for preparedness on tech transfer, that's the only way we can speed up the base at which tech transfers can happen otherwise we will always be saying: Yeah, there is a recipient side but their staff doesn't fully speak my language because they are so far behind in the analytical chemistry than I am, and therefore I will not start a tech transfer. And we will have to avoid that to be better prepared for the future. Anyways that is my way of thinking about it.

Minute 47:02 Marcella Distrutti: Thank you Prashant, super insightful to learn more about how the government can get involved and also this call for this pool of specialists super interesting and super aligned with some other proposals that we've seen before with technology, knowledge transfer heads up and things like that, thank you. Ferdinando, I hand it over to you, to continue the discussion.

Minute 47:25 Ferdinando Regalia: Thank you Marcella and I am going to follow up but also, I'm going to warn the panelists that I'm going to mix a little bit all the questions that we received from the audience. One question, of course there is a lot of asymmetrical information Esteban, and we are reading news from newspapers, we hear the position of pharma companies, etcetera. We also heard that there are companies that already produce a lot of vials but there are some problems with the quality control requirement and the speed for them to send these vials out. Can this process be expedited without compromising vaccines safety and quality? and, what is being done right now in your knowledge?

Minute 48:16 Esteban Corley: I agree that we are all very anxious and all want to be vaccinated an one of the reasons we are in a webinar an not sitting together in a room, is that we do not consider it completely safe, so, we all want this to be expedited but on the other hand, safety comes first, and I think that what was mentioned by Matthew in terms of technology transfer, what we are seeing is that a lot of groups have capacity to develop a vaccine from the scientific point of view, that is one of the aspects, but the industrial challenge is gigantic and I think we spend most of the morning speaking about that.

And in that sense the demonstration that your process is robust that is consistent, that it can be compared between sites because in many cases, a lot of sites are producing the same product, I think this is probably one of the first times that we have so many CMOs or contract manufacturing organizations producing different vaccines for different big pharma companies, and this all has to be absolutely the same standards, the same safety, they have to be completely comparable and a lot of the analytic tests take quite a few days, there are tests that take 40 days, 45 days, 20 days, etcetera, and they have to be done.

So, I think, really, that the authorities have done a great job of expediting analysis of the rolling evaluation of dossiers, is something that was existing or preexisting but I think it has never been used in such a massive way, but again, analytics have their time, setting up the technology has a time, and demonstrating without a shadow of a doubt that what you are producing is robust, is consistent and is comparable between plants takes its time, so if you consider that most of this has been compressed to 6 or 7 months… We have done technology transfers to Brazil in the past, to China, and for us are normal technology transfers that would take 18 to 24 months and here we have compressed everything into something like 6.

So, vaccines are coming, this I can guarantee you; we are really moving very fast and very soon we will have them in the Latin market, at least the ones I'm involved with. And I think really is extremely fast, but nothing is as fast as our expectation this is bad news, I have to share with you today.

Minute 51:08 Ferdinando Regalia: Thanks very much Esteban and better to be honest and blunt in this space. Prashant a question for you, I remember to read, I think in the middle of last year, some work done by CGD regarding the estimation for success rates, now we already have 81 or more than 80 candidates in clinical trials, many have already passed the regulatory approval of many agencies and there is a large volume of doses promised over the next couple of years.

What does this really mean for the future changes in the vaccine markets, what we are observing right now?

Minute 51:51 Prashant Yavad: So, firstly I think that the work that we have done at CGD which is led by my colleague Anthony McDonnell I think, it wasn't an attempt to say we know and we are trying to make a bet on which of the vaccines will succeed, it was trying to help people understand that if you have to buy an optimal portfolio what would that portfolio look like? You can't put all your bets in one particular platform, and there was an attempt to provide some scientific basis for it.

Now, what happens when the second wave of vaccines come out, I think, we will see in my opinion a Covid vaccine market and a vaccine market, I mean both are connected but the interest thing is, the second division vaccines for Covid, I mean clearly the bar for them to demonstrate either higher efficacy or higher field effectiveness on some way, and field effectiveness whether it is being able to work with less stringent temperature requirements, easier to administrate doses requirements, if those things are met, then I think we will see update, otherwise, I think the update of the first initial vaccines, that is already reaching fairly high and, from the stand point of market share leaders, they may continue to be market share leaders, now, the part that we do not know of course is the big wildcard character for everybody is efficacy against new variants including some of the variants of concern, and whether the first emission vaccines or would a second generation vaccine, especially the ones which have different pathways, are non-expire based or something else, that may change the future shape of the Covid vaccine market dramatically, but that is a big degree of uncertainty.

The group that did this work on estimating the probability of success, we have gone back and ask the question, should we repeat this and say which of the second-generation vaccines are more likely to succeed for variants of concern? things like that, but it is something we have to go back to.

One last thing I want to mention is that the future of the vaccine market has to keep in mind that the big question is to in case we do not need that 10 billion doses in a year from now or two years from now, in many ways that would be an exciting time, right?

The fact that we have controlled the pandemic that we don't need that much volume of doses, but then what happens to this capacity, like I mean it sits largely with contract manufacturers, in some cases with the vaccine developers themselves, what would it be used for? Would it be used or reprogramed to do things where then we will not be able to bring it back to make vaccines? would they all go into making large and growing monoclonal antibody market? I mean those are the sort of questions which are worth asking.

And also, it fits for nucleic acid vaccines what would their drug substance capacity for nucleic acids likely to be used for if it is not as needed for Covid vaccines and there are very promising areas there too.

Minute 55:20 Ferdinando Regalia: Thank you Prashant, to finish up, we are running out of time but we have a lot of questions I'm trying to summarize a couple for Matthew, one is the issue of variants, I know CEPI is actively working in this phase with manufacturers, what can you tell us regarding the way this threat is being approached by the industry? and the last question is: if you go back ten months and we were all talking about financing Advance Market Commitment to scale up capacity enough, what could we have done better as international financial architecture, as banks, as Covax, as other national authorities?

Minute 56:14 Matthew Downham: I recognize there is only a few minutes left, I will try to be as fair and concise as I can, in terms of new variants, you are actually right there is a concern regarding some specific new variants in the UK, from Brazil, from South Africa and various other places on the planet, and certainly what we are hearing is that manufacturers and manufacturers organizations are developing vaccine candidates to those novel strains at risk pending decision to transition from the current vaccine that is being used, based on the Wuhan strain originally, to another virus strain.

So, there's a similar kind of situations to what happened with influenza on a seasonal basis and the trigger will be caused by, let's say a depreciation of the efficacy, damageable mismatch and the escalation of one particular strain that threatens to be a resurgent pandemic or such. So that's where certain activities are with new variants, there was a meeting earlier today actually by the WHO [The World Health Organization] to try and leverage the WHO influenza's network, GISRS System [Global Influenza Surveillance and Response System], the national influenza centers which have been in operation since about February last year for Covid, it's thinking through how to leverage that more readily in the future so there is a lot of activity going on, there is concern regarding new variants.

In terms of lessons learned in manufacturing scale up and capacity, this comes back to some the agility topics we have talked about today in terms of how to increase manufacturing capacity and capability particularly in LMICs [Low and middle-income countries].

I noticed some of the questions in the Q&A from this session are related to autonomy for example from China, so, how would you create more independence and better response capability in Latin America and the Caribbean? A way to do that would be to improve the manufacturing capacity and capability, that autonomy, that flexibility and that agility is kind of one of the lessons learned from the Covid pandemic, i.e.: the lack of reliance on core global geographies to provide the rest of the planet, having more autonomy within countries and regions is key.

And that is some of the lessons learned, the need to drive towards the manufacturing scale up in respect of what vaccine platforms technology is used and geographically where it is, it's all about that autonomy, that independence, that speed, that agility to better respond in the future.

Minute 58:57 Ferdinando Regalia: I think with this we came to a closure; it was a very difficult time, and you were very compact, very difficult question with very little time to answer. We finish up our space and we really want to thank Esteban, Matthew, and Prashant we learned a lot it was a very informative panel we thank you for your time, we know how busy you are right now and thanks again for your contribution.

And I also want to thank the audience for the time they spent with us, this hour I hope it was very useful and informative and I want to remind you that we are going to have very soon on April 6 a new panel session where we are going to discuss about the challenges of vaccine deployment with a panel with the experience of Chile, Israel and the state that maybe is not very well known in the U.S. which is West Virginia with a lot of characteristics similar to our countries, we will present their experience. Thanks very much to all.

Minute 1:00:00

Matthew Downham: Thank you very much, have a good day.
Prashant Yavad: Thank you.
Esteban Corley: It has been a pleasure, thank you, an honor.
Ferdinando Regalia: Thank you very much, a pleasure.

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