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Reference: EMA Concept Paper on the development of a Guideline on the 4 quality aspects of mRNA vaccines (EMA/CHMP/ BWP/211968/2023)

The number of clinical trial applications for human products and marketing authorisation applications for mRNA containing products significantly increased over the last few years and is expected to increase further in the future. Furthermore, a lot of experience with mRNA vaccines was gained during the COVID-19 pandemic. From an analytical and regulatory perspective, mRNA vaccines are interesting since their classification depends on the target and/or whether they are obtained chemically or biologically. In response to this, the European Medicines Agency (EMA) distributed the *Concept Paper on the development of a Guideline on the 4 quality aspects of mRNA vaccines* for public comment from 23 June 2023 to 30 September 2023. (https://www.ema.europa.eu/documents/scientific-guideline/concept-paper-development-guideline-quality-aspects-mrna-vaccines_en.pdf)

A team of PDA members convened in order to provide a response to the comment solicitation. The comments submitted to the EMA are provided below for reference and as a record of PDA's ongoing commitment to promote regulatory convergence as well as provide information to PDA's members and the pharmaceutical manufacturing community.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts representing our Biopharmaceutical Advisory Board and Board of Directors.

PDA (Parenteral Drug Association®) Response to EMA's Concept paper on the development of a Guideline on the quality aspects of mRNA vaccines

1. General comments on the concept paper

General Comments
The concept paper scope is mRNA vaccines and is clear that therapeutics are currently out of scope. Quality requirements for mRNAs are more related to the technology that its therapeutic applications, limiting the scope to infectious diseases does not correspond to any foundational quality differences in the mRNA product characteristics – which remain similar regardless of the target application. Scope should include therapeutics. Clarify why vaccines would be called out separately.
The guidelines should consider ICHQ12 principles, including use of post-approval change management protocols (PACMP) for post approval changes (e.g., strains update).
Please consider including in the guideline a detailed discussion on the Platform technology, including clear definition of a "platform technology" for mRNA and RNA/LNP products, manufacturing process and analytical methods, and context for use of prior and platform knowledge. Of interest strain changes and new targets use of vaccine technology, and a master file for human mRNA vaccines (in line with EMA guidance on vaccine platform technology master files for veterinary marketed vaccines). Include information on using platform knowledge/prior knowledge to support dossier and post approval changes as well as new variants. The master file could contain all data related to the platform for which there is a reasonable scientific certainty that they will remain unchanged regardless of the antigen(s)/gene(s) of interest manufactured and tested using the platform.
The guideline could address regulatory considerations related to the use of matrixing approaches for Performance Process Qualification (PPQ) batches (for starting materials, active substance, and finished product intermediates).
Consider elaborating on approaches for multivalent vaccines for multiple targets and multivalent vaccines against either different serotypes or mutational variants of the same parent pathogen.
When discussing quality and regulatory considerations related to the control strategy, please include discussion on the approaches for release specifications, characterization, and stability testing of finished product intermediates (i.e., encapsulated mRNA-LNP intermediates) and on how to assess the impact of intermediates (considering their quality attributes level and stability over process execution) on final product quality. The guideline should be defining approaches covering the broad industrial practices applied for LNP manufacturing (considering that LNP formulation processes may differ among applicants.
Please consider including regulatory considerations for starting materials (e.g., plasmid DNA), including characterisation and stability testing. Clarify GMP Principles to be used throughout the development process as they apply to topics such as cell bank control, raw material control, and manufacturing control.
Please consider including a definition for a drug substance and intermediates as it relates to unencapsulated mRNA and LNP encapsulated. This definition should be globally aligned to promote harmonization of regulatory expectations.

2. Specific comments on text

Introduction *(lines 13-29)*

Line number(s) of the relevant text (e.g., 20-23)	Comment and rationale for change	Proposed guidance text change
22-25	Text modification proposed to include "starting material" in addition to drug substance and drug product	It is therefore proposed to establish a guideline addressing those specific aspects regarding the manufacturing process, characterization, specifications and analytical control as well as the definition of starting material, active substance and finish product.
26-27	The document refers to mRNA and self-amplifying RNA. Are these the only two RNA types it will apply to? I am specifically thinking of circular RNA but it could be others as well.	...limited to mRNA vaccines against infectious diseases (including self- amplifying mRNA, circular RNA, and other RNA types manufactured in a similar manner).
46	As part of the "Control of starting materials," please consider and clarify requirements for the method of product of a plasmid (PCR vs cell culture), and how changes to this product should be viewed.	N/A

Discussion (on the problem statement) *(lines 33-72)*

Line number(s) of the relevant text (e.g., 20-23)	Comment and rationale for change	Proposed guidance text change
42-43	Consider rewording the sentence and replace 'quality control' with 'control strategy'. Rationale: This gives more flexibility vs tests categorization (e.g., in specifications, in-process, characterization) which could be dependent on the nature of the tested attribute (e.g., strength and on the control strategy in place. The proposed scope seems to align with the EDQM mRNAVAC Working Party program; there might be duplication of efforts if both EMA and EDQM work on the same topic in parallel.	The proposed guideline will provide information and regulatory considerations regarding the following key aspects of the manufacture and control strategy:

44-45	Please consider adding the definitions of raw materials. Provide clarification of what starting materials encompasses, based upon the processing steps of the plasmid Consider the difference between outsourced activities and purchased materials in relationship to the starting materials/plasmid. If performed at a CMO/vendor, does the agency consider the plasmid to be outsourced activity under the responsibility of the sponsored to disposition? (as per chapter 7, volume 4)	• Definitions of raw materials, starting materials, active substance, finished product intermediate, excipients and finished product • Guidance around Chapter 5 vs. Chapter 7 applicability around plasmid
46-47	When using de novo synthesis of plasmid DNA, set up guidance for changing from batch to batch and the definition of the first step associated with the drug substance process (i.e., linearized plasmid vs. IVT). The proposal is also to include in the scope of the guideline the *manufacturing requirements for starting material/ linear template DNA* (e.g., appropriate non-GMP environment, appropriate traceability of materials and appropriate documentation of operations). -Missing guidance about master cell bank or working cell bank	• Control and delineation of starting materials (linear DNA template for the preparation of mRNA transcript and plasmid DNA where relevant) and the minimal requirements for the preparation of starting material (pDNA, linearized DNA)
67	Please include the definition of RNA Platform technology and add reference to use of "platform analytical methods". The use of platform prior knowledge is an element that mRNA technology can easily leverage because the information vehicle CQAs/CPPs/CMAs can remain the same whatever the encoded sequence is. It is an easily platform-able technology; however, the whole industry could benefit from other technologies platform knowledge. -Define the term platform technology and how to utilize platform knowledge to support filings/ dossier forming more effectively. -Also set up clear guidance when to inform agencies about changes to the platform, and how the assess impact on these changes for the products that have already been approved using the prior “platform design.”	• the definition and use of platform technology/prior knowledge approach and platform analytical methods for new targets