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Navigating an uncertain regulatory environment for mRNA-based products

The development of effective vaccines to combat COVID-19 has showcased the potential of mRNA technology, which is now under exploration for various clinical areas, including oncology, HIV, rare diseases, and personalized medicine. Given that the application of mRNA technology is relatively new, regulatory guidelines and industry standards that address specific aspects of mRNA quality during process development are still evolving, with existing resources primarily focused on mRNA vaccines.

How this guidance will translate for developers of mRNA products for other therapeutic modalities remains to be seen. Developers will need to remain nimble during this period of evolution and stay aware of emerging regulatory guidelines applicable for their unique therapies. Collaborating with a strategic Contract Development and Manufacturing Organization (CDMO) partner that has the appropriate industry knowledge and experience can help developers navigate these challenges and bring novel mRNA products to market faster.

Current and developing regulatory guidance for mRNA products

mRNA-based products are currently regulated within existing frameworks of both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). US FDA oversees mRNA-based products under its Center for Biologics Evaluation and Research (CBER) and the responsible review division is assigned based on indication (e.g., vaccine, oncology). In Europe, mRNA-based vaccines can fall under different regulatory statuses depending on their target (infectious disease or not).

The regulatory framework for Advanced Therapy Medicinal Products (ATMPs) includes both Gene Therapy Medicinal Products (GTMPs) and Somatic Cell Therapy Medicinal Products (sCTMPs). mRNA-based products may be classified under either category, depending on their intended use. To help navigate the regulatory complexity in Europe, the Committee for Advanced Therapies, an advisory committee that reports into EMA, provides non-binding opinions including classifications of ATMPs. This legal status is critical to understand as it can have implications for different controls and other specificities that are intended to limit risks for different product types.

Navigating a region's regulations can be challenging and sometimes cause for confusion. Guidance documents serve an important role in providing industry with the health authority's interpretation of policy on a regulatory issue while not being legally enforceable. Naturally, guidance documents become an important part of the region's regulatory framework. The process for the development and issuance of guidelines is based on policy itself, involves public consultation, and can be quite lengthy.

As of March 2024, neither the FDA nor the EMA have issued specific guidelines related to chemistry, manufacturing, and control (CMC) considerations for mRNA-based products. Past guidance issued by FDA, such as the *2018 FDA Final guidance on liposome drug products* and the *2022 Final guidance on drug biological products containing nanomaterials*, offers some regulatory insight to mRNA developers that employ liposome delivery strategies, but these guidelines are written broadly and are not specific to mRNA.

The integration of mRNA-based vaccines into clinical and market settings during the COVID-19 pandemic highlighted the need for a collaborative approach to standardize quality expectations, facilitating their successful development. Early efforts are focused on vaccines for infectious disease, but undoubtably there will be principles and considerations that will be relevant to other mRNA therapies.

In June 2023, the Biologics Working Party, who provides quality and safety recommendations to EMA's scientific committees, issued a concept paper to industry on the development of a guideline on the quality aspects of mRNA vaccines. The concept paper acknowledged the novel nature of mRNA vaccines for infectious disease, which do not fully align with existing general guidance for human vaccines. Specific quality considerations for future guidelines will address topics such as starting material definition and controls, potency testing, and formulation strategies.

On the US front, the United States Pharmacopeia (USP), the not-for-profit organization involved with establishing quality standards for drugs, issued their *2nd edition for Analytical Procedures for mRNA Vaccine Quality (Draft Guidelines)* in April 2023. A key objective of the USP initiative is to create a shared understanding of mRNA quality attributes through the development of a set of methods for mRNA quality to enable accelerated product development.

While these recent efforts have focused on regulatory expectations for mRNA-based vaccines, significant work is still needed to clarify requirements for other mRNA products, which may vary greatly by treatment type in terms of dosing, route of administration, and clinical targets. These variations point to the need for the consideration of different or more stringent quality control elements.

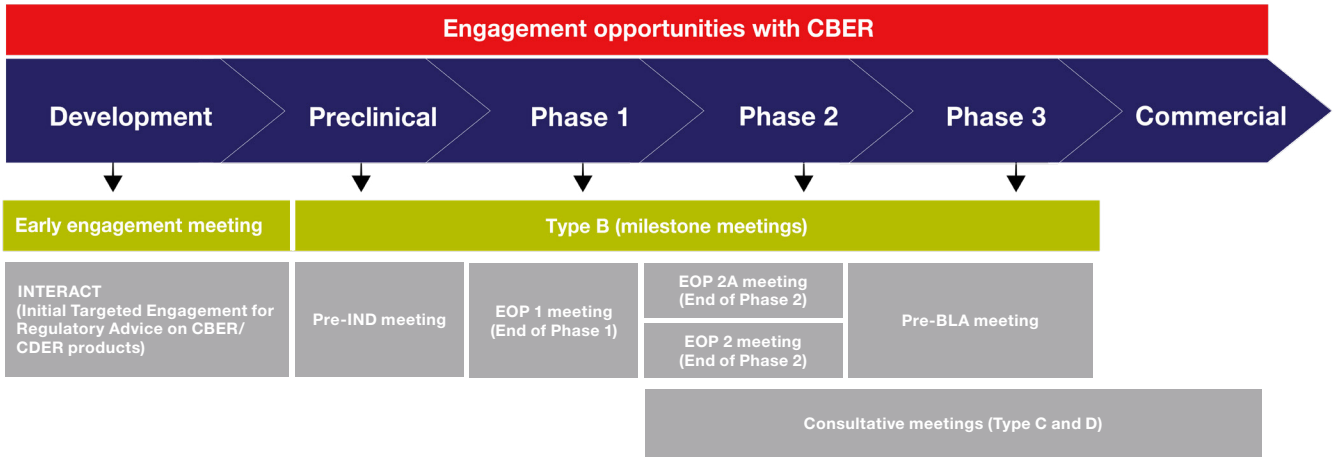
As regulators continue to refine and develop guidelines, developers should engage with these initiatives by actively participating in consultation activities, providing their input, and joining industry groups involved in regulatory development within their target markets for effective collaboration and compliance.

Importance of early engagement with regulators

Engaging with regulators for product-specific guidance is an important strategic element of a drug development program, especially for novel products and where guidelines are lacking. Seeking a scientific advice meeting early in the development process serves as an initial step toward building a strong working relationship. It helps the review division become acquainted with both the product and the process, and it also offers a chance to mitigate risks associated with development strategies. However, the success of such meetings hinges on the sponsor's preparedness. The information package presented to regulators must be thorough, with questions framed precisely to solicit constructive feedback. The most effective meetings occur when sponsors are well-prepared, willing to discuss their development strategy in detail, and ready to tackle tough questions.

As product development progresses to meet new clinical milestones, additional check-ins with the regulator are often critical to ensure that the CMC remains on track with regulatory expectations. Meeting with the FDA to discuss development topics can occur at a milestone meeting (end of phase) or planning an ad hoc technical meeting (type C or D). A schematic of meeting engagement opportunities with FDA during clinical development is presented in the figure below.

Figure 1: Click on the gray boxes to reveal more information about the meeting opportunities across phases.



Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products

Choosing a strategic partner for mRNA development

To navigate the specific challenges and regulatory landscape of mRNA therapy development, some companies opt to collaborate with a Contract Development and Manufacturing Organization (CDMO). This approach can mitigate risks by leveraging the CDMO's expertise and experience. Involving your manufacturing partner in the planning of regulatory meetings is particularly beneficial, as their prior experiences can enrich discussions with regulatory agencies, potentially enhancing agency discussion and feedback.

Given the fluid nature of the mRNA landscape, a strategic CDMO partner should demonstrate their experience with mRNA development as well as their ability to remain informed and responsive to regulatory advancements along the way. Various guidance is available to support developers in choosing a CDMO partner, including this *checklist of key attributes*.

Conclusion

mRNA technology presents an exciting prospect for innovative therapies addressing a variety of clinical areas and challenging disease states. In light of the lack of specific guidelines for mRNA, leading to potential regulatory ambiguity, strategic collaborations and early and frequent one-on-one engagement with regulators are key to facilitating the best path forward for your unique product.