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Vaccine manufacturing: COVID-19 and beyond

In 2020, the biopharmaceutical industry set a historic pace at which new therapies have been taken from research to full-scale manufacturing and distribution in the race to find treatments for SARS-CoV-2, the virus which causes COVID-19.

After approximately a year of research and technology development, two RNA based vaccines, produced by Moderna and Pfizer/BioNTech respectively, received emergency use authorization in the United States and European Union[1]. In China, emergency use has been granted for just one vaccine, produced by Sinopharm[2], and Russia has also granted one vaccine approval to date[3]. A pipeline of more than 800 therapies[4] are still under evaluation for how they may also be used to alleviate the effects of COVID-19 on different patient populations.

In this interview, Nandu Deorkar, Vice President R&D, Biopharma Production at Avantor, shares insight about the different vaccines' technologies and the lessons we can learn from the industry's historic ramp-up from research to manufacturing.

So far, it would seem that DNA and mRNA vaccines have been the most successful modalities to inoculate against COVID-19. What has contributed to their success?

An array of therapeutics have been in development to address the COVID-19 pandemic, with five different vaccine modalities, all relying on different viruses or viral parts:[5]

- Recombinant protein vaccines
- DNA vaccines
- mRNA vaccines
- Non-replicating viral vector vaccines
- Inactivated vaccines

Recombinant vaccines are manufactured using well-established technology, proven to be both safe and effective, but take longer to develop. The most promising vaccines in development are protein-based, with 81 in the pipeline at the time of this publication[4]. Inactivated vaccines have been on the market for much longer, so a lot of knowledge has been developed but the production processes are often outdated. So far, rapid production of these vaccines has not been possible.

Unlike recombinant vaccines, DNA or mRNA vaccines use information from the genome of the virus to create a blueprint of select antigens. Those molecules hold the genetic instructions that, after being injected into human cells, are used by the cell's machinery to make virus antigens which cause the immune system to react. These vaccines aim to do one of two things: 1) the vaccine exposes the body to an antigen that won't cause a disease but will provoke an immune response that can block or kill the virus if the person becomes infected; or 2) the vaccine provides instructions to an antigen (as in case for mRNA), inducing an antigen-specific B and T cell response.

Speed has been and will continue to be the biggest determinant in how quickly the world can begin to recover from the pandemic, first related to discovery and scale-up, now continuing the pace of manufacturing and distribution of the proven vaccines into the hands of medical professionals worldwide. Clearly, what has stood out for mRNA vaccines has been the combination of both speed and efficacy. DNA and mRNA vaccines have a very short construction and development time: they can be designed on the computer in a matter of hours. Since small doses are needed, small bioreactors can be used, speeding up the whole process. For example, CureVac and Tesla are promoting "RNA micro factories," a technology which could be reproduced around the world to deliver a vaccine in a short period of time.[6]

Additionally, significant funding and collaboration have taken place, furthering platform technologies and innovation. Biopharma companies are working together and sharing knowledge about technologies collaboratively in consortiums like the Coalition for Epidemic Preparedness Innovations (CEPI), co-founded and co-funded in 2017 by the Bill & Melinda Gates Foundation and other partners. Partnerships and consortiums like these will not only help support the industry's pathway to the nine billion COVID-19 vaccine doses required to help meet global demand but also keep ahead of and prevent global outbreaks of COVID-19 and other pandemics in the future.[7]

How did the availability of existing platforms help the progression of clinical trials?

In a typical clinical stage testing format, vaccines go through multiple years of testing before being approved for the general public. The vaccine for mumps in 1948 was the fastest developed prior to last year, taking four years from the collection of viral samples to an approved and licensed drug.[8] In 2020, modern technology allowed companies to accomplish the same in a quarter of the time.

The development period for COVID-19 vaccine candidates was substantially compressed by the use of modern platform technology to develop the vaccine in pre-clinical stages, followed by historically fast authorization by regulatory agencies for clinical trials. Moderna, as an example, initiated clinical trials within two months of sequence analysis of the virus of their new generation vaccine (mRNA-1273)[9]. This would have normally taken more than two years without platform technology to develop such a vaccine.

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Many developers also ran clinical trials in parallel (phases I and II) to shorten the time for approval. Some have started collecting data on efficacy from phase II itself (IIb). There is a debate on whether challenge studies are ethical in COVID-19, assessing the risk to a healthy volunteer. It also has to be considered that vaccine development is a high-cost and high-risk involvement, and the success rate is rather low. A 2016 study showed that typically, around 20% of vaccine clinical trials make it from phase I to license[10]. Regardless, it remains understood that no matter how quickly we move, there can be no compromises to patient safety in the process.

What are some of the challenges still being faced in scaling-up the vaccines under development to meet requirements to have more than nine billion doses of approved vaccines by the end of 2021?

One of the major challenges for mRNA and DNA vaccines is to physically deliver genetic material into cells. The pDNA has to deliver the material into the nucleus, passing different barriers along the way. Electroporation devices have been investigated to overcome this delivery challenge.

By contrast, an mRNA vaccine does not need to be carried into the nucleus. It can be carried into cell cytoplasm but has to be protected; otherwise, the mRNA can be easily attacked by enzymes. There is inherent instability with mRNA, so manufacturers need to make chemical modifications to the mRNA base in order to enhance stability. Lipid-based nanoparticles (LNPs) are used by both approved RNA vaccines for delivery. To prove safety and stability is a challenge both types of nucleoid vaccines will face.

Another issue is immunogenicity: mRNA vaccine manufacturing has created a need for pDNA, nucleotides, and enzymes. In particular, the demand for LNPs will grow significantly. These LNPs contain components like ionizable amino-lipid, cholesterol, a phospholipid (also termed helper lipid), and lipid-anchored polyethylene glycol (PEG). For clinical translation of these mRNA LNP systems, it will also be critical to meet pharmaceutical and regulatory product requirements during scale-up manufacturing under GMP conditions, quality control of these products, stability testing, and good safety and efficacy assessments during the preclinical stage in relevant animal models.

Expedited development of treatments can put increased pressure on the supply chain of materials such as salts and buffers. Also, some of these raw material requirements still have to be scaled up to meet cGMP requirements (e.g. enzymes), where previously a cGMP material did not exist or was limited. Using high purity, cGMP raw materials can significantly increase safety, efficacy and stability of the final vaccine product as well as prevent scale-up challenges along the way.[11] Several raw materials used in vaccine manufacturing are of animal origin and not suitable for long-term use. We are developing semi-synthetic processes to manufacture these at required scale.

How is Avantor supporting therapy scale-up and production of COVID-19 vaccines?

Overall, collaboration with suppliers is one of the major areas that biopharma companies can use to help enhance their regulatory compliance, minimize risk, drive cost-effectiveness and improve time-to-market for any product, but now especially for novel therapies that will help mitigate the impact of the COVID-19 pandemic. As a supplier to our customers in the biopharma industry, spanning all the way from the lab to production stages, we are proud to offer many products and services that are essential in the development of these critical vaccines and other treatments.

Practicing what we preach in terms of collaboration within the biopharma industry, we help set up and optimize workflows in manufacturing and formulation steps. One area in which we have specifically focused has been downstream bioprocessing. Here, we are working with customers on how to overcome potential processing bottlenecks by implementing new approaches to buffer management, like utilizing pre-packaged buffer materials to help streamline buffer exchange steps. Clear benefits of reduced quality testing, reduced buffer preparation time, reduced tank volume used and enhanced process efficiency can be gained with the implementation of a new buffer management strategy.

We are also supporting biomanufacturers who are looking to make wider use of data analysis tools, allowing them to gain deeper insight into complex raw material interactions in downstream processing. We have started to work with customers on how they could make better use of the data we collect during development and manufacturing. This allows them to better characterize raw

material variability, and anticipate and mitigate any impact this might have on their manufactured batches.[12]

What lessons learned can be taken from the past year of vaccine development and applied to how the industry will move forward post-COVID-19?

Over the past year, the convergence of science, engineering and technology along with global collaboration made it possible to develop effective vaccines at unprecedented speed. Breakthroughs were achieved, but we have not yet achieved a complete victory. If the primary goal over the last year was to develop a product that is safe and efficient, the next challenge was to reach and sustain scale, which we are still in the process of doing. Much work still needs to be done to reach a goal of nine billion doses (with some vaccines requiring repeated doses) across different vaccine modalities by the end of 2021, enough required to vaccinate a global population against the virus.

The industry will look to the increased adoption of single-use for its ability to provide flexible, localized infrastructure. Formulation improvements will be another important factor in vaccine design, considering the cold-chain requirements of existing vaccines. Immunization programs will only be successful if end-to-end supply chains and logistics systems are installed and can be sustained. There is undeniable room for improvement in the global infrastructure and supply chain if we are to meet ongoing demands of research, scale-up, manufacture and delivery – especially if we were to see a situation like this unfold again, which experts agree that if we don't change our lifestyles we will face pandemics like this in the future. Vaccines of the future will need to be efficient, safe, easy to manufacture, stable and convenient to deliver to meet the requirements of sudden global pandemics.

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During his more than 25-year career in materials technology research & development, Dr Deorkar has worked on various aspects of chemical/polymer R&D, drug development, formulation, drug delivery technologies, process development, and technology transfer. Dr Deorkar earned his PhD in chemistry from the Indian Institute of Technology, Bombay, and his MBA from Fairleigh Dickinson University, New Jersey (USA).