mRNA: THE STATE OF PLAY IN **ONCOLOGY AND INFECTIOUS DISEASE**

Report 2024

DATWYLER

INTRODUCTION

Advances in genomics are shaping the next generation of vaccines and therapeutics. Within this field, mRNA has enormous untapped potential stretching far beyond COVID-19.

A new era of drug development is emerging, one where genetic material such as DNA and RNA can be delivered into the body to deliver transformative – even curative – therapeutic effects. While such therapies have been dreamed of for decades, they only became possible after the Human Genome Project was completed in 2003. Spanning 13 years and with contributions from thousands of researchers, the $2.7bn project paved the way for rapid advancements in genomic medicine.

To demonstrate just how far we've come, it is now possible to sequence a whole human genome on a desktop machine in just over 24 hours, at an approximate cost of $600. Such advancements are transforming the way we define diseases and develop and prescribe treatments for them, enabling a more targeted approach with fewer side effects.

In GlobalData's annual survey of biopharmaceutical industry professionals, genomics, immuno-oncology, personalised/precision medicine, and cell and gene therapies (CGT) were identified as the four trends likely to have the largest impact on the sector in 2024.[1] Such fields are closely related, not only in science but also their potential to completely reshape disease treatment paradigms:

"Genomics will continue to play a significant role in understanding, preventing, and treating diseases. The genomics market will benefit from the growth of the personalized medicine market. Genomics will also support precision medicine, making these trends more entangled over time." - GlobalData, The State of the Biopharmaceutical Industry 2024

Amid all this progress, messenger RNA (mRNA) – a long-studied genomic medicine modality with links to immuno-oncology, precision medicine, and CGTs – has found its moment to shine. Messenger RNA (mRNA), a genetic molecule that instructs cells to make therapeutic proteins, is one of the most exciting emerging technologies in biopharma right now.

While the COVID-19 vaccines were the first and currently only mRNA drugs to gain approval, mRNA's history extends far before the pandemic. More importantly, many believe it has a place in the future of medicine for generations to come. But where did it all start, and what's next for mRNA?

This report covers the rise of mRNA and explores the modality's potential in a broad range of applications within the infectious disease and oncology fields. Leveraging GlobalData's proprietary data and insights, the report will analyse the current state of play in both infectious disease and oncology pipelines and discuss the opportunities and challenges in both. While exploring challenges, the report will focus on primary packaging considerations, which play a critical role in getting these innovative new drugs to patients safely and effectively.

[1] GlobalData. The State of the Biopharmaceutical Industry 2024

THE STORY OF mRNA: **PAST, PRESENT, FUTURE**

Most people became aware of mRNA in 2020, but the concept is far from new. In this section, we chronicle major breakthroughs across mRNA's history and attempt to pinpoint the modality's next big success.

The rise of mRNA

While mRNA molecules were first discovered in the early 1960s, R&D took off in the 1990s when a group of scientists published a landmark paper showcasing the molecule's feasibility as a tool for in vivo therapeutic protein expression.[2] The big challenge was figuring out the best delivery system for transporting highly unstable mRNA molecules to cells. Around this time, lipid nanoparticles were emerging as promising new drug delivery vehicles. The two fields intersected in 1993 with the first mRNA-LNP delivery system encoding an influenza virus protein.[3]

The next significant hurdle was figuring out a way to avoid the immune-stimulatory effects of the mRNA components.[4] To this end, a huge leap forward was made in 2005 when two scientists at the University of Pennsylvania – now Nobel Prize winners – discovered a way to modify mRNA to make it an effective therapeutic without activating the immune response. This brought the community much closer to a clinically viable mRNA platform, laying the groundwork for numerous mRNA-based candidates to be tested in humans over the next 15 years, the first of which was an immunotherapy intervention for metastatic melanoma.

While no drug candidates advanced very far through the clinical pipeline, by the time the coronavirus pandemic struck all the essential elements for an mRNA vaccine were in place. The technology developed in 2005 was identified by Pfizer/BioNTech and Moderna as the best way to develop a vaccine rapidly. Leveraging it meant that two mRNA-LNP drugs could be developed within only three months of first sequencing the SARS-Cov-2 genome.[5]

Pfizer/BioNTech's Comirnaty was granted emergency use authorisation (EUA) by the Food and Drug Administration on 11 December 2020. Moderna was right behind, receiving EUA for Spikevax just one week later. Both have had huge clinical and commercial success, with Pfizer distributing more than 3.7 billion doses of Comirnaty to 180 countries and territories through 2022 alone.[6]

In December 2023, GlobalData reported declining sales revenues in the COVID-19 vaccine market. Comirnaty, which had global revenues of $42.4bn in 2022, generated just $13.9 billion in 2023 – a decrease of 67%.[7] Over the next five years, the decrease in sales is forecasted exponentially, falling to approximately $7.3bn by 2029.

What's more, there have been no new approvals for mRNA vaccines or therapeutics to follow. mRNA certainly had its moment during COVID, but as the pandemic winds down, is this the last we will hear of this novel modality?

[2] Wolff, J. et al. Science 247, 1465–1468 (1990).
[3] Martinon, F. et al. Eur. J. Immunol. 23, 1719–1722 (1993).
[4] https://www.nature.com/articles/s41565-023-01347-w
[5] https://www.nature.com/articles/s41565-023-01347-w#ref-CR11
[6] https://www.nature.com/articles/s41587-022-01643-1
[7] GlobalData. mRNA Vaccines in Infectious Diseases Market Overview. December 2023. Report code: GDHCHT448

Predicting the next success story

That would be unlikely. Excitement is still going strong for mRNA, with the success of Comirnaty and Spikevax reinvigorating mRNA development for a variety of infectious diseases. According to GlobalData, "mRNA vaccines have an opportunity to be widely used for treatment of different infectious disease indications outside of COVID-19", including influenza, respiratory syncytial virus (RSV), and cytomegalovirus (CMV). Late-stage trials for mRNA-based influenza vaccines have already demonstrated positive efficacy and safety profiles, suggesting this could be the next field to benefit.

mRNA vaccines are such an exciting possibility because they work very differently from traditional vaccine strategies that rely on weakened viruses or pieces of viruses. Instead, mRNA molecules contain the instructions to direct our cells to produce specific therapeutic proteins for fighting infections. This approach uses a non-infectious and non-integrative platform, making it a potentially safer option. It is also made through a cell-independent process. This offers additional safety advantages by reducing the risk of contamination and could also translate to faster large-scale production than viral vectored vaccines, for example.

As Pfizer/BioNTech and Moderna recognised in 2020, one of the biggest advantages mRNA has over other modalities is its potential to enable rapid vaccine development. This is because mRNA platforms are sequence-independent, meaning they can be adapted to different pathogens within hours. Lower development timelines mean lower costs, which will only continue to reduce as the technology matures.

For all these reasons, mRNA could revolutionise vaccine developments, making it a key tool for fighting future epidemics and pandemics. But scientists are not stopping at infectious disease. According to GlobalData, "RNA-based therapeutics can be useful in personalized/precision medicine for their abilities to restore or inhibit gene expression without the risk of genomic integration."

THE mRNA LANDSCAPE: **WHERE IS INNOVATION FOCUSED?**

Infectious disease and oncology therapeutics dominate the mRNA landscape. In this section, we dive into each area to understand what, where and when the next approval for an mRNA-based drug may be.

According to GlobalData, as of 12 March 2024, there are currently 1,035 mRNA drugs in the pipeline (Figure 1), though almost one-fifth of these are either inactive or discontinued. Of the active candidates, the majority are in early-stage development. There is a total of 220 in clinical trials, representing 27% of the active pipeline.

Segmented by therapy area (Figure 2), there are two clear frontrunners, and it is no surprise which one currently takes the lead – 45% of the drugs are for infectious disease indications, followed by 27% in oncology.

The COVID-19 pandemic did wonders for the infectious disease mRNA market. GlobalData analytics shows that in 2019 there were 2.5 times the number of mRNA trials initiated in oncology than there were for infectious disease. Between 2019 and 2021, the increase in new oncology trials was four-fold, jumping from 15 new trials in 2019 to 61 in 2021. In infectious diseases, the jump was 59-fold, showing the huge impact the COVID-19 pandemic had on that space.

But it is possible that oncology could overtake infectious disease one day. By continuing to look at clinical trials by start year, new infectious disease trials contracted in 2023, with the final-year total of 117 trials marking a 42% decrease from the previous year. Meanwhile, in oncology, 29 trials were initiated in 2023 – a 53% increase from 2022.

Moreover, 11 oncology trials have already been initiated or are planned to begin in 2024 as of mid-March. This is exactly half the amount of initiated or planned infectious disease trials in 2024, which is currently at 22. While oncology is still a smaller market than infectious disease, with less therapies in the pipeline and nothing yet on the market, R&D activity is gaining pace.

FIGURE 1: THE mRNA PIPELINE BY DEVELOPMENT STAGE

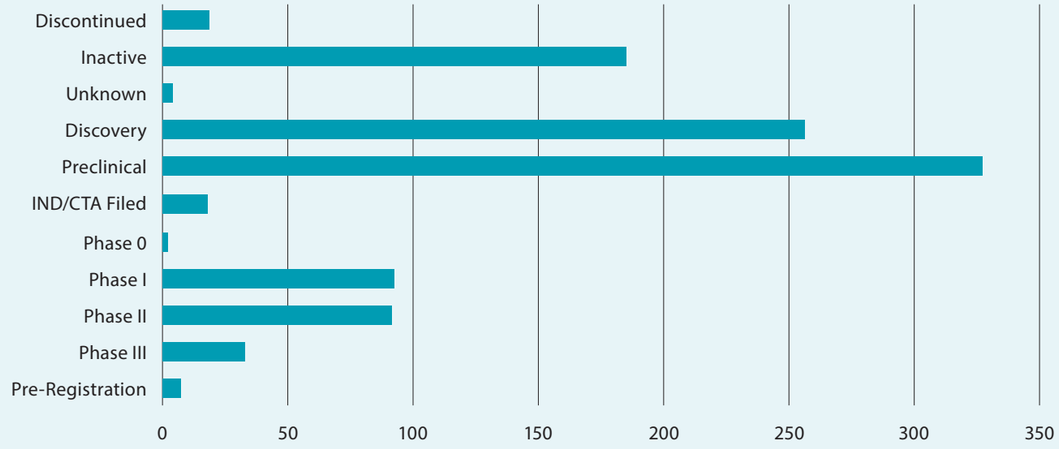
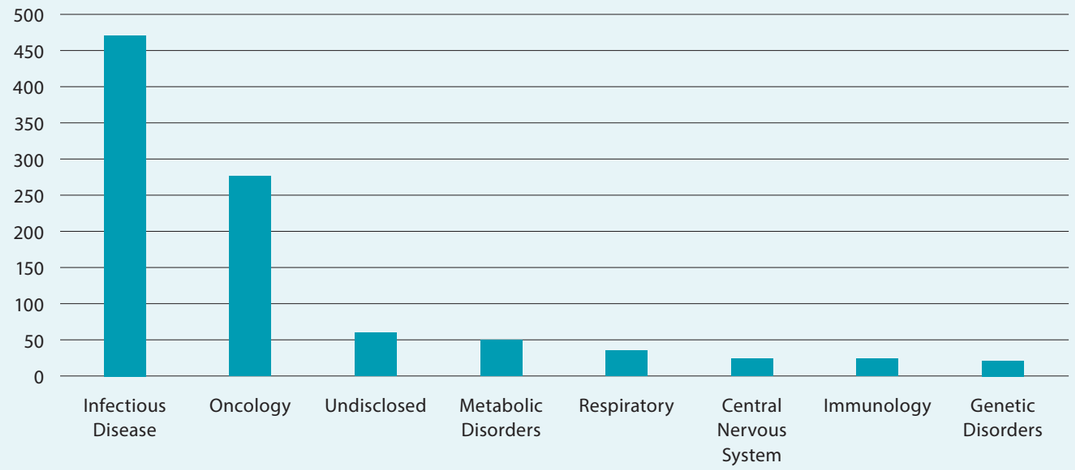


FIGURE 2: THE mRNA PIPELINE BY TOP 8 THERAPY AREAS



Focus on infectious disease

In the infectious disease space, the majority of mRNA candidates are in the preclinical stage, followed by discovery. In trials, there is not much difference in the numbers for Phases I and II, then roughly half the amount in Phase III. Meanwhile, 7 drugs are in the pre-registration stage.

Breaking down the active infectious disease candidates by indication, it is no shock which disease accounts for the highest number. The top 10 specified indications are presented in Table 1, with COVID-19 on top due to the rush of activity in that space during the pandemic.

Moderna currently has an RSV mRNA vaccine in pre-registration (mRNA-1345). However key opinion leaders (KOLs) interviewed by GlobalData in its ***mRNA Vaccines Infectious Disease Market Overview*** report predicted very limited commercial success for the vaccine. This is because two traditional (protein subunit) vaccines with high efficacy were approved in 2023, beating Moderna for first-to-market in that indication. Since mRNA-1345 will have a higher price tag, one KOL said its only chance of success in that market would be to become part of a seasonal combination vaccine, perhaps combining the RSV agent with COVID-19 and influenza ones.

This raises an interesting point, since most of the mRNA candidates target single indications. Moderna is the only company with a combination vaccine in Phase III trials (mRNA-1083, targeting influenza and COVID-19). Meanwhile, in Phase II, there is still a lack of combination products from major industry players.

While not listed in Table 1, the future for mRNA looks more hopeful in CMV, where there is currently a huge unmet need for a reliable and effective treatment. According to GlobalData, Moderna commenced a Phase III clinical trial for its CMV candidate mRNA-1647 in 2021, though no study data is currently available.

Another key theme in GlobalData's report is Moderna's dominance in the late-stage mRNA vaccine landscape for infectious disease. Moreover, the company is the only player investigating this modality in a very wide range of indications, including non-viral infections such as Lyme Disease.

TABLE 1: mRNA INFECTIOUS DISEASE PIPELINE - TOP 10 SPECIFIED INDICATIONS

Indication	No. of active drug candidates
Coronavirus Disease 2019 (COVID-19)	156
Unspecified Influenza Virus Infections	30
Respiratory Syncytial Virus (RSV) Infections	23
Seasonal Influenza	15
Human Immunodeficiency Virus (HIV) Infections (AIDS)	11
Herpes Zoster (Shingles)	11
Influenza B Infections	11
Influenza A Virus, H1N1 Subtype Infections	10
Malaria	9
Rabies	8

TABLE 2: mRNA ONCOLOGY - TOP 10 SPECIFIED INDICATIONS

Indication	No. of active drug candidates
Melanoma	19
Non-Small Cell Lung Cancer	14
Pancreatic Cancer	12
Pancreatic Ductal Adenocarcinoma	11
Colorectal Cancer	10
Ovarian Cancer	9
Glioblastoma Multiforme (GBM)	9
Cervical Cancer	8
Gastric Cancer	8
Head and Neck Squamous Cell Carcinoma (HNSC)	8

Focus on oncology

Like the infectious disease landscape, the vast majority of mRNA candidates for oncology are in early-stage development (discovery and preclinical). Those in clinical trials are mostly split between Phases I and II, to which there is little difference in the numbers. There is currently just one candidate in Phase III – that being Moderna's mRNA-4157, which is under development for the treatment of a range of solid tumours including melanoma, metastatic melanoma, non-small cell lung cancer, and squamous non-small cell lung cancer. GlobalData has designated mRNA-4157 a 24% likelihood of approval score in squamous non-small cell lung cancer.

Breaking the active pipeline drugs down into indication is challenging, as many of the drugs are under development for multiple specific cancers. 'Solid tumours' and 'unspecified cancer' are both highest on the list. Of those that reference specific indications, the ten most targeted cancer types are listed in Table 2.

German-based BioNTech currently has the highest number of both completed and ongoing trials under its belt for mRNA-based oncology therapeutics. The runner-up is another German company, CureVac, followed closely by Moderna.

THE NEXT STAGE: **OVERCOMING mRNA CHALLENGES AND WELCOMING A NEW WAVE OF THERAPIES**

High costs, public uncertainty, and stability challenges could threaten the success of mRNA. Ultra-low temperature storage supported by sub-zero-compatible primary packaging components can help address drug delivery concerns, but recipe optimisations must be made to improve the stability of the next wave of mRNA products.

While mRNA comes with many exciting opportunities and advantages, there are still numerous challenges to overcome. In crowded marketplaces where traditional-modality drugs are already succeeding, mRNA will face stiff competition, with drug sales hindered by the modality's current limitations. Some mRNA vaccines only offer short-term protection against infectious diseases due to the high mutability of the target virus, for example. Production is still costly, meaning higher price tags than traditional vaccines, though there is strong potential to reduce manufacturing costs as the technology matures. There is also general scepticism from specific population groups surrounding mRNA. This is due to the short development period and rapid approval of the COVID-19 vaccines.

Moreover, mRNA molecules are extremely fragile. There is a need to continue optimising LNP-based drug delivery vehicles to ensure vaccines and treatments remain stable over a range of temperatures. Storage conditions for Pfizer/BioNTech's COVID-19 vaccine was less than ideal. While most vaccines can remain stable at refrigeration, Comirnaty required ultra-cold storage conditions of -80°C. Arranging deliveries to all corners of the world demanded speciality distribution services with dry ice, which was difficult to manage in many regions.

When it came to making packaging decisions for the COVID-19 mRNA vaccines, multi-dose vials were chosen by Pfizer to ensure a fast time-to-market. Moderna opted for vials while also making the vaccine available in pre-filled syringe format. The vast majority of mRNA infectious disease vaccines currently in development are intended for intramuscular injection. Indeed, out of the 223 pipeline drugs where route of administration data is currently available in GlobalData's Drugs database, 190 (85%) of the candidates are intended for intramuscular injection. In the oncology arena, most mRNA developers have selected the intravenous route of administration. Out of the 135 drug candidates with available route of administration data, 54 (40%) were intravenous. This was followed by 22 (16%) that were intratumor.

TESTING THE IMPACT OF ULTRA-COLD STORAGE ON ELASTOMER SEALS

Extreme cold chain conditions and the freeze-thaw cycle can have impacts on the mechanical performance and container closure integrity of primary packaging. mRNA's ultra-cold storage requirements prompted primary packaging companies to evaluate whether their components were fit for purpose in this scenario. Leading elastomer component provider Datwyler set to studying the thermal expansion coefficient of its three different plunger materials to assess their performance at sub-zero temperatures. It was found that even after storage at -50°C for one week, all three plungers maintained their integrity, with very minimal impacts on gliding force.

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Material matters

With injectable packaging a common choice in this growing space, the pressure is on for parenteral packaging providers to ensure their components function as intended in the ultra-low temperature conditions required by mRNA developers. Material choice can have a huge impact on container closure integrity (CCI) during deep frozen storage. Glass is recommended for vials, while in a prefilled syringe it is better to use plastic barrels to achieve CCI.

Rubber/elastomer components are well-suited for ultra-low temperatures in both vials and syringes, but coating decisions are important. Uncoated elastomer components have become the preferred choice for both vials and prefilled syringes, with Datwyler's clean uncoated rubber formulations proving their compatibility with mRNA vaccines through limited chemical interactions at ultra-low temperatures. Indeed, in June 2021, Datwyler was recognised by BioNTech as a "pivotal partner" in supporting the company to provide a vaccine for COVID-19.

"It is an honour to be recognised for our role in supporting the leading pharmaceutical companies of the world in their fight to combat this global pandemic."

– Dirk Lambrecht, Datwyler CEO

Recognising the growing need for coated stoppers that are suitable for ultra-low storage conditions, Datwyler launched its UltraShield™ fluoropolymer film coating in April 2023. Film coating with UltraShield can offer additional advantages to mRNA manufacturers, since it minimises silicone levels and is applied within Datwyler's highly controlled FirstLine™ facilities, benefiting from a range of additional quality measures such as extreme particulate reduction and 100% camera inspection. The launch of UltraShield made Datwyler the only company capable of offering both film and spray-based fluoropolymer coating options for vial stoppers. This extended range is designed to meet the highest demands of quality and performance for large and sensitive molecule drugs.

There are two specific situations where film coatings demonstrate an advantage over spray coatings, says Geert Moens, Datwyler's Global Platform Leader Vial Closure Systems: "One is the fact that the untreated sealing area provides a very robust seal," Moens explains. "At ambient temperatures or even frozen temperatures this will not generate any difference versus a spray coating, but once beyond the glass transition temperature of rubber - around -60°C, when the rubber loses its elasticity - it may make a difference.

"Therefore, in deep frozen storage conditions like -80°C we would typically recommend the film coating over the spray coating," he continues. "The other parameter that supports a preference for film coating is in extreme cases with aggressive solvents. Here, the thicker film barrier, roughly double the thickness of the spray barrier, generates more robust protection against highly concentrated solvents."

Conclusion

Since the possibilities of mRNA are only just becoming clear, there is still a significant journey ahead, with challenges to overcome along the way. The need for more temperature-stable vaccines is perhaps at the top of that list. Nevertheless, the potential of this new modality cannot be denied. mRNA saved millions of lives during the COVID-19 pandemic. With its exciting prospects in oncology and its newfound place in future pandemic response toolboxes, it could save many millions more.

As a key primary packaging partner for the pharmaceutical and biotechnology industries, Datwyler is following advancements in the mRNA market very closely. With a wide portfolio of high-end parenteral drug packaging solutions made from advanced pharmaceutical rubber compounds produced in best-in-class manufacturing facilities, the company has everything needed to support the next wave of mRNA drugs – whenever they arrive.

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