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HMA

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NOTICE TO STAKEHOLDERS

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

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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 reprioritisation 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 GMP INSPECTIONS, CERTIFICATES AND WORK OF THE QUALIFIED PERSON ("QP")

1.1. 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 2023 without the need for further action from the holder of the certificate.([1]) This automatic extension 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 2023 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 2023 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 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.

Important remarks

Pre-approval or routine on-site inspections will resume as soon as COVID-19 restrictions are

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

lifted([2]) according to risk-based inspection planning, taking into account the date of the last inspection.

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.

1.2. 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 paper-based 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. PHARMACOVIGILANCE, INCLUDING ADVERSE EVENT REPORTING

2.1. Is there any impact on submitting "Adverse event reports" (AERs) to the Union pharmacovigilance database or on the signal management process?

According to Article 76(2) of Regulation (EU) 2019/6, MAHs shall submit electronically to the Union pharmacovigilance database all suspected adverse events and human adverse events relating to the use of veterinary medicinal products that occur in the Union and in third countries without delay and no later than within 30 days of receipt of the adverse event report. This includes adverse events that result from use outside the terms of the marketing

([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/veterinary-regulatory/post-authorisation/pharmacovigilance-veterinary-medicines#guidance-applicable-from-28-january-2022-section

authorisation (off-label use) and adverse events in humans after treatment(s) of an animal.

MAHs shall carry out a signal management process[5] and inform the competent authority or the Agency, as applicable, without delay for emerging safety issues (and no later than 3 working days following their identification) and, for other signals, within 30 days of identifying a change to the benefit-risk balance or a new risk. The MAH shall also record in the Union pharmacovigilance database, at least annually, all results and outcomes of the signal management process.

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 or signal management operations, they should temporarily—until the pandemic is resolved—prioritise their reporting or signal management 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.

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

According to Art. 79(4) of Regulation (EU) 2019/6, the national competent authorities have the obligation to verify, by means of controls and inspections referred to in Articles 123 and 126 that marketing authorisation holders and pharmacovigilance system master files comply with the requirements related to pharmacovigilance laid down in Section 5 of the Regulation.[6]

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 the guideline for remote pharmacovigilance inspections of MAHs during a crisis situation – points to consider and should also take into consideration the limitations imposed by using a remote process.[7] 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.

[5] Guideline on veterinary good pharmacovigilance practices (VGVP) – Signal management (EMA/522332/2021)

[6] See also Commission Implementing Regulation (EU) 2021/1281 on good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products.

[7] Remote pharmacovigilance inspections of MAHs during a crisis situation- Points to consider (europa.eu)

3. GDP Flexibility

3.1. Which adaptations to the work of the Responsible Person (RP) are possible considering travelling, absenteeism and other restrictions arising from COVID-19 pandemic?

(i) Remote working of the RP

If a regional or national government authority has implemented quarantine measures such as stay-at-home restrictions for entire regions or the whole country resulting in cancellation or prohibition of travelling, then remote working of the RP is permissible, limited to the duration of the restrictions, provided that :

• the RP has timely access to all information necessary to ensure that the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.

• the RP can fulfil responsibilities specified in Article 8 of Regulation (EU) 2021/1248 on GDP for VMP .

(ii) Delegation of duties and responsibilities of an RP to another RP?

In case of comparable size, structure and complexity of distributor's activities and with prior approval by the competent authority, it could be acceptable for a RP designated by a wholesale distributor to temporarily take over the duties and responsibilities of another RP designated by a wholesale distributor in:

- Another branch(es) of the same group / company.
- Another company within the same group of companies.

When temporarily designated to the role, the RP should fulfil his responsibilities of the role personally. After a risk assessment has been performed to determine that the person has the resources and capacity to take on the additional responsibilities, a written job description should define those responsibilities and the authority to make decisions relevant to the role, in compliance with Regulation (EU) 2021/1248 on GDP for VMP.

(iii) Delegation of duties of an RP to a person who is not a RP

When necessary, it is acceptable for a RP to delegate duties to an appropriately trained person designated by a wholesale distributor according to Article 9 of Regulation (EU) 2021/1248 on GDP for VMP. However, responsibilities for the correct execution of the duties remain with the RP.

(iv) Replacement of the RP at short notice

It is recognised that under exceptional circumstances, like quarantine measures travel restrictions or longer absence due to sickness, it may become necessary to replace the RP at short notice. Agreement of the National Competent Authority should be sought in advance for replacement of the designated RP by an employee with appropriate competence, experience, knowledge and training in GDP or a third party RP. If the newly designated RP within the timeframe of the COVID-19 crisis does not meet all the qualifications and conditions provided for by the legislation of the Member State concerned, the RP should at least have appropriate competence and experience as well as knowledge of and training in GDP to fulfil all delegated responsibilities. Prior notification of the supervisory authority is necessary. In all cases, the RP should have appropriate knowledge about the QMS of the new company. It is stressed that the obligations/responsibilities of the RP remain unchanged.

3.2. Is it possible to use new equipment or newly authorised premises for storage and distribution of medicinal products with limited prospective qualification?

Yes, when relocation of veterinary medicinal products is necessary to meet demand within the timeframe of COVID-19 pandemic, new equipment or re-purposed equipment may be used with limited prospective qualification to allow it to be used as soon as possible. Where prospective validation has been limited for premises and equipment used for the storage and

distribution of veterinary medicinal products then this should be compensated by employing sufficient ongoing monitoring such that there is evidence that veterinary medicinal products are stored and transported under the required conditions. The principles of Quality Risk Management as per Article 7 of Regulation (EU) 2021/1248 on GDP for VMP should be employed to determine the extent of ongoing monitoring required and the approach should be approved by the RP. Special attention should be paid to equipment and premises used for the storage and distribution of products with specific handling instruction or storage conditions. Agreement of the National Competent Authority should be sought before using any new premises for wholesaling activities. The full qualification and validation should be completed without delay following this period.

3.3. Can I introduce planned deviations from normal practice (temporary change controls) in the context of the COVID-19 pandemic?

Yes, when documented within the quality system, approved by the RP and assessed on a case by case basis in accordance with a quality risk management process as per Article 7 of Regulation (EU) 2021/1248 on GDP for VMP, temporary flexibility can be introduced as follows:

(i) Remote working of the RP

The timeframe for the performance of routine Standard Operating Procedure (SOP) reviews can be extended during the period of the pandemic.

(ii) Audits and internal audits

Where on-site audits of contract acceptors are not possible, the RP can rely on paper-based audits also and take into consideration the results of inspections or audits performed by third parties. Remote audits should provide confidence that the contracted party is fit-for-purpose and will not negatively affect the wholesale distribution process. The internal audit (self-inspections) schedule can be adapted, where necessary and under quality risk management, in order to free personnel for tasks deemed critical during the period of the pandemic crisis. However, each situation should be assessed, documented and authorised on a risk based approach.

(iii) Non-conformities and CAPA management

Following a risk assessment approved by the RP to determine the impact of a deviation or non-conformity, the implementation of CAPAs to address a deviation determined to have low risk to product quality or wholesaling activities, can be deferred. Investigations into events classified as ‘minor’ can also be deferred provided that the deferrals are tracked and resumed once pandemic restrictions are lifted. The issuing of change management documentation in relation to CAPA implementation can be postponed in order to facilitate a faster and more flexible change management process, however, the approval of the change should be recorded. Remaining change management documentation should be completed retrospectively.

(iv) Training

The company’s training plan may be adapted with respect to routine retraining of experienced personnel to reflect prioritised needs during the period of the pandemic crisis. Training of new and recently hired personnel should be conducted and special emphasis should be given to any current atypical working conditions. The principles of quality risk management should be applied in determining appropriate prioritisation of training needs to ensure competence of the personnel with respect to the duties assigned to them

4. 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.

European Commission Directorate-General Health and Food Safety	Heads of Medicines Agencies European Medicines	Agency