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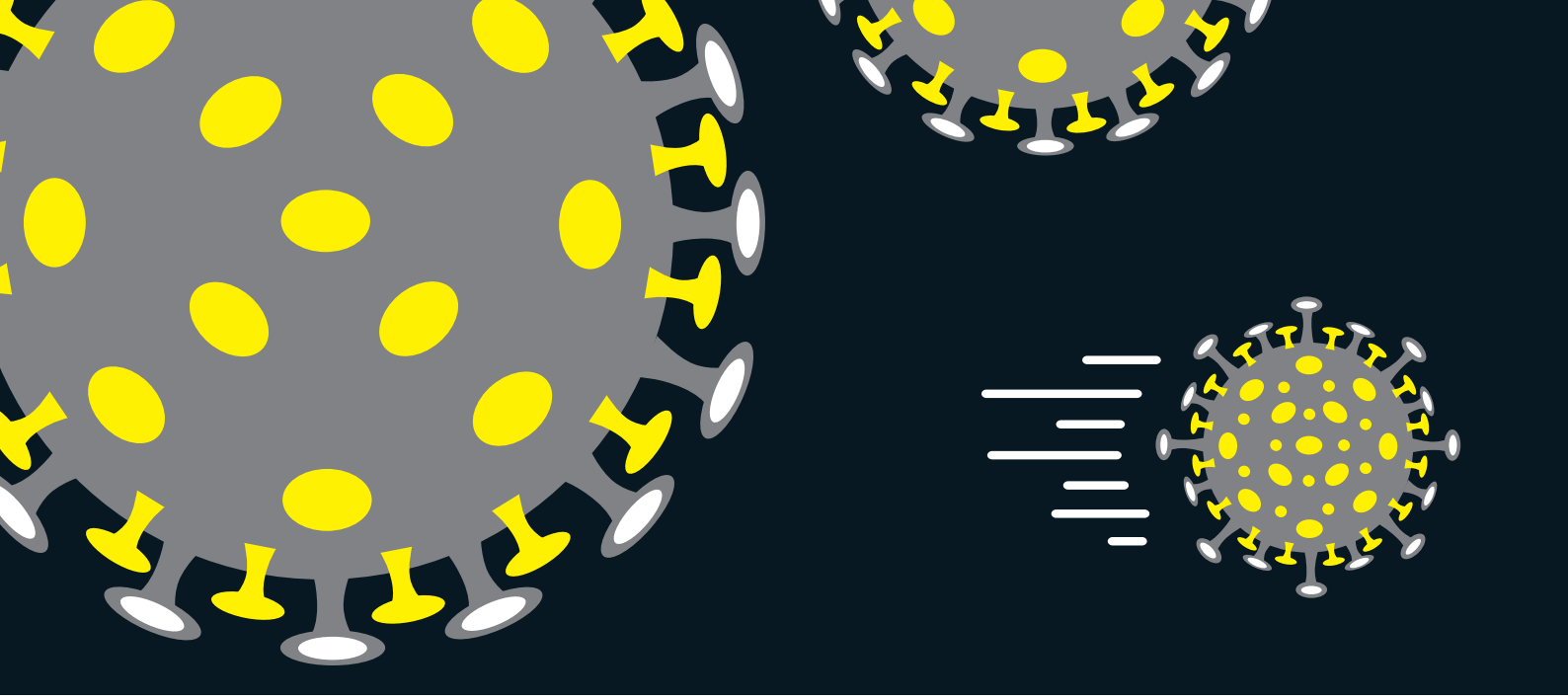
Can mRNA Disrupt The Biopharma Industry?

Abstract

As the world continues to reel from the impact of the COVID-19 global pandemic, health experts around the world are trying to identify a potential vaccine that can combat the international threat before a second wave of the virus inevitably hits. This process traditionally requires years or even decades to not only develop the drug but also move it through the clinical trial phases necessary to ensure it is safe and effective. However, the pharmaceutical industry is facing unprecedented expectations to accelerate the delivery of a vaccine for COVID-19 in the face of a death toll that is rising daily.

One technology some companies were investigating even before COVID-19 is mRNA (messenger RNA)-based vaccines. Due to several benefits, including the ability to quickly scale up in the case of a large disease outbreak, mRNA has the potential to revolutionize the field of vaccine development. Going from a niche corner of the market to an innovative disruption, though, requires a better understanding of how the manufacturing process for mRNA vaccines differs from traditional vaccines, what challenges exist, and any other factors that could impact the successful entry of mRNA vaccines into today's market.



Existing Vaccine Manufacturing Versus mRNA

With traditional manufacturing, it is often "one drug for one bug." In other words, the manufacturing process for a vaccine must be tailored for that one disease because the manufacturing process includes the production and the purification of the pathogen itself. Therefore, every time you tackle a new disease, you must start from the beginning and learn everything about the pathogen to determine how to produce it on a larger scale. This presents several technical challenges as well as other complications. Yield often becomes an issue, which means you must have enough capacity to produce the amount of vaccine needed to make it available and affordable to a large population, especially in low- and middle-income countries. Even worse, it is not a given that a microorganism or virus can be produced in a bioreactor at large scale. When developing a vaccine for the human papillomavirus (HPV), it was not possible to grow the virus in a bioreactor, so vaccine developers used a recombinant approach instead (the production of virus-like particles in a bioreactor). The lack of a manufacturing process that can be utilized for multiple diseases has led to long development timelines, limiting the industry's ability to respond quickly to an outbreak or, in the case of COVID-19, a pandemic.

Safety is also a concern with traditional vaccine manufacturing processes. Typically, when developing a vaccine, you must first propagate the pathogen that is generating the disease, resulting in large quantities of the product within a facility, which poses a major risk to the operators. Preventing exposure means investing in the resources needed to maintain a high level of biosafety to ensure your facility has the appropriate engineering controls in place to prevent cross contamination. Patient safety must also be considered, since, with existing processes, you must be sure the virus in the vaccine they receive has actually been inactivated or, with attenuated vaccines, you must ensure the virus cannot revert back to its pathogenic form.

Alternative Approaches To Vaccine Development And Manufacturing

Driven by a mutual commitment to overcoming the challenges of vaccine production today, industry experts have identified alternative approaches to vaccine development and manufacturing. One breakthrough has been the development of recombinant subunit vaccines, used for viruses like hepatitis B and HPV. Here, researchers identify an antigen, often a protein, that is specific to the pathogen and able to generate a strong immune response. The vaccine's antigen is produced in a recombinant way, relying on an expression system, such as E. coli, yeast, CHO, etc., without using the disease-causing microorganism or virus in the manufacturing process. This eliminates safety issues as well as technical hurdles during the production of the pathogen. However, you need to develop the right expression system for your protein and tailor the downstream development process

to the antigen specific to the disease you are targeting. Every protein is unique in terms of property; therefore, a lot of optimization is required for any new process.

A Simplified Approach: mRNA

A second and newer breakthrough is the use of mRNA vaccines. To understand the principle of mRNA vaccines, it is important to remember the basis of molecular biology. Our genetic code is stored in the nucleus of our cells in our DNA. The first step of gene expression is transcription, where a copy of the DNA, called a messenger RNA (mRNA), carrying the information is produced. The mRNA is then transported out of the nucleus and translated into a protein. From a manufacturing perspective, a mRNA is a simple structure made of nucleotides that can be chemically synthetized, while proteins or complex molecules are produced using only recombinant technologies.

The principle of the mRNA vaccine is to deliver the sequence coding for the antigen, in an mRNA, to the patients, rather than the antigen itself. When delivered to the patient, the mRNA enters the cells, which start producing the antigen.

The complex antigen is produced by the patient cells, while the simple mRNA can be produced within a true manufacturing platform (although the process may need to be slightly adjusted, depending on the disease). To produce the mRNA, a genetic sequence from a DNA plasmid containing the sequence coding for the antigen is mixed in a reactor with nucleotides and enzymes. This enzymatic reaction produces the mRNA using a DNA plasmid as a template. The mRNA is then encapsulated in a lipid nanoparticle for delivery.

Because mRNA is developed using an enzymatic synthesis rather than a cell culture, processes are simpler and more straightforward. For example, you know what your contaminants are, and there is no need to remove cells or assess the removal of host cell proteins or DNA. The result is a simplified vaccine manufacturing process compared to traditional or recombinant strategies, including those used for viral vectors. Therefore, mRNA vaccines are easy and extremely rapid to develop and manufacture, improving speed to clinic and to market. Just as with any vaccine manufacturing, though, you need to control critical process parameters and ensure the process is robust enough to yield the same drug substance quality at varying scales, no matter the production site.

mRNA vaccines offer new promise, but we must also recognize and consider any potential challenges. Adjusting to this new strategy will require innovative solutions and expertise similar to when the pharmaceutical industry used chemical-based drug development processes to advance biopharmaceutical drug development. Approaches used in other industries, such as how to use bioreactors in food and beverage manufacturing and chemical engineering, were modified to fit today's biopharmaceutical industry and single-use approaches. The same sharing of information across biopharma may be necessary to move mRNA vaccine development into the future.

Challenges In mRNA Vaccine Development And Manufacturing

While mRNA vaccines offer several benefits, there are some limitations that must be considered. For example, the supply chain for raw materials, such as plasmid, could be an issue when it comes to achieving an acceptable level of quality and even the right quantity. Traditionally, plasmid DNA was used mainly for research purpose and for inserting the antigen into vectors or cell line for protein productions. With mRNA, plasmid becomes a critical raw material to start any new batch, which can create a capacity crunch in sourcing DNA plasmid, as the number of producers and scale needed are limited worldwide. Proprietary enzymes used in mRNA production could also present intellectual property challenges for the manufacturer, especially when a vaccine needs to be produced at a large scale. As demand increases, it is likely these issues will improve with time, but they are important to consider in early stages of mRNA adoption, such as with the development of a COVID-19 vaccine.

With the elimination of live microorganisms in the development process (due to the chemical-based reaction), manufacturers can also expect a decreased cost of goods. Moreover, raw materials not typically used in existing vaccine manufacturing, such as oligonucleotides, lead to opportunities for new suppliers to enter the space. Although this

strengthens the supply chain, it also means manufacturers must remain vigilant in ensuring a sufficient amount of quality supply will be consistently available, especially in the case of a pandemic like COVID-19. Contract development and manufacturing organizations may even adjust their focus and offerings to accommodate the new market, just as they have for the increased demand for viral vector supply in cell and gene therapy, leading to a need for stricter vetting processes when selecting a partner. Overall, you must ensure that, with any partnership you enter into, both parties share the same end goal of the highest level of product quality and safety.

The current process development expertise for mRNA in this industry is not widespread. Therefore, many other companies do not have, to some extent, the mindset to develop and scale mRNA. For new entrants in this field, process expertise and scale-up should be built inside the organization. There is some industry speculation about the efficacy of mRNA vaccines, with some strongly believing they offer a solid alternative to the challenges of existing vaccine manufacturing and others skeptical due to early failure of mRNA targeting, such as with cancer or other therapeutic applications.[1] As of early April, though, the Coalition for Preparedness Innovations reported there were 115 COVID-19 vaccine candidates in varying stages of preclinical testing, with 78 confirmed as active programs.[2]

Overall, 9 percent of these candidates are based on mRNA technology.[3] The pending clinical outcomes of these candidates will ultimately reveal the true efficacy of mRNA. Beyond COVID-19, mRNA has the potential to expand access to vaccines across the world, potentially revolutionizing the industry's ability to rapidly respond to the urgent need for life-saving preventive care.

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Sales and Service Contacts

For further contacts, visit www.sartorius.com

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

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