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Committee for Veterinary Medicinal Products (CVMP)

Project for dosage review and adjustment of selected antibiotic veterinary medicines

1. Background

Due to the impact of antimicrobial resistance (AMR) development in pathogens affecting both human and animal health, there have been numerous activities within the European regulatory network over the last 15 years aiming to improve the quality of antibiotic prescription for veterinary use (e.g. limiting the conditions of use of fluoroquinolones, 3rd- and 4th-generation cephalosporins, colistin; the "Human Reserved List"; and conditions for the use of certain antibiotics under the "cascade"). The effectiveness and availability of the older veterinary antibiotics - often used as first-line treatment - is essential to keep a range of safe and efficacious treatment options for bacterial diseases in animals in the European Union (EU). Safeguarding the continued availability of established veterinary antibiotics is important for the veterinary sector, especially since it is likely that very few new antibacterial active substances will be developed for use in veterinary medicine. The recently updated strategy of the European medicines agencies' regulatory network is to modernise the product information (PI) (Summary of Product Characteristics (SPC), package leaflet and labelling) of existing antibiotics for veterinary use and consider additional options for guiding prescribing practices in accordance with the terms of their marketing authorisation (HMA/EMA, 2025).

It is acknowledged that the authorised PI for some established veterinary antibiotics may not be up to date with current scientific knowledge. In some cases, emerging AMR has resulted in changed susceptibility distributions of the pathogens for which these antibacterial veterinary medicinal products (VMPs) are indicated. Therefore, the dosage regimens (i.e., dose, frequency and treatment duration)[1] described in the authorised PI of these VMPs may require a critical evaluation in order to be updated for the desired level of efficacy and safety, whilst limiting the selection for resistant pathogenic bacteria, under current animal production conditions.

A change in the dosage regimen of a VMP, in particular an increase in the dose or in the dosing frequency, can have implications for target animal safety (TAS), possibly for the user safety assessment (URA) and also, in the case of food-producing species, for the withdrawal periods (WP), as well as for the environmental risk assessment (ERA). If the review and adjustment of dosages is handled *via* variations using current dossier (study data) requirements for new marketing authorisation applications, then this would require a substantial investment. It is considered unlikely that this would be a viable approach due to resource constraints and it, if imposed, may consequently lead to a decreased availability of established veterinary antibiotics. Overall, this would have a negative impact

[1] The intention is to review/adjust both the dose and the treatment duration, if possible. Whilst the proposed PK/PD approach will only address dose adjustment, the treatment duration could also be modified only if clear scientific evidence is available.

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on animal health, potentially increase the occurrence of antimicrobial resistance, and it may lead to overreliance on other antibiotics.

In a reflection paper (CVMP, 2021), the CVMP recognised that the current regulatory environment does not stimulate the realisation of the desired dosage review and adjustment of established veterinary antibiotics. The CVMP therefore explored non-experimental approaches to refine their PIs, i.e. not necessitating the generation of new data. Although such options might be less established (as compared to traditional study data), they may still be helpful in improving the dosage regimen in the PIs, which would in turn facilitate harmonisation of national marketing authorisations of individual VMPs across EU Member States (MSs). The non-experimental approaches proposed by the CVMP include pharmacokinetics/pharmacodynamics (PK/PD) integration for dose review and adjustment, PK modelling for WP adjustment, and scientific review approaches to address the safety of both target animals and the environment, and the treatment duration, if possible.

During 2024, the CVMP, in consultation with stakeholders (National Competent Authorities (NCAs) and Industry) *via* a survey/questionnaire, established the main criteria for selecting a combination of ''antimicrobial substance-target species-route of administration-pharmaceutical form-disease'' to create a priority shortlist. Based on this list, the Committee will compile all VMPs considered candidates for dosage review and adjustment. Thereafter, in consultation with stakeholders, the CVMP will start with the actual assessment which will rely on existing data and will largely follow the methodology described in the above-mentioned CVMP reflection paper (CVMP, 2021).

The present document describes the processes, timelines and resources for this activity.

2. Goals

The main goals of this activity are to minimise the occurrence of resistance in the Union and to safeguard the availability of first-line treatment veterinary antibiotics in the EU, ensuring they remain efficacious and safe when used in accordance with the approved terms of use as described in the PI. Refined dosages in the PI of VMPs will further ensure the prudent use of antibiotics in veterinary medicine. In general, the review should aim to preserve efficacy and availability while avoiding unnecessary loss of VMPs or indications.

3. Legal basis

It is proposed that the actual assessment for the dosage review and adjustment will be conducted in accordance with Article 141(1)(i) of Regulation (EU) 2019/6: ''*provide scientific advice on the use of antimicrobials and antiparasitics in animals in order to minimise the occurrence of resistance in the Union, and update that advice when needed''.*

The use of Article 141(1) (as opposed to e.g. a referral procedure), has the advantage that there are no legal timelines and deadlines and the CVMP self-mandates the task.

Following the publication of the CVMP's scientific advice(s) provided under Article 141(1)(i) of Regulation (EU) 2019/6, the recommendations would be implemented as a second step, i.e. the PI of the concerned veterinary antibiotics should be updated in line with recommendations. This second step, at national level, can be performed under the following provisions of Regulation (EU) 2019/6:

- Article 58(4) (responsibility of MAHs to keep PIs updated in line with the latest scientific knowledge),
- Article 70 (SPC harmonisation procedure) for different national marketing authorisations of a single VMP.

The NCAs would be responsible for overseeing any national implementation of the conclusions of the scientific advice(s) on existing or subsequent marketing authorisations that would fall within the scope of that advice.

Further tools foreseen in the Regulation may be actioned case by case, if necessary.

4. Procedure under Article 141(1) (i) of Regulation (EU) 2019/6

Under Article 141(1)(i) of Regulation (EU) 2019/6, the CVMP will provide scientific advice on the use of antimicrobials in animals in order to minimise the occurrence of resistance in the Union.

A clear scope should be identified before starting the procedure, including which VMPs will fall under the scope of each scientific advice (a group of VMPs containing a specific active substance, administered *via* the same route and indicated for a target species and a particular disease), so that all relevant applicants/MAHs can be identified.

The work for each scientific advice will be performed by the CVMP which will consult a group of experts (Ad-hoc expert group (AhEG)) with relevant expertise for this activity. The expertise needed includes PK/PD modelling, efficacy of antibiotics, TAS, WPs/WP modelling, ERA. This AhEG will develop and advise on aspects including methodology and data collection (including data mining in scientific literature) and will report to the Committee through a rapporteur and a co-rapporteur appointed to assist with the assessment. This approach aligns with Article 140(6) of Regulation (EU) 2019/6 which allows the CVMP to designate rapporteurs for procedures under Article 141: *"the Committee may appoint, for the purpose of performing its tasks referred to in Article 141, one of its members to act as rapporteur. The Committee may also appoint a second member to act as a co-rapporteur".* The CVMP will ultimately be responsible for preparing the scientific advice(s) under Article 141(1)(i), together with the EMA staff and experts from its Working Parties.

Article 141(1)(i) places the task of collecting scientific information on the CVMP for the purposes of providing its scientific advice. This can be published studies or unpublished proprietary data provided by stakeholders such as MAHs or NCAs as well as studies from authorised marketing authorisation dossiers. In all cases, consent from the MAHs will be always required and confidential information should be redacted from the eventual scientific advice report. All available data will be used for the assessment and can be combined to reach the scientific conclusions. By and large, conclusions need to be generally formulated, rather than targeted at specific VMPs, but in any case should be unambiguous for implementation in the PIs of specific VMPs.

Within the Article 141(1)(i) procedure, the CVMP (as per the norm for assessment procedures) will ask the concerned MAHs to provide relevant, already available information, including data from existing proprietary experimental studies and results from modelling. All MAHs of the concerned VMPs containing the selected combination of ''antimicrobial substance-target species-route of administration-pharmaceutical form-disease'' will be given the opportunity to be involved during the assessment (e.g. responding to lists of questions), including the MAHs of generic VMPs which may have more up-to-date PK (bioequivalence) studies and ERA data that are useful for the assessment.

In addition, an open stakeholder consultation on the draft scientific advice could take place, like the ones for reflection papers and guidelines. This public consultation would also allow academia to provide any relevant data for the scientific assessment (to be confirmed within each procedure, as appropriate).

Based on all the above information and past experience, it is intended to start this activity with the forecast of one procedure per year; i.e. CVMP to deliver one scientific advice per combination of

"antimicrobial substance-target species-route of administration-pharmaceutical form-disease", which would facilitate the assessment and ultimately the national-level implementation of the outcome. Where feasible, the pharmacokinetic modelling used for that combination could be applied for additional diseases, which would be part of the same scientific advice outcome, thereby optimising the use of resources. This approach will be followed on a case-by-case basis.

5. Identification of limitations

The legislation provides a framework for the CVMP to provide scientific advice on the use of antimicrobials in order to minimise the occurrence of resistance. Article 141(1)(i) provides sufficient flexibility in terms of scope, timelines, and stakeholder interactions. Legal aspects of the (conditions of) use of proprietary data have been confirmed as long as consent from the MAHs is sought. The new EMA fee Regulation[2] which entered into force on 1 January 2025 does not foresee fees for MAHs involved under indent (i) of Article 141(1).

The scientific assessment may be limited by data availability, either because there is no relevant data or, based on experience from referral procedures, because not all MAHs decide to engage in providing data. Older MA dossiers may not be fully available anymore within companies or NCAs, or may not contain useful data. Researchers do not often publish studies on old molecules, and if they do, it is often in new target species. Literature data on established antibiotics in the standard target species will therefore often be relatively old. However, useful PK data and ERA data may be available from MA dossiers of more recent generic VMPs, assuming that it is made available during the procedure. In any case, the available data will differ in each situation. Indeed, the assessment approach must be flexible and focus on the possibilities with the (limited) data available.

Availability of resources may be a limiting factor. Whereas the expertise is likely to be present in the European Medicines Regulatory Network, the number of experts in certain areas, such as PK/PD modelling and WP modelling, may be relatively low. The future progression of the activity will largely depend on resource investment and on the return on investment, i.e. is it achieving implementation all the way through to changes to PIs of VMPs at the national level in practice.

6. Phasing of activities

6.1. Preparation phase

The current document and the brainstorming sessions which took place in 2024 and 2025 are part of this preparation phase, which also includes:

- Set up the CVMP/EMA preparatory work expert group;
- Check limitations (data, resources);
- Confirm the assessment approach during the Article 141(1)(i) procedures;
- Analyse the list of antimicrobial candidate substances, define criteria, and propose assessment order (could start with a relatively easy one, combine logical combinations);
- Effective stakeholders engagement, including timings for industry and NCAs consultation and discussion.

[2] Regulation (EU) 2024/568 of the European Parliament and of the Council of 7 February 2024 on fees and charges payable to the European Medicines Agency, amending Regulations (EU) 2017/745 and (EU) 2022/123 of the European Parliament and of the Council and repealing Regulation (EU) No 658/2014 of the European Parliament and of the Council and Council Regulation (EC) No 297/95 (europa.eu)

6.2. Scientific advice

See section 4 for details.

6.3. Implementation phase

Since the concerned VMPs are nationally authorised, the implementation of the outcome of this activity will be the responsibility of: a) the concerned MAHs to apply the 'current scientific knowledge' to their affected VMPs (as per Article 58(4) of Regulation (EU) 2019/6), and b) the NCAs in the Member States to follow-up with MAHs not submitting in due time the anticipated variations.

The SPC harmonisation procedure foreseen under Article 70 of Regulation (EU) 2019/6 only allows for harmonising the same nationally authorised VMP (and its generics afterwards), for which the PI is disharmonised across the different Member States where it is authorised. Therefore, the SPC harmonisation procedure cannot be the main mechanism for implementation of the CVMP's scientific conclusions that will almost certainly reach across several, separate VMPs. However, it could still contribute to implementation, e.g., if a CVMP scientific advice outcome covers in its scope a VMP which will go on to be part of an SPC harmonisation (according to the CMDv's prioritisation), then this will facilitate the work of the CMDv. Furthermore, it might pave the way for the CMDv to consider including VMPs on their prioritisation list for harmonisation if the main assessment work on the most complex areas has already been done by the CVMP.

Harmonisation of PIs of antimicrobial VMPs is acknowledged as a desirable goal and hence, further tools foreseen in the Regulation may be actioned case by case, as appropriate.

6.4. Tentative timelines

The preparation phase has already started and would last to July 2025, approximately. The start of the first scientific advice procedure under Article 141(1)(i) will likely be in September 2025.

Implementation of the CVMP's scientific recommendations by MAHs or by competent authorities could start as soon as the scientific advice(s) will become available.

7. Interaction with stakeholders

During the preparation phase as well as within the development of the scientific advice, the interaction with stakeholders, in particular the veterinary pharmaceutical industry, is essential. MAHs will have valuable input, including useful data, results of modelling, and proposals for dosages or withdrawal periods and should be involved from the outset. MAHs will be requested to provide any relevant data for the assessment and to respond to any questions that the CVMP is trying to solve in the scientific advice. On the other hand, the industry will need clarity in the list of VMPs falling within the scope of each scientific advice and the time schedules in order to prepare their input. It is therefore proposed to organise an information session with the industry during the preparation phase to discuss all these matters, to anticipate and solve concerns, before initiating any scientific advice assessment. This information session will take place in May 2025.

8. Outcome of assessment procedure

Overall, with regard to high-level aim of the project to potentially refine the dosage regimen of antimicrobials substances within veterinary medicinal products, it is important to note that even if a procedure under Article 141(1)(i) is started, if there is lack of sufficient data to support the achievement of robust conclusions, the scientific outcome could be that the CVMP was not able to

safely recommend any (changed) dosage regimen compared to what is authorised. This could also serve as an opportunity to address the lack of data for those antimicrobials and highlight the need for future research projects.

9. References

CVMP (2021). Reflection paper on dose review and adjustment of established veterinary antibiotics in the context of SPC harmonisation. EMA/CVMP/849775/2017. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-dose-review-and-adjustment-established-veterinary-antibiotics-context-spc-harmonisation-first-version_en.pdf

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