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Reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6

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Table of contents

1. Introduction

Regulation (EU) 2019/6[1] (VMP-Reg), which lays down the rules for the marketing of veterinary medicinal products (VMPs) in the European Union (EU) and the European Economic Area (EEA), will be applicable from 28 January 2022 and replace Directive 2001/82/EC[2], which has been the Union's main VMP-related legislation during the last 20 years.

Article 18 of the VMP-Reg generally lays down provisions related to the granting of a marketing authorisation for generic VMPs, with Article 18(7) specifically concerning provisions for the performance of an environmental risk assessment (ERA) for generic VMPs. The present reflection paper aims at providing an approach to applying Article 18(7).

With regard to the ERA of generic VMPs, the VMP-Reg contains specific provisions that imply a significant shift compared to the situation under Directive 2001/82/EC. Article 18(7) states that "[a] competent authority or the Agency, as applicable, may require the applicant to provide safety data concerning the potential risks posed by the generic veterinary medicinal product to the environment where the marketing authorisation for the reference veterinary medicinal product was granted before 1 October 2005". In addition to that, Annex II of the VMP-Reg mentions in Section IV.1.1 (which pertains to generic VMPs) that "[if] required, pursuant to Article 18(7) an environmental risk assessment shall be included".

Furthermore, Recital 35 of the VMP-Reg states that "[i]t is recognised that the potential effect of a product on the environment may depend on the volume used and the resulting amount of the pharmaceutical substance that may reach the environment. Therefore, where there is evidence that a constituent of a medicinal product, for which an application for a marketing authorisation for a generic veterinary medicinal product has been submitted, is a hazard for the environment, it is appropriate to require data on the potential effect on the environment in order to protect the environment". For the purposes of this reflection, the constituent(s) of a generic medicinal product will be considered a hazard with the potential for effects on the environment when the constituent(s) of the product have not been subject to full ERA in line with VICH guidance in the context of either the marketing authorisation for the reference product (RP) or the marketing authorisation of a similar VMP (same active substance, same pharmaceutical form, indicated for use in the same target species when administered at the same or a higher total dose).

2. Discussion

Generic VMPs rely on the safety and efficacy data presented in the dossier of their RP. However, although technically a part of the safety section of the application dossier (i.e. part 3), under the provisions of Directive 2001/82/EC, the ERA of generic VMPs was excluded from this general principle (Title III, point 1 of Directive 2009/9/EC specifies that for every marketing authorisation application [MAA] submitted for a generic VMP, an individual ERA has to be provided). The VMP-Reg no longer requires that an ERA is provided routinely with a generic application, effectively bringing the ERA in line with the rest of the safety aspects in part 3 of the dossier. A derogation from this principle is provided for in Article 18(7), which states that "[a] competent authority or the Agency [...] may require the applicant to provide safety data concerning the potential risks posed by the generic veterinary medicinal product to the environment where the marketing authorisation for the reference veterinary medicinal product was granted before 1 October 2005". This is the date of coming into

[1] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC. OJ L 4, 7.1.2019, p. 43–167.
[2] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. OJ L 311, 28.11.2001, p. 1–66.

effect of VICH guideline (GL) 38 ("Guideline on environmental impact assessments for veterinary medicinal products — Phase II" [CVMP/VICH/790/03-FINAL]).

The CVMP considers that Article 18(7) provides for a possibility ("may require") and not an obligation to require ERA data. Therefore, competent authorities (CAs) should only require the submission of ERA data from generic applicants under Article 18(7) on an exceptional basis. As Article 18(7) does not provide any specific criteria, it is left at the discretion of the national competent authorities (NCAs) or the European Medicines Agency (the Agency) to decide whether the provision of ERA data is necessary for a particular generic application.

The underlying principle of this reflection paper on the interpretation of Article 18(7) of the VMP-Reg is that an ERA should only be requested from generic applicants in case no ERA has been performed for the same active substance and exposure level in the EU/EEA in accordance with VICH GL38.

As a general principle, the CVMP considers that the submission of an ERA under Article 18(7) should be understood to relate to a phase II ERA in line with VICH GL38. It should be noted that the performance, submission, and, respectively, assessment of a phase I ERA in line with VICH GL6 ("Environmental impact assessment [EIAs] for veterinary medicinal products — Phase I" [CVMP/VICH/592/1998]) would not be formally necessary. Furthermore, in its introduction, VICH GL6 states that "[s]ome VMPs that might otherwise stop in Phase I may require additional environmental information to address particular concerns associated with their activity and use" (the so-called "however" clause). The considerations of this reflection paper also apply to such products.

For generic applications citing an RP that was authorised before 1 October 2005, the applicant should check the Union Product Database (UPD) for VMPs with the same active substance and the same pharmaceutical form indicated for use in the same target species when administered at the same or a higher total dose as the proposed generic VMP, and which have been authorised after 1 October 2005. The outcome of this check should be provided and discussed in the dossier under part 3A.6 ("Environmental risk assessment"). If such products are authorised in the EU/EEA, then it will be considered that an ERA according to VICH GL38 and/or any other relevant guidelines in effect at that time has been performed by a CA, that the ERA data package provided has been found to be satisfactory and that appropriate risk mitigation measures are in place (if applicable). Based on the principle of mutual trust, the CA receiving the application for a new generic VMP should recognise the outcome of this assessment and should not request the generic applicant to provide an ERA under Article 18(7) of Regulation (EU) 2019/6.

While the dossiers for RPs authorised before 1 October 2005 will not have a phase II ERA in line with VICH GL38 at the time of initial authorisation, such an ERA might have been provided during a post-authorisation procedure, e.g. via an extension, a renewal or a referral. Therefore, alternatively, the applicant can contact the relevant CA or the Agency, requesting that the CA checks whether a guideline-compliant ERA is available for the RP. If it is confirmed that an ERA is available for the reference product, and based on the principle of mutual trust, the CA receiving the application for a new generic VMP should recognise the outcome of this assessment and should not request the generic applicant to provide an ERA under Article 18(7).

Where,

- the cited RP is authorised before 1 October 2005, and
- the relevant CA advises that an ERA is not available for the RP, and
- no similar VMP (same active substance, same pharmaceutical form, indicated for use in the same target species when administered at the same or a higher total dose) was authorised after 1 October 2005,

no conclusions will be drawn regarding the environmental safety of the proposed generic VMP. In this case, the CA will request that an ERA be provided under Article 18(7). The ERA should be provided as part of the MAA dossier and should be submitted before the authorisation procedure starts.

It is recognised that the product information (PI) of RPs authorised prior to 1 October 2005 and for which an ERA according to VICH GL38 has not been performed might not contain risk mitigation measures to protect the environment or environmental information in line with current standards. Article 18(6) of the VMP-Reg states that "[t]he summary of product characteristics of the generic veterinary medicinal product shall be essentially similar to that of the reference medicinal product […]". Therefore, the generic applicant is expected to adhere to the authorised PI of the RP. The CVMP considers that the lack of risk mitigation measures in the proposed PI of the generic VMP should not be used as a justification for CAs to require a generic applicant to provide an ERA under Article 18(7). Nevertheless, when there is public information available (from European public assessment reports [EPARs], public assessment reports [PuARs], referrals or the PI of already authorised VMPs) related to inherent environmental properties of the active substance (e.g. persistence or leaching potential), an NCA or the Agency might request the applicant to complete the PI with such information for the sake of environmental protection. Any such information included in the PI of the generic product can be included in the RP in future variations that require an amendment of the SPC. The inclusion of this environmental protection information will imply neither a risk characterisation nor a deviation from the principle that generics' summaries of product characteristics (SPC) should be "essentially similar" to the RP's SPC. Should a concern regarding the environmental safety of a generic VMP be identified, indicating the need for inclusion of risk mitigation measures and/or environmental information in the PI, these would in principle also apply to the RP and would therefore be beyond the scope of the generic application. This concern should hence be addressed in a Union interest referral procedure under Article 82 of the VMP-Reg. This would allow for an assessment of all available data and for reaching harmonised conclusions for all relevant products, which would ensure better protection of the environment. As an alternative to a referral, CAs might consider applying Article 130(3)(a) of the VMP-Reg in order to request the marketing authorisation holder of the RP to submit a variation to update the PI with the appropriate risk mitigation measures and/or relevant environmental information.

In situations where the need for an environmental risk assessment cannot be clearly determined based on the guidance provided above, applicants are strongly advised to liaise with the relevant CA(ies) before submission, in order to clarify whether or not an ERA needs to be provided as part of the authorisation dossier.

For clarification, the Annex to this reflection paper contains a schematic figure exemplifying the situations where an ERA should or shouldn't be requested by an NCA or the Agency for a generic VMP.

3. Annex

In Article 18(7), the VMP-Reg states that CAs may require applicants of generic applications to provide an ERA. **Figure 1** depicts in which situations an ERA should or should not be required.

Whenever an ERA is not required for a generic application, its PI will be essentially similar to the one of the RP, which does not exclude the possibility of including publicly available environmental information related to inherent properties of the active substance (e.g. persistence, leaching potential or toxicity to non-target organisms). The alignment of the PI of concerned products in terms of environmental information and/or risk mitigation measures can be carried out by the CAs by means of a Union interest referral or by applying Article 130(3)(a).

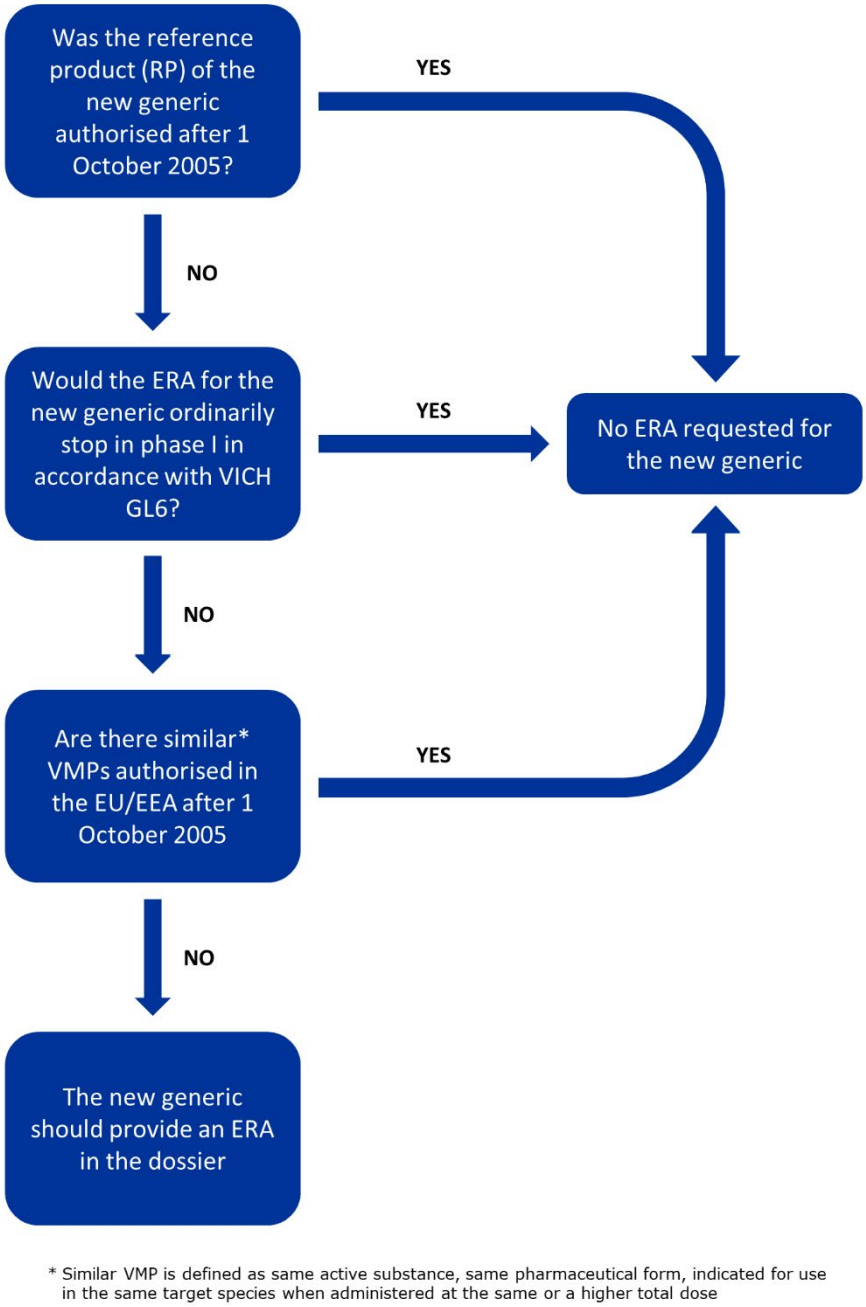

Figure 1. Schematic representation depicting when an ERA should be requested from a generic VMP applicant.