JEFFREY BUGULISKIS: Welcome to GenCast, a sponsored podcast series brought to you by *Genetic Engineering & Biotechnology News*. I am your host, Jeff Buguliskis.

Van Gogh. Renoir. Monet. These Impressionist Masters created some of the most iconic works of art the world has ever known. But what if you wanted to recreate some of their most famous paintings, a scenario that has been tried by skilled forgers for centuries in many instances. But let us say, just for a moment, that it was not illegal to create copies of the artworks and sell them. How close would the copies have to be to their original in order to have any real value?

Well, thankfully for the artworld, this is not a scenario that they have to contend with. Yet, for the biotech and pharma space, this is a scenario that is part of the new normal as the biosimilar market, which is looking to recreate some of the most iconic approved drugs, is poised to topple over $3 billion by 2023.

For emerging biotech companies in early-stage clinical development, accessing the market as quickly as possible is extremely important. One example of these burgeoning companies is Turgut Pharmaceuticals, located in Istanbul, which in 2013 initiated an ambitious plan to become a

global leader in the development and manufacture of high quality biosimilars for regulated markets.

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However, to achieve their enthusiastic goal of accelerating the clinical progression of biosimilars, the Turgut team sought to partner with a group possessing strong scientific knowledge and expertise, that were also capable of providing a full range of contract development and manufacturing services, from process and analytical development to pilot and commercial scale manufacturing and regulatory support.

This is where the M Lab Collaboration Centers stepped in to provide expert assistance on training in the single-use systems that would be used in Turgut's new GMP facility located in Turkey. Let us meet our panelists for today's podcast, who are here to discuss the successful collaboration that span across functions and geographies, which made the original laid out vision a reality.

SEBASTIEN RIBAULT: Good morning, afternoon, everyone. Sebastien Ribault, I am Senior Director in charge of our BioReliance End-to-End Solutions organization, providing CBMO services primarily to emerging biotech, although we work also with large companies. I have been within the

biotech industry for about 25 years now and I am speaking today out of our Burlington facility in Massachusetts.

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ADAM SOKOLNICKI: Good morning, good afternoon, good evening, everyone. My name is Adam Sokolnicki. I am a Biomanufacturing Engineer Manager in the Manufacturing Sciences and Technology Group. I am based in our Burlington, Massachusetts office, adjacent to our M Lab Collaboration Center.

DR. SERDAR ALPAN: Hi, everyone, this is Serdar Alpan. I am the head of the Turgut Biopharmaceuticals group and I am a medical doctor and molecular pharmacologist. I am from the beginning of this establishment, we first founded and now developing at different levels of a certain number of molecular antibodies.

JEFFREY BUGULISKIS: Great. Thanks, guys. In a recent interview with OncLive, former FDA Commissioner Scott Gottlieb talks about the barriers the biosimilar market must overcome despite its impressive growth. One of the major challenges he mentioned is the cost of development and manufacturing. So what made Turgut decide to enter the biosimilar space and how do you plan to overcome these challenges?

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DR. SERDAR ALPAN: So the issue is that the biotechnology is very rapidly growing area and two good strategies is to develop high quality biosimilars for local and also the regulated markets. We believe that if the market is as large as possible, then the cost is more manageable. On the other hand, if production is not for local markets but also regulated markets are considered on the cost-wise. The second one is that, Turgut considers itself as an R&D based company, which currently has a strong R&D team, which continuously working on improving the process and also decreasing the costs.

SEBASTIEN RIBAULT: I think I can relate to what Serdar just mentioned maybe indicating within the company we are trying to achieve working with companies like Turgut. Our company experience overall is more than 32 years in process development and manufacturing for our organization. But we also have experience in using single-use products in general to make sure that when we develop biosimilars and large molecules in general, we are going to make sure that the cost of goods are as low as possible so that the local markets that Serdar just mentioned can be addressed. And we do not develop a process that will not be financially accessible on some of the local markets.

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So by putting together the experience of our team in process development and manufacturing, our single-use environment, our organization designing facility, we can bring a package to our customers to make sure that not only we will be able to transfer the process to their facility that we supported in terms of design, but also, we are making sure that long-term our clients, including Turgut Ilaç, are going to be able to make that manufacturing and be totally autonomous.

We see that much more as a collaboration than anything else, because it really takes a partnership to put in place in parallel a facility, develop a process and transfer that process. So we really have to work hand-in-hand to make that possible.

JEFFREY BUGULISKIS: Great, so Serdar, what specific challenges do you face when you decided to build a biosimilar business from the ground up?

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DR. SERDAR ALPAN: So we at Turgut are developing biosimilar monoclonal antibodies for global markets, so this means that we are developing high quality biosimilar monoclonal antibodies. So the universal challenge here is that first the monoclonal antibodies are large molecules,

150,000 Dalton molecules, and in order to make a biosimilar version of this molecule is scientifically a challenge.

Therefore, this absolutely requires a strong R&D platform. So in this regard, we are using a different cell line, a different process, different analytical methods, different production methods, but at the end of the day, we need to make a highly similar monoclonal antibody. So again, this requires basic experience, R&D experience plus the cell line development, process development, and analytical methods development, and also the scale-up and production experience.

So all these things should be put together and this is what exactly we did. This was the most important challenge, where we managed to do that and at the end of the day, now we are at different levels, developing five high quality monoclonal antibodies at different levels.

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JEFFREY BUGULISKIS: Then Sebastian, what approach did the BioReliance End-to-End Solutions team take to support Turgut's ambitious goals?

SEBASTIEN RIBAULT: Actually, we put together not one approach but several approaches that were running in parallel, because we had to work on the strategy on which we supported the team from Turgut. And I remember many

workshops and meetings Serdar and I had together with our team. But in parallel, we were working on the technical aspects, and in parallel of these first workstreams, we also were working on the facility.

I remember our very first meeting, which on the top of my head was at the very end of 2013, and at the end of the discussion in our facility in Martillac next to Bordeaux in France, Serdar told me, "What do you think it takes to replicate Martillac in Istanbul," which was an interesting challenge.

So we really had to look at the best way to take the facility we had in Martillac and transfer a similar facility to Istanbul, but also make sure that that facility would be able in that strategic aspects to take care of one biosimilar at the beginning and five biosimilars midterm and maybe, you know, ten molecules running in parallel along the long-term.

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So we worked a lot on the strategic aspect at the very beginning and this strategic aspect included as I just mentioned a vision for this facility, moving from one to five and many more molecules, but also what should be the structure of the team, which molecule should be the first, the second, the third, and so on.

In parallel, we had that work with the engineering team to design the facility and make sure it would not only be able to support clinical manufacturing but also commercial manufacturing, quality control activities, but also in the future process development because we were sure from the discussions that Turgut team would like to start process development activity, and all of that obviously being approved from a quality and regulatory standpoint.

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In parallel, the teams in our facilities were working on the development of the process so that this process could not only give us a molecule that is biosimilar but also make sure that this process could be scaled up and transferred to Turgut's team in Istanbul so that once we finalized the process and development and the phase one clinical manufacturing, then Turgut's team would be able to make the phase three and commercial manufacturing. So as I said, not really one approach but several approaches running in parallel.

JEFFREY BUGULISKIS: So then Adam, I am going to turn it over to you now and ask how did the M Lab Collaboration Centers support this project?

ADAM SOKOLNICKI: So Jeff, end-user training is really one of the final stages in project execution for these

large investment projects which we are talking about here. It typically comes after the systems are delivered to the facility. However, we do have the capability to conduct comprehensive trainings at one of our nine M Lab Collaboration Centers, which are spread across the globe, typically in biotech and biopharma hubs around the globe.

So working with our system and automation specialists, such as the MSAT group of which I am a member, the end-user can receive hands-on experience with our single-use technology, focusing on aspects such as hardware features, insulation of the Flexware or single-use assemblies, system operation, and then familiarizing engineers and operators with our software control platform.

Turgut visited our M Lab Collaboration Center in Burlington, Mass in the United States in October in 2018 for a week of hands-on training with our MSAT team. They brought a full team representing process owners, senior process development scientists and engineers, as well as the system operators for both the upstream and the downstream manufacturing processes.

So this week of training not only helped Turgut fulfill the requirement for CGMP manufacturing to have trained and qualified operators, but it also positioned

them for success as they began their startup operations at their new facility.

Furthermore, our regional team of process and system experts is available to support engineering and performance qualification runs, which will come down the road.

SEBASTIEN RIBAULT: If you will allow me a comment, what Adam just mentioned is the complement of some of the other activities we provide through the BioReliance End-to-End organization. We have several organizations within the company who can actually support the customers when they put together a facility. The hands-on training that Adam mentioned is very important to make sure that our customers really understand how to use the different ... [STATIC] [?] operations. It is really important to make sure the customers will be ready to execute as soon as the process is ready.

As a complement, we provide GMP training within the end-to-end organization since we have GMP facilities as well. So by putting together our various organizations, not only we can provide a process, we can provide a facility design, we can make sure that an adequate training is provided on the equipment, as Adam just mentioned. And we can also make sure that the operators are ready for GMP operation.

I remember a discussion we had with Serdar years ago, and more or less the conclusion of the discussion was we are going to take care of everything and we will be together when we cut the ribbon at the grand opening.

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JEFFREY BUGULISKIS: So gentlemen, what is the next step for the project?

DR. SERDAR ALPAN: The platform for the development of high quality monoclonal antibody development has been established now. And also, the production plant, which is the largest monoclonal antibody production plant in Turkey, Turgut's production plant and it will, the construction and also the equipment and utilities and the green rooms and everything, the laboratories, everything, the constructions are completed.

And now the documentation, qualification and validation studies are going on. And we expect to get the Turkish MOH GMP approval next year and start the production of the first, and later on the following products, monoclonal antibodies. So in this regard, this is a very important milestone in Turkish pharmaceutical industry because this is the first monoclonal antibody API production facility in Turkey. And this facility designs at the global standards, therefore fulfilling the EMA and

hopefully FDA regulations, and as well the Turkish Ministry of Health regulations. And therefore, this is a very important milestone.

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And the capacity of this production plant is expandable, and the first phase is now being opened. And the second phase is also under planning and it will be completed in two years' time. The building, the block of the production plant, one block of the production plant is for this large-scale production, we call it. Therefore, this will be an important production plant for local and regulated markets in the near future.

SEBASTIEN RIBAULT: So I guess the next step for us is to make sure we can support Turgut in the activities that Serdar just mentioned. As we discussed earlier, not only we make sure that there is a facility and the process is developed and ready for manufacturing, but we want to make sure that there is long-term success, that the capacity can be expanded, that the process development can continue and that manufacturing will go on to commercial activity.

So next steps, support these activities. And recently, we had discussions with Serdar on the regulatory aspect and some quality documents that were necessary for filing, and obviously very much looking forward to seeing

Turgut being successful on the market with the first molecules.

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JEFFREY BUGULISKIS: Well, thank you gentlemen, for joining this GenCast today. We appreciate your time and we look forward to the future of this collaboration.

Thanks for listening to GenCast. For *Genetic Engineering and Biotechnology News*, I am Jeff Buguliskis.

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