

# Analytical Sensors for Process Control

## In mRNA Vaccine Production

**Messenger RNA (mRNA) technology represents a flexible and accurate method in the biopharmaceutical industry for developing vaccines and therapeutics by enabling rapid design and production of proteins that can trigger immune responses or treat diseases. Effective production depends on well-defined workflows and sophisticated analytical techniques to uphold product quality. Real-time monitoring and regulation of critical variables are essential for sustaining process control and adhering to regulatory requirements. Meticulous regulation of manufacturing conditions, along with innovative single-use and in-line sensor technologies, helps maintain mRNA stability and optimizes yield. These technological innovations form the basis for consistently delivering potent mRNA-based therapies to meet the growing needs of healthcare.**

### Background

mRNA is emerging as a promising platform in biopharmaceuticals due to its flexibility, safety, and precision compared to traditional methods of vaccine development and therapeutic protein production. An increasing number of clinical trials in various therapies reflect growing industry interest in bringing these vaccines to market. They offer the advantage of rapid, large-scale manufacturing suitable for clinical applications, making them ideal for responding quickly to epidemic outbreaks.

The success of mRNA-based products has driven demand for scalable, clinical-grade manufacturing processes supported by robust analytical methods to ensure safety, potency, and purity. Sensors play a vital role in monitoring key parameters such as temperature, pH, oxygen level, pressure, and flow during production. Their integration into automated control systems enables prompt detection of deviations, enhancing process reliability, product consistency, and compliance with regulatory standards.



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## Process

The production of mRNA vaccines consists of two key phases: the upstream phase, where mRNA is enzymatically synthesized in the lab, and the downstream phase, which involves purification. The purification process starts with diluting the mRNA mixture, followed by chromatography methods that leverage mRNA's distinctive features such as its negatively charged backbone and poly-A tail. Affinity chromatography employs oligo dT ligands to bind the mRNA by targeting its poly-A tail, while salts adjust charge interactions to eliminate impurities like enzymes, DNA, and proteins. Additional ultrafiltration and diafiltration steps refine and cleanse the mRNA, with size exclusion chromatography used to assess purity.

A pH gradient can separate full-length mRNA from shorter fragments based on size during elution[1]. This thorough purification produces high-quality mRNA—about 3 mg per mL with 80% efficiency—ready for encapsulation in lipid nanoparticles that assist delivery into the body, forming the final vaccine[2].

Maintaining strict temperature control throughout production and storage is vital due to RNA's sensitivity to temperature; it safeguards mRNA stability and integrity, ensuring the vaccine remains effective and safe[3]. This requires rigorous cold chain management and continuous temperature monitoring during manufacturing, storage, and distribution.

## Challenges

Key critical process parameters (CPPs) in chromatography for mRNA vaccine production include flow rate, temperature, and pH of buffers. The flow rate affects binding efficiency and resolution, with an excessively fast flow risking inadequate impurity separation. Temperature influences binding kinetics and mRNA stability, while buffer pH affects the charge interactions between the mRNA and the resin.

Among these parameters, temperature regulation, as mentioned, stands out due to the fragile nature of mRNA molecules. They are highly susceptible to degradation caused by heat, light, or even minor temperature fluctuations. Elevated temperatures accelerate enzymatic activity and RNA instability, potentially compromising the vaccine's efficacy and safety. Thus, strict temperature control is essential throughout the manufacturing process

to maintain mRNA integrity, potency, and stability, ensuring consistent product quality.

Similarly, precise pH control is vital for ensuring the overall safety and effectiveness of the vaccine. Optimal pH levels enable enzymes involved in transcription to function efficiently, prevent mRNA degradation, support effective capping crucial for translation and protection, and influence downstream purification and lipid nanoparticle formulation.

## METTLER TOLEDO Solutions

### Flow Meter

METTLER TOLEDO Pendotech offers a variety of flow meters and monitors specifically designed to meet the needs of bioprocessing applications. Our high-accuracy Coriolis Flow Meter maintains precision regardless of changes in viscosity or conductivity, and its compact design enhances its adaptability across different applications. These flow meters play a vital role in purification processes, delivering accuracy within 1%. Additionally, our Single Use Rotary Flow Meters provide a reliable method for flow measurement within various processes. When paired with tubing, they present an economical alternative to traditional reusable rotary flow meters. Incorporating advanced DSP technology, these meters guarantee dependable performance even under demanding conditions and integrate effortlessly with OEM equipment. Constructed from biocompatible, gamma-sterilizable polypropylene, our single-use flow meters meet FDA and other regulatory standards. Designed for long-term use, the Single Use Rotary Flow Meters connect to monitors via a 3-foot cable, making them a versatile and practical solution for numerous process applications.



### Temperature Sensor

Our Single-Use Temperature Sensors offer highly accurate temperature measurements tailored for single-use processes, minimizing the risk of cross-contamination while maintaining durability for multiple cleanings. Designed specifically for in-line applications, these sensors are ideal for filtration, chromatography, tangential flow filtration (TFF), filling operations, and general process monitoring. They are compatible with various monitoring devices such as the TEMP-340 handheld unit, and monitors capable of handling up to four temperature readings, as well as other pre-qualified third-party equipment, and feature reusable cables for straightforward connectivity.

Available with hose-barb fittings, a 1-inch sanitary flange, or luer fittings, these sensors ensure an unobstructed fluid pathway. Thanks to the well-defined temperature-to-resistance profile of their thermistor elements, calibration is not required. They deliver high sensitivity and accuracy, better than  $\pm 0.2$  °C (often surpassing  $\pm 0.1$  °C) over the 0-70 °C range. Constructed from polysulfone for hose-barb and flange models and polycarbonate for luer fittings, they meet USP Class VI standards. Manufactured in an FDA-registered, ISO 9001-certified facility, each sensor is supplied with a certificate of quality.



### pH Sensor

METTLER TOLEDO Pendotech provides single-use in-line pH sensors equipped with advanced InSUS™ 307 probes, delivering accurate and reliable pH measurements for downstream bioprocessing. These sensors function precisely within a pH range of 3 to 10 and achieve an accuracy of  $\pm 0.10$  pH when calibrated at a single point within  $\pm 1.50$  pH units. They offer rapid response times, detecting pH changes in less than 20 seconds between pH 4 and 7, which allows for effective monitoring of swift process variations. Built to endure temperatures from 5 to 60 °C and pressures of 4 bar at 25 °C, 2 bar at 40 °C, and 1 bar at 60 °C, the InSUS 307 sensors provide versatile and dependable performance across a range of bioprocessing settings.

## Conclusion

The integration of advanced industrial sensors and meticulous process control is fundamental to the scalable and reliable manufacturing of high-quality mRNA therapeutics. By precisely monitoring critical parameters such as flow, temperature, and pH in real time, manufacturers can uphold product integrity, safety, and efficacy. METTLER TOLEDO single-use pH and temperature sensors exemplify the technological advancements supporting these rigorous standards. Together, these solutions enable consistent production of potent mRNA vaccines, addressing the growing demand for effective biopharmaceuticals in healthcare.

## References

- 1) Optimizing Process Chromatography for mRNA Production, Sartorius.
- 2) Development of mRNA manufacturing for vaccines and therapeutics: mRNA platform requirements and development of a scalable production process to support early phase clinical trials, Whitley, Jill et al., Translational Research, Volume 242, 38 – 55.
- 3) Factors Affecting Stability of RNA – Temperature, Length, Concentration, pH, and Buffering Species, Urmi Chheda et al., Journal of Pharmaceutical Sciences, Volume 113, Issue 2, 2024, Pages 377-385, ISSN 0022-3549, <https://doi.org/10.1016/j.xphs.2023.11.023>.

### METTLER TOLEDO Group Process Analytics

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