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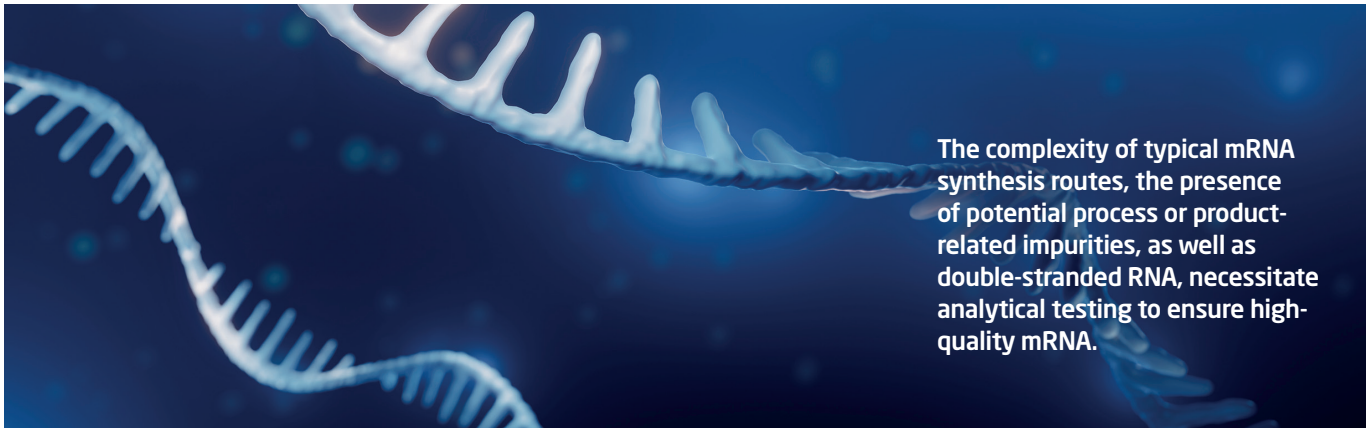
mRNA VACCINE AND THERAPEUTIC PRODUCTS ANALYTICAL DEVELOPMENT SERVICES

CMC Development Support, Characterisation, Stability, and Quality Control Services



Analytical Development and Chemistry, Manufacturing and Controls (CMC) Support

mRNA therapeutics and vaccines have the potential to revolutionise multiple areas of medicine, including the prophylaxis of infectious disease and cancer.

mRNA products present promising alternatives to conventional vaccine approaches because of their high potency, capacity for rapid development, and potential for low-cost manufacture and safe administration. Recently, their value has been demonstrated vividly through applications as vaccines to prevent SARS-CoV-2 infection.

Challenges

Due to the complexities associated with typical mRNA synthesis routes (in vitro transcription (IVT)) and the presence of impurities, analytical testing should be performed to assess the quality of the mRNA product. Potential process-related impurities include residual DNA templates or enzymes, and potential product-related include truncated RNA fragments or aberrant mRNA species such as double-stranded RNA (dsRNA).

mRNA vaccines are, however, a relatively new concept, and there are no specific ICH or FDA guidance documents. However, the principles of existing regulations can be applied, including FDA CFR Title 21 for CMC information as well as ICH guidelines for cGMP, method validations, elemental impurities, residual solvents, and setting specifications. As mRNA therapies have been considered as gene therapies in clinical trials by the FDA and EMA, guidelines relating to these products can also be applied.

Our Solutions

Our experts deploy strategic science-led analytical programs and to assess critical quality attributes, including determination of identity, purity, stability, homogeneity, and immunogenicity, supporting an mRNA product from early development, authorisation, and ongoing production.

Our scientists at our GLP / GCP / GMP laboratories characterise and test mRNA drug substances or drug products to help you confidently assess batch-to-batch manufacture and process repeatability as well as the quality of mRNA produced.

We are adept in establishing GMP validated analytical methods, including general methods, such as identification, residual solvents and elemental impurities, and compendial methods (appearance, pH, osmolality, particulate matter, container closure integrity, sterility, and bacterial endotoxins) (Table 1).

Additionally, we provide mRNA-specific methods, including integrity, potency, capping efficiency, residual DNA template, residual dsRNA, and delivery system testing. These comprehensive characterisation services provide data to determine protein expression and product purity, which can be directly linked to translation efficiency and immunogenicity.

Integrity

An important quality consideration for mRNA is overall product integrity, as this can have a direct effect on potency. We apply several different chromatographic approaches to assess integrity, including size exclusion chromatography, ion pair, reverse phase HPLC, or capillary gel electrophoresis.

COMPENDIAL METHODS	GENERAL METHODS	mRNA SPECIFIC METHODS
Appearance	Identification	Integrity
pH		Sequence
Osmolality		Potency
Particulate Matter	Residual Solvents	Capping Efficiency and Poly(A) Tail Characterisation
Container Closure Integrity	Elemental Impurities	Residual DNA Template
Sterility		Residual dsRNA
Bacterial Endotoxins		Delivery System Testing

Table 1: Specification tests for batch release and stability study testing of mRNA

"For the analytical development of mRNA therapies, a best practice approach should be based on orthogonal techniques that are sensitive, accurate, and linear over a broad range."

Identity and Sequence

Additionally, to ensure quality control, confirmation of mRNA identity and sequence is vital to ensure correct protein expression. We use next-generation sequencing (NGS) to confirm identity and sequence, as well as to confirm any potential variants.

Potency

We develop potency assays for mRNA therapies and vaccines based on the transfection of cell lines appropriate to the target construct. Relative potency is then demonstrated by quantitative and/or functional assays of the expressed protein. While the initial cell stage is often common between constructs, the readout typically requires the development of a bespoke functional assay or ELISA.

Capping Efficiency and Poly(A) Tail Characterisation

Capping efficiency and properties of the Poly(A) Tail length also requires careful monitoring. For example Poly(A) Tail length variations are likely to effect potency. To assess these structural features, we would typically involve digesting the mRNA with enzymes that allow isolation of the relevant 3' or 5' end and analysis using chromatographic approaches coupled to UV or MS detection.

Specific Impurities

Alongside conducting impurity testing for residual solvents or trace metals (ICP), we also conduct tests for specific impurities such as dsRNA, which can be determined by ELISA methods.

Advanced Delivery Technologies

Encapsulation of mRNA inside Lipid Nanoparticles (LNPs) provides stability, delivery, and safety advantages. In April 2018, the FDA published liposome drug guidance for the industry. Although this was published by the Centre for Drug Evaluation and Research rather than the Centre for Biologics, many of the scientific principles described in the guidance can also be applied to biological therapies.

To help you meet the requirements of the FDA CMC guidance, our scientists provide a package of analytical services aimed at the assessment of critical quality attributes (CQAs), such as physicochemical properties, lipid content/composition, encapsulation efficiency, and the release of drugs from the LNP formulation which is necessary to support the submission of an Investigational New Drug Application (IND).

The potential for administration through inhaled delivery routes has been steadily growing in importance. This presents a more desirable mode of non-invasive route for self-administration of mRNA therapeutics, not only for the treatment of respiratory diseases through targeted delivery to the lungs but also as an alternative route to parenteral administration. Our experts provide development support, including device selection/compatibility and analytical development from both the molecule (structure, physicochemical properties, potency) and delivery performance aspects (delivered dose, delivery rate, aerodynamic droplet size distribution, etc).

Total Quality Assurance

At Intertek, we believe a best practice approach to supporting the analytical development of mRNA therapies involves orthogonal techniques that are ideally, sensitive, accurate, and linear over a broad range. In addition, methods should be validated appropriately to support the relevant phase of clinical development, regulatory submission requirements, or to support ongoing quality control of the approved product. With a heritage of supporting advanced pharmaceutical product development coupled with a comprehensive range of state-of-the-art analytical technology, our experts offer Total Quality Assurance to help you ensure the safety, efficacy, and quality of your mRNA therapy.

WEBINAR ON-DEMAND

Superhero Analytics - Understanding the Fantastic Four: Capping Efficiency, Sequencing, Poly(A) Tail, and dsRNA

Scan the QR code to watch the video

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