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How CDMOs are Adapting to New mRNA Tech Demands

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From 2020, coinciding with the outbreak of COVID-19, there's been a steady upsurge in demand for new technologies such as messenger RNA (mRNA). Contract development and manufacturing organisations (CDMOs) are compelled to rapidly expand capabilities to cater to this upsurge. Let's see how CDMOs have prepared for the new wave of technologies on the horizon, and the challenges they faced in welcoming a new era of such technologies.

The COVID-19 pandemic highlighted the successful development and utilisation of mRNA vaccines. This has encouraged biopharmaceutical companies to explore and utilise these technologies for other diseases. There are a significant number of new therapeutic programmes that are based on mRNA and lipids, which is encouraging CDMOs to invest in new expertise to deliver end-to-end solutions.

CDMOs have been building new capacity, while simultaneously building out capabilities, to better prepare for the new wave of technologies. Many CDMOs have invested in new processes and resources to safeguard product integrity, minimise waste, enable safe and efficacious supply to patients without delay.

"In the area of mRNA technology, we have seen CDMOs do almost exclusive internal builds, while others are making strategic acquisitions to develop their mRNA capabilities. Many CDMOs, like the Center for Breakthrough Medicines, are expanding to include this dedicated and segregated capacity. It is extraordinarily complex and a different process from other processes CDMOs are currently running, so you must make sure to segregate these operations as much as possible from your existing manufacturing," said **Joerg Ahlgrimm, President and CEO, Center for Breakthrough Medicines, US.**

With mRNA-based drugs witnessing a surge in popularity in such a short time frame, companies supporting their development and manufacturing had to adapt quickly as mRNA- based vaccines required cold chain capabilities and more robust aseptic fill-finish technologies.

Weathering the storm

Even though COVID-19 fuelled the growth for the CDMO market, it also brought its fair share of challenges. Managing supply chains was perhaps the biggest challenge as the pandemic had a sudden and extreme impact on the supplier / distributor network.

“This challenge demanded the fast, yet precise, expansion of clinical supply chains, which would need to be informed by data and expertise and underpinned by a global infrastructure and network,” said **Kevin Cheong, Director, Clinical Operations-Asia, Almac Clinical Services, UK**. Kevin is based in Singapore.

As mRNA-based technology is a newer modality in the industry, few CDMOs have the extensive experience and a historical track record to point to. However, CDMOs with teams of scientists that have the expertise in the area could mediate the challenges and address the growing mRNA market much more quickly.

“mRNA-based technology challenges are not necessarily unique. All cell and gene manufacturing technologies have faced obstacles that needed to be overcome. That said, for mRNA I see these two challenges. The first is building or acquiring the capacity to scale up manufacturing, as well as being able to source high quality mRNA synthesis. The other is mastering and being able to replicate the technology process, which is a key element to being a successful CDMO,” said Joerg.

During the pandemic, production capacity and yields had to be dramatically increased, which came with obvious challenges. “Capacity is another hurdle for DNA and plasmid production, a process that uses fermentation alongside E. coli. Suite dedication is a key issue as carrying out a fermentation process in a suite that also runs a mammalian cell culture would lead to a risk of cross-contamination. As a result, alternative manufacturing platforms such as synthetic plasmid DNA (doggy bone) may grow in prominence,” said **Lawrence Yap, Global Head, Technical Operations, Hilleman Laboratories, Singapore**.

The unique nature of mRNA also creates analytical challenges in drug development. It is important to remember that mRNA technology itself is advancing rapidly and evolving on a continual basis. Developers of analytical methods for mRNA therapeutics and vaccines are therefore challenged not only by the complexity of these biomolecules and their delivery vehicles, but also by the need to develop flexible methods that can accommodate the ongoing changes in mRNA structures and final formulations.

“There is also the analytical challenge to identify appropriate tests that can monitor the quality of each intermediate. This requires highly specialised assays and analytical testing to properly characterise the molecule, and select the most appropriate formulation, which may include lipid nanoparticle manufacturing,” added Lawrence.

Shortage of skilled workforce is another bottleneck. CDMOs need highly technically skilled talents to develop, produce, and test each mRNA-based entity. “It has been challenging to find talents who can support the rapid build-out in manufacturing, analytics, manufacturing science and technology (MST), tech transfer and chemistry, and manufacturing and controls (CMC). We are seeing a growing demand for talents who have skill sets and deep knowledge in microbial fermentation and also the biocatalytic enzymatic synthesis process,” said Lawrence.

Lessons learnt

The pandemic and the resulting fast approval of vaccines has highlighted the ability of the industry to move much more quickly through the drug development process than was ever thought possible. It also shows the importance and power of strategic collaborations.

“One of the most important lessons we learnt about preparing for the future stems from our experience with COVID-19 vaccines. It is clear that both innovator companies and CDMOs, with the right amount of public support, can develop a product and bring it to market extremely quickly. That said, all the stars were aligned. Every government and health agency wanted a rapid-fire solution - a product that worked and worked safely, so the normal barriers to fast track a product to market were eliminated,” said Joerg.

Another important lesson is to have robust supply chain management processes in place. “One of the lessons learnt is in supply chain management to avoid disruptions. Manufacturers should ensure that there is always a reliable supply of raw materials and consumables. At the same time, we need to identify potential sources of equipment and consumables as alternative options in the event of delays from their primary source,” said Lawrence.

Contract manufacturers are now evolving into the space of Contract Research and Manufacturing Services (CRAMS), becoming valued partners to pharma players in every sense of the word. “The model involves working with Contract Research Organisations (CROs) to generate data supporting the pathway to enter into the clinic, followed by partnering with an innovator to provide the resources for subsequent drug development. The small biotech-innovator relationship will ideally turn into a tripartite agreement where the execution component continues to come from an integrated service provider (CRO-CDMO) with end-to-end capabilities,” said **Dr Mahesh Bhalgat, COO, Syngene International, India**.

Much of what CDMO could achieve during this crisis is also because of technology and digitisation of the development and manufacturing process, and moving forward technology will play an even more important role in the functioning of the CDMOs.

The challenges faced by the sector throughout the pandemic highlighted how important it is to be nimble and flexible to ensure consistent and cost-effective delivery. CDMOs that demonstrated agility and ability to respond to the shift in market dynamics, as well as adapt their manufacturing capabilities for new technologies, are best suited for the future.

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