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2 EMA/CHMP/ BWP/211968/2023
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept Paper on the development of a Guideline on the**
5 **quality aspects of mRNA vaccines**
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Agreed by Biologics Working Party	14 June 2023
Adopted by CHMP for release for consultation	22 June 2023
Start of public consultation	23 June 2023
End of consultation (deadline for comments)	30 September 2023

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10 Comments should be provided using this EUSurvey [form](#). For any technical issues, please contact the [EUSurvey Support](#)

Keywords	Guideline, mRNA, Vaccine, Development and Manufacture, Starting Materials, Active Substance, Finished Product
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13 **1. Introduction**

14 This concept paper addresses the need to establish a Guideline on the quality aspects of mRNA
15 vaccines. The number of clinical trial applications for human products and marketing authorisation
16 applications for mRNA containing products significantly increased over the last few years and is
17 expected to increase further in the future. Furthermore, a lot of experience with mRNA vaccines was
18 gained during the COVID-19 pandemic. From an analytical and regulatory perspective, mRNA vaccines
19 are interesting since their classification depends on the target and/or whether they are obtained
20 chemically or biologically.

21 mRNA vaccines against infectious disease have to align with the general guidance for human vaccines,
22 however the new technology is not fully accounted for in the existing guidance. It is therefore proposed
23 to establish a guideline addressing those specific aspects regarding the manufacturing process,
24 characterisation, specifications and analytical control as well as the definition of active substance and
25 finished product for mRNA vaccines for the prevention of infectious disease.

26 The scope of the guideline will be limited to mRNA vaccines against infectious diseases (including self-
27 amplifying mRNA). mRNA-based therapeutics will be out of scope of the document. It is not intended
28 to address specific requirements for mRNA vaccines to be used in clinical trials, however the scientific
29 principles described may also be applicable during pharmaceutical development.

30 **2. Problem statement**

31 Currently there is no guideline which reflects the quality requirements for regulators and industry on
32 mRNA containing vaccines.

33 **3. Discussion (on the problem statement)**

34 mRNA vaccines and their manufacturing process are novel and differ from other types of vaccines.
35 They consist of mRNA (either non-replicating or self-amplifying, and either nucleoside-modified or not)
36 encapsulated in lipid nanoparticles or other kind of delivery systems. Whereas the production of mRNA
37 vaccines has to align with the general guidance for human vaccines, specific quality considerations may
38 apply to these novel products.

39 The proposed guideline will follow the structure of CTD Module 3 where relevant. Additionally, finished
40 product considerations (e.g. choice of excipients, formulation & manufacturing aspects) relevant to
41 finished product formulations containing mRNA will be addressed.

42 The proposed guideline will provide information and regulatory considerations regarding the following
43 key aspects of the manufacture and quality control:

- 44 • Definitions of starting materials, active substance, finished product intermediate, excipients
45 and finished product
- 46 • Control of starting materials (linear DNA template for the preparation of mRNA transcript and
47 plasmid DNA where relevant)
- 48 • Development of an integrated control strategy for the active substance and finished product
49 manufacturing process to ensure consistent quality of mRNA vaccines, based on relevant
50 critical quality attributes (CQAs)
- 51 • Characterisation approaches including investigation of the impurity profile

- 52 • Purity control strategy: process-related and product-related impurities as well as other
- 53 potential contaminants and methods to control them
- 54 • Active substance and finished product specifications
- 55 • Potency testing: different tests may be required to control various aspects of potency also
- 56 including functionality (e.g. mRNA expression, protein expression in transduced cells)
- 57 • Various aspects with respect to the formulation strategies including considerations on
- 58 formation and method of manufacturing of lipid nanoparticles (LNPs) and their stability
- 59 • Stability studies for active substance and finished product

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61 The proposed guideline will also discuss relevant regulatory considerations and challenges relating to:

- 62 • the development and testing of bivalent and multivalent vaccines, as well as to changes in the
- 63 existing mRNA vaccine strains
- 64 • self-amplifying mRNA (sa-mRNA) packaged in LNPs
- 65 • other delivery systems (i.e. non-LNPs)
- 66 • the use of platform technology/prior knowledge approach for new targets

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69 The WHO guidance document, Annex 3 “Evaluation of the quality, safety and efficacy of messenger
70 RNA vaccines for the prevention of infectious diseases: regulatory considerations”, WHO technical
71 report Series, No.1039, 2022 will be taken into account. Furthermore, reference will be made to
72 current and future Ph. Eur. chapters and/or monographs, where applicable.

73 **4. Recommendation**

74 The Biologicals Working Party recommends the establishment of a Guideline on the quality aspects of
75 mRNA vaccines.

76 **5. Proposed timetable**

77 This concept paper will be published for a three-month public consultation period.

78 BWP will take account of all comments received during the public consultation on the concept paper
79 when preparing the draft guideline. The draft guideline will be published for a six-month public
80 consultation period.

81 BWP will take account of all comments received during the public consultation on the draft guideline
82 when preparing the final guideline text. It is expected that the final guideline will come into operation
83 six months after publication following adoption by CHMP.

84 **6. Resource requirements for preparation**

85 The development of the guideline will involve the EMA-BWP Secretariat, the Biologicals Working Party,
86 the CHMP, and the Quality Working Party and GMP/GDP Inspectors Working Group, who would be
87 consulted, as necessary.

88 The BWP should appoint a rapporteur and a drafting group.

89 **7. Impact assessment (anticipated)**

90 The guideline will clarify requirements for regulators and pharmaceutical industry with respect to the
91 quality aspects of mRNA containing vaccines taking into account the concepts of recent development.

92 The guideline will not introduce new requirements on medicinal products already authorised and on the
93 market.

94 **8. Interested parties**

95 Academia, Pharmaceutical Industry, EU Competent Authorities

96 **9. References to literature, guidelines, etc.**

- 97 • Relevant ICH Quality & Multidisciplinary Guidelines
- 98 • Reflection paper on the regulatory requirements for vaccines intended to provide protection
99 against variant strain(s) of SARS-CoV-2 (EMA/117973/2021)
- 100 • Guideline on process validation for the manufacture of biotechnology-derived active substances
101 and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014)
- 102 • Guideline on quality aspects included in the product information for vaccines for human use
103 (EMA/CHMP/BWP/133540/2017)
- 104 • Toolbox guidance on scientific elements and regulatory tools to support quality data packages
105 for PRIME and certain marketing authorisation applications targeting an unmet medical need
106 EMA/CHMP/BWP/QWP/IWG/694114/2019
- 107 • Guideline on process validation for finished products - information and data to be provided in
108 regulatory submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.
- 109 • Guideline on the sterilisation of the medicinal product, active substance, excipient and primary
110 container EMA/CHMP/CVMP/QWP/850374/2015
- 111 • Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of
112 infectious diseases: regulatory considerations, WHO/RNA/DRAFT/22 DECEMBER 2020,
- 113 • Relevant Ph. Eur chapters and/or monographs