# The Rise of mRNA: New Era, New Challenges

**mRNA vaccines have provided one good answer to humankind's latest grand challenge, but the technology has yet to mature. If the success story of these nucleotide-based drugs is to continue, manufacturers must look to ease the headaches associated with their manufacture.**

*By Amelie Boulais, Nitin Chopra, and Jay Zhang*

Within just a few decades, industry perspectives on mRNA-based therapeutics have drastically changed. In the early 1970s, only a handful of scientists were exploring the potential of mRNA and their work attracted little attention. Today, however, the power of mRNA vaccines is undeniable; they have dominated the industry's response to COVID-19 and questions are being asked about their influence on the broader therapeutic landscape. mRNA-related research is filling pipelines as manufacturers seek to be part of the industry's next success story; meanwhile, the achievements have piqued the interest of investors, who are keen to support the development of the next generation of successful mRNA-based products.

The relative newness of the market means there is still uncertainty surrounding the best approaches to process development and manufacturing – and there are many challenges to face.

## Perfecting processes

To start any commercial journey off on the right foot, manufacturers must have a clear understanding of the processes that underpin their products. However, this is hard to do for very new products, such as mRNA-based therapeutics, which have not been commercially used before.

The processes for producing mRNA-based vaccines are very different compared to traditional vaccines. mRNA vaccines rely on an enzymatic reaction, which is, in essence, simpler than cell culture, but still in its infancy; innovations are still required to improve yield, stability, or translation efficiency. In addition, there is no reference or standard in vitro transcription (IVT) protocol available for all mRNA-based products. Therefore, manufacturers must develop and optimize their own IVT, leading to a considerable number of process variations in both upstream and downstream processes. As the field is still evolving, it is important that the toolbox of solutions is adjusted to meet market needs.

Once manufacturers are ready to put their process development plans into motion, Sartorius offers a toolbox of products ready to cover their end-to-end process needs. Our solutions include:

- The high throughput process development platform Ambr® to improve customers' understanding of IVT reactions and gather data
- A new generation of analytical column providing clear insight on IVT reactions by HPLC, to monitor target molecule production and reagent consumption
- A toolbox of monolithic columns for purification of mRNA, addressing most production scenarios with seamless scalability covering everything from product development to commercial needs

## Controlling costs

An accelerated journey to market doesn't begin and end with access to the right equipment; we also help customers to map out their processes; for example, we highlight how process steps can be optimized, where cost-savings can be achieved, and how scalable development techniques can be used to tackle manufacturing woes.

Though all these services are of importance, we believe that cost awareness is a crucial factor in the product development process. The reason? mRNA-based products can be expensive to produce – in part due to the use of high-priced reagents. Around 80 percent of the cost of goods for mRNA-based products is tied up in raw materials, with roughly 60-65 percent of the cost attributed to the IVT reaction. An additional 15- 20 percent of the cost is tied to the formulation step, where mRNA is enclosed in lipid nanoparticles.

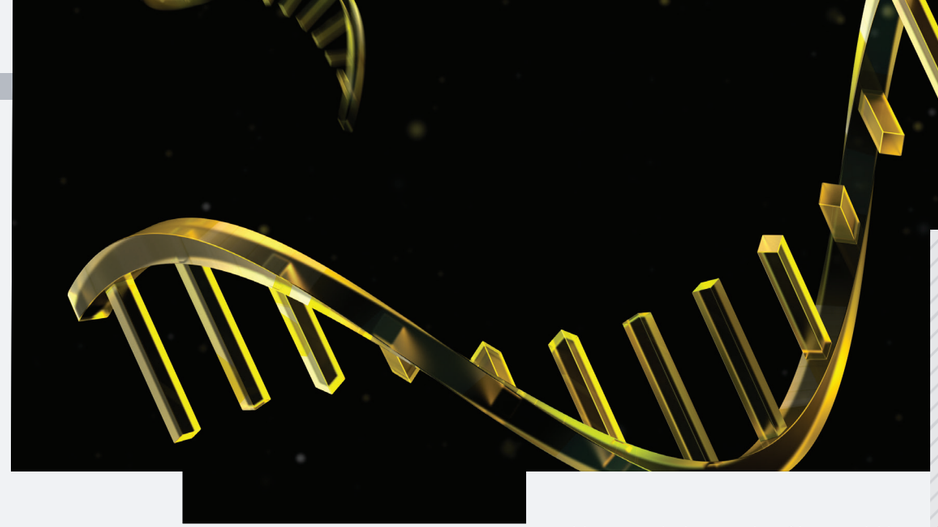
We support manufacturers in the optimization of costs with a small-scale high throughput platform for IVT, combined with our Design of Experiments software, helping developers to find the best protocol that results in the lowest utilization of costly reagents.

Facility design is another key aspect of our services. Our consultants ensure the best process solutions are selected, based on a product's properties and the customer's requirements. We work with developers to pick the right technology and equipment, estimate the yields and material requirements, and create timelines for efficient process scheduling. This approach allows us to work collaboratively with customers to make adjustments to either new or existing facilities to help them make the right decisions for their budget and in accordance with the latest regulation for biopharmaceutical production.

## Managing tactical complexities

To add further complexity, mRNA products are inherently unstable molecules. Although significant progress is being made to maintain the integrity of the product over time (with new mRNA constructs and improved formulations), there are still two challenges that need to be addressed during manufacturing: RNase free processing and storage.

mRNA vaccines are unstable at room temperature and hence require cold



chain infrastructure to prevent spoiling and wastage. This is a significant hurdle for modern manufacturers, but they can draw inspiration from other product types as the field continues to mature. Take viral vectors for example; today, viral vectors can be stored at temperatures between 2-8 °C, but a few short years ago, temperatures as low as -20°C were necessary to maintain them. Over time the stability and storage facilities for mRNA will certainly improve. At Sartorius, we're constantly exploring how this can be achieved. We have 15 years of experience in designing freeze and thaw solutions from lab scale to large commercial scale. Our Celsius® portfolio offers an end-to-end, integrated approach that enables monitoring and controls to assure product quality and integrity at scale. This experience is invaluable when designing frozen storage and transportation solutions for these sensitive mRNA molecules – helping to tackle some of the issues manufacturers face today.

Another solution that is tailored for mRNA-based drugs is our tangential flow filtration technology. By providing an option for gamma sterilized ready-to-use format, we can help mitigate the risk of contamination by RNAse/DNAse – a challenge specific to mRNA production.

## The road ahead

As we look ahead, we're optimistic about the possibilities that mRNA products could hold – and the pandemic has provided us with a practical example of how quickly mRNA products can be manufactured and distributed. Now, drug developers are eagerly looking at indications beyond COVID-19, including how mRNA-based products could influence the future of oncology and personalized medicine.

Industry suppliers and regulators will also have a role to play as the field continues to evolve. We are likely to see updated regulatory guidelines as regulators resume business as normal and analyze learnings from the mRNA COVID-19 vaccines. On the supplier side, there will be a need for innovative equipment specifically suited to mRNA manufacture. At Sartorius, for example, we are working collaboratively with industrial partners to develop the next generation of single-use products and solutions tailored to the needs of mRNA manufacturers.

The world can already see the promise; mRNA vaccines are already out there, protecting countless lives. As our customers continue to innovate, we will remain flexible to help support their success. An adaptable mindset and out-of-the-box thinking will help support the discoveries that will inform the future of the field. And as the field continues to evolve, we will remain reliable partners to the manufacturers aiming to bring life-saving medicines to patients in need.

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## Domain Expertise

The newness of mRNA products means that the talent pool (the technical aptitude and skills required to respond to the challenges) is limited. In fact, most of the industry's expertise with mRNA sits with a few key players, such as BioNTech, Moderna, and Curevac, but many other manufacturers are now receiving investment and entering the mRNA space.

Even before the mRNA vaccines were considered for the COVID-19 pandemic, BIA Separations (a company recently acquired by Sartorius) had been working on this budding technology. With labs dedicated to analyzing and conducting extensive research on the purification of mRNA. Why? Because mRNA was attracting increased attention in the industry and held the potential for developing new therapeutics. In the past few years, Sartorius has invested in infrastructure, technologies, and experience that have helped our customers build their mRNA expertise and processes without compromising their current development pipelines. Put simply, our Cornerstone® process development services enable rapid product development by offering effective tools and expertise so that customers can feel supported as they pursue new therapeutic avenues