Advanced Digital Strategies to Meet mRNA Therapy Production Challenges

Utilising Digital Tools to Support Accelerated Drug Development and Scale-up

Messenger ribonucleic acid (mRNA) therapies represent a promising frontier in medicine. However, developing and producing mRNA therapies presents significant challenges including complex manufacturing processes, high costs, regulatory requirements and precision required in the development and commercialisation phases. Utilising advanced digital tools with a well-defined digital strategy can mitigate these challenges and ensure both stability and efficacy throughout production, efficient operations and the ability to scale-up to meet demand, while maintaining high-quality standards.

Key aspects explored:

- **Challenges of mRNA therapy production.**
- **Digital strategies for mRNA manufacturing:** Best practices to support production scale-up.
- **Implementing digital strategies:** Utilising Emerson software solutions to facilitate optimized business performance.

Manufacturing mRNA Therapies

The manufacturing process for mRNA therapies has several meticulously controlled steps. It begins with the design and synthesis of a DNA template that encodes the desired mRNA sequence, utilising recombinant DNA technology. This DNA template is then used in an in vitro transcription process, where enzymes like T7 RNA polymerase transcribe it into mRNA. The resultant mRNA undergoes a purification process to eliminate any impurities, such as residual DNA, enzymes and by-products, often using chromatographic techniques and filtration. After purification, the mRNA is encapsulated in lipid nanoparticles (LNPs) to protect it from degradation and enhance its delivery into target cells. This encapsulation step is crucial for ensuring the stability and bioavailability of the mRNA therapy. The formulated mRNA-LNP product is then subjected to rigorous quality control tests to confirm its potency, purity and safety. Finally, the finished product is filled into vials or syringes, ready for distribution and clinical use, ensuring that each batch meets stringent regulatory standards.

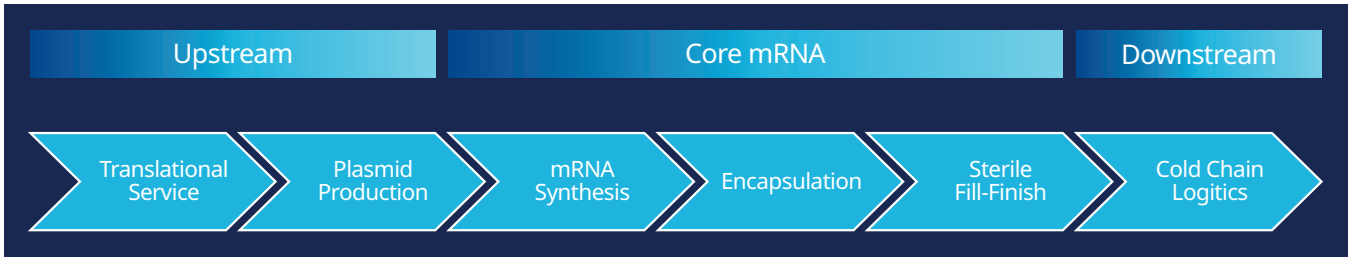

Figure 1: *The different steps involved in manufacturing mRNA therapies.*

Key Challenges in the Production of mRNA Therapies

Despite being a cell-free process, mRNA production remains less established than DNA and viral vector production. Key challenges include:

- **Double-stranded RNA (dsRNA) impurities**, requiring extensive and complex purification methods.
- **Variability in associated testing**, complicating process understanding and tolerances.
- **Additional contaminants**, such as residual DNA and enzymes, necessitating rigorous purification steps and testing.
- **Ineffective purification methods**, adapted from protein purification techniques, are less suited for nucleic acid removal due to differences in size and biophysical properties.

Ensuring compliance with Good Manufacturing Practices (GMP) is another challenge:

- **Variability, contamination and deviations**, often caused by human interactions, pose significant compliance risks.
- **Minimising human involvement**, through cost-effective and sustainable automation strategies, is crucial to reducing errors and improving consistency.

Scaling up mRNA production introduces additional complexities:

- **mRNA instability** requires precise handling, rapid processing and strict temperature control to prevent degradation.
- **Mixing, shear forces, reaction kinetics and temperature control** become more challenging at larger scales.
- **Post-production encapsulation in lipid nanoparticles (LNPs)** can lead to variability in particle size distribution, affecting the lipid-to-mRNA ratio and overall product quality.

Key Components of a Digital Strategy

These complexities are also illustrative of how data-intensive the mRNA development and production process are, underscoring the critical need for advanced technologies to ensure safe, reliable and consistent production. A well-designed digital strategy is essential to address these challenges effectively.

Digital Twins

mRNA manufacturing processes are highly complex and have multiple stages/steps. However, many of the individual steps are well understood and based on established technologies and engineering principles. This enables the creation of empirical and mechanistic digital twins. Digital twins help to reduce risk when scaling up the unit production processes of certain mRNA molecules. Where reliable digital twins can be modelled well, scaleup can be an effective strategy. Manufacturers may choose a scale-out strategy for processes that are difficult to build digital twins, leading to a hybrid scaling approach in this market space. Regardless of the scaling options, digital twins can be designed for training and used to decrease any remaining variability from human interactions.

Enhanced Process Automation and Efficiency

Automation of manufacturing steps can be used to standardise processes, reduce human error and improve reproducibility. Advanced process control (APC) systems can use a model-based control strategy built on digital twins to precisely control the fragile mRNA manufacturing processes, especially for scaled-up unit operations. For processes that are scaled out by adding multiple parallel lines, an overarching process automation system to coordinate activities between the parallel lines may be beneficial to promote efficiency and control.

Real-Time Monitoring
Due to the fragility of the mRNA molecule, the manufacturing processes require highly precise conditions. This requires real-time monitoring of vessel conditions such as mixing, pH, temperature gradients, freeze-thaw rates and enzymatic activity using process analytical technology (PAT).

Process Knowledge Management
mRNA products are highly equipment specific. They are also particularly sensitive to raw material variability. Establishing a clear line of sight to commercial equipment scales and available materials is essential, as this may influence the product development roadmap and equipment choices. Process Knowledge Management software can facilitate process, product and platform-specific information sharing between R&D and commercial, ensuring a smooth transfer of steps, processes, specifications and parameters from clinical to commercial.

Advanced Analytics and Knowledge Management
Due to the complexity of mRNA production processes and the multitude of unit operations, equipment and analytical processes, copious amounts of data are created. However, due to the infancy of mRNA production processes and lack of equipment standardisation, there are data siloes spread across multiple systems, making analytics a challenge. A well-architected data aggregation, contextualisation and visualisation framework is critical to enable data access. Inmation™ software from AspenTech is an expandable, extensible data integration, contextualisation and visualisation tool designed to support this type of application.

Flexible Batch Records and Manufacturing Execution Systems
While paper-based batch records enable flexibility in generation and execution, there is a significant downside regarding the time to collate, review and approve paper documentation. A significant advantage of a manufacturing execution system (MES), when integrated with equipment execution or online tests, is the ability to improve right first-time production and reduce the risk of progressing to a next stage of manufacture without all aspects being completed correctly. An electronic batch record system (EBRS) is an essential tool to enable regulatory compliance, demonstrate control and adhere to procedures and controls.

Digital Tools Supporting mRNA Production Scale-up

Although the various teams across the lifecycle of the product have a very different focus, digitalisation and digital excellence enable systems to functionally share pertinent data and learnings across organisational boundaries. Emerson and AspenTech have developed a comprehensive set of technologies and software tools that support product discovery and development, clinical manufacturing to scale up/new product introduction (NPI) and commercialisation. These include the scalable DeltaV™ Distributed Control System (DCS) for managing clinical and commercial production processes; DeltaV Process Knowledge Management for managing recipes across the product lifecycle, streamlining technology transfers and simplifying risk assessments; AspenTech Inmation for the ingestion, processing, contextualisation and storage of diverse data; and asset process performance management tools such as Aspen Unscrambler™, Aspen MTell®, Apsen ProMV® and Plantweb Insight.

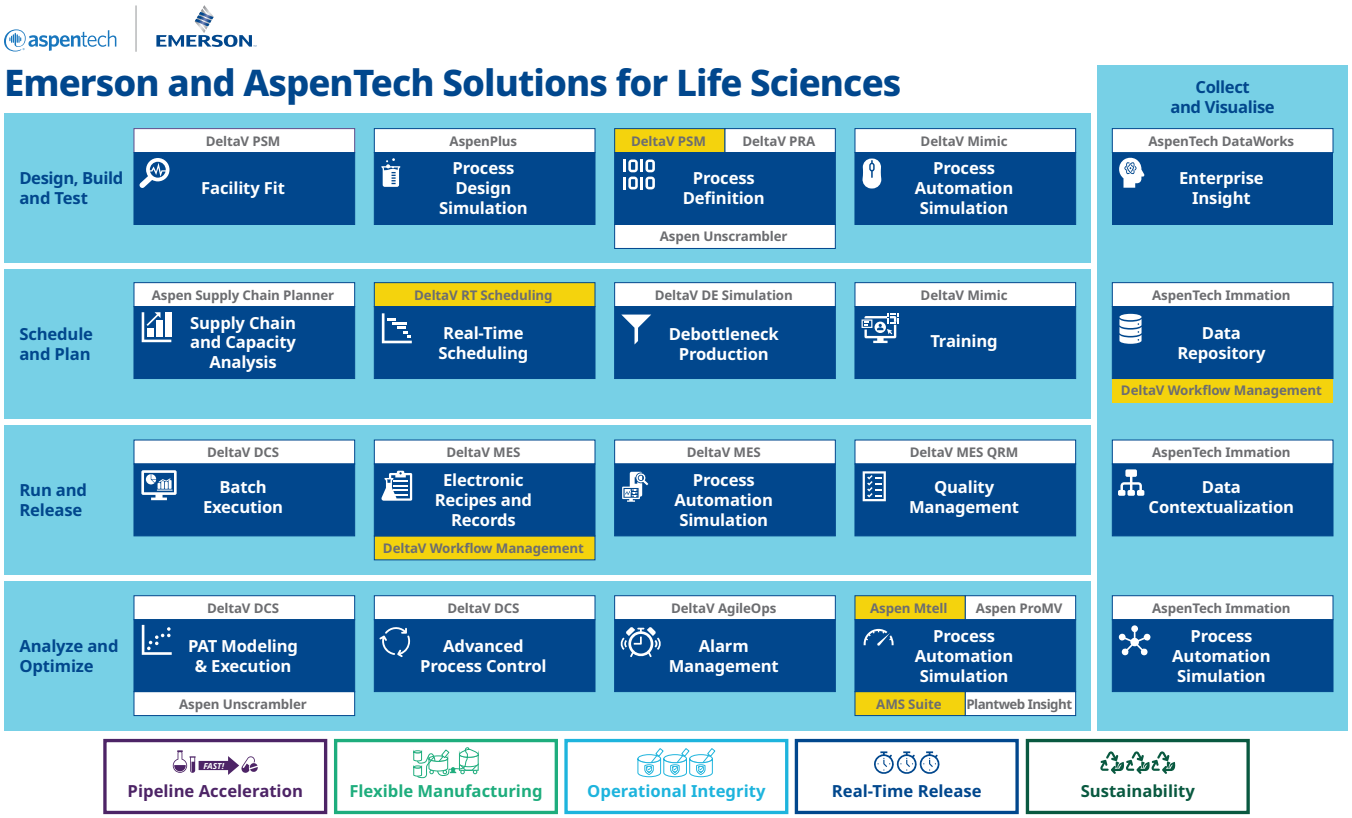

Figure 2: *Emerson and AspenTech software support design, build and test, scheduling and planning, run and release, analysis and optimisation, data collection and visualisation.*

These software tools support the unique activities of the process development organisation, and as companies go through the scaling up process, also empower the clinical and commercial operations teams with capabilities such as:

- Facility fit, process design and automation simulation, throughput and bottleneck assessments and early gap identification (between process design and manufacturing capabilities) to reduce risk and maximise operational efficiency.
- Product knowledge lifecycle management (PKLM) to capture and preserve process definition, unit operations, critical process parameters (CPPs), critical quality attributes (CQAs), material attributes and equipment capabilities, and provide product design version control and risk management.
- Recipe management, batch execution, electronic recipes, records, equipment tracking, materials tracking and quality management to ensure GMP and regulatory compliance.
- Modelling, real-time monitoring and process control, alarm management, and PAT to accelerate and optimise design, scale up and facility start up, and predict and prevent issues for improved operational efficiency.
- Data availability and alignment to support experiments and process development. Predictive and prescriptive analytics to enhance process performance and decision-making.

Figure 3: *High-level capabilities and coverage of Emerson technologies that support life sciences product development, design, and commercialisation.*

Boundless Automation℠ Enables Seamless Access to Data

Although the focus, activities and requirements will vary for different parts of the organisation, there is a need for seamless data sharing to enable software, systems and people to drive optimised business performance. Emerson's Boundless Automation℠ approach (see white paper: `A Journey to Boundless Automation in Life Sciences') enables an open yet inherently secure-by-design automation architecture, where information is shared with context. This helps to prevent functional departmental silos, where each functional role only has access to information specified for them. Boundless Automation liberates data to unleash the power of software and is a key enabler for addressing major pillars in the life sciences industry—pipeline acceleration, flexible manufacturing, operational integrity, real-time release and sustainable operations.

Conclusion

Developing and producing mRNA therapies presents significant challenges, but a well-defined digital strategy can mitigate these challenges and enhance operational efficiency. By leveraging data management, automation, digital twin technology and regulatory compliance tools, organisations can scale up to meet demand, while maintaining high-quality standards. Collaboration, pilot projects, training and continuous improvement are essential to a robust digital strategy. Emerson's Boundless Automation strategy and a comprehensive suite of digital solutions and services position Emerson as a key partner in driving innovation and ensuring the successful commercialisation of mRNA therapies.

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