



1 20 February 2026
2 EMA/CVMP/IWP/128476/2025
3 Committee for Veterinary Medicinal Products (CVMP)

4 **Guideline on quality aspects of mRNA vaccines for**
5 **veterinary use**
6 **Draft**

Draft agreed by Immunologicals Working Party	22 October 2025
Adopted by CVMP for release for consultation	12 February 2026
Start of public consultation	20 February 2026
End of consultation (deadline for comments)	31 August 2026

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Keywords	mRNA, vaccine, development and manufacture, starting materials, active substance, quality, veterinary, finished product
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20 **Executive summary**

21 The aim of the guideline is to outline the information which should be included for mRNA vaccines in
22 the marketing authorisation application (MAA) dossier of veterinary vaccines as required in Section IIIb
23 of Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December
24 2018 on veterinary medicinal products (repealing Directive 2001/82/EC), referred to as Annex II to
25 Regulation (EU) 2019/6 throughout the document.

26 The data requirements and points for consideration for the demonstration of quality of veterinary
27 mRNA vaccines are discussed, and guidance is provided on the information to be included in Part 2 of
28 the MAA dossier.

29 **1. Introduction (background)**

30 In the last years, experience with mRNA vaccines has increased in the field of human vaccines in the
31 course of the COVID pandemic and the corresponding development of mRNA vaccines for human use.

32 mRNA vaccines can be beneficial in terms of safety (no reversion to virulence, little to no use of
33 biological material in the manufacturing process and consequently no contamination with extraneous
34 agents) and may also offer the possibility for a more easily adaptable and scalable and therefore more
35 cost-efficient manufacturing process.

36 They also may provide a wider stimulation of the immune system, cellular and humoral, including the
37 stimulation of a cytotoxic T cell response.

38 mRNA vaccines for veterinary use must align when relevant with the general guidance for veterinary
39 vaccines, however this new technology is not specifically addressed in the existing guidelines.
40 Therefore, this guideline addresses those specific aspects regarding the manufacturing process,
41 characterisation, specifications and analytical control as well as the definition of active substance and
42 finished product for mRNA vaccines for veterinary use intended for the prevention of infectious
43 diseases.

44 mRNA-based vaccines are amenable to platform technology approaches and the use of vaccine
45 platform technology master files (vPTMF), which may enable the rapid development of new vaccines,
46 facilitating timely responses to emerging infectious diseases. Specific guidance on data requirements
47 for vPTMF is provided in the respective guideline (EMA/CVMP/IWP/286631/2021).

48 **2. Scope**

49 This guideline is applicable to mRNA vaccines against infectious diseases, based on messenger RNA
50 (mRNA) and self-amplifying mRNA (sa mRNA). The guideline mainly addresses the requirements for
51 development, manufacture and control which are specific to mRNA vaccines for veterinary use.

52 It is not intended to address specific requirements for replicon mRNA vaccines, although some of the
53 principles described in this guideline may also be applicable.

54 mRNA-based veterinary medicinal products other than vaccines against infectious diseases are out of
55 scope of this guideline.

56

57 **3. Legal basis and relevant guidelines**

58 Requirements for a marketing authorisation application are laid down in Article 8(1) (b) of Regulation
59 (EU) 2019/6 and are specified in Title IIIb 'Requirements for immunological veterinary medicinal
60 products' of Annex II of the Regulation.

61 This guideline should be read in conjunction with the introduction and general principles of Annex II to
62 Regulation (EU) 2019/6, the European Pharmacopoeia (Ph. Eur.) and all other relevant EU and VICH
63 guidelines.

64 The specific EMA guideline (draft) and Ph. Eur. chapters relevant to mRNA vaccines for human use
65 have been also taken into account.

66 **4. General considerations**

67 RNA substances for mRNA vaccines are non-viral, nucleic acid-based substances manufactured from a
68 linear DNA template via in vitro transcription (an enzymatic, cell-free process).

69 There are two types of mRNA: non-replicating mRNA and self-amplifying mRNA.

70 Non-replicating mRNA (NRM) constructs encode the coding sequence (CDS) and are flanked by 5' and
71 3' untranslated regions (UTR's), a 5' cap and a 3' PolyA – tail. The self-amplifying mRNA (sa mRNA)
72 construct encodes additional replicase components able to direct intracellular mRNA amplification.

73 For a successful delivery of the mRNA to the cell, a delivery system is necessary to protect the mRNA
74 from RNase degradation and to allow uptake into the cytoplasm. Currently, LNPs (lipid nanoparticle -
75 based delivery systems) are mainly used. LNPs consist of lipid and lipid-like components and are able
76 to encapsulate the mRNA based on self-assembly.

77 mRNA vaccines mimic infection with a live microorganism and induce a response of the immune
78 system.

79 **5. Data requirements for Part II (Quality)**

80 The data requirements for veterinary vaccines have to be addressed in the application dossier. The
81 information must be presented in accordance with the format set out in Annex II to Regulation (EU)
82 2019/6. The following are points to be addressed, as appropriate, in the various sections of the
83 dossier.

84 **Qualitative and quantitative composition (IIIb.2.A1.)**

85 The mRNA /sa mRNA itself is considered as active substance.

86 The name of the active substance and the concentration per dose should be stated. "mRNA" or
87 "saRNA" is not considered an adequate description of the active substance.

88 The minimum concentration of mRNA / sa mRNA used to establish efficacy should be given.

89 **Product development (IIIb.2.A2.)**

90 The full mRNA sequence including the 5' cap, the 5' and 3' UTR regions and the poly(A)-tail needs to
91 be provided as well as information on the encoded antigen(s). The functional features of the different
92 elements of the molecular sequence should be described in detail, and the amino acid sequence should
93 be provided for the encoded antigen(s) and additional encoded proteins (if relevant).

94 Modifications/alterations to nucleosides should be indicated.

95 Components like nucleotides and the 5' cap or capping reagents are defined as starting materials for
96 mRNA vaccines. Additionally, the linear DNA template is defined as a starting material (even though it
97 is not part of the active substance itself, but it defines the sequence of the mRNA).

98 Characterisation:

99 Characterisation of the mRNA is intended to determine structure, physico-chemical properties, purity
100 and functionality (ability to be translated into the protein of interest).

101 Batches used for characterisation studies should be clearly identified (development, pilot, full scale).

102 Batches used in clinical studies should also be included in characterisation studies, since clinical
103 experience is highly relevant for justification of specifications.

104 Delivery systems:

105 To ensure protection of the mRNA and effective entry into the cell, a suitable delivery system is
106 necessary. Currently, lipid nanoparticles (LNPs) are used.

107 LNP delivery systems contain the active substance encapsulated in LNPs which are composed of lipid
108 and lipid-like components which are capable of encapsulating the mRNA. Encapsulation guarantees
109 stability of the mRNA (protection from enzymatic degradation) and delivery into the cytosol.

110 The mRNA active substance and the selected excipients in the formulation, including for example the
111 lipids used for the LNP-formation, should be described and defined. The formulation development
112 studies should be sufficiently described to justify the selection of suitable lipids and other excipients for
113 a robust LNP formulation of the mRNA vaccine finished product. The lipid-based nano delivery system
114 of the mRNA vaccine (i.e. LNP) needs to be sufficiently characterised.

115 Other possible delivery systems could be used and should be also sufficiently characterised.

116 **Description of the manufacturing method (IIIb.2B.)**

117 A comprehensive flow chart of the manufacturing process should be provided and all manufacturing
118 steps and materials used in general should be described in detail.

119 Information on process parameters should be presented, relevant in-process controls should be
120 identified, and acceptance criteria should be established. These may include, but are not limited to
121 bioburden and endotoxin, identity, purity and mRNA yield.

122 Clearance capacity for the removal of contaminants will be established for the purification process by
123 the difference in impurity levels before and after critical purification steps. Batch acceptance will be
124 established based on compliance with the upper acceptance limits defined for each impurity. Validation
125 studies for clearance capacity will be required. Suitable in-process controls for any potential
126 contaminants of concern should be developed and routine batch test upper acceptance limits
127 established, based on data from tests showing the safety of that concentration. Appropriate limits may
128 be set for e.g. residues of DNA template, enzymes or presence of dsRNA.

129 **Production and control of starting materials (IIIb.2C.)**

130 As the linear DNA template is defined as a starting material, detailed information about the following
131 aspects should be provided:

- 132 • The origin of the DNA template
- 133 • The full sequence of the entire DNA template
- 134 • Information about the host cell line if applicable
- 135 • Information on the cell bank system if applicable

136 Reference is also made to Ph. Eur. general chapter 5.40 DNA templates for the preparation of mRNA
137 substances.

138 For other starting materials, the suppliers should be stated, and certificates of analysis should be
139 provided.

140 In case starting or raw materials of biological origin are used they must comply with the relevant
141 guidance, e.g. Ph. Eur. chapter 5.2.5 and the "Note for Guidance on Minimizing the Risk of
142 Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
143 (EMA/410/01)" and other relevant guidance documents.

144 The absence of bacterial and fungal contamination, as well as mycoplasma and spiroplasma where
145 relevant, should be determined.

146 **Control tests during the manufacturing process (IIIb.2D.) and control tests on the finished**
147 **product (IIIb.2E.)**

148 Specifications for the active substance and finished product should be established and justified.
149 Descriptions of analytical methods and acceptance limits for in-process and finished product testing,
150 including information on assay qualification or validation, should be provided.

151 A summary of the results of the testing on all relevant batches produced should be provided. The
152 appropriateness of performing tests on the bulk of purified plasmid versus the formulated vaccine
153 should be considered on a case-by-case basis and justified.

154 At least three batches of vaccine should be characterised as fully as possible to determine consistency
155 of the manufacturing process and to demonstrate conformity with specifications. Any differences
156 between batches should be noted.

157 The specifications should take into account the results from the characterisation studies. The control
158 steps should include mRNA integrity, mRNA identity and mRNA content, functionality, polyA-tail-
159 length, 5' capping efficiency, bacterial endotoxin content and bioburden. Potential process- and product
160 related impurities should also be considered. Where relevant, limits should be set.

161 The specifications at the finished product level should also include appearance and some
162 physicochemical properties (e.g. pH, osmolality, particle content, extractable volume) and carrier (LNP)
163 attributes.

164 Batch potency/ Functionality:

165 The potency of each batch of finished product should be established using a suitably validated test. The
166 most appropriate approach will vary depending on the composition of the vaccine, the nature of the
167 disease, the expressed antigen(s) and the immune response being sought. Thus, the design of a
168 potency assay will require careful consideration and will be assessed on a case-by-case basis. An
169 appropriate potency test should include a combination of tests, e.g. mRNA content, encapsulation
170 efficiency, mRNA integrity or cell-based in vitro expression assays.

171 Where possible, an approved in-house reference preparation should be established, from an
172 appropriately characterised batch of vaccine that has been shown to be efficacious (or of the same
173 quality as the efficacious batches).

174 An appropriate level of functionality of the mRNA should be demonstrated at least during the
175 developmental phase. A qualitative assay can be used to detect the expression of the protein of
176 interest in a cell line of the target species origin, the assay may not be required to be performed on a
177 routine basis for batch potency testing.

178

179 **Batch to batch consistency (IIIb.2F.)**

180 Results from three consecutive batches of finished product from three production runs representative
181 of routine production should be provided or otherwise justified. The three batches of vaccine should be
182 prepared from at least two different active substance batches. Manufacturing batch protocols for each
183 of the batches should be provided.

184 **Stability tests (IIIb.2G.)**

185 The requirements as stated in VICH GL17 'Stability testing of biotechnological/biological veterinary
186 medicinal products' generally apply to mRNA vaccines.

187 However, due to the specific characteristics of mRNA vaccines, establishment of an appropriate
188 stability testing program considering those characteristics may be necessary.

189 The batches used in the stability studies should be representative of commercial material and should
190 be manufactured using the same process. They should be formulated with the same buffer, have the
191 same RNA concentration and should be stored in the same container closure systems as the
192 commercial batches. Stability indicating parameters must be linked to the characterisation testing but
193 should generally include purity (mRNA integrity), concentration and poly(A)-tail. On the finished
194 product level, also quantitative detection of degradation and testing of functionality should be
195 considered.

196 In-use stability studies are of high importance to ensure maintenance of the functionality during use.
197 In case freeze/thaw cycles are foreseen, the influence on integrity of the product has to be considered.
198 Duration of storage in a refrigerator and/or at room temperature should be included in the stability
199 study.

200 Stability data should be based on long-term, real-time stability studies under all claimed temperature
201 conditions.

202 Data from development or clinical batches may be used as long as their representativeness of the
203 commercial material can be confirmed.

204 **6. References**

205 Ph. Eur. general chapter 5.36 mRNA vaccines for human use

206 Ph. Eur. general chapter 5.39 mRNA substances for the production of mRNA vaccines for human use

207 Ph. Eur. general chapter 5.40 DNA templates for the preparation of mRNA substances