Submission of comments on Concept Paper on the development of a Guideline on the quality aspects of mRNA vaccines

Fields marked with * are mandatory.

* Name of organisation or individual

Vaccines Europe (VE) and International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

* Country of organisation or individual

Belgium & Switzerland

* Email

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

VE and IFPMA

Please click here to be redirected to the guideline text. The public consultation is launched on 23 June 2023 until 30 September 2023.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 September 2023) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency. Please note that in this survey some of your personal data will be processed by the EMA in accordance with Regulation (EU) 2018/1725. By submitting this survey, you are providing your consent to this processing of your personal data. For additional information, please consult EMA's Privacy Policy (https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-privacy-statement-public-targeted-consultations_en.pdf).

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

Kindly note that the comments and the name of the commenting organization or individual will be published unless a specific justified objection is received (the country and email address will not be published). All comments considered during the public consultation process will be published at the time of publishing the final guideline.

☑ Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.

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1. General comments on the Concept Paper on the development of a Guideline on the quality aspects of mRNA vaccines

	Stakeholder name *(to be repeated in all rows)*	General comment
1	VE and IFPMA	It is acknowledged the efforts of EMA and importance of this guidance for regulators and developers, in order to harmonize and create confidence among development program based on breakthrough technologies such as mRNA-based vaccines. New technologies played a critical role in the recent rapid development of COVID-19 vaccines. Clear procedures and quality frameworks related to these technologies are essential, but also how rapid developments are possible, and how flexible and efficient the guidance are, in order to accommodate technology advancements, leading to faster science-based EMA approvals. In the end, world citizens and patients will benefit from

		science advancements in the right time with the best quality technologies.
2	VE and IFPMA	Please consider including in the guideline a detailed information 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 with specific reference to both strain changes and new targets use of vaccine technology master file for human mRNA vaccines (in line with EMA guidance on vaccine platform technology master files for veterinary marketed vaccines*). *https://www.ema.europa.eu/en/data-requirements-vaccine-platform-technology-master-files-ptmf-scientific-guideline
3	VE and IFPMA	The guidelines should consider ICHQ12 principles, including use of post-approval change management, protocols for post approval changes (e.g., strains update). In line with comment in row 2, please consider including information on using platform knowledge/prior knowledge to support dossier and post approval changes as well as new variants. The master file would 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.

4	VE and IFPMA	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).
5	VE and IFPMA	Please 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, and suggest the guidance include how manage multivariant vaccines.
6	VE and IFPMA	When discussing quality and regulatory considerations related to the control strategy, 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).
7	VE and IFPMA	Proposal to include regulatory considerations related to the banking system for the starting material, including its characterization and stability testing.

8	VE and IFPMA	Proposal to include regulatory consideration on the production, characterization and use of reference material for DS and DP. Consider providing guidance on the harmonization of use of reference standard as applicable (e.g.: reference standard to be used for characterization of double stranded RNA content). Clarification on whether the classification will depend on the manufacturing process or the target.
9	VE and IFPMA	The proposed scope in this Concept Paper seems to be aligned 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. It is proposed to consult this Working party to align efforts.
10	VE and IFPMA	Although we understand the scope of this guideline is focused on vaccine against infectious diseases, it would be interesting to consider this guideline as a future reference to be applied to all mRNA products, as there is no real quality difference in the mRNA product characteristics, which can remain very similar regardless of the different target applications.
11	VE and IFPMA	VE and IFPMA would like to be informed and consulted before the final draft guideline get into force.
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2. Specific comments on text

2.1 Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	21	VE and IFPMA	Please consider including appropriate references to general guidance for human vaccines and WHO guidelines 2005 and 2013 (i.e., WHO guidelines on non-clinical evaluation of vaccines Annex 1, TRS 927 (2005)*, WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines, Annex 2, TRS No 987 (2014)**). *https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccines-annex-1-trs-no-927 **https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987	N/A
2	22-25	VE and IFPMA	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…

3	26-27	VE and IFPMA	Quality requirements for mRNAs are more related to the technology specificities than its therapeutic applications. mRNAs are information vehicles that can code for target proteins playing a vaccine role or a therapeutic enzyme substitution role, likewise.	Noting only sa-mRNA is limiting, should be expanded to include circular RNA and alternatives to mRNA.
4	21-29	VE and IFPMA	It is understood that mRNA therapeutic vaccines against diseases caused by infectious agents will be in the scope of this guideline, in compliance with the new proposed vaccine definition (i.e., Article 4 (28) in the proposed Directive relating to medicinal products for human use, and repealing Directive 2001/83/EC).	mRNA vaccines have to align with the general guidance for human vaccines, however the new technology is not fully accounted for in the existing guidance. It is therefore proposed to establish a guideline addressing those specific aspects regarding the manufacturing process, characterisation, specifications and analytical control as well as the definition of active substance and finished product for mRNA vaccines for the prevention, including post exposure prophylaxis, or treatment of diseases caused by infectious agents. The scope of the guideline will be limited to mRNA vaccines (including self-amplifying mRNA).
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2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.3 Discussion (on the problem statement)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	42-43	VE and IFPMA	Consider rewording the sentence and replace ‘quality control’ by ‘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 guideline will provide information and regulatory considerations regarding the following key aspects of the manufacture and control strategy:
2	44-45	VE and IFPMA	Please consider adding the definitions of raw materials.	Definitions of raw materials, starting materials, active substance, finished product intermediate, excipients and finished product
3	44-47	VE and IFPMA	What the starting material is defined as, should be discussed.	Circular Plasmid should be considered instead of Linearized Plasmid, as a starting material.
4	46-47	VE and IFPMA	When using de novo synthesis of plasmid DNA, set up guidance for changing from batch to batch. Proposal is also to include in scope of this 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).	Control 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).

5	46-47	VE and IFPMA	Consider including information and regulatory considerations on master cell bank or working cell bank.	N/A
6	52-53	VE and IFPMA	Proposal to include the possibility to have a process related control strategy for impurities	Purity control strategy: process-related and product-related impurities as well as other potential contaminants and manufacturing process strategies or methods to control them
7	55-56	VE and IFPMA	Please consider elaborating within the guideline on the applicability of vaccine potency concept to RNA vaccines. Rationale: For this class of vaccines, the appropriate use and combination of quantitative biochemical and biophysical methods at DS and DP level can be appropriate as vaccine quality surrogate. Candidate vaccine functionality is being addressed as part of product design and development, while confirmation of the ability of finished product to express antigen with functional active properties is part of batches specification. Functionally active properties of the antigen need to be defined on individual case-by-case, based on the expected immunological response and targeted disease.	Potency-determining attributes testing different tests may be required to control efficacy related product properties, including the verification of expression of functionally active antigen in transfected cells. Rather than committing to establish rules for mRNA products "Potency Testing"; EMA could recognize the debates ongoing on the topic in the frame of the EDQM mRNAVAC Working Party. The underline part above could be deleted or reworded as: "The relevance of "Potency Testing" for information based medicines conveying the code for the therapeutic protein like mRNAs". (To the difference of traditional vaccines and biotech products, the final active protein is not within the mRNA product itself but produced in situ in vivo by patient cells).

8	55-56	VE and IFPMA	Please consider elaborating on the control strategy approaches for multivalent vaccines (multiple targets and multivalent vaccines against either different serotypes or mutational variants of the same parent pathogen).	N/A
9	59	VE and IFPMA	Include guidance for reference materials (generic and/or product specific).	Propose to change into: “Stability studies and shelf-life claims for active substance and finished product”
10	61-67	VE and IFPMA	Please include discussion on nonclinical safety evaluation and information package to be provided in context of new targets produced with platform technology (in alignment to the WHO Guideline mentioned in line 69)	The proposed guideline will also discuss relevant regulatory consideration and challenges relating to: - … - The use of platform technology/ prior knowledge approach for new targets, including what level of changes in the mRNA and /or carrier (LNP) quality attributes would trigger the request for additional nonclinical safety studies
11	63-64	VE and IFPMA	Clarify whether multiple mRNA combinations targeting different (infectious) diseases (e.g. Flu + Covid) are also considered multivalent vaccines.	Include multi-target vaccines (vaccine targeting different infectious diseases) in the definition of multivalent vaccines.
			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	

12	67	VE and IFPMA	CQAs/CPPs/CMAs can remain the same whatever the encoded sequence is. It's an easily platformable technology; however, the whole industry could benefit of 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. EMA might want to consider developing a separate guideline on the topic applicable to all technology platforms.
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2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5 Proposed timeline

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6 Resource requirements for preparation

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.8 Interested parties

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	95	VE and IFPMA	See comment in section 1, row 9: "The proposed scope in this Concept Paper seems to be aligned 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. It is proposed to consult this Working party to align efforts."	EDQM (mRNAVAC Working Party)
2	95	VE and IFPMA	Based on the reliance project EMA is moving forward, it is important to consider consulting other international Competent Authority in order to ensure harmonization at global level.	Academia, Pharmaceutical Industry, EU and other international Competent Authorities
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2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	96	VE and IFPMA	See comment in section 2, row 1: "Please consider including appropriate references to general guidance for human vaccines and WHO guidelines 2005 and 2013 (i.e., WHO guidelines on non-clinical evaluation of vaccines Annex 1, TRS 927 (2005) , WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines, Annex 2, TRS No 987 (2014))"	WHO guidelines on nonclinical evaluation of vaccines, Annex 1, TRS 927 (2005)* *https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccines-annex-1-trs-no-927
2	96	VE and IFPMA	See comment in section 2, row 1: "Please consider including appropriate references to general guidance for human vaccines and WHO guidelines 2005 and 2013 (i.e., WHO guidelines on non-clinical evaluation of vaccines Annex 1, TRS 927 (2005) , WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines, Annex 2, TRS No 987 (2014))"	WHO - Guidelines on the non-clinical evaluation of vaccine adjuvants and adjuvanted vaccines, Annex 2, TRS No 987 (2014)* *https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987
3	96	VE and IFPMA	See comment in section 2.8, row 2: "Based on the reliance project EMA is moving forward, it is important to consider consulting other international Competent	USP Analytical Procedures for mRNA Vaccine Quality (Draft Guidelines) - 2nd Edition*.

			Authority in order to ensure harmonization at global level."	*https://www.uspnf.com/notices/analytical-procedures-mrna-vaccines-20230428
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10. Other comments

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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Thank you for your contribution.

Contact

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