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Concept paper on the revision of annex 4 of the guidelines on good manufacturing practice – manufacture of veterinary medicinal products other than immunologicals

Agreed by GMP/GDP IWG and PIC/S	September 2021 (IWG) October 2021 (PIC/S)
Start of public consultation	9 November 2021
End of consultation (deadline for comments)	9 January 2022

The proposed guideline will replace:

- 'Eudralex Volume 4: manufacture of veterinary medicinal products other than immunologicals
- for PIC/S participating authorities: PE 009-14: annex 4 - manufacture of veterinary medicinal products other than immunologicals

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

Keywords	GMP, veterinary medicinal product, annex 4
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1. Introduction

1 This concept paper addresses the need to update Annex 4 (manufacture of veterinary medicinal
2 products other than immunologicals) of the good manufacturing practice (GMP) guide. Annex 4 is
3 common to the member states of the European Union (EU)/European Economic Area (EEA) as well as
4 to the participating authorities of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The
5 original version has not been revised since it was originally issued in 1992. Since that time, there have
6 been significant changes in GMP following the adoption of the International Council for Harmonisation
7 of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8, Q9, Q10 and Q11 guidelines,
8 International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary
9 Medicinal Products (VICH) guidelines. Additionally, there have been significant development in
10 veterinary product manufacture, technologies, products types such as anticancer products, flavoured
11 products, antiviral, veterinary medicinal products without marketing authorisation (registered
12 homeopathic veterinary medicinal products, veterinary medicinal products exclusively for pets¹) and
13 others dosage forms (e.g. spot-on, collar, intramammary products, infusion products, bee-hive strips).

14
15 The revision of the current text of Annex 4 is considered a priority for the following main reasons:

- 16 • to facilitate the implementation of the principles set by the aforementioned ICH guidelines and
17 ad hoc VICH guidelines;
- 18 • to extend the underlying concepts to include new areas of technology (e.g. novel therapy
19 products), new processing methods, new products not previously covered;
- 20 • to clarify areas that have been highlighted as ambiguous due to the age of the document.

21
22
23 The current Annex 4 is focused on the manufacture of veterinary medicinal products “other than
24 immunologicals”. The title and scope of the annex need to be clarified or re-defined to take into
25 consideration the concomitant revision of Annex 5 on manufacture of immunological veterinary
26 medicinal products which could be extended to all biological veterinary medicinal products in order to
27 avoid any gap, redundancy or inconsistency between both annexes. Moreover, a change in title and
28 scope is required also to clearly focus on veterinary special and specific dosage forms.

29
30 Moreover, since the update and split of GMP Part I and II in 2005, a number of Annexes have been
31 revised (e.g. Annex 2 and 15) or are under revision (Annex 1). This revision has provided the
32 opportunity to indicate if specific requirements are applicable to those described in GMP Part I and II.
33 The current Annex 4 does not similarly indicate if requirements are applicable to Parts I and II.

34
35 Finally, it is noted that unlike the situation for medicines intended for use in human clinical trials, there
36 is no universal legislative requirement for GMP manufacture of medicines for use in veterinary clinical
37 trials in the EU or PIC/S member states. However, national legislation in some countries may require
38 this. Therefore, it is suggested that the revised guidance acknowledges this and makes clear that
39 where required nationally, the guidance may be applicable, as appropriate to the manufacture of
40 investigational veterinary medicinal products.

41 2. Discussion

42 Since Annex 4 was published in 1992, the manufacturing and regulatory background has changed
43 significantly and an update is required to this Annex to reflect this change in technical/scientific and
44 regulatory environment.

45
46 The introduction of relevant ICH and VICH concepts, consequential regulatory changes and
47 technological advancements have occurred, which are not reflected in the current text. In addition, and
48 in keeping with greater international convergence, opportunities will be taken where appropriate to

¹ aquarium or pond animals, ornamental fish, cage birds, homing pigeons, terrarium animals, small rodents, ferrets and rabbits

49 align this guideline with international requirements. The opportunity will also be taken to ensure
50 maintenance of coherence with other EU or PIC/S pharmaceutical guideline documents.

51
52 The current GMP Annex on the manufacture of veterinary medicinal products other than
53 immunologicals was established before the development of ICH Q8, Q9 and Q10 guidelines and main
54 VICH guidelines. Specifically, ICH Q9 (i.e. EU GMP Part III and PIC/S GMP Annex 20) provides
55 principles and examples of tools for quality risk management that can be applied to different aspects of
56 pharmaceutical quality, while ICH Q10 describes a modern quality system in order to establish and
57 maintain a state of control, the realisation of product quality and facilitation of continual improvement
58 over the entire product life cycle. The revised Annex will clarify to what extent principles of Q8, Q9 and
59 Q10 and VICH guidelines should be followed in the design and implementation of facilities, equipment
60 and processes for the manufacture of veterinary medicinal products other than biologicals.

61
62 As the Annex 4 was published back in 1992, it does not reflect advances in the manufacture of
63 veterinary medicinal products and the development of new dosage forms; indeed, the revised Annex
64 will embrace the use of new technologies to make products and processes even safer and also will
65 endeavour to support the introduction of new manufacturing techniques through additional guidance.
66 Furthermore, the requirements for the manufacture of dosage forms which are specific to the
67 veterinary sector (e.g. Intramammary products, teat dips, bee-hive strips, ectoparasiticide collars,
68 etc.) or for products which have veterinary specific manufacturing issues (e.g. small batch size, large
69 volume / weight pack sizes, etc.) are not currently or partially covered by the Annex. This will be
70 addressed in the revised Annex and the title, scope and content of the revised document will need to
71 be broadened to encompass this.

72
73 The current Annex already gives guidance on the prevention of cross contamination for the
74 manufacturing of specific products (Ectoparasiticide and Penicillins) and the opportunity to derogate,
75 in certain conditions from some requirements of EU/PIC/S GMP Part I at that time. The revised
76 document will be harmonised with the current chapters 3 and 5 which provide improved guidance on
77 the prevention of cross contamination and introduce a quality risk management approach. Adaptations
78 for the manufacture of some specific veterinary medicinal products will also be addressed.

79
80 Other changes will allow for harmonisation with other GMP Chapters and Annexes (Chap. 1, Chap. 4,
81 Chap. 6, Annex 11, Annex 15 and Annex 19), international pharmacopeia (USP, Ph. Eur. monograph)
82 (e.g. Intramammary products, intrauterine preparations for veterinary use, veterinary liquid
83 preparations for cutaneous application, etc.) and other relevant international documents.

84
85 Veterinary medicinal products can be tested or used as a reference, including as a placebo, in a
86 veterinary clinical trial in order to examine under field conditions their safety or efficacy (or both)
87 under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose
88 of obtaining a marketing authorisation or a change thereof. In these clinical trials, there may be added
89 risk to the subjects compared to animals treated with authorised medicinal products. Extending the
90 scope of this guideline to good manufacturing practice for the manufacture and import of
91 investigational veterinary medicinal products used in veterinary clinical trial may ensure, when it is
92 required by national law, that subjects and users are not placed at undue risk, and that the results of
93 clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory
94 manufacture or import such as:

- 95 • inconsistency between batches of the same investigational medicinal product used in the same
96 or different clinical trials,
- 97 • changes during the development of an investigational medicinal product inadequately
98 documented and justified,
- 99 • increased risk of product cross-contamination and mix-up due to randomisation and blinding
100 process, or
- 101 • incomplete knowledge of the potency and toxicity of the product and a lack of full process
102 validation.

103 This Annex may also include guidance on importing, exporting, ordering, shipping, and returning
104 clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical
105 Practice (VICH 9).

106

107 A change is also necessary in order to make clear that this Annex 4 is applicable to medicinal product
108 manufacturers (GMP Part I) and not to API manufacturers (GMP part II).

109
110 Finally, the revision of Annex 4 will correct inaccuracies and areas of ambiguity contained in the
111 existing "outdated" document and will offer a higher level of a clearer interpretation of GMP
112 expectations.

113 **3. Recommendation**

114 The PIC/S WG on VMP and EMA GMP/GDP IWG recommend that the current version of Annex 4, on the
115 manufacture of veterinary medicinal products other than immunologicals, is revised to reflect changes
116 in the regulatory environment (e.g. enforcement of new EU Veterinary Medicines Regulation -
117 Regulation (EU) 2019/6) and technological progress, to cover the manufacture of dosage forms which
118 are specific to the veterinary sector and to extend the scope to the manufacture of veterinary
119 medicinal products used for veterinary clinical trial when required by national law.

120
121 The revised Annex should clarify how manufacturers can take advantage of new possibilities deriving
122 from the application of an enhanced process understanding by using innovative tools as described in
123 the ICH Q8, Q9 and Q10 guidelines and VICH guidelines.

124
125 The scope of the project will be limited to Annex 4 but the revision of Annex 4 should also take into
126 account related changes in other GMP chapters and annexes as well as in other regulatory documents.
127 It should also state its applicability to GMP guidelines part I only.

128 **4. Proposed timetable**

129 Preparation of draft concept paper – June 2021
130 Approval of draft concept paper – September 2021
131 Release for consultation – 2 month
132 Deadline for comments – December 2021
133 Discussion in PIC/S Committee – March 2022
134 Discussion in EMA GMDP IWG - March 2022
135 Discussion with other Working Parties - during 2022 & 2023
136 Proposed date for release of draft guideline – March 2023
137 Deadline for comments – 3 months from above date
138 Re-discussion in EMA GMDP IWG – November 2023
139 Re-discussion in PIC/S Committee – November 2023

140 **5. Resource requirements for preparation**

141 A drafting group will be established by GMP/GDP Inspectors Working Group and the PIC/S WG on VMP
142 representing the PIC/S committee with a rapporteur and supporting experts from other EU member
143 regulatory authorities and from non-EU PIC/S participating authorities.

144
145 It is expected that most of the work will be completed by email and by teleconference.

146
147 The guideline will be discussed at GMP/GDP IWG and the PIC/S Committee as necessary and at other
148 involved working parties and groups. Further discussions are expected with interested parties.

149 **6. Impact assessment (anticipated)**

150 The updated Annex 4 is intended to benefit both industry and regulators by incorporating new
151 regulatory concepts, clarifying requirements and taking the opportunity to adopt a common approach
152 between EU and non-EU regulatory authorities. Revision of the Annex will facilitate a better
153 understanding of expectations which will lead to more consistent and improved manufacture of
154 veterinary-specific medicinal products and thereby enhancing the continuity of supply.

155
156 No adverse impact on industry with respect to either resources or costs is foreseen, although
157 clarification on the use of new systems may require some facilities, equipment and processes to be
158 modified over a period of time.

159 **7. Interested parties**

- 160 • EMA (GMP/GDP Inspectors Working Group, Quality Working Party, Biologics Working party)
- 161 • PIC/S (Committee, Sub-committee on GMDP Harmonisation, WG on VMP)
- 162 • National competent authorities of EU/EEA member states
- 163 • PIC/S participating authorities
- 164 • EDQM
- 165 • Pharmaceutical Industry

166 **8. References to literature, guidelines, etc.**

- 167 • ICH Q8 (R2) Pharmaceutical development
- 168 • ICH Q9 Quality Risk Management
- 169 • ICH Q10 Pharmaceutical Quality System
- 170 • ICH Q11 Development and manufacture of drug substances
- 171 • VICH Guidelines
- 172 • EU Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)
- 173 • EU Guideline on setting health based exposure limits for use in risk identification in the
- 174 manufacture of different medicinal products in shared facilities (EMA/CHMP/ CVMP/
- 175 SWP/169430/2012) / PIC/S PI 046 Guideline on Setting Health Based Exposure Limits for use in
- 176 Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities
- 177 • REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December
- 178 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
- 179 • Pharmacopeia
- 180
- 181