EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2020
EMA/CVMP/179874/2020
Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP strategy on antimicrobials 2021-2025

Draft

Adopted by CVMP for release for consultation	18 June 2020
Start of public consultation	1 July 2020
End of consultation (deadline for comments)	30 September 2020

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

Keywords	antimicrobials, CVMP, strategy

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

CVMP strategy on antimicrobials 2021-2025

Table of contents

1. Introduction 4

2. Summary 4

3. CVMP's strategic aims and proposed actions in relation to antimicrobials 2021-2025 5

4. Annex 10

Acronyms

ADVENT	Ad hoc Expert Group on Veterinary Novel Therapies: Established under the CVMP to provide guidance on the requirements for authorisation of novel veterinary medicines.
AMEG	Antimicrobial Advice Ad hoc Expert Group: Established jointly under CVMP and CHMP to provide guidance on the impact on public health and animal health of the use of antibiotics in animals, and on the measures to manage the possible risk to humans.
AMR	Antimicrobial resistance
CHMP	Committee for Medicinal Products for Human Use
CIA	Critically Important Antimicrobial
CMDv	Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary
CVMP	Committee for Medicinal Products for Veterinary Use
EARS-Net	European Antimicrobial Resistance Surveillance Network: Network of national surveillance systems providing reference data on AMR from clinical laboratories in the EU/EEA. Supported by ECDC.
ECDC	European Centre for Disease Prevention and Control
ECHA	European Chemicals Agency
EFSA	European Food safety Authority
EMA	European Medicines Agency
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption: ESVAC collects data from European countries on the sales and use of antimicrobial medicines in animals. Supported by the EMA.

EURL-AR	EU Reference Laboratory – Antimicrobial Resistance: Body providing scientific advice to the Commission in relation to monitoring schemes for AMR.
FAO	Food and Agriculture Organization of the United Nations
HMA	Heads of Medicines Agencies: Network of the heads of National Competent Authorities responsible for the regulation of human and veterinary medicinal products in the EEA.
JIACRA	Joint inter-agency antimicrobial consumption and resistance analysis: Collaboration between ECDC, EFSA and EMA to analyse the relationship between the consumption of antimicrobials in humans and animals and the occurrence of AMR.
OIE	World Organisation for Animal Health
PKPD	Pharmacokinetic-pharmacodynamic
RONAFA	EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety
SPC	Summary of Product Characteristics
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance: Collaboration between government agencies from Canada, EU, Norway and the US to promote mutual understanding and information exchange on activities and best practices relating to prevention and control of AMR.
VetCAST	Veterinary sub-committee of European Committee on Antimicrobial Susceptibility Testing
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary Medicinal Product

21

22

1. Introduction

It is estimated that in 2015 there were more than 670,000 human infections with antibiotic-resistant bacteria in the EU/EEA and that these accounted for 33,000 deaths, according to a study based on data from the European Antimicrobial Resistance Network (EARS-Net) (Cassini et al., 2019). The European One Health Action Plan against antimicrobial resistance (AMR), adopted in 2017 (European Commission, 2017), acknowledges this serious social and economic burden and provides a framework of concrete actions, certain of which have been ratified as measures in the veterinary medicinal products regulation (Regulation (EU) 2019/6) (Official Journal of the European Union, 2019), adopted by the European Parliament and Council at the end of 2018 (Official Journal of the European Union, 2018). Considering the CVMP's regulatory responsibility to ensure the safety and efficacy of antimicrobial veterinary medicines and to provide scientific advice to the Commission on AMR, many of the CVMP's activities proposed for the next five years focus on assisting with the effective implementation of the new legislation to ensure it achieves its objective to strengthen the EU's actions in the fight against AMR. Related tasks have already started in 2020, building on foundations laid down by CVMP whilst fulfilling its preceding strategies on antimicrobials. An overview of the activities undertaken by CVMP in 2016-2020 (EMA/CVMP, 2016a) is presented in the Annex to this document.

Furthermore, the EMA has recently published its strategic reflections on regulatory science, developed in consultation with key stakeholders (EMA, 2020). Addressing the health threat from AMR is a key strategic goal and the recommendations will feed into the European Regulatory Network Strategy to 2025. These recommendations have been taken into consideration for the CVMP's antimicrobials strategy presented below.

CVMP's Mission Statement on antimicrobials

The CVMP's mission is to ensure the availability of effective antimicrobial medicines for the treatment of infectious diseases of animals while, at the same time, minimising the risks to animals or humans arising from their use.

An 'antimicrobial' is defined in Regulation (EU) 2019/6 as 'any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals'.

2. Summary

Aim 1: To provide opinions for the **authorisation of effective antimicrobial veterinary medicinal products** ensuring that the necessary **risk management measures** are applied so that products can be used safely and sustainably.

Actions: CVMP will update its existing guidance documents in line with the definitions relating to antimicrobial use provided in the new veterinary medicines legislation and will review the indications for antimicrobial medicines authorised via centralised procedure for prophylactic/preventive use.

Aim 2: To consider and advise on the **risk to public health** that could arise from the use of antimicrobials in animals, and to balance this against the need to protect animal health. To provide advice in a One Health context, considering the interaction between humans, animals and the environment as sources of antimicrobial resistance genes.

Actions: The AMEG's categorisation will be reviewed as required to take account of evolving patterns of AMR and antibiotic usage in human and veterinary medicine.

Aim 3: To **maintain the effectiveness of antimicrobial substances that are already authorised** in veterinary medicinal products by monitoring and analysing their **sales and usage**, encouraging surveillance for changes in susceptibility of target pathogens and zoonotic bacteria, and subsequently **reviewing the authorisation** of substances and/or products, especially when there is evidence that there may be a related change in the benefit-risk of the authorisation.

Actions: CVMP will provide support to ESVAC in its preparations to receive data on sales and use of antimicrobials by animal species and will provide appropriate governance over the ESVAC and JIACRA reports. Recommendations will be taken forwards on dose review and adjustment for established antibiotic products.

Aim 4: To encourage the **development of new and existing antimicrobial veterinary medicinal products.** To encourage the development of **alternatives to antimicrobials.**

Actions: The CVMP will provide regulatory and scientific advice on the development of new and existing antimicrobial medicinal products and will progress options for the regulatory framework for alternatives to antimicrobials.

Aim 5: To support the **responsible use** of antimicrobials both in accordance with Marketing Authorisations and under the **cascade**.

Actions: Scientific advice will be provided on the implementation of the new legislation pertaining to restrictions on the use of antimicrobials under the cascade. A reflection will be made on use and availability of diagnostic tests to improve the responsible use of antimicrobials.

Aim 6: Recognising that **AMR is a global problem** affecting both animal and human health, to work in partnership with the European Commission and its agencies, competent authorities in the Member States, international regulatory bodies, human and animal health organisations and the pharmaceutical and livestock industries to provide science led guidance on the responsible use of antimicrobials in animals.

Actions: CVMP will continue its engagement with its diverse stakeholders and to collaborate with colleagues in EU agencies and international regulatory bodies in developing guidance and advice on antimicrobial-related issues.

Additional actions relating to the implementation of the veterinary medicinal products regulation (Regulation (EU) 2019/6) are included in the detailed strategy below.

3. CVMP's strategic aims and proposed actions in relation to antimicrobials 2021-2025

Aim 1. Provide opinions to support the authorisation of effective antimicrobial VMPs with measures ensuring safe and sustainable use

The veterinary medicinal products regulation (Regulation (EU) 2019/6) seeks to promote the responsible and prudent use of antimicrobials and eliminate their misuse. In this respect it introduces important controls around the use of antimicrobial products for 'prophylaxis' and 'metaphylaxis' (Article 107), reflecting recommendations in the joint EMA/EFSA RONAFA opinion (EMA/EFSA, 2017). Differing interpretations of the terminology, which have led to lack of clarity for users in the past, have been addressed by provision of definitions in the regulation. In relation to prophylaxis, the regulation states that use of antimicrobial medicines is not allowed other than in exceptional cases, for administration to

an individual or a restricted number of animals and when the risk of infection is high and the consequences are likely to be severe. Guidance may be needed around the application of this provision and a review of existing marketing authorisations for consistency with the new definition and restrictions will be required.

CVMP's proposed actions:

CVMP's existing **guidelines will be updated** in line with the **definitions provided in Article 4 of Regulation (EU) 2019/6** ('antimicrobial', 'antibiotic', 'metaphylaxis', 'prophylaxis').

CVMP will consider the need to provide **guidance/criteria for the 'exceptional cases' when antimicrobial medicines may be used for prophylaxis** (Article 107(3)). Related indications for **existing centrally authorised VMPs will be reviewed** and amended where necessary.

Advice will be provided on the data requirements for a **variation demonstrating a reduction in antimicrobial resistance** that will benefit from an **additional period of data protection** (Article 40(5)).

Aim 2. Advise on the risk to public health of the use of veterinary antimicrobials and balance it against the need to protect animal health

At the beginning of 2020, the EMA published an update of the Antimicrobial Advice Ad hoc Expert Group (AMEG) Categorisation of antibiotics according to the risk to public health from their use in veterinary medicine in the EU (EMA/CVMP/CHMP, 2019a). This developed upon the previous categorisation (2014), including all EU-authorised antibiotic substances and strengthening the One Health approach by placing greater emphasis on the availability of alternative antibiotics in veterinary medicine for the treatment of important animal diseases. The report recognises, as came to attention in relation to colistin in 2016, that antimicrobial resistance and usage is a dynamic environment, and hence timely review of the categorisation is recommended.

Consideration of the role of the environment as a reservoir for dissemination of antimicrobial resistance genes has been high on the agenda of international organisations such as the WHO, OIE and FAO in recent years (FAO, 2016; OIE, 2016; WHO, 2015). At EU level, the Commission presented in 2019 its Strategic Approach to Pharmaceuticals in the Environment, reinforcing the need for the measures included in Regulation (EU) 2019/6 aimed at limiting the preventive use of antimicrobial veterinary medicines as a direct approach to reduce the exposure of the environment. The CVMP has reviewed its approach to the environmental risk assessment of VMPs in respect to AMR (EMA/CVMP/ERAWP/AWP, 2018), identifying knowledge gaps and concluding that the risk assessment methodology needs to be further developed.

Depending on the outcome of the considerations of the CVMP's working group drafting advice to the Commission on antimicrobials to be reserved for human use only, CVMP may reflect on the use of non-antibiotic antimicrobials in animals[1].

CVMP's proposed actions:

At the request of the Commission, the EMA/CVMP will collaborate with other EU Agencies in a **review of the AMEG's categorisation of antibiotics** as recommended in the AMEG's advice (2020) (within 5 years) and in particular to **respond in a timely way to any emerging health threat relating to AMR**.

[1] To be updated after the public consultation.

CVMP will consider developing **guidance on the assessment of the risk to public health** due to the use of antimicrobials in **companion animals.**

As outlined in the **EU's strategic approach to pharmaceuticals in the environment,** the CVMP will take action to ensure correct implementation of Regulation (EU) 2019/6 in order to **limit preventive use of veterinary antimicrobials** as a measure to reduce environmental exposure.

CVMP will explore the development of **improved or alternative methodologies** to assess if improvements can be made to the **environmental risk assessment** for antimicrobial VMPs.

An action may be entered relating to a review of the (potential) use of **non-antibiotic antimicrobials** in veterinary medicine and e.g. potential for transfer of resistance to humans and impacts on public health.

Aim 3. Take measures to ensure the on-going availability and effectiveness of authorised veterinary antimicrobials

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project has been collecting antimicrobial sales data from European countries on a voluntary basis since 2010. This information, together with data from EFSA and ECDC, forms the basis for the joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) report, identifying important trends and associations between the consumption of antimicrobials in humans and animals and the occurrence of AMR. The third JIACRA report will also present a series of agreed outcome indicators, designed to assist Member States to assess progress made in the implementation of their action plans against AMR. Recognising the important need for more detailed and standardised data, Regulation (EU) 2019/6 introduces harmonised collection of 'use' data and reporting by specific animal species at EU level. The reporting of these data, alongside collection and reporting of data on antimicrobial sales, which has been voluntary since 2010, will become mandatory, with stepwise requirements for specific species/categories of animals being introduced from 2022. Further consideration will need to be given to the methodology for analysis of these data, to ensure best use can be made by policymakers and also considering approaches under development internationally. In future the CVMP will take responsibility in cooperation with Member States and other EU agencies for the analysis of the data provided in the associated ESVAC and JIACRA reports.

Under the previous strategy, the CVMP published a reflection paper (EMA/CVMP, 2018b) which investigated the use of non-experimental approaches to review and adjust doses for established antibiotics, hence avoiding the need for new animal studies; recommendations from this report will be finalised and taken forwards as found appropriate. The CVMP will assist with implementation of further measures introduced into the veterinary medicines regulation to ensure that antimicrobial veterinary medicines already on the market remain effective with a positive benefit-risk for as long as possible. CVMP will also investigate the barriers preventing access to, and use of, certain Category D[2] antibiotics that could reduce the use of critically important antimicrobials in animals.

CVMP's proposed actions:

From 2022, the CVMP will take responsibility for **adoption of the annual ESVAC report of the analysis of sales and use of antimicrobial medicinal products** to be prepared by the Agency in cooperation with the member states (Regulation (EU) 2019/6, Article 57(2)).

[2] According to the AMEG's categorisation (EMA/CVMP/CHMP, 2019a) Category D includes antibiotics that should be used where possible as first line treatments.

CVMP will provide further **support to ESVAC** in its preparations to receive **data on sales and use of antimicrobial medicinal products relating to certain animal species** (Article 57(5)).

The EMA/CVMP will continue to **report antimicrobial use and consumption data to the JIACRA group for the purpose of integrated analysis of antimicrobial consumption and resistance surveillance data from ECDC, EFSA and EMA.** In line with Regulation (EU) 2019/5, the joint interagency report should be updated at least every 3 years.

At request from EFSA, the EMA/CVMP will contribute to a scientific opinion for the **listing and categorisation of transmissible animal diseases caused by AMR bacteria** within the framework of the Animal Health Law and European One Health Action Plan against AMR.

The CVMP will provide guidance on the circumstances and requirements for **post-authorisation studies** for antimicrobial veterinary medicines to be required at the time of granting of a marketing authorisation in order **to ensure that the benefit-risk remains positive** given the potential for development of AMR (Article 36(2)).

The CVMP will finalise and take forward the recommendations from its Reflection paper on **dose review and adjustment of established veterinary antibiotics,** including development of a procedure for prioritisation of candidate products for review.

If requested by the Commission, the CVMP will **assist the CMDv** in the implementation of Article 70 of Reg (EU) 2019/6 by providing recommendations on the **prioritisation of classes or groups of antimicrobial reference VMPs that should undergo SPC harmonisation** in order to protect human or animal health (Article 70(4)).

Through dialogue with colleagues in the European Medicines Regulatory Network, industry and veterinary professionals, the CVMP will **investigate the barriers preventing access to, and use of, certain Category D antibiotics** in veterinary medicine.

The CVMP will undertake a review of its **reflection paper on Macrolides, Lincosamides and Streptogramins** (EMA/CVMP/SAGAM, 2011) in order to update its recommendations, as required, to reflect recent developments in AMR and the importance of these classes to animal and human health.

Aim 4. Encourage the development of antimicrobial veterinary medicinal products and foster the development of alternatives to antimicrobials

The first AMEG opinion acknowledged that new veterinary-only classes of antimicrobials have the potential to decrease the animal and public health risk from AMR and the O'Neill report (2015) also highlighted the need to encourage further development of antimicrobials for animals, in particular substances found not viable for use in humans. The European One Health action plan against AMR aims to support the development of new antimicrobials and alternative products for animals as well as for humans. In 2019 the EMA published advice on a preliminary risk profiling (PRP) which considers the AMR risk to public health from new antimicrobial substances or veterinary medicines; this has now been introduced into the CVMP's scientific advice process (EMA/CVMP/CHMP, 2019b). The intended benefit is to increase regulatory predictability at an early stage of product development and thereby encourage the pharmaceutical industry to develop new antimicrobial medicines for animals.

The RONAFA opinion provided a review of the evidence supporting a range of potential alternatives to antimicrobials. Based on a recommendation from this report, CVMP has conducted an analysis to identify gaps in the regulatory framework supporting the authorisation of these alternatives and the topic has also been discussed with stakeholders in the context of development of the EMA's regulatory science strategy. It is understood that novel paradigms will be needed and a series of measures for

consideration by the network has been proposed in the CVMP's draft reflection paper published in 2019 (EMA/CVMP, 2019b).

CVMP's proposed actions:

The CVMP will provide regulatory guidance through the **Innovations Task Force** and the **ADVENT group**, and **scientific advice including Preliminary Risk Profiling** on request from marketing authorisation applicants on the development of new antimicrobial products and alternatives to antimicrobials for the treatment of microbial infections.

In addition, CVMP will provide advice on the circumstances and type of data that could support **demonstration of a reduction in AMR** and hence a variation to the terms of the marketing authorisation that would benefit from an additional **4 years' data protection** (Article 40(5)).

The CVMP will **collaborate with other EU Agencies** (EFSA, ECHA) on the **classification and regulation of alternatives to antimicrobials (ATAm)**. Further guidance will be developed on **data requirements and** potential **claims for ATAm,** and how demonstrated treatment benefits should be factored into the benefit/risk assessment for veterinary medicines. CVMP will promote **international cooperation** and exchange of information with other regulatory regions to assist the global development and alignment of the approach to authorisation of ATAm.

The CVMP will continue to take into consideration **data requirements for limited markets** when reviewing marketing authorisation applications for designated products and will consider if the related guidance can be revised to improve the availability of antimicrobials for minor uses and minor species.

Aim 5. Support responsible use of antimicrobials both in accordance with marketing authorisations and under the cascade

Regulation (EU) 2019/6 recognises that there is a need to reserve for human use only certain critically important antimicrobials (CIAs) that are of last resort to treat life-threatening infections. Taking into account the work of international and regional expert groups, CVMP has provided advice to the Commission on the criteria for designating these substances and will propose candidate antimicrobials for the 'reserved list' based on their importance to human health, the risk for transfer of resistance to the substance from animals to humans and the availability of alternative treatments for animals (EMA/CVMP, 2019a). Furthermore, the CVMP will provide advice on restrictions on the cascade use of other specific antimicrobial substances to ensure that associated AMR risks to animal and public health are balanced with the availability of treatments, especially for limited market indications, and potential impacts on aquaculture and farming if the associated condition cannot be treated.

The CVMP supports the development of evidence-based national and regional treatment guidelines, which take account of local trends in antimicrobial susceptibility, animal health status and product accessibility. The updated AMEG categorisation is a useful tool for those preparing such guidelines or when prescribing under the cascade. The CVMP will continue to ensure that the guidance it provides in SPCs facilitates the development of treatment guidelines and responsible antimicrobial prescribing. Use of antimicrobial susceptibility testing, especially before administration of CIAs, 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.

CVMP's proposed actions:

EMA/CVMP will provide scientific advice to the Commission on the **implementing act** to establish **a list of antimicrobials which either shall not be used under the cascade or shall only be used subject to certain conditions** (Article 107(6)).

The CVMP will continue to ensure that the **advice provided in SPCs facilitates the development of treatment guidelines** and will continue to support the development of **clinical breakpoints**.

The CVMP will develop a reflection paper to consider the **availability and characteristics of diagnostics tests** that could be used to inform better targeted therapy to improve the responsible use of antimicrobials in animals.

Aim 6. Work in partnership with EU/EEA and international human and animal health organisations to tackle the global problem of AMR

The EU Member States and EEA countries collaborate through shared legislation and the work of the EMA and HMA in tackling AMR. However, as a result of increasing international trade and travel, AMR is an expanding global issue. Recognising the need for collaboration between human health, animal health and agricultural sectors, the WHO has published a Global Action Plan (WHO, 2015), which outlines the roles and responsibilities of stakeholders in relation to AMR. The overall public health goal of the action plan is to ensure, for as long as possible, continuity of treatment and prevention of infectious disease with effective safe medicines that are quality-assured, used in a responsible way and accessible to all who need them. A number of International intergovernmental bodies and EU industry and professional organisations such as WHO, World Organisation for Animal Health (OIE), Codex Alimentarius, EFSA, ECDC and Federation of Veterinarians of Europe (FVE) already produce guidance on risk assessment and responsible use recommendations. It is important that the CVMP continues to collaborate with international bodies such as VICH and Codex to harmonise regulatory frameworks and to ensure that progress made through controlling AMR within Europe is not put at risk through importation of resistant bacteria (or determinants) from regions with less rigorous controls.

CVMP's proposed actions:

The CVMP will continue to **consult with stakeholders** (including the pharmaceutical and livestock industries and veterinary associations) when developing guidance documents and reflection papers relating to antimicrobials issues.

CVMP will aim to increase collaboration with colleagues across the European Medicines Regulatory Network, in **EU agencies** (e.g. EFSA, ECDC, EURL-AR) and with **international regulatory bodies** in developing guidance and advice (e.g. OIE, TATFAR and WHO).

4. Annex

4.1. CVMP status report on activities undertaken on antimicrobials

In order to facilitate the development of the new CVMP strategy on antimicrobials from 2021-2025, a review was conducted of the activities carried out to implement the previous strategy in place from 2016-2020 (EMA/CVMP, 2016a).

Strategy 2016-2020	Actions undertaken by CVMP and the network
Aim 1 **Provide opinions to support the authorisation of effective antimicrobial VMPs with measures ensuring safe and sustainable use**	The revised Guideline for the demonstration of efficacy of veterinary medicinal products containing antimicrobial substances (EMA/CVMP/261180/2012) was finalised and published in 2016 (EMA/CVMP, 2016b). Updated guidance is provided on provision of PK and PD data and on study requirements to support claims for prevention of disease and for metaphylaxis. The draft Guideline on the SPC for antimicrobial veterinary medicines (EMA/CVMP, 2018a) was released for consultation in 2018 (finalisation Apr 2021*). Additional information about epidemiological conditions for initiation of antimicrobial metaphylaxis and the demonstrated extent of treatment benefit should now be included in the SPC. Training for regulatory assessors on the application of CVMP guidelines relating to antimicrobial VMPs was provided by ANSES (2017) in conjunction with EUNTC.
Aim 2 **Advise on the risk to public health of the use of veterinary antimicrobials and balance it against the need to protect animal health**	The joint EMA/EFSA RONAFA opinion on measures to reduce the use of antimicrobial agents in animal husbandry and impacts on food safety was adopted in 2016 and published in the Official Journal (EMA/EFSA, 2017). It has been presented at various Agency fora. Recommendations from the opinion relating to antimicrobial prophylaxis and metaphylaxis have been taken forward in Regulation (EU) 2019/6. The EMA/CVMP has provided advice to the EC on the delegated act on the *Criteria to designate antimicrobials for human use only* (EMA/CVMP, 2019a), and is preparing advice for the implementing act on the related list of substances (for adoption Oct 2020). A focus group meeting was held in 2018 to discuss comments received during the first public consultation of the *guideline on the assessment of the risk to public health due to the use of antimicrobial VMPs in food animals* (EMA/CVMP/AWP, 2015). Following the second consultation, finalisation is anticipated in Apr 2021*. The CVMP's reflection paper on Aminoglycosides was published in 2018 (EMA/CVMP/AWP, 2018b). A draft reflection paper on Aminopenicillins was adopted in 2018; finalisation is expected by Dec 2020* (EMA/CVMP/AWP, draft). The draft reflection paper on AMR in the Environment (EMA/CVMP/ERAWP/AWP, 2018)has been published and further revision following the public consultation (ended Aug 2019) is expected to be completed by Dec 2020*. The AMEG's Categorisation of antibiotics (first published in 2014) was updated in 2020 using modified criteria to provide a

Strategy 2016-2020	Actions undertaken by CVMP and the network
	balanced One Health approach and to include all antibiotic substances used in the EU. The updated advice (EMA/CVMP/CHMP, 2019a) has been published on the EMA website, along with an infographic translated into all EU languages to assist vets in their prescribing.
Aim 3 **Take measures to ensure the on-going availability and effectiveness of authorised veterinary antimicrobials**	The revised guideline on the SPC for antimicrobial VMPs proposes updated information and warnings to be included to support responsible use by veterinarians. A memorandum of understanding has been agreed between the EMA and ESCMID to allow collaboration with VetCAST experts over the establishment of clinical breakpoints for veterinary antimicrobials/pathogens for both new and existing antimicrobials/products. The JIACRA II report was published in 2017 and is based upon data provided by ESVAC, ECDC and EFSA surveillance (ECDC/EFSA/EMA, 2017b). The report allows progress to be monitored against key outcome indicators of antimicrobial consumption and AMR in the human and animal sectors. Data from ECDC, ESVAC and EFSA surveillance have also been used to inform advice provided to the Commission, e.g. in relation to the AMEG's review of the impact of colistin use in animals on public health and recommendations on risk management. The EMA/CVMP provided advice to the Commission on the delegated act on the requirements for the collection of data on antimicrobial medicinal products used in animals (Regulation (EU) 2019/6, Article 57(3)) and on the implementing act on the format of the data to be collected (Article 57(4)). The CVMP conducted [nine†] referral procedures for established antimicrobial VMPs, leading to recommendations for withdrawal of products/indications only when it was considered that the evidence (or absence thereof) led to serious concerns in relation to lack of efficacy or AMR. In many cases, dosing regimens and prudent use warnings have been improved allowing products to be maintained on the market. The CVMP collaborated with industry on a pilot project (PPHOVA) to investigate the use of non-experimental approaches to optimise doses for established antimicrobials. A reflection paper on this topic (EMA/CVMP, 2018b) was discussed with stakeholders at a focus group meeting and published for consultation in 2018 and will be finalised in 2020*.

Strategy 2016-2020	Actions undertaken by CVMP and the network
	Training for regulatory assessors on principles and application of PKPD modelling was provided by MEB and ANSES in conjunction with the EUNTC in 2019.
Aim 4 **Encourage the development of antimicrobial veterinary medicinal products, especially for minor uses and minor species, and foster the development of alternatives to antimicrobials**	The Committee has provided [xx†] scientific advice reports relating to AM VMPs and held [xx†] ITF meetings for applicants wishing to develop antimicrobials or alternatives. In response to a request from the Commission, the CVMP/CHMP published in 2019 advice on a methodology for 'preliminary risk profiling', intended to increase regulatory predictability and hence encourage the development of new antimicrobial substances or products for use in animals (EMA/CVMP/CHMP, 2019b). A draft reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU was published for consultation until April 2020 (EMA/CVMP, 2019b). This topic also features in the EMA's Regulatory Science Strategy to 2025, for which the recommendations and approach have been discussed with stakeholders at workshops held in 2018 and 2019. In 2016, CVMP established an *ad hoc* expert group on vaccine availability (CADVVA) to support implementation of the actions arising from the EMA/HMA steering group on this topic, including consideration of a risk-based approach to extraneous agent testing, the feasibility of introducing the vaccine antigen masterfile (VAMF) and recommendations on the need for field efficacy trials.
Aim 5 **Support responsible use of antimicrobials both in accordance with marketing authorisations and under the cascade**	CVMP's reflection paper on off-label use of antimicrobials in veterinary medicine in the EU was published in 2018 (EMA/CVMP/AWP, 2018a). Recommendations relate to responsible prescribing under the Cascade and encouragement for the development of evidence-based treatment guidelines by regional/sectoral professionals. Implementation of the revised guideline on the SPC for antimicrobial veterinary medicines is intended to improve the information available to those developing treatment guidelines. Annex II of the document also includes recommendations on appropriate pack-sizes to support prudent use.
Aim 6 **Work in partnership with EU/EEA and international human and animal health organisations to tackle the global problem of AMR**	The CVMP has continued with open public consultations on guidelines and reflection papers relating to AMR topics and has received and addressed extensive responses from international organisations and regulatory bodies, professional bodes, academia and pharma and livestock industry groups. The EMA/CVMP has collaborated extensively with ECDC and EFSA on the implementation of the EU One Health Action Plan

Strategy 2016-2020	Actions undertaken by CVMP and the network
	against AMR, assisting with compilation of inter-agency reports (e.g. AMEG advices, RONAFA, JIACRA) (ECDC/EFSA/EMA, 2017a; ECDC/EFSA/EMA, 2017b; EMA/CVMP/CHMP, 2019a; EMA/CVMP/CHMP, 2019b; EMA/EFSA, 2017) and provision of advice to the Commission on the new legislation on VMPs and Medicated Feed. CVMP is represented under the EMA at the Codex TFAMR and VICH and has input to discussion on antimicrobials issues including revision of guidance.

*Dates subject to impacts of BCP and Covid-19. To be updated after public consultation, prior to publication of the adopted strategy.

†Figures to be finalised after public consultation, prior to publication of the adopted strategy.

4.2. References

Cassini, A., L.D. Högberg, D. Plachouras, A. Quattrocchi, A. Hoxha, G.S. Simonsen, M. Colomb-Cotinat, M.E. Kretzschmar, B. Devleesschauwer, and M. Cecchini, 2019. 'Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis', The Lancet Infectious Diseases, Vol. 19 (1), pp.56-66.

ECDC/EFSA/EMA, 2017a. 'Joint Scientific Opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals', https://www.ema.europa.eu/en/documents/report/ecdc-efsa-ema-joint-scientific-opinion-list-outcome-indicators-regards-surveillance-antimicrobial_en.pdf

ECDC/EFSA/EMA, 2017b. 'Second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals (JIACRA II)', https://www.ema.europa.eu/documents/report/ecdc/efsa/ema-second-joint-report-integrated-analysis-consumption-antimicrobial-agents-occurrence_en.pdf

EMA, 2020. 'Regulatory Science to 2025 (EMA/110706/2020)', https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

EMA/CVMP, 2016a. 'CVMP strategy on antimicrobials 2016-2020 (EMA/CVMP/209189/2015)', https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/cvmp-strategy-antimicrobials-2016-2020

EMA/CVMP, 2016b. 'Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)', https://www.ema.europa.eu/en/demonstration-efficacy-veterinary-medicinal-products-containing-antimicrobial-substances

EMA/CVMP, 2018a. 'Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/383441/2005-Rev.1)', https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-guideline-summary-product-characteristics-spc-veterinary-medicinal-products-containing_en.pdf

EMA/CVMP, 2018b. 'Reflection paper on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation(EMA/CVMP/849775/2017)', https://www.ema.europa.eu/en/dose-optimisation-established-veterinary-antibiotics-context-summary-product-characteristic-spc

EMA/CVMP, 2019a. 'Advice on implementing measures under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products. Criteria for the designation of antimicrobials to be reserved for treatment of certain infections in human (EMA/CVMP/158366/2019)', https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/advice-implementing-measures-under-article-374-regulation-eu-2019/6-veterinary-medicinal-products-criteria-designation-antimicrobials-be-reserved-treatment-certain_en.pdf

EMA/CVMP, 2019b. 'Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU (EMA/CVMP/461776/2017)', https://www.ema.europa.eu/en/cvmp-reflection-paper-promoting-authorisation-alternatives-antimicrobials-eu

EMA/CVMP/AWP, 2015. 'Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013)', https://www.ema.europa.eu/en/assessment-risk-public-health-antimicrobial-resistance-due-use-antimicrobial-veterinary-medicinal

EMA/CVMP/AWP, 2018a. 'Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union (EMA/CVMP/AWP/237294/2017)', https://www.ema.europa.eu/en/off-label-use-antimicrobials-veterinary-medicine-european-union

EMA/CVMP/AWP, 2018b. 'Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/721118/2014)', https://www.ema.europa.eu/en/use-aminoglycosides-animals-european-union-development-resistance-impact-human-animal-health

EMA/CVMP/AWP, draft. 'Reflection paper on the use of aminopenicillins and their beta-lactamase inhibitor combinations in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/842786/2015)', https://www.ema.europa.eu/aminopenicillins-their-beta-lactamase-inhibitor-combinations-animals-european-union-development

EMA/CVMP/CHMP, 2019a. 'Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017)', https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf

EMA/CVMP/CHMP, 2019b. 'Preliminary risk profiling for new antimicrobial veterinary medicinal products (EMA/CVMP/CHMP/682199/2017)', https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/answer-request-european-commission-updating-scientific-advice-impact-public-health-animal-health-use_en-0.pdf

EMA/CVMP/ERAWP/AWP, 2018. 'Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products (VMPs) (EMA/CVMP/ERA/632109/2014)', https://www.ema.europa.eu/en/antimicrobial-resistance-environment-considerations-current-future-risk-assessment-veterinary

EMA/CVMP/SAGAM, 2011. 'Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMEA/CVMP/SAGAM/741087/2009)', https://www.ema.europa.eu/en/use-macrolides-lincosamides-streptogramins-food-producing-animals-european-union-development

EMA/EFSA, 2017. 'Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)', 15:1. https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals/reducing-use-antimicrobial-agents-animal-husbandry

European Commission, 2017. 'A European One Health Action Plan against Antimicrobial Resistance (AMR)', https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf

FAO, 2016. 'Drivers, dynamics and epidemiology of antimicrobial resistance in animal production', http://www.fao.org/3/a-i6209e.pdf

O'Neill, J., 2015. 'Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste - The Review on Antimicrobial Resistance - December 2015', http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf

Official Journal of the European Union, 2018. 'A European One Health Action Plan against Antimicrobial Resistance. European Parliament resolution of 13 September 2018 on a European One Health Action Plan against Antimicrobial Resistance (AMR) (2017/2254(INI))', https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018IP0354&from=EN

Official Journal of the European Union, 2019. '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', https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN

OIE, 2016. 'The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials', https://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/PortailAMR/EN_OIE-AMRstrategy.pdf

WHO, 2015. 'Global action plan on antimicrobial resistance', https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/