ReciBio Pharm

Transforming xRNA Manufacturing with Digital Technologies and Continuous Processing

Many companies that have entered the RNA field since the COVID-19 pandemic are finding that development and manufacturing of diverse RNA formats cannot be simply realized. There is no one-size-fits-all manufacturing process for different RNA formats for vaccine and therapeutic applications. ReciBioPharm's unique, flexible, and digitally powered, continuous production platform for xRNA will transform biomanufacturing, substantially reducing the time and cost for process development and manufacturing and afford higher-quality products. With cloud-based central command and automated continuous operation, this platform can be implemented anywhere in the world, enabling equal access to advanced therapies and vaccines for all patients.

Aaron B. Cowley
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Advancing RNA Technologies: From Rapid Vaccines to Complex Therapies

The rapid development and approval by the U.S. Food and Drug Administration (FDA) of two messenger RNA (mRNA) vaccines to combat COVID-19 underscored the potential of RNA as a powerful modality for both therapeutics and vaccines. This highly accelerated timeline was made possible by decades of prior mRNA research, substantial government funding, and an unprecedented collaborative effort among various organizations — a synergy unlikely outside the pressures of a global pandemic.

In the intervening years, interest has broadened from traditional mRNA to novel RNA forms with enhanced properties for therapeutic use, such as circular RNA (circRNA) and self-amplifying mRNA (samRNA). While lipid nanoparticles (LNPs) were adequate for initial vaccine formulations, they exhibit limitations, particularly with regard to tissue targeting, prompting significant advancements to improve the delivery mechanisms for various RNA types, not just in vaccines but also in oncology, enzyme replacement, gene therapy, and other fields.

Post-pandemic entrants into the RNA space face unique challenges, unlike established players like Moderna and Pfizer/BioNTech who can leverage their existing validated manufacturing processes. The endeavors of these new entrants reveal that RNA development and manufacturing, especially of diverse RNA formats, is more complex than initially perceived. The investor community's misconception that RNA production is straightforward has been debunked by the real-world intricacies encountered, including the need for customized manufacturing processes for different RNA types such as circRNA, samRNA, and guide RNA. Moreover, therapeutic RNA products, which are administered in significantly higher doses than vaccines — sometimes a thousand-fold greater and frequently over short intervals — require much stricter purification standards due to the lower tolerance for impurities.

Heavy Reliance on Outsourcing for RNA Production

In the embryonic stages of the RNA sector, the complexities of RNA technologies compel most drug developers to rely heavily on contract development and manufacturing organizations (CDMOs) for developmental and production support. At present, few companies possess the in-house capabilities necessary for autonomous RNA product development. Nonetheless, there is a keen interest among these companies to collaborate with CDMOs.

Given the emerging clinical pipeline and the substantial potential for market expansion, it's hardly surprising that CDMOs are drawn to RNA therapeutics. For pharmaceutical and biotech firms, the challenge lies in choosing a CDMO that not only grasps the unique challenges associated with RNA technologies but also possesses the expertise and innovative solutions to navigate these complexities effectively. Partnering with the right CDMO can dramatically enhance a company's project outcomes in terms of speed, product quality, and cost-efficiency.

ReciBioPharm's Pioneering RNA Manufacturing Vision

Leveraging differentiating expertise and resources, ReciBioPharm has established itself as such an enabling partner in the RNA manufacturing landscape. Formed through the strategic merger of advanced therapy specialists Arranta Bio, Vibalogics, and GenIbet Biopharmaceuticals, ReciBioPharm combines capabilities in microbiome-based treatments, nucleic acids, and viral vector development to provide a seamless and comprehensive service offering. This consolidation has enabled the company to guide early-stage customers from scale-up to the industrialization of advanced therapies, all while maintaining rigorous GMP compliance.

With deep experience spanning plasmid creation, LNP production, formulation, and fill/finish across multiple RNA constructs, ReciBioPharm's operations in the United States and Europe ensure efficient tech transfers and consistent, high-quality output. Seamless collaboration between our facilities in Watertown, Massachusetts, and Oeiras, Portugal, further enables mirrored services across two continents, ensuring that challenges in xRNA manufacturing are effectively managed.

At the forefront of manufacturing innovation, we are developing a continuous manufacturing solution that integrates machine learning (ML) and advanced in-line process analytical technologies (PAT). This state-of-the-art platform, crafted in collaboration with the Massachusetts Institute of Technology and supported by an $82 million FDA grant, is set to revolutionize xRNA production by enhancing product purity while significantly reducing both time and costs associated with development.

Our approach leverages cutting-edge digital technologies to fuse process development with manufacturing, thereby slashing the time required for both process and analytical development. Extensive real-time monitoring through PAT tools further accelerates the manufacturing phase, culminating in a dramatic reduction in the time from target sequence identification to clinical trial material readiness.

A pivotal element of our platform is the Knowledge Hub, a centralized control center that archives comprehensive historical data on xRNA molecules and manufacturing processes. This hub continuously receives data from PAT tools and high-throughput screening, facilitating real-time process adjustments and improvements. Machine learning algorithms analyze these data to simulate manufacturing processes and create digital twins, vastly reducing the need for physical experimentation. These simulations ensure that only essential design-of-experiment studies are conducted to confirm predictions before full-scale manufacturing begins. The ML algorithms are also leveraged for predictive process control. As each project is pursued and completed, the generated data provide feedback to the system, leading to continuous improvement. Real-time product release should also be possible once platform performance is clearly demonstrated.

Projected to shorten typical xRNA development timelines from 9–12 months to merely three to four months — and eventually to mere weeks — our infrastructure is poised to transform the landscape of RNA therapy development. We anticipate services being available in early 2025 for xRNA candidates. As we look to the future, our goal is to expand this innovative digital architecture to encompass other advanced therapies, including antibody–drug conjugates, viral vectors, and cell therapies.

From the initial steps of plasmid DNA linearization and *in vitro* transcription through chromatographic purification, tangential-flow filtration, and production of the RNA–LNP drug substance to the final stages of sterile filtration and fill/finish, every process is meticulously designed to ensure the highest standards of quality and efficiency. The platforms, CP1 and CP2, will respectively handle non-GMP lab-scale (~0.5 grams of mRNA per day) and cGMP manufacturing (up to 40 grams of mRNA per day), readying ReciBioPharm to meet the urgent demands of tomorrow's medicine.

Crafting a Tailor-Made Manufacturing Platform

ReciBioPharm's new manufacturing platform has been built from the ground up, meticulously designed with custom-built equipment, hardware, and software to provide comprehensive visibility and seamless data integration into the Knowledge Hub. Unlike traditional setups, where PAT tools are embedded within individual pieces of equipment, ReciBioPharm has centralized all PAT tools onto a single skid. This allows the tools to be used flexibly across multiple unit operations for various xRNA molecules, optimizing both versatility and efficiency.

The development process extends beyond standard technologies, as we explore cutting-edge innovations, such as lasers and other robust options, to further refine our platform. Off-the-shelf solutions from traditional bioprocess tool providers rarely meet our exacting requirements, and while some existing products come close, we work directly with vendors to customize them to our needs. In many cases, we are developing our own solutions to ensure the highest performance standards.

A dedicated team of 25–30 experts is leading the design, development, and construction of the system, supported by highly skilled and knowledgeable contractors. This team is crucial in addressing the challenges of reducing the technological footprint, as many desired technologies for real-time monitoring are not yet available as inline solutions. This necessitates innovative partnering to adapt these technologies for real-time PAT applications.

One of the critical bottlenecks is real-time product release, where we have already developed PAT tools capable of detecting approximately 80% of the critical quality attributes we monitor. Our ongoing efforts focus on advancing the remaining technologies to meet our rigorous standards.

Additionally, the evolving regulatory environment for xRNA therapies presents its own set of challenges, particularly the uncertainty surrounding which impurities and attributes are critical. The FDA's funding and continuous feedback on our strategy and specific PAT tools have been invaluable, helping us navigate these regulatory complexities and ensuring our solutions are both effective and compliant.

Enhancing Efficiency with Continuous Manufacturing

Continuous manufacturing revolutionizes the traditional multi-suite production process by centralizing operations within a single suite, significantly enhancing efficiency. This streamlined approach is supported by advanced PAT tools and a central digital control center, which together enable a continuous flow of products. Traditional RNA manufacturing often requires multiple suites, which complicates logistics and can extend timelines. Additionally, quality control testing is typically conducted in separate laboratories that may not even be located on-site, further complicating the process.

In contrast, continuous manufacturing integrates all processes and quality control testing within a single operational suite. This setup not only facilitates real-time monitoring and control but also significantly mitigates risks associated with process discontinuities, thereby enhancing both process reliability and product quality.

Specifically for RNA, continuous manufacturing addresses the uncertainties of this evolving modality. The system's inherent flexibility allows it to adapt to the rapidly changing regulatory landscape regarding different RNA isoforms — such as circRNA, mRNA, and samRNA — and their diverse quality specifications. This adaptability is crucial for tailoring the manufacturing process to meet the specific needs of various end-use applications, whether for vaccines or therapeutic treatments.

Moreover, continuous manufacturing proves to be a cost-effective method for producing high volumes of xRNA therapies, facilitating standardized production protocols that can be replicated globally. This standardization ensures consistent product quality across different manufacturing sites, expanding patient access to these vital therapies. Additionally, the ability to reduce typical production times from 21 days to just 5 days is particularly advantageous for RNA molecules, which are inherently unstable and prone to rapid degradation.

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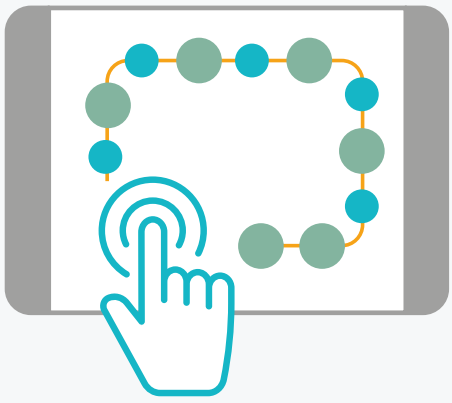

Strategic Enhancements in Efficiency, Cost-Savings, and Quality

ReciBioPharm aims to establish a continuous xRNA manufacturing solution scalable from research to commercial production, adaptable to needs such as rapid pandemic responses, and deployable globally. This bespoke platform is engineered to achieve significant enhancements in manufacturing duration, cost efficiency, and product quality.

Utilizing digital twins and advanced simulations, the platform can decrease process development timelines by up to 90%. The continuous operation, supported by real-time PAT and intelligent processing, reduces the need for extensive human operation while promoting consistency and elevating quality across production cycles. This system also minimizes the necessity for batch release testing and material handling, and it allows for scalability with minimal additional investment — production can simply be extended over longer periods to increase output.

When compared with traditional batch manufacturing methods, our process development duration will be dramatically reduced from 6–9 months to under a month, and product release timing from 2–3 months to just 1–2 weeks. Furthermore, the GMP-compliant platform is expected to produce up to 40 grams of xRNA per day, requiring only a fraction of the cleanroom space that conventional batch processes would necessitate.

This approach is designed not only to streamline development but also to expedite the clinical trial process, allowing companies to more quickly determine the viability of their candidates. The platform's inherent flexibility facilitates the integration of emerging technologies — like advanced PAT for immediate product release and superior delivery methods surpassing LNPs. It also ensures resilience against supply chain disruptions by accommodating various raw materials.

Clear Roadmap for Transforming the xRNA Manufacturing Paradigm

By April 2025, ReciBioPharm is poised to integrate client programs into its pioneering systems, utilizing the Knowledge Hub, simulator, high-throughput Screening (HTS), and the CP1 lab-scale system housed within our process development laboratory. The more expansive CP2 system, also situated at our Watertown facility, is slated for installation by the end of the second quarter of 2025, with full operational capability expected by Q1 2026. This timeline sets us on course to support clients seamlessly as their therapeutic candidates advance from clinical trials toward regulatory approval and eventual market launch.

Once operational, the profound influence of our innovative manufacturing platform on the biopharmaceutical industry will become evident. The platform is designed to expedite development timelines, reduce production costs, and enhance product quality, with these advantages being accessible to companies regardless of geographic location. Our central command center and automated continuous operations allow for deployment in regions lacking robust biomanufacturing infrastructure or skilled personnel, thereby democratizing access to advanced therapies and vaccines globally, including precision medicines.

About us

ReciBioPharm, a division of Recipharm, is a contract development and manufacturing organization (CDMO) specifically established to focus on serving companies seeking to develop and commercialize advanced therapy medicinal products (ATMPs). ReciBioPharm's specialized CDMO capabilities include pre-clinical to clinical and commercial development and manufacture for new biological modalities encompassing technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, nucleic acid-based mRNA and plasmid DNA production. Led by a management team and technical experts with a proven track record in both process development and contract manufacturing, ReciBioPharm offers the knowledge and resources necessary to help customers develop and manufacture promising new therapies to meet the needs of patients across the world.