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White Paper

Regulatory Frameworks for mRNA Therapeutics: Implications for Development and Manufacturing

The market for RNA therapeutics and vaccines has expanded rapidly in recent years and continues to grow. In 2018, the first siRNA-based therapeutic was approved, and just a few years later, mRNA-based and self-amplifying mRNA vaccines were introduced in the fight against SARS-CoV-2. Emerging mRNA technologies are now also being leveraged as the basis for a broad range of applications, such as cancer vaccines, protection against a wide range of pathogens, as well as therapeutics such as targeted antibody expression, enzyme replacement therapies, and CRISPR/Cas subunits used in gene editing.

In parallel, the regulatory environment for this modality continues to evolve. Currently, regulations governing mRNA-based drug substance and drug product are not yet fully defined, creating uncertainty for the biopharmaceutical industry. Developers of mRNA-based therapeutics and vaccines must remain agile and stay ahead of current improvements and changes to align on requirements and definitions for products and raw materials. Keen understanding of current regulations, despite being in flux, is essential to ensure that the appropriate set of information regarding quality of drug substance and drug product is provided in Investigational New Drug (IND) dossiers (US) and Investigational Medicinal Product Dossiers (IMPD; EU). Novel excipient regulations may also apply, for example when using novel or non-compendial lipids, or compendial lipids with first-in-human use, or new routes of administration. Accordingly, extensive details, comparable to information provided for active pharmaceutical ingredients (API), must be provided in dossiers.

This white paper provides an overview of the current regulatory landscape for mRNA-based therapeutics and vaccines and describes how current guidance may translate into practice. The content reflects our understanding of the mRNA manufacturing process and the quality topics of application dossiers, a critical part of the clinical trial application process for mRNA drug substance and drug product.

Components of mRNA-based Therapeutics and Vaccines

Integral components of mRNA-based therapeutics and vaccines must be manufactured according to GMP or cGMP requirements, as summarized in **Table 1**.

For drug substances categorized as biologicals, such as mRNA-based drug substances, generally neither active substance master file (ASMF), nor drug master file (DMF) apply. The respective CMC information required for Investigational Drug Applications (IND), is outlined in module 3.2.S, the contents of which are described in ICH M4Q(R1) and the US Food and Drug Administration's CMC Information for Human Gene Therapy Investigational New Drug Applications.

Lipid nanoparticles (LNPs) which consist of different kinds of lipids, can be compendial and/or novel lipids, serving as the delivery vehicle for mRNA drug substance cargo. LNPs are categorized as excipients which in the US are DMF type IV applicable. Generally, novel or non-compendial lipids are described to the extent of content similar to APIs, respectively in CMC module 3.2.P.

mRNA drug substances and LNPs are formulated into the mRNA-LNP, at which point they can then be considered the final drug product. The required CMC information compilation for the final mRNA-LNP drug product are collected in CMC module 3.2.P.

Table 1. Integral components of mRNA-based therapeutics and vaccines manufacturing.

mRNA Therapeutic and Vaccine Components	Regulatory Requirements
Drug Substance: mRNA	– GMP/cGMP requirements – No ASMF/DMF procedure available for biologics – CMC-Module: 3.2.S
Excipients: Lipids	– GMP/cGMP requirements – US: DMF IV applicable – Non-compendial/novel lipids described like APIs in CMC-Module 3.2.P
Drug Product: mRNA + Lipids including fill & finish	– GMP/cGMP requirements – CMC-Module: 3.2.P

The mRNA Regulatory Landscape

The regulatory landscape for mRNA-based therapeutics and vaccines includes national and global agencies such as the US Federal Drug Administration (FDA), the European Medicines Agency (EMA), the World Health Organization (WHO), and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. These agencies define legislations governing the quality, safety, efficacy and manufacture of drug substances and drug products. Additionally, organizations such as the European Directorate for the Quality of Medicines & HealthCare (EDQM), the British, Japanese and United States Pharmacopeia (BP; JP and USP) all set compendial standards applicable to quality, safety, efficacy, and manufacturing, as well. Additionally, consensus agencies such as the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH), the Pharmaceutical Inspection Convention (PICS) and the International Standard Organization (ISO) publish guidance that are mutually recognized and acknowledged as applicable in several countries. Industry organizations such as BioPhorum, the Parenteral Drug Association (PDA) and the International Society for Pharmaceutical Engineering (ISPE) also offer the industry perspective on guidance.

Regulatory Categorization of mRNA-based Therapeutics and Vaccines

Figure 1 illustrates the differences in the categorization of mRNA-based therapeutics and vaccines in the EU and US with a primary focus on the regulations pertaining to manufacturing drug substance, drug product, and Advanced Therapy Medicinal Products (ATMP) starting material. In the EU, mRNA-based vaccines that protect against infectious diseases are categorized in a separate class from mRNA-based therapeutics and ex vivo cell and gene therapies. Different EudraLex Guidelines apply to each of these categories. In contrast to the convoluted three-part approach in the EU, the US approach appears to be lean, combining all applications into a single category underlying FDA's CFR 210, 211 and 600 and respective FDA guidelines.

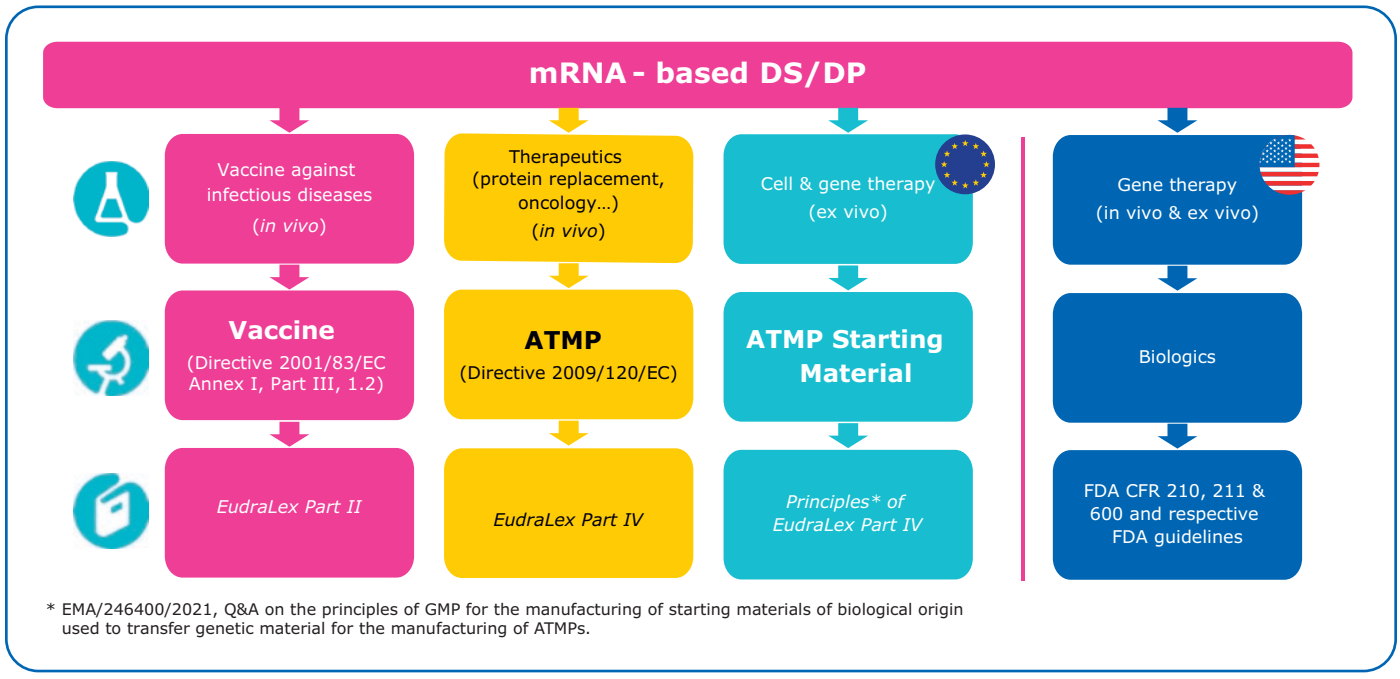

Figure 1. Categorization of mRNA therapeutics and vaccines in the EU and US.

A comprehensive view of the regulatory framework and overarching regulations pertaining to manufacturing and GMP is shown in **Table 2**.

ICH Q7—GMP for APIs and EudraLex Vol 4, Part 2 pertains to basic requirements for APIs including vaccines, and EudraLex Vol 4, Part 4 to GMP requirements for ATMPs, respectively. Annex 1 provides information on the manufacture of sterile medicinal products. Recently revised Annex 1 extended its scope to include low-bioburden drug substances based on risk-based approaches and risk assessments. Additionally, EMA Q&A (EMA/246400/2021) provides additional information on the principles of GMP for the manufacturing of starting materials of biological origin used for the manufacturing of ATMPs, applicable to mRNA for ex vivo cell and gene therapy.

WHO Guidance Technical Report Series No. 1039, Annex 3 remains high-level informative regarding quality, safety, and efficacy and its scope is limited to mRNA-based vaccines against infectious diseases and exclude therapeutic purposes.

In conjunction with the overarching guidance stands Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP Guidance. While PIC/S GMP guidance and EudraLex Vol 4 are fundamentally similar (PIC/S Annex 2A to EudraLex Vol 4 Part, 4 and PIC/S Annex 2B to EudraLex Vol 4, Part 2). While there are no fundamental differences there are some slight differences between PIC/S Annex 2A and EudraLex Vol 4, Part 4, particularly regarding ATMPs. E.g., the EudraLex Part 4 has a strong focus on risk-based approaches which are not highlighted within the PIC/S Annex 2A.

Details on specific guidance applicable to the manufacturing of mRNA drug substance, many of which are currently available in draft form still progressing or evolving, are summarized in **Table 3**. For example, EDQM recently proposed three general texts pertaining to mRNA, 5.36, 5.39, 5.40, inter-linked through sequential cross-references and published simultaneously as a complete package.

However, currently the most developed guidance with practical relevance is published by USP, e.g., *Analytical Procedures for Quality of mRNA Vaccines and Therapeutics*, 3rd edition draft guidelines. The 3rd ed. draft, published at the end of July 2024, contains proposed quality attributes for mRNA drug substance, and drug product such as for identity, integrity, purity, content, as well as for the starting material now including integrated quality considerations for plasmid DNA adapted from proposed USP Chapter <1040> *Quality Considerations of Plasmid DNA as a Starting Material for Cell and Gene Therapies*. Additionally, the USP 3rd ed. draft guideline proposes characterization, release, and stability relevant testing for mRNA drug substance, drug product, and starting material that may be translated to critical quality attributes (CQAs). USP will turn this 3rd edition draft into an effective guideline, and furthermore validate the proposed analytical methods to advance as compendial methods. Also, the USP Expert Panel currently continues their work on implementation of informational chapters on mRNA.

Table 2. Overarching regulations applicable to mRNA therapeutics.

Guidance document		Document title
EMA		
EudraLex Vol 4	Part 2	Basic Requirements for Active Substances used as Starting Materials (vaccines)
EudraLex Vol 4	Part 4	GMP requirements for ATMPs
EudraLex Vol 4	Annex 1	Manufacture of Sterile Medicinal Products (revised)
Q&A		On the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs
FDA		
CFR title 21	Part 210	Current Good Manufacturing (cGMP) Practice in Manufacturing, Processing, Packing, or Holding of Drugs: General
	Part 211	cGMP for Finished Pharmaceuticals
	Part 600	Biological Products: General
WHO		
TRS No 1039	Annex 3	Evaluation of the quality, safety and efficacy of mRNA vaccines for the prevention of infectious diseases: regulatory considerations (vaccines)
PIC/S		
GMP Guide	Annex 2A	Manufacture of ATMPs for human use (EudraLex Vol 4 Part 4)
GMP Guide	Annex 2B	Biological active substance and medicinal products (EudraLex Vol 4 Annex 2)
ICH		
ICH Q7		GMP for APIs – scientific guideline

Table 3. Draft guidance on the manufacturing of mRNA drug substance.

Reference no.	Title
EDQM	
5.2.12	Raw materials of biological origin for the production of cell-based and gene therapy medicinal products (Ph.Eur. 11.5 as of 07/2024*) *becoming General Monograph (3186) Gene Therapy Medicinal Products For Human Use in Ph. Eur. 11.7 as of 04/2025
5.40 Draft	DNA Template For The Preparation Of mRNA Substances
5.39 Draft	mRNA Substances for the production of mRNA vaccines for human use
USP	
Draft Guideline	Analytical Procedures for Quality of mRNA Vaccines and Therapeutics – 3rd Edition (incl. information on quality requirements for drug substance & drug product)
PF 49(6) <1040> Draft	Quality Considerations Of Plasmid DNA As A Starting Material for Cell And Gene Therapies* *commenting closed

Additional guidance applicable to lipids for LNP formulation is a reflection paper on data requirements published by the EMA and a document on liposome drug products published by the FDA (**Table 4**).

In the EU and US, non-novel compendial lipids typically do not have to be registered; this is not the case, in other countries e.g., China. For novel lipids in the EU, excipient quality has to be described extensively as individual parts of the registration dossier (3.2.S. section) while, in the US a DMF Type IV may be applied.

It is important to note that novel excipient regulations apply for lipids that have not been used in human applications in the same route of administration before. In this case, details of the characterization and controls with cross-referencing to supporting safety data must be provided according to the drug substance CMC format and content.

Table 4. Specific guidance on lipids for LNP formulation.*

Reference no.	Title
EMA	
EMA/CHMP/806058/2009/ Rev. 02 (2013)	Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product
FDA	
FDA-2016-D-2817 (April 2018)	Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

* For lipids that have not been used in human applications in the same route of administration, or are not described in compendia, novel excipient regulations apply.

Regulations applicable to mRNA drug product are summarized in Table 5 and include EDQM's general chapters 5.14 and draft 5.36, USP draft analytical procedures for mRNA vaccine quality, and the FDA CMC Information for Human Gene Therapy INDs.

US guidance is considered the standard in terms of establishing critical quality attributes, testing, and establishing a common set of standards applicable to mRNA-based therapeutics, vaccines, and cell and gene therapy.

Table 5. Specific guidance on the manufacturing of mRNA drug product.

Reference no.	Title
EDQM	
5.14	Gene Transfer Medicinal Products For Human Use (Ph.Eur. 11.5 as of 07/2024)
5.36 Draft	mRNA Vaccines For Human Use* *commenting closed
USP	
Draft Guideline	Analytical Procedures for Quality of mRNA Vaccines and Therapeutics – 3rd Edition (incl. information on quality requirements for drug substance & drug product)
FDA	
2008-D-0205	CMC Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Translating Regulatory Frameworks into Practice

A simplified manufacturing scheme of an mRNA drug product helps to put the regulatory framework into context. **Figure 2** shows the mRNA drug product manufacturing process beginning with the drug substance starting and raw materials used to prepare the linearized DNA template.

- Dark blue boxes represent the ATMP or drug substance starting materials.
- Yellow boxes represent GMP grade materials, including materials which are compendial to a pharmacopoeia or GMP standards, like ICH Q7.
- Teal boxes are the basic raw materials which need to be fit for the manufacturing of pharmaceutical products.

According to EDQM guidance, plasmids and primers are considered active substance starting materials, as they include information present in the linearized DNA template and translated into the mRNA. Deoxynucleotide triphosphates (dNTPs), additional enzymes, and processing materials are considered raw materials. Beginning with the in-vitro transcription the mRNA drug substance manufacturing process enters the GMP environment for drug substances. Enzymes used in the manufacturing process should be process materials with high requirements on the quality, origin and documentation (if available). Subsequently, the mRNA drug substance is mixed with lipids which are substances for pharmaceutical use to formulate the mRNA-LNP drug product.

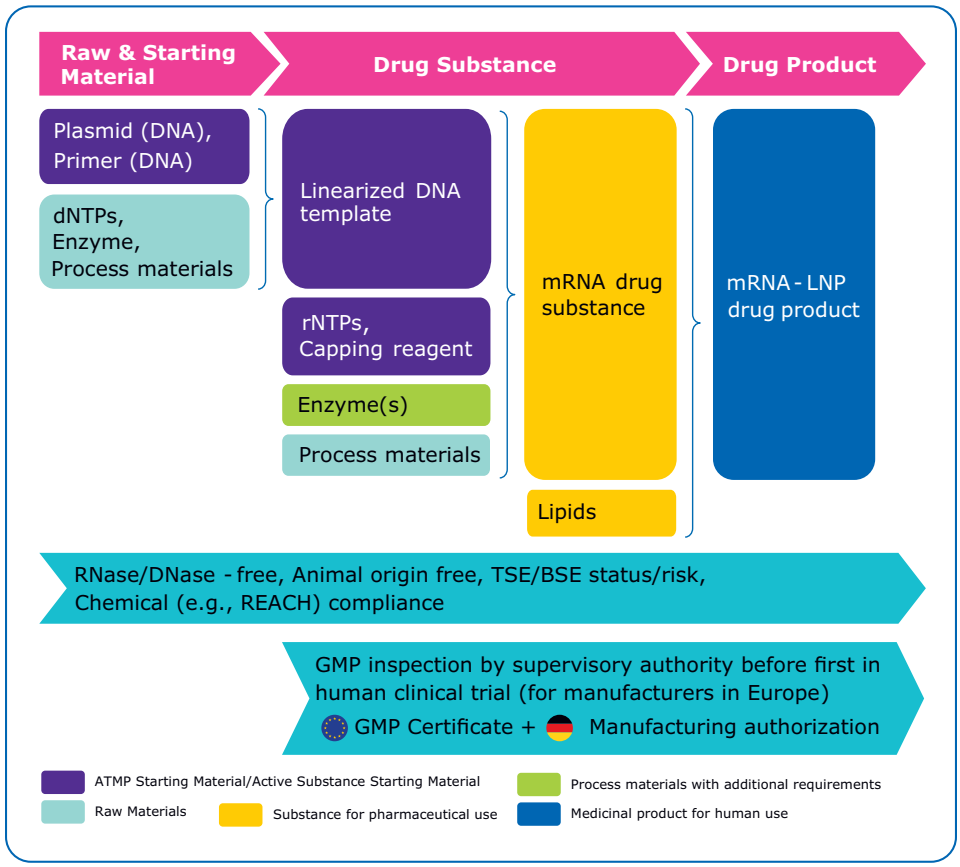

Figure 2. Manufacturing of mRNA drug substance and drug product is regulated.

Compliance with respective GMP regulations for drug substance and drug product processes must be certified upon inspection by the relevant supervisory authority. For manufacturers located in Europe, this takes place before the release of material for first in human clinical trials. Upon successful completion, a GMP certificate will be granted; in Germany, the manufacturer will also receive a manufacturing authorization.

Another important consideration highlighted in **Figure 2** is the quality of materials used in the production process as some (especially enzymes) may not yet be available in a pharmaceutical grade. Manufacturers should look for RNA- and DNA-free materials to protect the process intermediates and drug substance from degradation. Materials of animal origin should be avoided but have to be checked for the bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathies (TSE) status and risk. Another consideration is that of chemical compliance. For example, Triton® X-100 is a detergent that has been banned in the EU based on Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulations and therefore cannot be used for the manufacturing of an mRNA therapeutic.

Flexibility in GMP Requirements in Early Development

It should be noted that there is flexibility with regard to these GMP requirements in early development stages. GMP requirements begin with first in human Phase 1. The requirements on data and documentation increases across clinical development (**Figure 3**). During Phase 3, GMP compliance should be fully in place, prior to submission of the marketing authorization application.

In terms of inspections, the timing is dependent on where the manufacturer or the manufacturing facility is located. In the EU, the GMP inspection and recurrent inspections take place as early as manufacturing of Phase 1 material. In the US, there is typically a pre-approval inspection around the time of Phase 3 activities. This timing aligns with the requirements for process validation as indicated in the ICH Q7 guidance, where process validation is required during Phase 3.

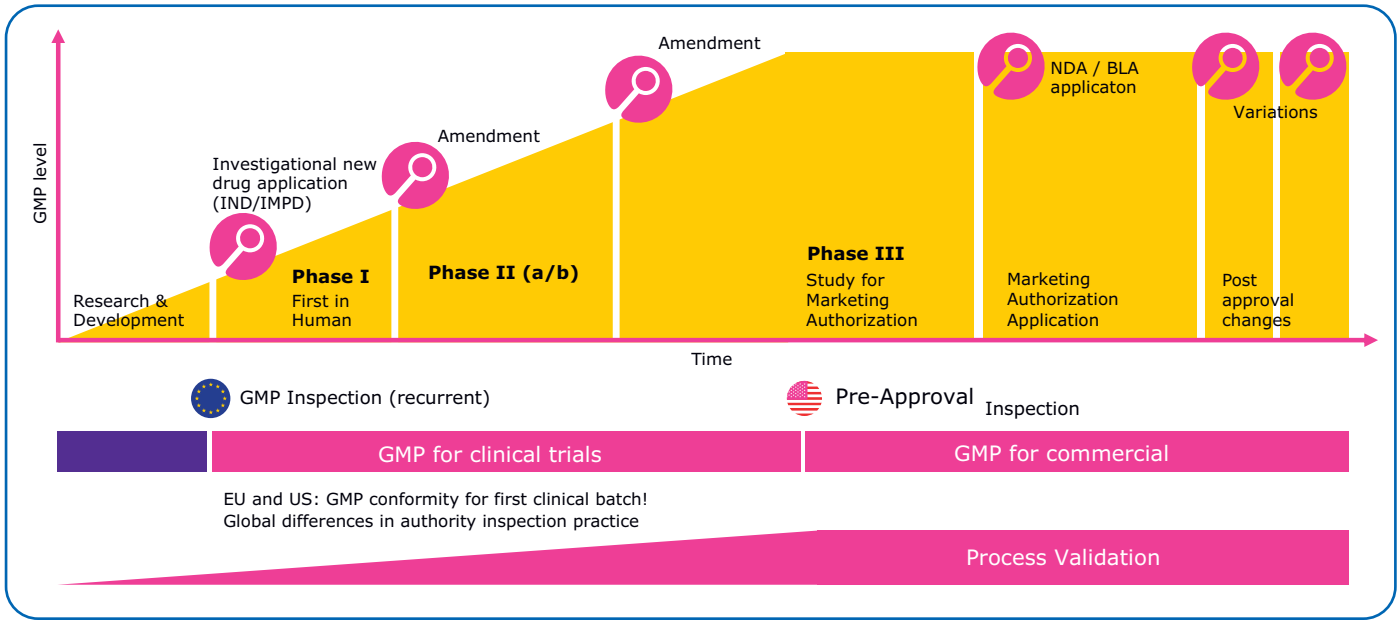

Figure 3. Increasing GMP level through clinical phases to commercial manufacturing.

Table 6 summarizes the regulation and control for manufacturing in the EU and the US. In both regions, phase appropriate GMP, on the basis of risk-based approaches, is generally expected from Phase 1 and onward. The difference, as noted above, is that in the EU, the initial inspection is at Phase 1 and there are continuous inspections throughout all clinical phases. This approach certifies quality and lowers the overall risk profile but also increases the demand for resources during clinical development.

In the US, the first inspection is typically expected in late Phase 3; prior to this point, it is the responsibility of the sponsor of the clinical trial to ensure compliance. While not having inspections in Phases 1 and 2 reduces the impact on resources, it means that early phase quality is not certified by a supervising agency and the risk of failing late-stage inspections may increase.

Table 6. Assessment difference between EU and US regulations on the mRNA API.

	EU	US
Regulation	• Phase appropriate **GMP** expected **from Phase 1 on**	• Phase appropriate **cGMP** expected **from Phase 1 on**
Control	• **First inspection** for **phase 1** to obtain GMP certificate/ ability to release product • **Continuous inspections** throughout all clinical phases	• **First inspection** in late **phase 3** (“pre-approval inspection”) • **Before, full responsibility of sponsor** to ensure compliance
Comparison	**Similar regulatory requirements** but **different control approach**	
Assessment	⊕ **Certified quality** through regulatory agency ⊕ **Lower risk profile** through continuous inspections ⊖ **Increased pre-load** to clinic	⊕ **Reduced pre-load** to clinic as no inspections in phase ½ ⊕ Increased **risk to fail late-stage inspections** ⊖ **Early phase quality not certified** through agency

Conclusion

The regulatory framework for mRNA-based therapeutics and vaccines continues to evolve. The regulatory requirements for production and materials are both complex and not yet fully described. mRNA-specific guidance also continues to evolve with the ongoing development of compendial chapters and guidelines specifying quality requirements for starting materials, mRNA drug substance, and drug product. Further complicating the regulatory landscape is that, depending on the therapeutic application of the mRNA drug product, there may be regional differences in the specific requirements.

As drug developers advance these novel modalities through development and into commercialization, it is essential to understand the regulatory environment and plan according to help ensure both near-term and long-term success. Collaborating with a reliable supplier who provides high-quality products backed by comprehensive documentation and extensive regulatory experience will help mitigate risks and navigate challenges in this rapidly evolving environment.

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