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Technical Brief

Regulatory Expertise and CMC Document Preparation to Support mRNA-based Therapeutic Development

Advancing a molecule through the clinical trials process presents many challenges, such as navigating the regulatory requirements that must be met for approval of a new mRNA-based drug product. A critical part of this process is the preparation of extensive documentation related to chemistry, manufacturing, and controls (CMC). These documents describe drug substance and drug product quality and must be included in investigational and commercial applications.

In addition to accelerating timelines, providing extended quality & capacity, and simplifying the journey to market, a contract testing, development, and manufacturing organization (CTDMO) can be an invaluable partner for the proper and thorough preparation of CMC documentation. An experienced CTDMO can mitigate the risk of not meeting regulatory expectations which can result in lengthy delays and extensive additional workload. CMC support can be particularly advantageous for mRNA drug products which require information on the mRNA itself, the lipid excipients, and the lipid nanoparticle (LNP).

This article provides an overview of the regulatory expectations applicable to mRNA drug substance and product, the need for phase-appropriate quality, and insights into the development of CMC documentation that help ensure compliance.

Regulatory Expertise Ensures Compliance

As with all drug modalities, the successful development and manufacturing of mRNA-based drug products requires an in-depth knowledge of regulatory requirements that evolve as the drug candidate advances towards regulatory approval and the preparation of phase-appropriate CMC documentation (Figure 1).

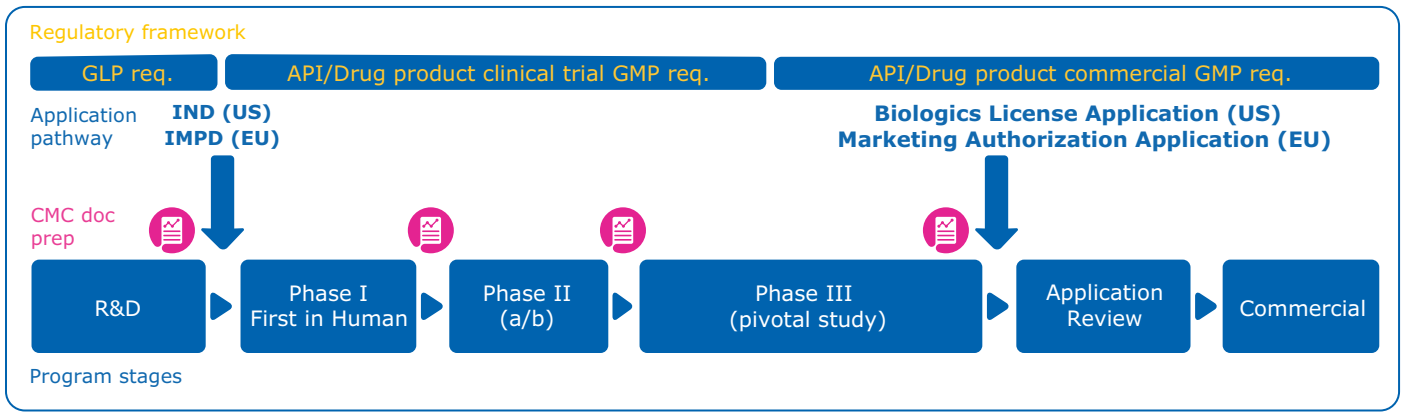

Figure 1.

GMP requirements increase as drug candidates advance towards commercial production and phase-appropriate CMC documents are prepared at several points.

Good manufacturing practice (GMP) requirements increase as clinical development advances, making experience in regulatory compliance essential. GMP is a risk-based approach and while management of several process-related risks are addressed in specific guidelines and are typically applicable for marketed products, it is useful to consider quality and regulatory aspects in early phases of development. For example, prior to first-in-human studies, appropriate documentation and quality expectations should be considered so that results of a toxicological study, for example, are obtained for a material that is representative of the material that will be used later in clinical studies.

The document icons in Figure 1 represent a review of dossiers needed to apply to advance into different clinical trial phases, marketing authorization, or variation once the product has been approved. Late in phase III, study results are used for the marketing authorization application; for mRNA drug substance used in these pivotal studies, full GMP requirements comparable to a commercial application must be met.

Assurance of clinical phase-appropriate quality should use a risk-based approach and encompass the following:

- Raw materials used for API production must be of an appropriate quality. The introduction of API starting materials determines the start of the GMP process, the point from which the detailed process description must be submitted to authorities, and where process validation should commence in preparation for commercial application.
- Process equipment and instruments should be qualified (IQ, OQ) for products used from phase I onwards.
- Facilities have been registered according to the country's requirements.
- The manufacturing process should be subject to phase-appropriate quality management. While process validation is not required for early phases, full traceability must be available, and the master batch record should be approved by the quality unit. The quality unit is also responsible for reviewing the executed batch records for completeness and accuracy.
- Analytical procedures should be qualified, all instruments and equipment should be calibrated with traceability to reference standards under scheduled controls or according to a preventative maintenance plan.
- All analytical methods for product release should be qualified from phase I onwards.
- Change control documentation requirements and rules of record keeping should be applied across all activities.

GMP inspection expectations evolve throughout clinical development. While the inspection processes may differ, both the European Union (EU) and the United States (US) expect GMP conformity for the first clinical batch. In the EU, the drug substance manufacturer is required to notify the National Competent Authority of each new clinical product; notification of taking on a production in a facility triggers an inspection by the authority and after a successful inspection, the GMP certificate is granted. In the US, the first inspection is typically a pre-approval inspection, which is later in the process.

Global expertise and familiarity with local regulations are also critical as the registration requirements of the mRNA manufacturing site differ across geographies:

- **EU:** A GMP certificate for the drug substance manufacturing site is required, and substances, products, organizations and referential (SPOR) data must be submitted as a prerequisite to start the clinical trial.
- **US:** The manufacturing site requires a Food and Drug Administration (FDA) drug establishment registration for the commercial application. This ensures that the FDA has the data necessary to start an inspection of the site and check the relevant GMP-compliant manufacturing processes.
- **China:** The manufacturing site must demonstrate the capability of GMP production.
- **Japan:** Foreign manufacturer accreditation is necessary and is accompanied by an extensive procedure in which details about the facility including floor plans, manufacturing equipment, and personnel must be provided. A GMP document inspection typically follows.

The Right Partner for Preparation of CMC Documentation

mRNA-based therapeutics and their associated regulatory requirements are still evolving. As your CTDMO partner, we offer expertise in optimizing the development and manufacturing of this novel modality backed by phase-appropriate guidance to ensure the proper GMP activities are performed at the right time. With extensive experience in CMC documentation preparation, we help you meet regulatory requirements by ensuring completeness and accuracy. Our in-house CMC experts provide expert counsel on which characterization studies are essential for risk mitigation and regulatory compliance and then design and execute those studies for inclusion in regulatory dossiers.

The CMC team operates in close alignment with our regulatory experts who support compilation of the appropriate quality information for every component of the mRNA drug product. Our global regulatory network includes a regional presence in the US, EU, Asia Pacific region, Latin America, Eastern Europe, Middle East, and Africa. This network is supported by a state-of-the-art electronic regulatory data management system, has access to registration pathways for submissions, and maintains active regulatory surveillance to ensure familiarity with any changes in requirements. Figure 2 shows the countries and regions where we have made regulatory submissions for our own active substances and hence have first-hand experience to support registrations on behalf of clients.

With this integrated approach, we can facilitate a smooth clinical trial application process, accelerate your timeline by enabling easier responses to regulatory authorities, and minimize the risk of failed applications and repeat application cycles.

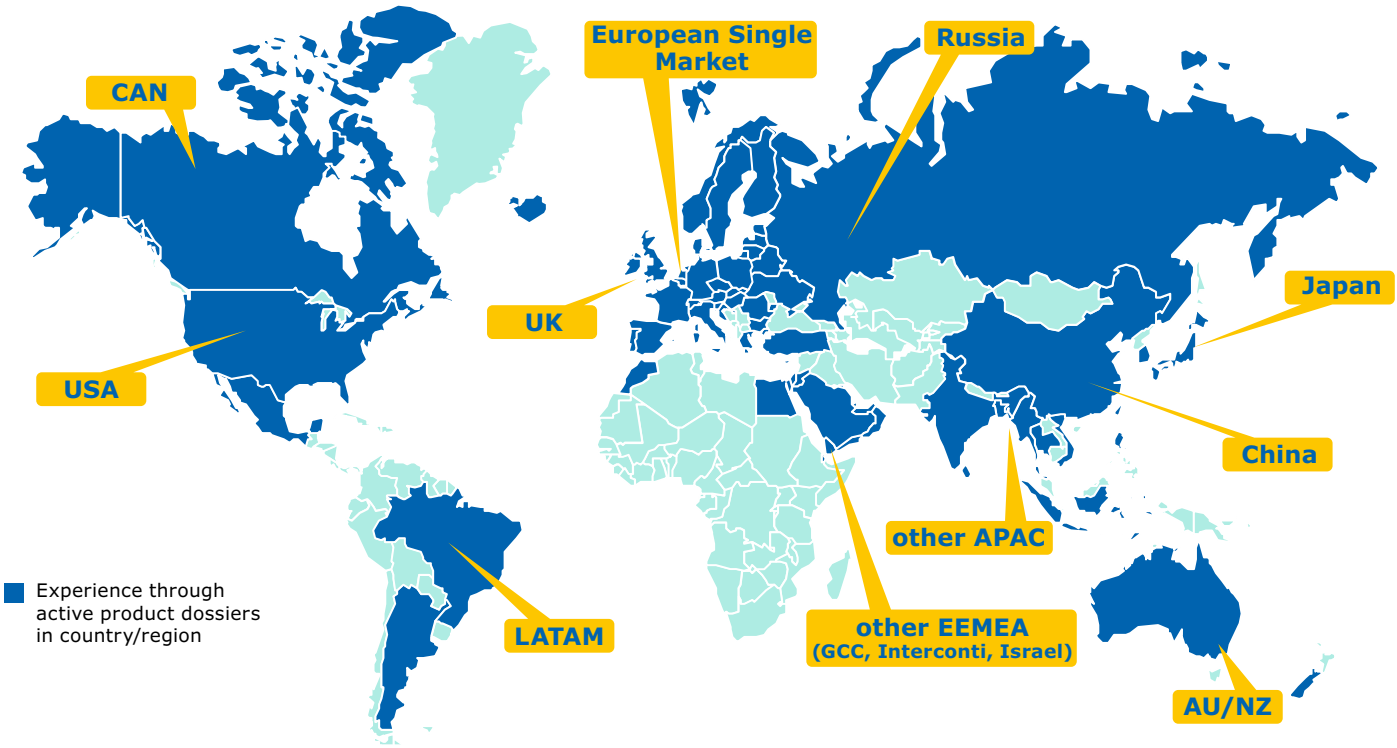

Figure 2.

Map of active regulatory submissions.

Your integrated CTDMO partner

The Millipore® CTDMO Services portfolio offers customized services to accelerate projects, mitigate risks, and expedite time to market all the way from mRNA, through lipids and Lipid Nanoparticles (LNP) to final Fill and Finish. Our services pave the way for robust, integrated, and consistent processes along all stages from pre-clinical to commercialization.

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