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Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products in the EU

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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
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Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products in the EU

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1. Introduction

Antimicrobial resistance (AMR) is recognised as a major threat to human and animal health. The European Union One Health Action Plan against AMR[i] (EU/OH Action Plan), published in 2017, presents a range of objectives aimed at tackling this problem, with the boosting of research, development and innovation being one of the key underlying pillars. The EU/OH Action Plan highlights that, in addition to developing new antimicrobials, there is a need to support the development of alternative and novel therapeutic approaches for the treatment or prevention of infectious disease. Considering the significant challenges associated with development of new antibiotics, 'alternatives' could have a particularly important role in veterinary medicine, and support the overall objective to reduce antimicrobial use in animals reflected in the Farm-to-Fork strategy of the 'European Green Deal'[ii].

Following on from the EU/OH Action Plan, in addition to measures to promote responsible antimicrobial use, the new veterinary medicines Regulation (EU) 2019/6[iii] (NVR) also provides incentives to stimulate innovation and increase the availability of veterinary medicinal products (VMPs).

Correspondingly, both the European Medicines Agency (EMA) and the wider network of European medicines agencies have emphasised the need to support research and incentivise the development of new antimicrobial agents and their alternatives in their recently published strategies covering the next 5-year period to 2025 (EMA Regulatory Science to 2025[iv], European Medicines Agencies Network Strategy to 2025[v]). It is recognised that in respect of innovative alternatives to antimicrobials, a consideration of the appropriate regulatory tools and pathways will be required, and that this should be done in collaboration with stakeholders, other EU agencies and international regulatory partners. The Committee for Medicinal Products for Veterinary Use (CVMP)'s newly published strategy on antimicrobials to 2025[vi] supports these ambitions and proposes an action to take them forwards, hence the importance of this reflection paper as the first step towards the implementation of CVMP's objectives and the aims of the EU/OH Action Plan.

2. Aim and scope

This reflection paper performs a gap analysis by reviewing the regulatory tools and measures currently in place to support the development and regulation of alternatives to antimicrobials (ATAm) in veterinary medicine, with particular emphasis given to alternatives to antibiotics, and identifying where and how these could be improved.

In line with the EMA's remit and the CVMP's mandate, the scope of the reflection paper is limited to VMPs that can be used as alternatives to antimicrobials in food-producing and/or companion animals, as per definition in section 3.

Potential gaps in the area of authorisation of ATAm were identified through reflection on previous experience with such products at the EMA, discussion with regulators from other regions such as the United States of America (USA), feedback from stakeholders, and review of the outcome of conferences on the subject jointly organised by the World Organisation for Animal Health (OIE) and the United States Department of Agriculture (USDA)[vii].

The EMA and the European Food Safety Authority (EFSA) published in 2016 a 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)[viii]. This opinion includes a review of both vaccination and of other alternative measures that formed the basis for the range of ATAm considered for this gap analysis. Appendix 1 presents a non-exhaustive list of examples of ATAm, mostly derived

from the RONAFA report, to illustrate the range of products and technologies covered within this discussion topic.

The RONAFA opinion, although it considers vaccines as an alternative to antimicrobials, does not formally include vaccination as an 'alternative' but rather categorises vaccination as a tertiary prevention measure to reduce the need for antimicrobials through creating more resilient animals. Other sources view vaccines as one of many alternatives to antimicrobials. In practice, the increased uptake of vaccination represents one of the most practical ways in which the use of antimicrobials in general and in particular the use of antibiotics can be reduced, both now and in the future. Ways to promote applications for marketing authorisations and effective use of vaccines[1] are therefore included within the scope of this document.

In 2015, EMA and Heads of Medicines Agencies established a joint steering group to foster and coordinate the implementation of an action plan to facilitate timely access to the EU market for new or improved veterinary vaccines. In line with the conclusion in the CVMP Strategy on Antimicrobials 2016-2020[ix] that vaccination of animals is an effective measure to reduce the need for antimicrobials, this joint action plan is also relevant to the objectives of increasing access to alternatives to antimicrobials.

3. Definition of terms

The terms 'veterinary medicinal product', 'antimicrobial' and 'antibiotic' are defined in the new Regulation (EU) 2019/6 as follows:

> ***Veterinary medicinal product:*** *'any substance or combination of substances which fulfils at least one of the following conditions:*
>
> *(a) it is presented as having properties for treating or preventing disease in animals;*
>
> *(b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; (…)'*
>
> ***Antimicrobial:*** *'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';*
>
> ***Antibiotic:*** *'any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases'.*

However, there is no internationally accepted definition of what constitutes 'alternatives to antimicrobials'. A working **definition of alternatives to antimicrobials** for the purposes of this document is proposed as follows:

> *'a veterinary medicinal product the use of which provides an alternative treatment approach to the use of antimicrobials in animals or that reduces the need for the use of antimicrobials by preventing or controlling infectious disease'.*

The definition limits the scope of this document to VMPs in line with the mandate of the CVMP. Two different categories of ATAm products should be distinguished:

[1] Autogenous vaccines are not within the scope of this Reflection Paper

i. VMPs that can be used as substitute treatment to antimicrobials i.e. used instead conventional antimicrobials for the treatment of infectious disease (e.g. bacteriophages, antimicrobial peptides)

ii. VMPs that are not a substitute treatment, i.e. cannot be used instead of antimicrobials, but could help reducing the need for their use, by acting in a preventive targeted (e.g. vaccines) or untargeted way (e.g. non-specific immunomodulators) or by having a synergistic or complementary effect.

As is evident from the definition, alternatives to antimicrobials include diverse therapies with different modes of action. Some of these substances may be capable of cross- or co-selecting for resistance to conventional antimicrobials, which according to the mechanism of resistance involved and their capacity to disseminate may have variable impacts on human and animal health. Any AMR risk, in addition to risks to users, consumers, target animals and the environment, should be part of the overall benefit-risk assessment at the time of evaluation for a marketing authorisation.

It is acknowledged that certain products containing the same active substance could be classified as a VMP, a feed additive or a biocide depending on the intended use and claims made. These products are frequently referred to as 'borderline products'. The classification of the product will determine the appropriate regulatory framework and standards under which it will be evaluated.

4. Discussion

Strategic objectives of introducing measures to support the authorisation of ATAm

The use of ATAm represents one way in which to reduce the use of antimicrobials, particularly antibiotics, in veterinary medicine. This reflection paper therefore explores ways by which to ensure that the EU is encouraging the authorisation of ATAm.

This will be achieved by:

- recognising the importance of alternatives to antimicrobials as a means to reducing the need to use antimicrobials, in particular conventional antibiotics, in veterinary medicine and adopting a pro-active approach to promote their authorisation;
- considering the provisions in the new Regulation (EU) 2019/6 and its Annex II[x] that are applicable to ATAm and ensuring that the necessary guidance is in place for authorisation of those categories of VMPs that can be used as ATAm. It is noteworthy that for some ATAm (e.g. vaccines) the legal framework is well established and adequate guidance is available currently;
- promoting international cooperation and exchange of information with other regulatory regions to assist global development of ATAm and to align the approach to authorisation where possible;
- providing advice and support to developers and applicants seeking to authorise ATAm within the EU.

4.1. Current measures

4.1.1. Support to developers

In general, the same range of support measures is available for applicants seeking to authorise ATAm as for any other new VMP, namely;

- Scientific advice to companies on the appropriate tests and studies in the development of a veterinary medicine.
- Pre-submission meetings for applicants to obtain procedural, regulatory and legal advice from the Agency.
- The Minor Use Minor Species /limited market (MUMS) Scheme (until 27 January 2022) to address the lack of veterinary medicines for the treatment of minor animal species and uncommon diseases in major animal species.
- Applications for Limited Markets (Article 23 of Regulation (EU) 2019/6; from 28 January 2022) aimed to promote availability of VMPs for markets of a limited size (e.g. products for minor species or for diseases that occur infrequently or in limited geographical areas). Where applicants consider that ATAm are intended for a limited market they can seek such classification by CVMP and receive confirmation of the eligibility for application for a limited market under Article 23, with the benefits in terms of reduction in data requirements that this may imply.
- The EMA's SME Office, set up by Commission Regulation (EC) No 2049/2005, which provides regulatory, financial and administrative assistance to companies designated as micro, small and medium-sized enterprises (SMEs). This is particularly relevant for ATAm where initial research and discovery is often carried out by SME companies.

In addition, and particularly as ATAm will often be innovative products that represent novel veterinary therapies, the following groups can provide advice and guidance:

- The Innovation Task Force (ITF) which acts as a forum for early dialogue with applicants on innovative aspects in medicines development. From May 2019, EMA has facilitated early engagement with medicine developers working on therapeutic approaches for the treatment and prevention of bacterial, viral and fungal infections.
- The Novel Therapies and Technologies Working Party (NTWP) providing guidance to the CVMP on all issues relating to veterinary novel therapies and technologies. One of the tasks in the mandate of the NTWP is to provide recommendations to encourage the development and authorisation of novel veterinary therapeutic approaches as an alternative to antimicrobial treatment. This working party replaces the former *Ad Hoc* Expert Group on Veterinary Novel Therapies (ADVENT).

These groups have complementary roles. ITF provides product-specific advice to applicants at early stages of product development in response to a request. NTWP identifies priority areas in the field of veterinary novel therapies and publishes general, non-product specific guidance.

4.1.2. International collaboration

AMR is a global phenomenon, as recognised by the WHO in the Global Action Plan[xi], Food and Agriculture Organization (FAO)[xii] and by OIE[xiii] in their corresponding strategy. In terms of meeting the need for new products to overcome this threat, a global response is therefore required that should involve cooperation between regulators at international level. EMA and CVMP experts participate in relevant international conferences on the topic of ATAm and EMA exchanges information with both the Food and Drug Administration (FDA) Centre for Veterinary Medicines and the USDA Centre for Veterinary Biologics. The discussion about the particular challenges related to authorisation of novel veterinary therapies presented as alternatives to antimicrobials has also been included as specific action item 3.3 in the work plan of the Trans- Atlantic Task Force on AMR (TATFAR).

4.2. Gaps identified and possible additional measures

Table 1 presents the results of a gap analysis between the measures currently available and possible additional measures.

5. Conclusions

This reflection paper has been endorsed by CVMP and represents a reflection on the measures that could be taken to deliver the objective in the CVMP's Strategy on Antimicrobials related to ATAm. It is clear that to make meaningful progress on this topic would require not only CVMP, but also the wider European Medicines Regulatory Network, to put in place a set of coordinated actions to promote development, authorisation and use of ATAm in the veterinary domain.

The gap analysis identified needs for the EU regulatory framework, the support given to developers and applicants and in the area of strategic collaboration with stakeholders. Difficulties in the classification of certain products and the lack of a clear framework, including guidance on general and specific technical requirements, are perceived as the main challenges for the authorisation of ATAm as veterinary medicines. Opportunities have also been identified in regard to additional support to developers and applicants, particularly SMEs, who would benefit from earlier and improved access to scientific, regulatory and procedural advice and to financial incentives (e.g. pull incentives). Establishing an adequate communication channel between regulators (including those at EFSA, ECHA), developers, applicants and other relevant stakeholders is considered of paramount importance to understand needs, set priorities and draft a roadmap to streamline the development and authorisation of ATAm. Finally, international cooperation with other regulatory regions is necessary to facilitate global development and align, where possible, regulatory pathways and requirements for authorisation, reducing the administrative burden and the number of studies that developers and applicants need to provide.

Possible measures and activities are proposed for the EMA secretariat, CVMP and its working parties, Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv), Heads of Medicines Agencies (HMA), the European Commission, other European Agencies, the animal health industry and national competent authorities. This initial gap analysis clearly shows that making progress on this topic will require a long-term approach and a set of coordinated actions with engagement of resources across the regulatory network, by industry and other relevant stakeholders.

Based on the results of the gap analysis and the reflection on the possible actions to address identified needs, recommendations for actions that could be taken to promote the development and authorisation of alternatives to antimicrobial VMPs in the EU are presented.

6. Recommendations

1. To establish a framework for collaboration between the CVMP, other EU Agencies (EFSA, ECHA) and the coordination group of Member States (CMDv) (described in Recital 89 of Regulation (EU) 2019/6) to discuss recommendations on classification and regulation of alternatives to antimicrobials (ATAm).
2. Noting that Regulation (EU) 2019/6 and the Commission Delegated Regulation (EU) 2021/805 provide a framework for authorisation of veterinary medicines, analyse the appropriateness of that framework for the authorisation of ATAm classified as veterinary medicines.

3. Establish a platform of communication to foster dialogue between the EU regulatory network, industry, veterinary professionals, international regulators and other relevant parties to identify diseases for which needs for ATAm are greatest and the types of ATAm that show greatest promise for future development and potential medicinal claims. A workshop or similar event is suggested to kick-off the activity.
4. To increase international cooperation and exchange of information with other regulatory regions with the ultimate goal to facilitate global development of ATAm and alignment of pathways and requirements for authorisation (e.g. TAFTAR).
5. To strengthen support to developers and applicants of ATAm: promote the Innovation Task Force (ITF), scientific advice and the Novel Therapies Working Party (NTWP) as the appropriate fora for scientific, regulatory and procedural advice related to development of ATAm.
6. To develop further guidance on data requirements and potential claims for ATAm, and how demonstrated treatment benefits should be factored into the benefit-risk assessment for veterinary medicines. In particular, approaches to demonstrate efficacy of ATAm with antimicrobial properties should be defined. Priorities for the development of guidance should be set.

7. Potential actions, Actors, Resource and Impact analysis

The gaps identified in the current analysis are categorised in three different areas:

a) Gaps in the EU regulatory framework
b) Gaps in support to developers and applicants of ATAm
c) Gaps in strategic collaboration and communication with stakeholders

Gap	**Activity No**	**Activity**	**Responsible *(and others involved*)**	**Timescale**	**Resource impact**	**Challenges, comments**
a) Gaps in Regulatory Framework						
Lack of consistent terminology causes confusion	1.	Define term 'Alternatives to antimicrobials' in the context of measure to promote their authorisation	CVMP	Short term	Minimal	Definition for ATAm might promote harmonisation of regulatory requirements at EU and international level. The term should include vaccination as vaccines have a significant potential for reducing use of antimicrobials in animal husbandry.
Companies developing ATAm are often unsure to which regulatory authority they should apply and what legal framework will apply (e.g. medicine, feed additive, biocide)	2.	Provide clarity to applicants on the classification of borderline products	CMDv Borderline Products Working Group National Competent Authorities (NCAs) EU Agencies	Current	Within the remit of existing Borderline Products Groups NCAs have in place systems to provide advice to applicants on classification of borderline products	In the new Regulation (EU) 2019/6, CMDv is mandated to provide recommendations as to whether a product falls within the definition of a VMP. CMDv readiness and capability to classify ATAm to be confirmed. Possibility of developing guidance with other EU Agencies exists (e.g. EFSA, ECHA), in consultation with stakeholders and EC. Would require mandate from EC. Need for harmonisation with NCAs having already systems in place.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
EU legal framework needs to support authorisation of ATAm by providing guidance on the technical requirements that need to be fulfilled	3.	Explore how the NVR provides framework for authorisation of ATAm as veterinary medicines and reflect on need for additional guidance	CVMP	Current-Medium term	Within work on NVR	Requirements for VMPs, including novel therapies, are specified in technical annexes to the NVR. Further guidance on data requirements for ATAm, should be developed, in particular data requirements to demonstrate efficacy and what can potentially be accepted as claims. Further guidance may also be needed on the assessment of the AMR, considering potential capability of ATAm to select for resistance to conventional antimicrobials.
Current lack of guidance increases uncertainty in a number of areas	4.	Generate additional guidance specifically intended to clarify requirements for ATAm. Specific examples are given in the rows below	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP working parties (WPs)	Prioritisation would be essential due to the limited resource available within the veterinary network to generate new guidance. Work in the area of ATAm would be particularly resource intensive as many topics are new to the area of veterinary medicines and would therefore require extensive reflection and consultation before guidance could be produced. Where relevant, possible development of antimicrobial resistance to ATAm needs to be considered during the authorisation process and monitored post-authorisation.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
						Consider need for guidance on GMP requirements for specific ATAm products (e.g. phages, gene-editing products).
		Explore how benefit risk assessment for VMPs (vaccines and other products) could take into account that a product reduces the use of antimicrobials Explore if/how the beneficial effect of ATAm products on reducing the use of antimicrobials could be reflected in the product information and, if relevant, define data required to support it.	EMA CVMP	Medium-long term	Would require including in the work programme of CVMP.	No specific regulatory framework currently exists for evaluation of claims that relate to products reducing the need to use antimicrobials or how to include evidence as part of B:R for authorisation. The possibility should be evaluated of developing an approach to assess efficacy of ATAm as their efficacy levels may be lower compared to conventional antimicrobials authorised for the same disease but still show an overall positive B:R balance and a beneficial effect in reducing the need to use conventional antimicrobials. SA and ITF tools should contribute to the development of appropriate and workable endpoints for efficacy and associated claims. OIE lists of vaccines[xiv,xv] that could reduce antimicrobial use may be a useful reference. Attention should be given to providing a regulatory framework for adjunct therapies which are

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
						effective when administered in association with another product (e.g. use of immunomodulator or phage lysins in conjunction with antibiotic therapy.
		Regulatory requirements for bacteriophages	EMA CVMP	Short term	Relevant topic for NTWP	Similar regulatory and scientific challenges exist for authorisation of bacteriophages as human medicines. The development of a guideline on quality, safety and efficacy of phages is included in the work plan of the NTWP for 2021/2022.
		Regulatory requirements for novel biologically active molecules that kill bacteria but are not classic pharmaceutical antibiotics (e.g. lysins, peptides, lysozymes and other enzymes), including MRL requirements	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs Relevant topic for NTWP	
		Regulatory requirements for non-specific immunomodulators	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs. Possible relevant topic for NTWP and/or IWP	To date, advice has been given on a case-by-case basis on products/ substances that modulate innate immunity to support resistance to infection or to promote the response to vaccination. The possibility of developing general guidance in this area could be explored. Conditions of use should be defined.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
						A framework is required to evaluate the impact of ATAm on the microbiome of animals and the consequent impact on innate resistance.
		Regulatory requirements/framework for gene editing technology presented as medicinal products (e.g. CRISPR-Cas9)	EMA CVMP	Long term	Unknown Relevant topic for NTWP	Need to improve knowledge in regulatory domain of potential use of gene editing technology to reduce use of antimicrobials (e.g. to target bacterial pathogens or to restore antimicrobial efficacy by targeting bacterial extrachromosomal genetic elements such as plasmids).
		Regulatory requirements (including establishment of MRLs) for herbals, phytochemicals and other non-biological active substances presented as alternatives to antimicrobial veterinary medicinal products	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs	Consideration of the MRL requirements for these substances should be given. Current legislation requires applicants (company, NCA) to submit an MRL application to EMA supported by an appropriate package of safety data with the intention to subsequently seek authorisation of a VMP. Quality standardisation of herbal active substances is a challenge.
Internationally aligned requirements are needed to promote global development programmes for ATAm	5.	Dedicated exchange of information in the context of TATFAR Action 3.3 on current activities in the area of ATAm and identify opportunities for further cooperation	EMA (TATFAR) USA Canada Norway	Long term Long term	Planned within TATFAR activities	Objective is to exchange information and thereby reduce duplication of effort. Scope currently limited to exchange of information and does not extend to harmonisation of requirements at this early stage of discussion.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		Harmonisation of requirements for ATAm	VICH OIE			Objective to harmonise requirements for ATAm products across regions from the outset.
b) Gaps in support to ATAm applicants and developers						
Companies seek early 'upstream' advice to reduce risk related to development of ATAm	6.	Promote ITF as the appropriate forum for scientific, regulatory and procedural advice related to development of innovative VMPs, including ATAm	EMA (V Division; Stakeholders Division) ITF NCA innovation contact points	Current	Additional work required for pro-active communication by EMA Increased workload for ITF related to ATAm	Challenges (i) to identify experts available to the Network with knowledge of ATAm (ii) to identify companies working on ATAm and target communication to them. Explore possibilities to engage national innovation offices via the EU Innovations Network on the specific topic of ATAm. Facilitate innovative approaches to the development of ATAm (e.g. use of digital technologies, in silico models, quality by design). Explore organisation of portfolio reviews with innovative companies to better understand upcoming developments, including those on ATAm in general and specifically to antibiotics.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
Many companies developing ATAm are SMEs unaware of regulatory requirements and of the assistance provided by EMA	7.	Promote EMA and NCA incentives to SMEs working in the area of ATAm	EMA (SME Office) NCA SME contact points	Current	Additional work required EMA SME office	Challenge would be to identify SMEs working in this area and target communication to them. EMA will include ATAm as a specific topic for consideration within the EMA framework for engagement with academia in the veterinary domain. New Regulation (EU) 2019/6 places an obligation on EU Member States to assist SMEs.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
Creation of 'pull' incentives	8.	Financial or other incentives to authorisation of ATAm	TBD	TBD	TBD	Industry has raised the possibility of 'pull' incentives for authorisation of ATAm. The view to date of EMA has been that financial or other procedural, regulatory incentives, over and above those already in place, are not the most significant factor reducing interest in developing ATAm. Furthermore, there is no clear legal basis on which EMA could systematically provide such incentives in the veterinary domain under the current legal framework. The wider EU Medicines Regulatory Network should discuss if there is interest in introducing financial or other "pull" incentives at national or European level to promote authorisation of ATAm and how this could be achieved. Specific calls for projects on alternatives to antimicrobials (for veterinary use) could be an important incentive and stimulus.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
c) Gaps in strategic collaboration and communication with stakeholders						
Communication with stakeholders on ATAm	9.	Create a platform of communication and dialogue with industry and other relevant stakeholders on the development and authorisation of ATAm	EMA, CVMP,HMA, EFSA, Academia	Short-medium term	Would require including in the work programme of CVMP, EMA, industry	If agreed that coordinated action is required then communication and engagement of stakeholders from the outset would be important. This would require dedicated resources. In view of the scope and scale of activity required to make progress on this topic, options should be explored for the creation of a public private partnership such as was formed for the European Technology Platform for Global Animal Health, including the DISCONTOOLS project. The development of veterinary antimicrobials and their alternatives is included as a priority topic in the EMA Regulatory Science Strategy to 2025 in terms of promoting ATAm technologies and the development of new regulatory tools. Fostering dialogue with developers of new antimicrobial agents and alternatives to streamline their development is one of the strategic goals in the European medicines agencies network strategy to 2025.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
Develop objective targets to monitor success of measures to promote ATAm	10.	Draft a roadmap with targets for development of veterinary ATAm in the EU including an impact assessment on potential reduction when reaching these targets	EMA, CVMP, HMA	Medium term	Would require including in the work programme of CVMP, WPs, EMA and possibly HMA	Identifying ATAm with the greatest potential for replacing or reducing use of antimicrobials and designing their roadmap from R&D to authorisation could be an objective measure of success. This would require a substantial investment of resources to achieve.

8. Appendix 1

Examples (not exhaustive list) of alternatives to antimicrobials*:

- Vaccines
- Antibodies (monoclonal, polyclonal, engineered)
- Immunomodulators
- Bacteriophages (wild-type, engineered)
- Lysins
- Peptides with antimicrobial properties (e.g. bacteriocins, host-defence peptides)
- CRISPR-Cas9-based products
- Probiotic and live organisms (e.g. probiotics, predatory bacteria, competitive exclusion)
- Prebiotics
- Symbiotics
- Postbiotics
- Interferons
- Phytochemicals
- Herbals/Botanicals/Natural extracts
- Organic acids
- Biocides
- Teat sealants
- Quorum sensing inhibitors
- Liposomes (cytotoxin inhibitors)

*Classification of ATAm products as VMPs, feed additives, biocides, etc. will depend on their presentation, intended use and claims made for the product.

9. References

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