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Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances

Draft

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1 Executive Summary

2 This reflection paper is intended to reflect the current experience of the Quality Working Party (QWP),
3 of the Committee for Medicinal Products for Veterinary Use (CVMP) and the Co-ordination Group for
4 Mutual Recognition and Decentralised Procedures-Veterinary (CMDv) concerning the definition of a
5 New Active Substance (NAS) in the context of preparation of dossiers and submissions of applications
6 for Marketing Authorisation (MAA) in the Centralised Procedure (CP), the Mutual Recognition Procedure
7 (MRP)/Decentralised Procedure (DCP) and purely national procedures for chemical medicinal products
8 for veterinary use under Article 12(3) of Directive 2001/82/EC as amended.

9 The paper describes the chemical structure and properties criteria to be taken into account by the
10 CVMP to qualify a chemical active substance as NAS, as well as the required elements to be submitted
11 by applicants to substantiate their claims.

12 1. Introduction

13 This reflection paper intends to provide clarifications for applicants on the elements that need to be
14 substantiated in relation to a claim of considering an active substance as NAS. Assessment of the NAS
15 status will be performed in light of principles defined in Article 13.2b of Directive 2001/82/EC and the
16 Chapter I - Volume 6A of Notice to Applicants, as well as the evidence required to substantiate the
17 claim of NAS in a MAA. However it cannot cover every scenario *a priori*, and therefore applicants are
18 invited to obtain scientific advice on the studies that may be appropriate to substantiate the NAS claim,
19 especially for scenarios not covered in this reflection paper.

20 The above assessment is without prejudice to any assumption at the time of eligibility to the CP,
21 MRP/DCP procedures, or to the grant of an International Non-proprietary Name (INN) by the WHO

22 Eligibility to the CP based on the claim that the medicinal product for veterinary use contains a new
23 active substance must be dissociated from the assessment of the scientific data submitted in support
24 of the NAS claim during evaluation of the marketing authorisation application. Agreement on
25 designation as a NAS can only be made after a detailed assessment of the application.

26 Applicants are invited to consult the 'pre-submission guidance' on the EMA website for further details
27 on the eligibility to the CP.

28 1.1. Scope

29 This reflection paper describes the chemical structure and properties criteria to be taken into account
30 to qualify a chemical active substance as NAS under Article 12(3) of Directive 2001/82/EC as amended
31 in light of principles defined in Article 13.2b of Directive 2001/82/EC, as well as the required elements
32 to be submitted by applicants. It applies to marketing authorisation applications including solely
33 chemical active substance(s) eligible to the centralised and MRP/DCP and purely national procedures.

34 Biological and biotechnological active substances are excluded from the scope of this reflection paper.

35 1.2. Legal basis and relevant guidelines

36 Directive 2001/82/EC

37 Article 13.2b of Directive 2001/82/EC states:

38 “[...] the different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an
39 active substance shall be considered to be the same active substance unless they differ significantly in
40 properties with regard to safety and/or efficacy. In such cases, additional information providing proof
41 of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active
42 substance must be supplied by the applicant [...].”

43 Further information can be found in the Annex III & IV, Volume 6A, Chapter 1 of the Notice to
44 Applicants (NtA).

45 **2. Discussion and guidance**

46 A chemical active substance that is not previously authorised in a medicinal product for veterinary use
47 in the European Union and that is from a chemical structure point of view not related to any other
48 authorised substances should be considered as a NAS. Such substance is considered to be new in
49 itself, when the administration of the applied active substance would not expose animals to the same
50 therapeutic moiety as already authorised active substance(s) in the European Union.

51 If the chemical active substance is structurally related as a salt, ester, ether, isomer, mixture of
52 isomers, complex or derivative of an already approved active substance(s) in the European Union, it
53 should be assessed whether it shares the same therapeutic moiety at the site of the biological activity
54 as the already approved active substance and if so whether it differs significantly in properties with
55 regard to safety and/or efficacy.

56 Guidance is provided below to define the elements taken into account to qualify a salt, ester, ether,
57 isomer, mixture of isomers, complex or derivative of an active substance as NAS in the context of the
58 NAS status claim.

59 **2.1. Isomers**

60 Isomers should in this context be understood as enantiomers. Other types of isomers are presumed
61 not to share the same therapeutic moiety unless they are able to isomerise *in vivo*. Stereoisomers
62 related to each other as enantiomers have the same connectivity but are non-superimposable mirror
63 images of each other. This implies that enantiomers have the same chemical and physical properties
64 (except their ability to rotate plane polarized light), i.e. act in exactly the same manner, except when
65 they interact with other chiral structures. In the case one enantiomer is applied for where the other
66 enantiomer is the active substance in a previously authorised medicinal product for veterinary use
67 within the European Union it has to be assessed whether they differ significantly with respect to safety
68 and/or efficacy properties. This assessment will be based on the data provided by the applicant.

69 When an isomer that is not the enantiomer of an already approved active substance (diastereoisomer,
70 geometrical isomer, regioisomer, constitutional isomer etc.) is applied for it is presumed that it will not
71 expose animals to the same therapeutic moiety, unless it is able to isomerise *in vivo*, and could be
72 considered as NAS. In such cases, evidence that the substance is not able to isomerise *in vivo* may
73 need to be provided.

74 **2.2. Mixtures of isomers**

75 Where a previously authorised medicinal product for veterinary use in the European Union includes a
76 racemate and a new application for only one of the two enantiomers of the racemate is submitted, this

77 enantiomer would have been a substantial part (50 %) of the racemate and would therefore not be
78 considered as NAS, unless the applicant provides evidence that the two substances differ significantly
79 in properties with regard to safety and/or efficacy.

80 This does also apply to other situations where mixtures of diastereoisomers or other isomers have
81 been authorised as medicinal products for veterinary use and a new application contains only one of
82 the isomers of the mixture.

83 **2.3. Complexes**

84 The term 'complexes' may be used to refer to a wide variety of structures. Two categories of
85 complexes used as medicinal products are discussed below:

- 86 a. Complexes intended to release an active substance that is entrapped by the complex in the blood
87 circulation or elsewhere. Examples of such complexes are e.g. Iron dextran or meglumine
88 antimoniate.
- 89 b. Another type of complexes is those that are intended to remain intact in the body and for which
90 examples can be found in human medicinal products, e.g. a number of gadolinium complexes, with
91 different complexing ligands, and with extremely low dissociation constant. They exhibit their effect
92 by distributing gadolinium to places where it enhances the images obtained by NMR imaging. Due
93 to the toxicity of free gadolinium they are designed to remain intact (not dissociate and release the
94 metal).

95 Complexes of the category a. above prepared from an already approved active substance are designed
96 to release the original substance *in vivo* and will consequently not be considered as NAS in themselves.
97 Therefore the NAS status will have to be justified by significant differences with regard to safety and/or
98 efficacy. On the contrary, complexes of the category b. exhibit their effect without dissociating, and
99 different ligands may be used to complex the same metal. Because they do not dissociate the
100 therapeutic moieties are presumed to be different and could be considered as NAS. In such cases,
101 evidence that the complex does not dissociate may need to be provided.

102 **2.4. Derivative**

103 The term derivative, in the context of this reflection paper, includes related active substances which
104 expose the animal to the same therapeutic moiety.

105 This includes notably situations:

- 106 a. Where the original substance or its active metabolite(s) *in vivo* will be derived from the new
107 applied substance in such a manner that the animals are exposed to the same therapeutic moiety
108 of the original substance (the applied substance is a prodrug).
- 109 b. Where the new applied active substance is the same substance as the therapeutic moiety that the
110 animals were exposed to when treated with the original active substance (the applied substance is
111 a metabolite).

112 In these situations, substances related as a "derivative" to the active substance of an already approved
113 medicinal product for veterinary use in the European Union will not be confirmed as NAS unless the
114 applicant provides evidence that the substance being evaluated differs significantly in properties with
115 regard to the safety and/or efficacy from the substance already approved.

116 The above mentioned situations also apply to stereoisomers which isomerise to authorised active
117 substances *in vivo*.

118 **2.5. Esters and ethers**

119 Converting an active substance to certain esters or ethers is a well-established way of preparing so-
120 called prodrugs. The purpose of a prodrug is to deliver the same therapeutic moiety to the patient,
121 possibly with some differences such as a different bioavailability, a different *in vivo* distribution
122 pattern, etc. Such esters or ethers of an already approved medicinal product in the European Union
123 that are designed to be hydrolysed *in vivo* and expose the animal to the same therapeutic moiety as
124 the original active substance will not be considered as NAS unless the applicant provides evidence that
125 the substance being evaluated differs significantly in properties with regard to safety and/or efficacy
126 from the one already approved.

127 If the applicant provides evidence that an ester or ether of an already approved medicinal product in
128 the European Union exerts its effect in an intact shape (is not hydrolysed *in vivo*), and the animals are
129 not exposed to the same therapeutic moiety as with the already approved medicine it could be
130 considered as NAS. In such cases, evidence that the substance exerts its effect in an intact shape (is
131 not hydrolysed *in vivo*) may need to be provided.

132 **2.6. Salts**

133 Salts usually dissociate in aqueous solution and the therapeutic moiety is no longer associated with the
134 counter ion but is rather surrounded by solvent molecules and ions present in the solution. A different
135 salt of an active substance previously authorised as part of a veterinary medicinal product in the
136 European Union would not be considered as NAS, unless the applicant provides evidence that the
137 substance being evaluated differs significantly in properties with regard to safety and/or efficacy from
138 the one already approved.

139 **2.7. Solid state forms and NAS status**

140 Since cocrystals, hydrates and solvates are held together by weak interactions that usually dissociate
141 in a similar way as salts upon dissolution they will expose an animal to the same therapeutic moiety.
142 As for salts, they will not be considered as NAS unless the applicant provides evidence that the
143 substance being evaluated differs significantly in properties with regard to safety and/or efficacy from
144 the one already approved.

145 Regarding the different crystalline polymorphs of an active substance in principle the differences
146 between such polymorphic forms will immediately disappear when dissolved and therefore will not be
147 presumed as NAS.

148 **2.8. Documentation**

149 Where an applicant submits a claim of NAS under Article 12(3) in light of the principles defined in
150 Article 13.2b of Directive 2001/82/EC, the applicant should demonstrate whether the active
151 substance(s) subject of the application shares the same therapeutic moiety with the active
152 substance(s) previously authorised in medicinal product(s) for veterinary use. This should include a
153 demonstration that the administration of the applied active substance would not expose the animal to
154 the same therapeutic moiety as an already authorised active substance in the European Union. It is

155 recommended that this is substantiated by comparison of structural substance/features which can be
156 obtained using established databases and discussion on the therapeutic moieties for any structurally
157 related already authorised substances in relation to the therapeutic moiety of the claimed NAS. Results
158 of such investigations should be provided within the dossier.

159 When a substance applied for exposes the animal to the same therapeutic moiety as the previously
160 active substance(s) as part of a veterinary medicinal product(s) authorised in the European Union, the
161 applicant should provide evidence that the related active substances differ significantly in properties
162 with regard to safety and/or efficacy. The documentation needed for such a claim will be dependent on
163 the particular case details; applicants are advised to seek scientific advice accordingly.

164 **3. References**

165 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the
166 Community Code relating to medicinal products for veterinary use.

167 Notice to Applicants (NtA), Volume 6A – Procedures for marketing authorisation - Chapter 1 marketing
168 authorisation.

169 EMA/CHMP/QWP/104223/2015: Reflection paper on the chemical structure and properties criteria to be
170 considered for the evaluation of new active substance (NAS) status of chemical substances.