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3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 **Guideline on data requirements for applications for**
5 **immunological veterinary medicinal products intended for**
6 **limited markets submitted under Article 23 of the**
7 **Regulation (EU) 2019/6**
8 **Draft**

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10 Comments should be provided using this [template](#). The completed comments form should be sent to Vet-Guidelines@ema.europa.eu

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29 **Executive summary**

30 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on
31 veterinary medicinal products and repealing Directive 2001/82/EC introduces specific provisions for
32 applications for limited markets (Article 23).

33 The general aim of this guideline is to define acceptable data requirements for the demonstration of
34 safety and efficacy in case of marketing authorisation applications for immunological veterinary
35 medicinal products (IVMPs) intended for limited markets submitted under Article 23 of Regulation
36 2019/6.

37 It is the intention of the guideline to indicate which data requirements can be reduced for this type of
38 applications; however, it is recognised that this is not always feasible as not all scenarios can be
39 addressed in a general guidance document.

40 The specific data requirements for the demonstration of safety and efficacy for immunological
41 veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation
42 2019/6 are presented in Table 1 of the guideline.

43

44 **1. Introduction**

45 From 2007 to 2017, the CVMP developed a guideline on data requirements for MUMS/limited market
46 for immunological veterinary medicinal products with the aim to stimulate research, development and
47 innovation of new veterinary medicines intended for minor uses and minor species (MUMS/limited
48 market). That guideline was developed with the purpose of reducing data requirements where possible
49 for products classified as intended for MUMS/limited market while still providing assurance of
50 appropriate quality, safety and efficacy and complying with the legislation in place and leading to an
51 overall positive benefit-risk balance for such products.

52 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on
53 veterinary medicinal products repealing Directive 2001/82/EC introduces specific provisions for limited
54 markets including definition of limited market and specific conditions for granting derogation to the
55 data requirements defined in Annex II of the Regulation. These provisions need to be taken into
56 account when defining the data requirements.

57 Therefore, the former MUMS/limited markets guidelines have been replaced by the current limited
58 markets guidelines, which were drafted in line with the new legal provisions.

59 It is the intention of the guideline to provide data requirements that can be reduced in accordance with
60 Article 23 of Regulation EU 2019/6, to facilitate the applicant's work for estimating the required
61 resources for a limited market application preparing the application dossier and provide for
62 predictability. However, it is recognised that this is not always feasible as not all scenarios can be
63 addressed in a general guidance document.

64 The general aim of this guideline is to define acceptable data requirements for the demonstration of
65 safety and efficacy for IVMPs (immunological veterinary medicinal products) for limited markets.

66 In addition, the reduced data requirements for limited markets will result in certain cases in the
67 reduction of the number of animals used in testing, which is in line with the Directive 2010/63/EU on

68 the protection of animals used for scientific purposes and the 3Rs principles of replacement, reduction
69 and refinement.

70 The guidance provided in this document is general. In addition, Scientific Advice is available upon
71 request to confirm precise requirements for a specific application.

72 **2. Scope**

73 This guideline applies to marketing authorisation applications for immunological veterinary medicinal
74 products intended for limited markets.

75 The objective of this guideline is to clarify the data requirements for applications for limited markets
76 and thereby provide applicants with information on safety and efficacy data requirements to support
77 applications for authorisation of immunological veterinary medicinal products under Article 23 of the
78 Regulation (EU) 2019/6.

79 According to Annex II to Regulation (EU) 2019/6, a novel therapy veterinary medicinal product could
80 also fall into the category of immunological veterinary medicinal products. This guideline also applies to
81 these cases.

82 Biological veterinary medicinal products other than immunological veterinary medicinal products are
83 out of the scope of this guideline. Data requirements for these products are discussed in the specific
84 revised guidelines on efficacy and target animal safety and on safety and residue data requirements
85 for veterinary medicinal products intended for limited markets.

86 This guideline is not intended to provide information on administrative procedures (including scientific
87 advice procedures).

88 **3. Definitions**

89 Definitions are provided in Article 4 of Regulation (EU) 2019/6:

90 **Limited market**

91 According to Article 4(29) of Regulation (EU) 2019/6, '*Limited market*' means a market for one of the
92 following medicinal product types:

93 (a) *veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or*
94 *in limited geographical areas;*

95 (b) *veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs,*
96 *chickens, dogs and cats.*

97 **Immunological veterinary medicinal product**

98 According to Article 4(5) of Regulation (EU) 2019/6 an '*Immunological veterinary medicinal product*'
99 *means a veterinary medicinal product intended to be administered to an animal in order to produce*
100 *active or passive immunity or to diagnose its state of immunity;*

101 **Clinical trial**

102 According to Article 4(17) of Regulation (EU) 2019/6, a '*Clinical trial*' is a study which aims to examine
103 *under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions*
104 *of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing*
105 *authorisation or a change thereof.*

106 **Pre-clinical study**

107 According to Article 4(18) of Regulation (EU) 2019/6, a 'Pre-clinical study' means a study not covered
108 by the definition of clinical trial which aims to investigate the safety or efficacy of a veterinary
109 medicinal product for the purpose of obtaining a marketing authorisation or a change thereof.

110 **4. Legal basis**

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

114 One of the intentions of the current legislation for the authorisation of veterinary medicines as laid
115 down in the preambles of Regulation (EU) 2019/6, recital no. 30, is to facilitate the authorisation of
116 veterinary medicinal products intended for limited markets:

117 "(30) Companies have less interest in developing veterinary medicinal products for markets of a
118 limited size. In order to promote the availability of veterinary medicinal products within the Union for
119 those markets, in some cases it should be possible to grant marketing authorisations without a
120 complete application dossier having been submitted, on the basis of a benefit-risk assessment of the
121 situation and, where necessary, subject to specific obligations. In particular, the grant of such
122 marketing authorisations should be possible in the case of veterinary medicinal products for use in
123 minor species or for the treatment or prevention of diseases that occur infrequently or in limited
124 geographical areas."

125 In addition, Article 23 of Regulation (EU) 2019/6 introduces a specific legal basis for veterinary
126 medicinal products intended for limited markets, also specifying the conditions, which need to be
127 fulfilled by applications for limited markets:

128 "1. By way of derogation from point (b) of Article 8(1), the applicant shall not be required to provide
129 the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the
130 following conditions are met:

131 (a) the benefit of the availability on the market of the veterinary medicinal product to the animal or
132 public health outweighs the risk inherent in the fact that certain documentation has not been provided;

133 (b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited
134 market.

135 2. Where a veterinary medicinal product has been granted a marketing authorisation in accordance
136 with this Article, the summary of product characteristics shall clearly state that only a limited
137 assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or
138 efficacy data."

139 This is also reflected in Annex II of Regulation (EU) 2019/6 under section IV.6 – Applications for
140 limited markets:

141 "A marketing authorisation may be granted for a limited market in the absence of comprehensive
142 safety and/or efficacy data when, as provided for in Article 23 of this Regulation, the applicant
143 demonstrates that the product is intended for use in a limited market and that the benefit of
144 availability of the new product outweighs the risk associated with the omission of some of the safety or
145 efficacy data required by this Annex.

146 For such applications, the applicant shall submit Parts 1 and 2 as described in this Annex.

147 *For Parts 3 and 4, some of the safety or efficacy data required by this Annex may be omitted. As*
148 *regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by*
149 *the Agency shall be taken into account."*

150

151 **5. Requirements for IVMPs for limited markets**

152 Generally, the requirements as mentioned in section IIIb of Annex II to Regulation 2019/6 and the
153 relevant European Pharmacopoeia (Ph. Eur.) general chapters and monographs apply to all IVMPs,
154 including those for limited markets. The CVMP guidelines concerning IVMPs (e.g. association guideline,
155 in-use stability guideline) are applicable to products for limited market products. Possible reductions in
156 requirements for new marketing authorisations and relevant variations (i.e. variations to add new
157 target species) are listed in Table 1.

158 For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs
159 containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant
160 parts of the safety and efficacy data requirements of Annex II to Regulation 2019/6.

161 For IVMPs containing a GMO, this guideline is only applicable for efficacy requirements. In addition to
162 requirements of Directive 2001/18/EC, the full set of safety data as required in Annex II to Regulation
163 2019/6 should be provided. Nevertheless, it is acceptable for an applicant to submit data, which has
164 been generated for similar GMO constructs already authorised to fulfil part of the requirements for
165 safety.

166 In addition to the data reductions listed in Table 1, the following general considerations regarding
167 reductions in requirements can be applied:

- 168 1. For pre-clinical safety studies (laboratory safety studies), the GLP requirements can be lifted
169 provided the protocols and reports allow a satisfactory assessment of the trials.
- 170 2. Literature may be used to support the safety and efficacy warnings and indications, provided
171 these data were generated using the product for which the application is made. Bibliographic
172 data should originate from acknowledged scientific literature ideally from peer-reviewed
173 journals.
- 174 3. Clinical trials (field trials) are required when sufficient data from laboratory (pre-clinical)
175 studies are not provided to validate safety and/or efficacy. Such studies may not need to be
176 conducted to current GCP requirements, provided the protocols and reports allow a satisfactory
177 assessment of the trials.
- 178 4. The applicant should test for treatment differences between vaccinated and control animals
179 using appropriate statistical methodology. It should be possible in all cases to demonstrate a
180 benefit of treatment. The practical limitations of data collection for a limited market product
181 will be taken into consideration.

182 **6. Summary of Product Characteristics**

183 Where a veterinary medicinal product has been granted a marketing authorisation in accordance with
184 Article 23 of Regulation (EU) 2019/6, the summary of product characteristics shall clearly state that
185 only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive
186 safety or efficacy data. In line with Article 35(1)(j)(i) of Regulation (EU) 2019/6, the SPC will carry the

187 following statement: *“marketing authorisation granted for a limited market and therefore assessment*
188 *based on customised requirements for documentation”*.

189 **7. References**

190 The following legislation, guidelines and notes for guidance are relevant to this guideline:

- 191 1. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on
192 veterinary medicinal products and repealing Directive 2001/82/EC
193
- 194 2. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the
195 deliberate release into the environment of genetically modified on the deliberate release into the
196 environment of genetically modified organisms and repealing Council Directive 90/220/EEC
197 [http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-](http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF)
198 [0baaf0518d22.0004.02/DOC_1&format=PDF](http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF)

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200 **Table 1: Reduced data requirements for IVMPs intended for limited markets**

201 Please note that the numbering of the table refers to the numbering in Section IIIb of Annex II to Regulation 2019/6.

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactiv.
3.A	General requirements	For inactivated IVMPs, use of standard batches in safety studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study.	N/a	✓
		For live IVMPs, the use of the least attenuated passage level is not required. The titre used in the studies should be adequately justified.	✓	N/a
3.B	Pre-clinical studies (Laboratory safety studies)			
3.B.2	Safety of one administration of an overdose	Safety of an overdose is not required.	✓	N/a
3.B.3	Safety of the repeated administration of one dose	Safety of first re-vaccination is not required. Demonstration of safety of the primary vaccination schedule is sufficient.	✓	✓
3.B.4	Examination of reproductive performance	Studies for the examination of reproductive performance may be omitted. If such studies are not performed, relevant warnings should be given in the SPC.	✓	✓
3.B.5	Examination of immunological functions	Studies for the examination of immunological functions may be omitted. If necessary, relevant warnings should be given in the SPC.	✓	✓
3.B.6.1	Spread of vaccine strain	Published literature may be used to fulfil this requirement. In the absence of adequate scientific literature, the relevant studies should be performed to evaluate spread to unvaccinated target animals and potentially non-target species which could be highly susceptible to the vaccine strain.	✓	N/a
3.B.6.2	Dissemination in the vaccinated animal	Data not required unless the vaccine strain is shown to spread. Published literature may be used to fulfil this requirement. In the absence of adequate scientific literature, the relevant studies should be provided.	✓	N/a

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactiv.
		Dissemination studies are required in all cases for zoonotic diseases and should take into account the persistence of the organism at the injection site.	✓	N/a
3.C	Clinical trials (field studies)	<p>If pre-clinical (laboratory) studies adequately demonstrate the absence of a significant target animal safety risk, clinical (field) studies are not required.</p> <p>It should be adequately justified that the data from the pre-clinical (laboratory) studies are representative for safety under field conditions. Appropriate justification includes the use of representative animals versus field conditions in the EU, e.g. body weight, physiological status and reproduction performance.</p>	✓	✓
4.B	Pre-clinical studies (Laboratory trials)	For inactivated IVMPs, use of standard batches in efficacy studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study.	N/a	✓
		For live IVMPs, the efficacy studies may be combined with one-dose pre-clinical (laboratory) safety studies. The use of the maximum passage level is not required. The titre used in the studies should be adequately justified.	✓	N/a
		For immunosera an immunological action should be demonstrated.	N/a	N/a
		Omission of studies such as duration of immunity is acceptable, provided that it is made clear in the SPC that the data are not available.	✓	✓
		Omission of studies such as effect of maternally derived antibodies (MDA), are acceptable, provided that it is made clear in the SPC that the data are not available, and it should be scientifically justified.	✓	✓

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactiv.
4.C	Clinical trials (Field trials)	Clinical (field) studies are not required if the pre-clinical (laboratory) efficacy studies adequately establish and validate the efficacy and it is justified that they are representative of efficacy under field conditions. Appropriate justification includes the use of a laboratory challenge model, which has been shown to be relevant to EU field situation and reproducing relevant clinical signs and / or microbiological outcomes.	✓	✓
		Clinical (field) efficacy studies may replace pre-clinical (laboratory) efficacy studies, if adequately justified.	✓	✓

202
203

N/a = not applicable
Relevant variations: those variations aimed to add new target species