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WHITEPAPER

mRNA vaccine development: Key insights for planning, workflow, and supply chain success

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Abstract

The rapid progression of mRNA-based COVID-19 vaccines from the laboratory to clinical reality validated the mRNA platform and stimulated substantial interest in its application for a wide range of indications. The unprecedented scientific innovation and cross-industry collaboration required to bring the vaccine to market signaled a paradigm shift in planning and execution that has the potential to speed the development of safe, high-quality mRNA-based products in the future. The shift entails eliminating nonessential steps, limiting non-GMP batch production, adopting new supply chain strategies, and performing several planning steps concurrently. Although there is some added risk, the benefits include streamlined development, early identification of challenges requiring manufacturing solutions, and the opportunity to address those challenges prior to full-scale manufacturing.

Executive summary

The unprecedented scale and speed of global vaccine research and development in response to the COVID-19 pandemic provides a dramatic case in point for a prediction shared by Steve Jobs more than a decade ago. In an interview with author Walter Isaacson, the Apple cofounder prophesized that the biggest innovations of the twenty-first century would come "at the intersection of biology and technology."

The accelerated development, evaluation, and clinical and commercial production at scale of mRNA vaccines—backed by decades of research into mRNA technology—sits squarely at that intersection. Enabled by continuous advances in basic and applied science, delivery systems, and manufacturing capabilities, safe and effective mRNA-based vaccines targeting SARS-CoV-2 were developed in less than one year, altering the vaccine manufacturing landscape and potentially setting the stage for a therapeutic revolution touching every phase of drug development.

Lessons learned during COVID-19 about the unique operational, technological, and scientific considerations needed to ensure a successful development program are integral to planning future programs and building a reliable, robust supply chain to support them.

The COVID-19 pandemic has served as a test-bed for what is scientifically and technically possible with mRNA vaccine development, but delivering on the promise of mRNA technology for other emerging and established pathogens requires solving for the complex formulation, delivery, and scale-up challenges that are beyond the scope of traditional vaccine production methods. Lessons learned during COVID-19 about the unique operational, technological, and scientific considerations needed to ensure a successful development program are integral to planning future programs and building a reliable, robust supply chain to support them.

In this report, we will review key insights derived from the development of mRNA-based COVID-19 vaccines and how they can be applied to accelerate progress in the manufacture of mRNA vaccines and therapeutics moving forward, focusing on the following:

- The unique attributes of mRNA vaccine development
- The planning paradigm shift to address major process challenges and streamline workflow
- Global supply chain implications and the investments and innovations needed to manage them

The future will tell us whether the successful development and mass production of mRNA vaccines for COVID-19 fundamentally alter vaccine science over the long term, but the potential is certain. Applying lessons from these early clinical success stories to future projects will help reveal the full promise of the technology.

Introduction

Messenger RNA, or mRNA, is a molecule carrying a single-stranded version of a gene, which is read by ribosomes in the cytoplasm of a cell to trigger the synthesis of proteins. By getting human cells to take in mRNA with genes encoding antigens, such as the SARS-CoV-2 characteristic spike protein, an mRNA vaccine can prompt a natural immune response to infectious disease. The mRNA is quickly broken down, leaving no risk of ongoing production of the protein or of viral replication, and the approach ideally creates a robust and lasting immune memory so that future challenges with the actual pathogen result in no illness or in less severe symptoms.

Since the successful development and distribution of mRNA-based COVID-19 vaccines, the concept of mRNA-based therapeutics has grown monumentally in popularity, with 218 assets under preclinical or clinical development in 2021—a growth rate of 182% over pre-pandemic numbers.[1] The vast majority of those are still preclinical, following very recent advances in mRNA manufacturing platforms and process solutions that have made mRNA-based therapies both practical to produce at scale and feasible from a clinical standpoint.

Unique aspects of mRNA development

While mRNA has been under study since its discovery in 1961, progress toward mRNA-based therapeutics and vaccines has been slow due to a wide range of practical and clinical challenges facing the operationalization of mRNA technologies.

Intrinsic mRNA limitations that historically hindered successful clinical development include:[2]

1. Molecule instability and degradability
2. Low uptake rate in vitro
3. Large molecular size
4. Low immunogenicity
5. High toxicity or inflammation potential
6. Cold chain manufacture and storage requirements

Undeterred, researchers and drug delivery experts whittled away at these challenges slowly but surely, primarily in the lab and in animal models. The COVID-19 pandemic prompted a dramatic influx in research dollars and scientific minds applied to mRNA vaccine work, which culminated in clever strategies to stabilize mRNA, increase cell uptake, reduce toxicity, and simplify production. These solutions to prior technological hurdles resulted in two successful COVID-19 vaccines that utilize mRNA-based delivery mechanisms.

Compared to the manufacturing of mRNA in the past, and even compared to some of the leading platforms used for other vaccine technologies, mRNA options now include simple development features. This is due in part to the flexible nature of mRNA-based vaccines, since a change in the encoded antigen does not affect the mRNA backbone's physicochemical characteristics, meaning production can be standardized.

Because generation from plasmid DNA enables laboratory-based mRNA production and refinement using bacteria such as E. Coli, raw materials no longer carry the risk, expense, and supply limitations inherent in vaccine starters derived from animal or human cell lines. In addition, the technology can now be scaled—even globally—fairly rapidly, owing to major advances in supply chain and logistics developed during the pandemic. This is due in part to advances in optimization of the manufacturing process for lipid nanoparticle formulations, which help protect and stabilize the mRNA and shuttle it into cells after injection). High-speed filling lines can boost the pace of production without negatively impacting product quality.

Despite these advantages, the solutions used to address mRNA's key limitations require complex processes and careful management. The molecules require specialty production, purification, formulation, dosing, and packaging approaches. mRNA's intrinsic instability, even when modified with stabilizers, still carries a high risk of degradation when not carefully controlled in both the properties of the solution and its temperature during development and storage. Intracellular delivery also requires mRNA modification and specific lipid nanoparticle encapsulation to ensure that the target organs take in the molecules efficiently and produce the antigen without unacceptable toxicity during mRNA breakdown.

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Promising research in other infectious disease programs are now underway around the world, as well as opportunities in oncology vaccines and, eventually, therapeutics for chronic conditions. Proactive planning and veteran networks will be crucial to address their likely challenges in development, manufacturing, and supply.

In this whitepaper, we discuss lessons learned from Thermo Fisher Scientific's COVID-19 mRNA vaccine experience and the insights and solutions developed to help apply these solutions to a variety of other mRNA products moving forward.

Shifting the planning paradigm

Traditional vaccine development usually starts in one decade and ends in the next,[3] due to a long road of technical feasibility hurdles, vaccine formulation and extensive preclinical safety studies, screening and quality control testing, and safety and efficacy clinical trials—not to mention scale-up and manufacturing work and regulatory approval. With developments in manufacturing capabilities and efficient planning and production processes, however, mRNA-based vaccines offer the chance to develop candidates in a reasonable timeframe: days are the order of magnitude instead of years, and, as the world has seen with COVID-19, viable vaccines can be launched with emergency approval from regulatory bodies around the world in less than a year.

Barriers to rapid production

The physical and chemical limitations of mRNA require a high level of purity and precision for all elements in the product and facility at all stages, as well as a production process with strict quality control and advanced understanding of the risks of degradation and contamination. mRNA vaccine production—or any RNA-based product—is subject to the notorious degradability of the material. mRNA can be destroyed by RNase within seconds, meaning every raw material, solution, and equipment that comes into contact with the product must be free of these enzymes or carefully managed to avoid unintended degradation by organic solvents.

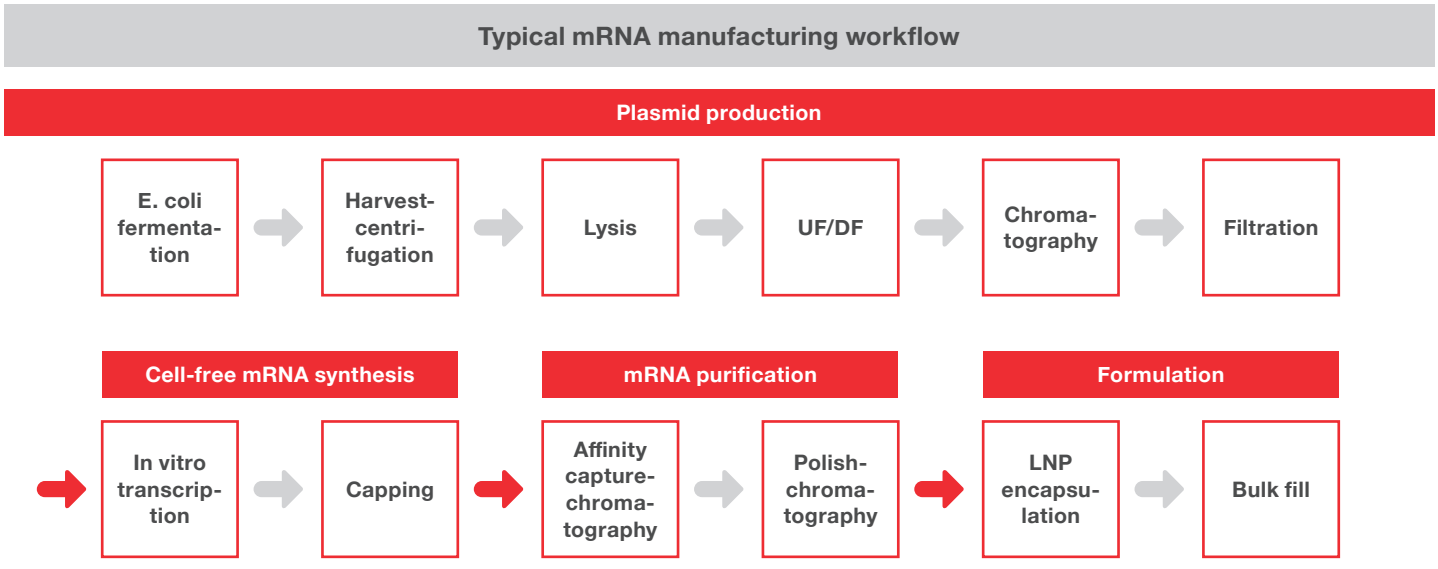
Sterile filtration and stability considerations can also change based on the unique mRNA product and target timeline, and when coupled with purification requirements, can be challenging to manage in large-scale manufacturing scenarios. Depending on the particular product, cold chain requirements may also come into play, which introduce storage and handling challenges beginning during manufacturing and continuing through the entire supply chain. CDMOs that offer support for the entire workflow have an advantage in overcoming some of these challenges due to their experience across the spectrum, from supplying raw materials and reagents to implementing and monitoring temperature controls across each phase of development and distribution.

Finally, capacity planning is essential, as no single laboratory can supply sufficient product for global vaccination efforts like those seen during the COVID-19 pandemic. Rather than a handful of facilities producing thousands of doses per year, manufacturing demand in the hundreds of millions of doses per year has required the use of multiple CDMOs with large and highly skilled networks of production facilities, capable of meeting the quality and production standards required for large-scale manufacture of commercial vaccines.

This prerequisite has favored companies with streamlined end-to-end, integrated services and advanced workstream management techniques. In addition, coordinated organizations with global networks that can produce vaccines at multiple locations hold an advantage for more opportunistic and geographically dispersed shipment bases, overcoming some potential supply chain limitations created by bottlenecks in transportation availability or raw material supplies.

Opportunities for efficiency

The rush for a COVID-19 vaccine resulted in a tight timeline and an avant-garde approach to planning and executing development, workflow, and manufacturing. When following classic formulation development pathways, for instance, developers aim to optimize the final product so that it can be stored in a shelf-stable liquid vial or produced in pre-filled syringes. During the pandemic, however, the race for a vaccine dictated that the most immediate possibility of a viable vaccine should proceed without delay—even if that resulted in the requirement of frozen or low-temperature vials with multiple doses.



Instead of taking time to simplify the delivery formulation to enable a single-dose, shelf-stable, pre-filled syringe, efforts centered on formulation development and early safety and efficacy data, process optimization, scale-up, and phase-appropriate method validation.

Preserving COVID-19-era planning lessons

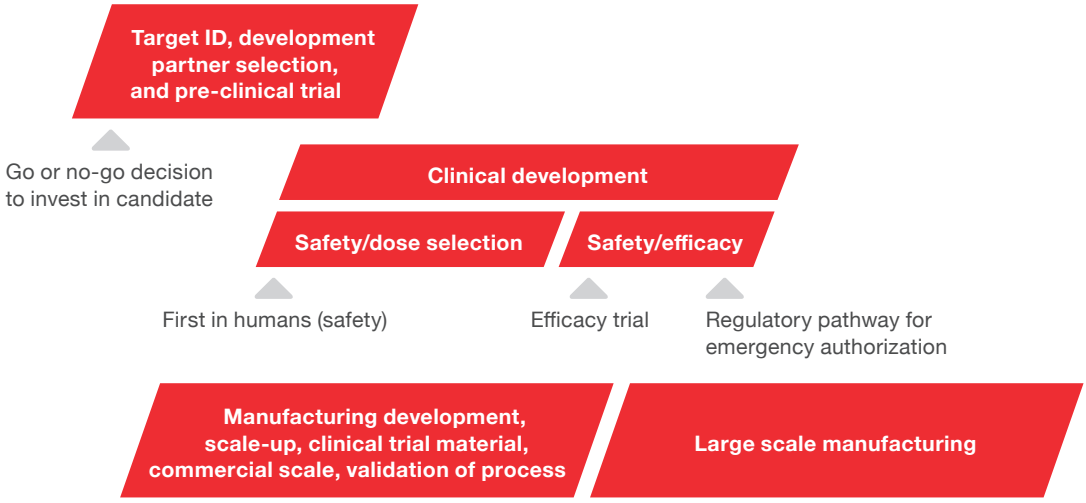
While the reinvention in planning and production steps seen during the COVID-19 pandemic may not be the future standard for all vaccines to come—especially as non-pandemic development endeavors will not enjoy the same degree of international collaboration among researchers, regulators, funders, the public, and health officials—the successful experience with COVID-19 suggests that faster entry into clinical trials and more immediate initiation of manufacturing solutions can speed up the overall timeline without sacrificing the quality of the end product.

This paradigm shift in planning and execution for mRNA vaccine development and production relies on performing previously sequential workstream processes in parallel, and deprioritizing steps when needed (such as formulation optimization) to secure faster market access. Although this approach results in more elements of the process conducted at risk, it streamlines development and results in early identification of challenges that will require manufacturing solutions. By the time full-scale manufacturing is appropriate, many of those process development challenges will have already been addressed.

Managing this whirlwind effectively requires insight and understanding as to which portions of the process should not be shortchanged, such as determination of the appropriate delivery system. This contributes to the efficiency of the vaccine or therapeutic and should be selected carefully. Once plasmid production and the delivery system are optimized, mRNA vaccine production has a major perk, even if the target disease is changed: the encoded antigen can be swapped out during synthesis and the remainder of the production process can remain the same. This opens the opportunity for numerous vaccines to be produced using a single delivery system and manufacturing process. When the workstream is managed by a single CDMO, further efficiencies arise from the existing processes for transitioning across development and production tasks within facilities or across coordinated teams.

This dramatic shift in timeline from initiation to approval has transformed the future of vaccine development, even for drug candidates without the urgency of a global pandemic to speed up regulatory review. Provided the foundation of the vaccine is sound, simultaneous movement in research, clinical studies, and manufacturing can dramatically speed up the overall process with less risk than in other areas of medicine.

Outbreak paradigm: Overlapping phases shorten development time



Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

Reinventing the global supply chain

Even when all of the technical and scientific aspects of vaccine development and manufacturing are decided, actual production and dissemination require that all the raw materials are available and that qualified transportation options have capacity to supply those materials and deliver the end product to clinics around the world. These requirements became painfully clear when COVID-19 impacted all aspects of the supply chain due to lockdowns, route closures, reduced personnel, less frequent commercial air traffic, raw good supply shortages, and lower shipping container availability. Even once mRNA vaccines were developed, the volume of shipments requiring ultra-cold temperature maintenance or dry ice shipping solutions was unprecedented.

To address these supply and transportation disruptions without compromising on quality, speed, custody, and temperature requirements, experts in pharmaceutical product supply chain turned to express carriers, collaboration, and proactive monitoring technology.

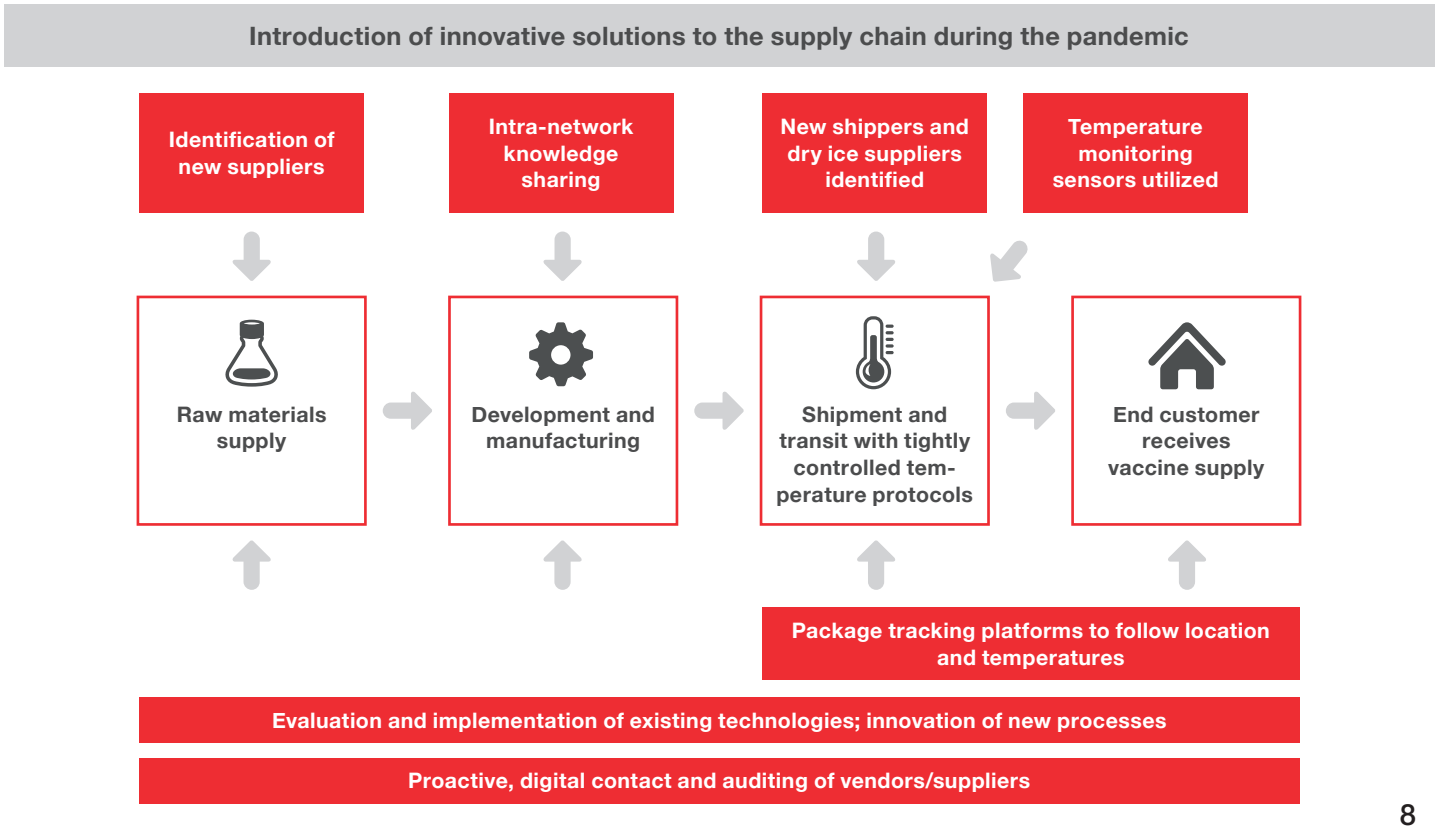
These adaptations allowed for rapid solutions to supply chain issues still plaguing many other industries, and have resulted in valuable adjustments to vaccine development and manufacturing that can be utilized in all vaccines moving forward, even if just to streamline the experience and reduce risk.

Expanding the supplier and carrier network

When key suppliers and transportation options became inaccessible due to unanticipated shortages, lockdowns keeping workers homebound, reduced commerce, and restricted travel, pandemic pharmaceutical work might have ground to a halt. CDMOs learned two key lessons:

1. By expanding transportation solutions to identify new cargo shipment options—such as using express carriers rather than commercial airlines for freight—much of that lack of access to transportation could be eased.

2. By employing virtual audits and digital monitoring technology, even suppliers and carriers without previous familiarity with cold chain requirements and other pharmaceutical-specific procedures could be utilized.



Enhancing partnerships and communication

While some of the new pandemic-prompted partnerships were made possible just by identifying creative alternatives to standard shipping methods, other solutions demanded early, frequent, and transparent communication with suppliers. As new needs arose—such as the tremendous anticipated increase in production of dry ice and ultra-cold shipping containers required once the vaccines were ready for distribution—proactive outreach from vaccine manufacturers allowed the relevant suppliers to adequately adjust production and supplement their quantities. The extra lead time and additional touchpoints ensured everyone along the supply chain had sufficient time to plan around shifting requirements, and frequent communication reduced waste and improved coordination.

Improving temperature and visibility monitoring

In the past, the transportation providers utilized most heavily for drug shipments (such as commercial airlines) often had formal protocols in place for handling large quantities of temperature-controlled goods. When new shipment solutions had to be employed, sometimes on short notice, it became essential to take out some of the opportunity for error inherent in highly controlled shipment processes so that nearly any carrier could adequately transport the vaccines without having to manually track temperature or initiate pharmaceutical-specific protocols required by the manufacturers.

This was done by eliminating reliance on carrier oversight and instead improving packaging and monitoring techniques. Use of digital monitoring for temperature departures, efficient cold chain packaging, and insertion of package-specific tracking devices put shipment visibility and excursion monitoring squarely in the purview of vaccine suppliers.

Post-COVID-19 mRNA vaccine and therapeutic production

The solutions employed to enable a successful distribution of COVID-19 vaccines included those listed in the following figure, most of which were underappreciated prior to the pandemic, and all of which will have a firm place in supply chain management moving forward. Although some apply more specifically to cold chain shipment, large-scale manufacturing, and distribution during supply and transportation disruptions, they each offer unique ways to enable quality assurance and continued supply during uncertain times. In addition, these pandemic-appropriate response techniques and tactics have been tested and will be ready in the event of a similar outbreak scenario in the future, while simultaneously improving the current end-to-end raw materials and product delivery network available for standard development.

Solutions to enable successful distribution of vaccines

Temperature sensors	Advanced monitoring platforms	Digitalization
Small sensors included in every shipment collect and keep a record of temperatures during transit, allowing accurate information about temperature excursions even when using new shipment options.	These programs allow remote monitoring and visual tracking of package location, all from a computer dashboard that can automatically inform users of problems with shipments. The technology can also be paired with temperature sensors. Together, the features enable proactive intervention for potential transit-related problems.	Digital connectivity with the entire network of suppliers, vendors, and collaborators allows for instant notifications, rapid communication, virtual audits, automated orders or updates, and more seamless transactions.

Coupled with proactive outreach and follow-up by logisticians and operations experts, these solutions demonstrated their worth during the pandemic. Their clear value-add under difficult circumstances has made them part of many manufacturing organizations' new best practices for supply chain management.

Conclusion

Moving mRNA vaccines from the lab to the clinic requires unique solutions to complex and often evolving challenges. The mRNA production and vaccine manufacturing world grappled with the pressure to solve these novel challenges under severe time constraints during the COVID-19 pandemic, resulting in rapid and unprecedented innovation in vaccine formulation, development planning, and supply chain logistics. The demand for deep expertise and immediate capacity required the experience of industry leaders with tried-and-true supplier networks and established facilities to be able to coordinate a swift and successful scale-up. Collaboration among pharmaceutical companies and strategic partners who could offer end-to-end support eased the way. The critical support and functionality included mRNA manufacturing capabilities spanning raw material supply for nucleotides and enzymes, plasmid manufacturing, mRNA synthesis, lipid nanoparticle formulation, fill and finish, and even packaging and transportation services.

mRNA vaccine manufacturing has required significant investment, integration, innovation, and collaboration from key industry players, as well as the expertise and commitment of thousands of talented and experienced individuals contributing across all sectors. Companies that can facilitate mRNA vaccine development with full-service solutions offer pharmaceutical partners the assurance of in-house scientific, manufacturing, and logistics expertise, and the reliability of tightly controlled processes, coordinated networks of facilities and high-level quality oversight. In addition, CDMOs that gained their experience during the most trying circumstances of materials shortages and transportation shutdowns have enhanced their ability to lead efficient and effective vaccine development and manufacturing for the next generation of therapeutics coming down the pipeline.

These industry leaders are prepared to apply the lessons learned from the pandemic to help streamline and simplify the experience for a wide range of future mRNA vaccines and therapeutics. As science and clinical research advance the potential of mRNA-based therapeutics, this network of support systems will help turn those development goals into reality.

Additional resources

On-demand webinar: mRNA technologies, trends and supply chain

Solutions overview: mRNA therapeutic services

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About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, cell therapy manufacturing, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic solution is designed to accelerate the journey from DNA to INA/IMPD and may help biopharma companies reach Phase I/First-in-Human trials and file for Investigational New Drug (IND) review in as little as 13 months from transfection. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Vincenza Pironti supports the Global Sales and Business Development teams in providing technical support, designing strategies and supporting new business opportunities for Thermo Fisher's sterile manufacturing business. Vincenza has more than 15 years of experience in the pharmaceutical industry with a consolidated experience on business development, product development, aseptic manufacturing and filling. She has extensive knowledge of all phases of product development from formulation screenings to sterile product commercial manufacturing with expertise in small and biologics in sterile formulation. Previously, Vincenza has worked as Business Development Manager in Pharmatex and CordenPharma managing multiple projects in sterile fields.

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Scott Emery holds the position of Global Commercial Director of Total Transportation Management (TTM) at Thermo Fisher Scientific. Scott joined Thermo Fisher Scientific in 2013 and was responsible for their global transportation network including the management of offices located in the United States, United Kingdom, Switzerland & Singapore, prior to moving into his current role. Scott has 21 years of experience in global transportation and logistics. Previous to Thermo Fisher Scientific, Scott held leadership roles in global development, sales and operations at DHL Express & National Air Cargo.

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