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NOTICE TO STAKEHOLDERS

QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR VETERINARY MEDICINAL PRODUCTS DURING THE COVID-19 PANDEMIC

Contents

INTRODUCTION

The current COVID-19 pandemic has a considerable impact on citizens, patients and businesses. It may force marketing authorisation holders ("MAHs") and regulatory authorities to operate under business continuity mode, impacting the standard way of working. Moreover, public and animal health needs may require quick actions or re-prioritisation of operations.

The ultimate aim of the EU legislation on medicinal products is to ensure a high level of public and animal health. The COVID-19 pandemic is posing unprecedented challenges and ensuring continuity of supplies of medicines is a priority for public and animal health. Therefore, it is necessary to articulate appropriate measures to minimise risks of shortages while ensuring that the high standards of quality, safety and efficacy of medicines made available in the EU are maintained.

The veterinary sector plays an integral and fundamental role in maintaining the health and safety of animals, as well as the security and sustainability of our food supply and thus contributes in an essential way to public health. It is therefore important to provide some flexibility for veterinary medicinal products to allow their continued manufacturing and distribution with minimal disruption and without affecting their availability.

This document provides guidance to MAHs of veterinary medicinal products on regulatory expectations and flexibility during the COVID-19 pandemic. The document will be updated to address new questions and to adjust the content thereof to the evolution of the pandemic. For queries related to procedures that are not specifically addressed in this document, MAHs are invited to address the European Medicines Agency ("EMA") (for centrally authorised products) or the relevant national competent authorities ("NCAs") (for nationally authorised products).

This document does not provide guidance on the potential use of veterinary medicinal products in humans affected by COVID-19.

This document remains valid until further notice. It has been developed in cooperation between the European Commission, the Heads of Medicines Agencies network ("HMA"), the Coordination group for Mutual recognition and Decentralised procedures – veterinary ("CMDv") and EMA.

The ultimate responsibility for the interpretation of EU legislation is vested on the European Court of Justice and therefore the content of this document is without prejudice to a different interpretation that may be issued by the European Court of Justice.

A LEGAL AND REGULATORY GUIDANCE

1. ISSUES RELATED TO MARKETING AUTHORISATIONS, MARKETING AUTHORISATION PROCEDURES

1.1. Can I postpone my renewal application?

According to Article 39 of Regulation (EC) No 726/2004 and Article 28 of Directive 2001/82/EC, the initial standard marketing authorisation is valid for five years. Such marketing authorisation may be renewed on the basis of a re-evaluation of the benefit-risk assessment. To this end, the MAH shall provide EMA or the NCAs with a

consolidated version of the file in respect of quality, safety and efficacy, at least six months before the marketing authorisation ceases to be valid.

MAHs facing difficulties to meet this deadline due to exceptional circumstances arising from the COVID-19 pandemic, are invited to contact EMA (for centrally authorised products) or the reference Member State (for products authorised under the MRP/DCP) before the deadline foreseen for the submission of the renewal application, with a justified request to postpone the submission of the complete dossier to a later point in time. The reference Member State will consult with the concerned Member State(s) and advise the MAH on any further steps to be taken before the foreseen deadline. In case of purely national marketing authorisations, MAHs should contact the relevant NCA.

1.2. Does the 'sunset clause' apply during a pandemic?

According to Article 28(4) to (6) of Directive 2001/82/EC and Article 39(4) to (6) of Regulation (EC) No 726/2004, any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State or on the Union market will cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Union is no longer actually present on the market for a period of three consecutive years, the authorisation for that product will cease to be valid.

Due to the current pandemic, initial market launch plans may need to be adapted in a way that could trigger the sunset clause mechanism. MAHs are reminded of the possibility to request an exemption in view of exceptional circumstances on human or animal health grounds.

For centrally authorised products, MAHs have to submit such a request under Article 39(6) of Regulation (EC) No 726/2004 to the European Commission. During the pandemic, the Commission may accept sunset clause requests that refer to the pandemic as a reason without the need for any further justification.

For nationally authorised products, MAHs have to submit such requests to the NCAs of the relevant Member State(s). NCAs will decide according to the national rules, considering the pandemic situation.

2. ISSUES RELATED TO GMP INSPECTIONS, CERTIFICATES AND WORK OF THE QUALIFIED PERSON ("QP")

2.1. Which measures will be taken in respect of GMP certificates and authorisations to manufacture/import in light of difficulties to conduct on-site GMP inspections due to restrictions linked to the COVID-19 pandemic?

The COVID-19 pandemic has triggered national and international restrictions that may affect and/or prevent the conduct of certain on-site GMP inspections. In light of the severity of the current circumstances, measures should be put in place to ensure availability of GMP certificates and authorisations to manufacture/import to support regulatory submissions, as well as to maintain the validity of current GMP certificates and authorisations to manufacture/import.

Specifically, the validity of GMP certificates that support the manufacture and importation of veterinary medicinal products in the EEA should be extended to avoid disruptions in the availability of these products. The validity of authorisations to manufacture/import should also be extended (in case they are time-limited). With a view to ensuring the quality of veterinary medicinal products marketed in the EU/EEA, a distinct approach should be taken for sites that are located in the EEA and sites located outside the EEA that have never been inspected by an EEA supervisory authority.

Sites located in the EEA

The validity of GMP certificates for manufacturing/importing sites of active substances and/or finished products in the EEA should be extended until the end of 2022 without the need for further action from the holder of the certificate.([1]) This automatic extension does not apply where restrictions on the validity period are stated in the clarifying remarks on the GMP certificate and does not cover changes in the scope of the GMP certificate (e.g. new buildings, new veterinary medicinal products).

The validity of time-limited authorisations/registrations to manufacture/import should also be extended until the end of 2022 without the need for further action from the authorisation/registration holder. This automatic extension does not cover changes in the scope of the authorisation/registration (e.g. new premises, new veterinary medicinal products).

For new sites/facilities in the EEA that have never been inspected and authorised, a distant assessment may be conducted in order to evaluate whether the site could be authorised without a pre-approval inspection. In such cases, it should be indicated that the certificate has been granted on the basis of a distant assessment. Moreover, an on-site inspection should be conducted once circumstances permit. If the outcome of the distant assessment does not permit the granting of the GMP certificate, a clock-stop will be triggered until an on-site inspection is possible.

Sites located outside the EEA

The validity of GMP certificates for manufacturing sites of active substances and/or finished products located outside the EEA should be extended until the end of 2022 without the need for further action from the holder of the certificate, unless the issuing/supervisory authority takes any action that affects the validity of the certificate. This automatic extension does not apply where restrictions on the validity period are stated in the clarifying remarks on the GMP certificate and does not cover changes in the scope of the GMP certificate (e.g. new buildings, new medicinal products).

For new sites/facilities in third countries where an inspection is required, and where there is no operational mutual recognition agreement (MRA) or the scope is not covered by the MRA, a distant assessment by an EEA supervisory authority may be conducted. A GMP certificate may be granted depending on the outcome of the assessment. In such cases, it should be indicated that the certificate has been granted on the basis of a distant assessment. Moreover, an on-site inspection should be conducted once circumstances permit. If the outcome of the distant assessment does not permit the granting of the GMP certificate, a clock-stop will be triggered until an on-site inspection is possible.

([1]) An explanatory footer has also been introduced in EudraGMDP database.

Important remarks

On-site inspections will be conducted according to risk-based inspection planning, taking into account any restrictions due to COVID-19. ([2])

It is stressed that the obligation of manufacturers and importers to comply with GMP is not waived. It is incumbent upon manufacturers and importers to continue complying with GMP. Supervisory authorities will remain vigilant to ensure the quality of veterinary medicinal products that are made available in the EEA. Inspections (including distant assessments) may be launched at any time and, in case of non-compliance, appropriate regulatory actions will be triggered.

2.2. Which adaptations to the work of the QP are possible considering travelling and other restrictions arising from the COVID-19 pandemic?

(i) Remote batch certification

Remote batch certification is permissible under EU GMP rules, provided that the QP has access to all information necessary to enable them to certify the batch.

While in some Member States additional requirements have been introduced which may preclude remote certification, considering the current restrictions of travelling linked to the COVID-19 pandemic, remote certification should be acceptable in all EEA Member States.

It is stressed that the obligations/responsibilities of the QP remain unchanged.

(ii) Remote audits of the active substance manufacturer

On-site audits should be conducted by the manufacturer or independent third party auditors where possible. If not possible the QP can rely on remote audits and also take into consideration the results of inspections from EEA authorities.([3])

Remote audits should provide confidence that the active substance is fit-for-purpose and will not negatively affect the safety and efficacy of the veterinary medicinal product. The QP is expected to justify the controls in place on a scientific basis and record a risk assessment on a product specific basis.([4])

([2]) Resumption of inspections will vary according to timing of the lifting of containment measures taken by each country and other factors such as restoration of transport links.

([3]) Guidance on good manufacturing practice and good distribution practice: Questions and answers. https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#eu-gmp-guide-part-ii:-basic-requirements-for-active-substances-used-as-starting-materials:-gmp-compliance-for-active-substances-section

([4]) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-template-qualified-persons-declaration-concerning-good-manufacturing-practice-gmp_en.pdf

3. PHARMACOVIGILANCE, INCLUDING ADVERSE REACTIONS REPORTING

3.1. Is there any impact on reporting "Adverse event reports" (AERs) into EudraVigilance Veterinary?

According to Article 49 of Regulation 726/2004 and Article 75(2) of Directive 2001/82/EC, MAHs shall submit electronically to the EudraVigilance Veterinary database all suspected serious adverse reactions and human adverse reactions relating to the use of veterinary medicinal products that occur in the Union and in third countries within 15 days following the day on which the MAH gained knowledge of the event.

This includes adverse reactions that result from use outside the terms of the marketing authorisation (off-label use) and adverse events in humans after treatment(s) of an animal.

During the current pandemic, there is a risk that the capacity of workforces in industry may be reduced e.g. due to high employee absenteeism. These exceptional circumstances may force companies to activate business continuity plans and prioritise activities. Therefore, in case MAHs are for justified reasons relating to the pandemic unable to continue standard reporting operations, they should temporarily—until the pandemic is resolved—prioritise their reporting obligations. In these circumstances, the MAHs are requested to immediately contact the EMA (for centrally authorised products) and the NCA of the Member State in which they hold a marketing authorisation.

3.2. Can I postpone the submission of a periodic safety update report (PSUR)?

According to Article 49(3) of Regulation (EC) No 726/2004 and Article 75(5) of Directive 2001/82/EC, unless other requirements have been laid down as a condition for the granting of the marketing authorisation, records of all suspected adverse reactions shall be submitted in the form of a PSUR, to the Agency and Member States immediately upon request or at least every six months after authorisation until the placing on the market. PSURs shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the Union market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.

MAHs facing difficulties to meet this deadline due to exceptional circumstances arising from the COVID-19 pandemic, are invited to contact EMA (for centrally authorised products) or the reference Member State (for products authorised under the MRP/DCP), in reasonable time before the deadline foreseen for the submission of the PSUR, with a justified request to postpone the submission of the PSUR to a later point in time. The reference Member State will consult with the concerned Member State(s) and advise the MAH on any further steps to be taken before the foreseen deadline. In case of purely national marketing authorisations, MAHs should contact the relevant NCA.

3.3. Which measures will be taken in light of difficulties to conduct on-site pharmacovigilance inspections during the COVID-19 pandemic?

According to Art. 80 (1)(d) of Directive (EC) 2001/82, the national competent authorities have the obligation to inspect the premises, records and documents of marketing

authorisation holders or any firms performing the activities relating to pharmacovigilance on behalf of a marketing authorisation holder (pharmacovigilance inspections)[5].

During the COVID-19 pandemic, on-site inspections may not be possible due to multiple factors, including difficulties and restrictions related to travelling between and within the countries, restrictions to accessing facilities and additional health risks for inspectors and inspectees. Regulatory authorities also may need to prioritise, reduce or postpone certain activities and look for alternative ways of supervision using a risk-based approach. For pharmacovigilance inspections that are part of pharmacovigilance inspection programmes and cannot be conducted on-site, a remote inspection may be considered if appropriate and feasible. Decision on "for cause" inspections should be considered on a case-by-case basis by inspectors and concerned assessors, as applicable, to determine whether a remote inspection is feasible, and it could fulfil the purpose of the requested inspection.

Remote inspections should follow, where applicable, the guidelines that already exist for the conduct of GxP inspections but should also take into consideration the limitations imposed by using a remote process. The compatibility of the systems operated by the MAH and the concerned NCA is fundamental to ensuring that the inspectee meets the technical requirements to provide remote access to electronic systems, as well as maintains communication with and provides support to inspectors. During the remote inspection initiation phase, the inspectee should provide detailed information as requested by the inspectors to allow a feasibility assessment by the inspection team.

4. PRODUCT INFORMATION AND LABELLING

4.1. Is there any flexibility in the labelling and packaging requirements to facilitate the movement of veterinary medicinal products within the EU?

It is necessary to facilitate the movement of veterinary medicinal products within the EU so that they can be made available in the Member States where they are needed the most. In the current exceptional circumstances, the regulatory flexibilities foreseen in the Directive 2001/82/EC should be fully utilised. Under Article 61(1) of Directive 2001/82/EC Member States may grant full or partial exemptions to certain labelling and packaging requirements for products intended to be administered only by a veterinarian.

During the COVID-19 pandemic, Member States may therefore accept, within the boundaries of Article 61(1), that the product information of products marketed in their territory may not be translated into the relevant official language if there are severe problems of availability of that veterinary medicinal product in the Member State.

In these exceptional circumstances, it may moreover be accepted that national specific information does not appear in the packaging/labelling, or that the presentation differs from the presentations authorised in the Member State where the product is marketed.

MAHs are required to notify the relevant national competent authorities in advance and should also provide a link to a website where the product information in the relevant

[5] Related information: Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (Volume 9B - Version October 2011).

official language may be obtained. Further guidance on specific national requirements/procedures will be developed by CMDv.

B. ADDITIONAL INFORMATION

The websites of the Commission (https://ec.europa.eu/food/animals/health/veterinary-medicines-and-medicated-feed_en) and of the EMA (https://www.ema.europa.eu/en/veterinary-regulatory/overview/covid-19-information-veterinary-medicines) provide additional information. For products authorised in accordance with the decentralised or mutual recognition procedures, the Coordination Group (CMDv) will provide additional information on its website. These pages will be updated with further information, where necessary.

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