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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**GUIDELINE ON DATA REQUIREMENTS TO SUPPORT IN-USE STABILITY CLAIMS
FOR VETERINARY VACCINES**

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26 EXECUTIVE SUMMARY

27 This guideline outlines the data that should be provided in support of in-use shelf-life claims for
28 veterinary vaccines. This guideline should be read in conjunction with Directive 2001/82/EC Title II,
29 as amended. The aim of this guideline is to provide a framework which will enable applicants to
30 maintain a consistent approach when generating data in support of allocating an appropriate in-use
31 shelf-life to a veterinary vaccine, based on existing regulatory requirements

32 1. INTRODUCTION

33 Veterinary vaccines may be marketed as either single or multidose presentations. There are various
34 recommended routes of administration for vaccines; e.g. parenteral use, oral administration following
35 reconstitution in drinking water or in feed, respiratory/oral route by spray application. The length of
36 time it takes for the user to administer the vaccine to the target species, and/or for the take of the
37 vaccine by the target species (e.g. in the case of vaccine administered via drinking water) can vary
38 considerably. The duration of this period for each vaccine is defined as the in-use shelf-life.
39 Appropriate data are required to demonstrate that the vaccine retains an acceptable quality profile and
40 remains efficacious throughout the in-use shelf-life.

41 2. SCOPE

42 This guideline outlines the data requirements which should be provided in support of claims for in-use
43 stability of veterinary vaccines.

44 3. LEGAL BASIS

45 This guideline has to be read in conjunction with the introduction and general principles (4) and part
46 six of the Annex I to Directive 2001/82 as amended.

47 4. MAIN GUIDELINE TEXT

48 4.1 *General concepts:*

49 The general principles for demonstrating an appropriate in-use shelf-life will be similar regardless of
50 the different pharmaceutical forms of the vaccine, consisting of data to demonstrate acceptable
51 potency and microbial safety under defined conditions of use for the duration of the proposed in-use
52 period.

53 For some vaccines, a recommendation to use immediately will be stated on the Summary of Product
54 Characteristics (SPC) instead of a defined in-use shelf-life. For such products, and if it is practical to
55 use immediately (e.g. single dose presentations), since an in-use shelf-life is not defined no data are
56 required. The warning use immediately should not be proposed by applicants as a substitute for
57 generating in-use stability data in circumstances whereby it is not possible to administer all the doses
58 in a short time frame, e.g. multidose presentations containing a large number of doses.

59 It is important that due consideration is given when proposing an in-use shelf-life, that the proposed
60 time will be sufficient to permit vaccination of the maximum number of target animals according to
61 the number of doses and according to the recommended conditions of use as instructed in the SPC.
62 The proposed in-use shelf-life shall not be longer than necessary to administer all doses to the target
63 animals. For multidose parenteral vaccines, it is generally accepted that a shelf-life of no longer than
64 one working day (8-10 hours) should be proposed, and the claim must be supported by relevant in-use
65 stability data.

66 4.2 *Design of the in-use stability study*

67 In support of the proposed in-use shelf-life, data from two different batches of finished product should
68 be provided. This data shall demonstrate compliance with the critical stability-indicating parameter(s)
69 at time zero (T0) (i.e. when the primary container is first opened or when the vaccine is manipulated
70 into final formulation for administration), and after T0 plus the proposed in-use shelf-life (T0 +X
71 hours). The vaccine should be tested after it has been prepared for use as per the instructions in the
72 SPC at T0 and T0+X hours.

73 The conditions for the in-use stability study should be designed to mimic use of the product in practice
74 taking into account the number of doses in the container and any dilution/reconstitution before use.
75 For example, reconstituted vaccine which should be administered in drinking water at ambient
76 temperatures in a poultry house, or vaccine which should be diluted in a water bath at a defined
77 temperature for administration by immersion to fish, should not be stored in a sterile refrigerated
78 environment during the in-use stability study. However, mimicking the conditions of use in the field
79 will not be applicable in all cases e.g. for an inactivated suspension for injection in a sealed immediate
80 container. The study design should be documented in the dossier and justified by the applicant.

81 Data from pilot scale batches are acceptable once it is confirmed that the method of manufacture is
82 identical to Part II of the marketing authorisation dossier, and provided that the batches conform to the
83 finished product specifications.

84 In-use stability data from a larger combination vaccine may be used in support of the in-use stability
85 of a vaccine for which the composition is identical with the exception that there are fewer active
86 ingredients. This would be acceptable provided that there is no reason to suspect that the in-use
87 stability would be any different on the basis of different antigen combinations, e.g. if the stability of
88 the finished product of the larger combination vaccine is demonstrated to be comparable to the smaller
89 vaccine.

90 The suitability of the tests conducted, and the acceptance limits chosen for the demonstration of in-use
91 stability should be justified.

92 4.3 *Potency testing*

93 For live vaccines, potency testing should be performed at T0 and T0+X hours and the results must
94 demonstrate that the potency will not decrease below the minimum guaranteed titre at T0+X hours.
95 Any loss in titre during the in-use period must not be of a magnitude that would permit a vaccine to
96 fall below the minimum guaranteed titre if it was a “worst case scenario” batch (i.e. a batch that was
97 released at the minimum release titre and that was used near the end of the finished product shelf-life).

98 For inactivated vaccines, if the proposed in-use shelf-life is within one working day (maximum 10
99 hours) it is acceptable to omit the potency testing from the in-use shelf-life stability study.

100 In the case of vaccines for which a suitable *in vitro* method is not available for the batch potency test,
101 in-use stability data from one batch, rather than two, may be submitted with the initial application.
102 This approach would be acceptable if the results from one batch are supportive of the proposed in-use
103 shelf-life. Justification should be provided by the applicant for the use of only one batch in the in-use
104 stability study, and a commitment should be made that at the next time the batch potency test is
105 conducted for routine release of the product, that the potency will also be tested at the end of the
106 proposed in-use shelf-life. The complete in-use stability study should be submitted when the
107 remaining data from the second batch are available.

108 4.4 *Microbial Safety*

109 The microbial safety of the vaccine should be demonstrated over the proposed in-use shelf-life. If
110 microbial safety data is not considered necessary in support of the proposed in-use shelf-life, this
111 should be justified by the applicant.

112 If an antimicrobial preservative is included in the vaccine, the efficacy of the antimicrobial
113 preservative under in-use conditions should be demonstrated, this may include evaluation of the
114 efficacy of the antimicrobial preservative at T0 and at T0+X hours. The efficacy of the antimicrobial
115 preservative should be evaluated as per the European Pharmacopoeia monograph *Vaccines for*
116 *Veterinary Use* (0062), which includes the requirement that samples are tested at suitable intervals
117 over the proposed in use shelf-life.

118 If there is no antimicrobial preservative in the vaccine, if the product cannot be used immediately and
119 an in-use shelf-life is proposed, the applicant should demonstrate that the product remains acceptable
120 for its recommended period of use. In this case, data to show that there is no increase in
121 microbiological contamination relative to an appropriate control (e.g. solvent or unmedicated drinking
122 water) between T0 and T0+X hours may be deemed supportive.

123 **DEFINITIONS**

124 In-use shelf-life: the maximum period of time recommended for use of one single presentation of a
125 veterinary vaccine as used under recommended conditions, for which the level of
126 quality, safety and efficacy of the vaccine has been demonstrated to be acceptable.

127 **REFERENCES**

128 European Pharmacopoeia Monograph *Vaccines for Veterinary Use* (0062).

129 European Pharmacopoeia Monograph *Efficacy of Antimicrobial Preservation* (50103)

130 7B1m14a Inclusion of Antimicrobial Preservatives in Immunological Veterinary Medicinal Products.

131 Position Paper on the Maximum In-Use Shelf-Life for Medicated Drinking Water.

132 EMEA/CVMP/1090/02-FINAL.