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Committee for Veterinary Medicinal Products (CVMP)

Concept paper for the development of a reflection paper on the availability and characteristics of diagnostic tests to improve the responsible use of antibiotics in animals

Agreed by CVMP Antimicrobials Working Party (CVMP AWP)	24 May 2023
Adopted by Committee for Veterinary Medicinal Products (CVMP)for release for consultation	17 July 2023
Start of public consultation	21 July 2023
End of consultation (deadline for comments)	31 October 2023

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	antimicrobial susceptibility testing, antimicrobial resistance, point of care test, genotyping, phenotyping, veterinary pathogens, biomarkers

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1. Introduction

The CVMP's work plan for 2023 [1] includes several activities intended to support the measures introduced in Regulation (EU) 2019/6 [2] directed at the problem of antimicrobial resistance (AMR), with a particular focus on antibiotic resistance. Amongst these activities is a proposal to develop a concept paper for the development of a reflection paper on the availability and characteristics of diagnostic tests to improve the responsible use of antibiotics in animals. This activity is likewise included in the CVMP's Strategy on Antimicrobials 2021–2025 [3] under Aim 5 (relating to support for the responsible use of antimicrobials) and carries forward the reflections in the European Medicines Agencies Network Strategy to 2025 and the EMA's Regulatory Science Strategy [4, 5].

The reflection paper will review available diagnostic tests for the identification or exclusion of the presence of bacterial diseases in animals. Tests currently available or in the validation process that can be used to determine causative pathogens that require antibiotic treatment will be discussed, with a view to the mitigation of antibiotic resistance threats for both animal and human health. Laboratory standards (quality control assays) and diagnostics for non-bacterial diseases will not be considered.

2. Problem statement

The guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances [6] states: 'One of the main requirements for the responsible use of antimicrobials is an accurate diagnosis before treatment'. This is considered to be a "gold standard" of good veterinary practice, aiming to move away from empirical towards a substantiated (calculated) therapy. Thus, diagnostic tests are key tools for prudent and rational use of antibiotics allowing a targeted and efficacious therapy as well as mitigating the risk of antibiotic resistance.

Humans, animals, and the environment act as a reservoir for antibiotic resistance which can spread through direct contact, food and environmental pathways and complicate therapy.

The CVMP's Strategy on Antimicrobials 2021–2025 [3] mentions that the use of antimicrobial susceptibility testing, especially before administration of critically important antimicrobials, is encouraged and a reflection will be made upon the use of currently available tests and novel rapid diagnostic testing methods as a means to improve rational prescribing. In particular, a current challenge for veterinary practitioners is related to the prerequisite for susceptibility testing for the use of some last resort compounds. In addition, other particular difficulties include the reliability of the test result and clinical usefulness of surveillance data in general (e.g. bias in surveillance data due to a selection of pathogens retrieved from animals that have already been treated with antibiotics, and thus an overestimation of antibiotic resistance).

Veterinary use of antibiotics may present a health risk to humans, animals and their environment, and thus restrictions are in place to use some agents as a second or last resort compounds. Currently the categorisation of antibiotics (e.g. such as that provided by CVMP/AMEG [7]) has been based upon a risk evaluation considering, amongst others, prevalence of resistance, risk of resistance transfer and co-and cross-resistance threats. In some European Member States, a susceptibility test is already mandatory before prescription of last resort agents, demonstrating that a substance from a lower AMEG category is not likely to be effective.

3. Discussion

The main driver for antibiotic resistance is the use of antibiotics and studies have found that the applied therapy is not always appropriate or needed because of wrongly targeted pathogens, involvement of other comorbidities, or because the infection is self-limiting. Even when applied rationally, resistance to antibiotic agents can evolve rapidly in both Gram-positive, Gram-negative, and anaerobic bacteria.

Testing has been traditionally based upon culture, whereas in recent decades non-culture identification methods have been introduced in the routine clinical and experimental setting. Both qualitative (presence) and quantitative (amount) assays have been developed and the utility and affordability for animal husbandry is driven by a balance between economics, animal health and animal wellbeing, as well as public health due to the zoonotic potential of the antibiotic resistome [8]. For farmed animals, a herd or flock-wide approach is often required, whereas companion animals are usually diagnosed individually.

We will aim to describe the currently available tests, both point of care and laboratory assays, that can support a rational antibiotic prescription and therapy.

4. Recommendation

The CVMP recommends the development of a "Reflection paper on the availability and characteristics of diagnostic tests to improve the responsible use of antibiotics in animals", taking into account the issues identified above.

The following items will be considered in a horizontal scanning review for livestock, aquaculture and companion animals, for major bacterial diseases and separating point of care tests (on farm/patient side) from routine sampling and clinical laboratory assays:

- Confirmative biomarkers for a bacterial infection
- Culture dependent vs culture independent assays
    - Identification of bacterial pathogens
    - Antimicrobial susceptibility testing

The reflection paper should also contain information on the

- clinical need for available tests and identification of gaps in availability
- turn-around time in the laboratory
- accuracy (false positive/negative results)
- feasibility of assays under field conditions (sampling procedure, storage, transport conditions)

Since development of syndromic testing (i.e. testing for a broad panel of infectious etiological pathogens within a specific organ system such as the respiratory tract) is expanding, allowing non-bacterial infections to be identified or ruled out, these assays will also concisely be reviewed. Finally future research topics, e.g. relating to the microbiome will be identified.

The reflection paper will also include recommendations based on the outcome of its review.

5. Proposed timetable

July 2023	Concept paper released for consultation
31 October 2023	Deadline for comments from interested parties
Q4 2024	Reflection paper released for consultation

6. Resource requirements for preparation

The development of the reflection paper will involve two AWP rapporteurs. Drafting group (physical and virtual) meetings will be organised, as needed.

7. Impact assessment (anticipated)

The Reflection paper will provide information on reliability of currently available diagnostic tests and information on future tests for the confirmation of infections with either antibiotic susceptible or resistant bacteria. This will support the responsible and targeted use of antibiotic agents by veterinarians. It will facilitate the One Health mitigation process to combat antimicrobial drug resistance, as outlined by the international (e.g. WHO, WOAH, FAO, UNEP) and European dedicated health organisations (e.g. ECDC, EFSA, EMA, EEA). Where appropriate, identification of the lack of diagnostic tests can encourage further development of such tests.

8. Interested parties

Veterinary pharmaceutical industry, regulatory consultants, EU national competent authorities and policy-makers, veterinary professional bodies, veterinarians and animal owners.

9. References to literature, guidelines, etc.

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