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Guideline on quality aspects of mRNA vaccines for veterinary use

Draft

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Executive summary

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

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

1. Introduction (background)

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

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

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

mRNA vaccines for veterinary use must align when relevant with the general guidance for veterinary vaccines, however this new technology is not specifically addressed in the existing guidelines. Therefore, this guideline addresses 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 veterinary use intended for the prevention of infectious diseases.

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

2. Scope

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

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

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

3. Legal basis and relevant guidelines

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

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

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

4. General considerations

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

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

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

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

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

5. Data requirements for Part II (Quality)

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

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

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

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

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

Product development (IIIb.2.A2.)

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

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

Characterisation:

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

Batches used for characterisation studies should be clearly identified (development, pilot, full scale). Batches used in clinical studies should also be included in characterisation studies, since clinical experience is highly relevant for justification of specifications.

Delivery systems:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Batch potency/ Functionality:

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

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

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

Batch to batch consistency (IIIb.2F.)

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

Stability tests (IIIb.2G.)

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

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

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

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

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

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

6. References

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

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

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