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Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU

Draft

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1. Introduction

Antimicrobial resistance (AMR) is now recognised as a major threat to human and animal health. The European Medicines Network Strategy to 2020[i] highlights that, with respect to veterinary medicines, controlling the risks of AMR arising from the use of antimicrobials, and particularly arising from the non-prudent use, is one of the highest priorities related to animal and public health. The European Commission has published a European One Health Action Plan against AMR[ii] which has as one of its objectives to develop new therapeutics and alternatives. Correspondingly, the CVMP Strategy on Antimicrobials (EMA/CVMP/209189/2015)[iii] has as an objective to encourage and foster the development of alternatives to antimicrobials with the specific action proposed:

> *"The CVMP will reflect further on measures that could be taken to promote the development and access to market of alternatives to antimicrobials, giving particular attention to vaccines (novel and improved) as part of the current initiative to promote availability of products that can reduce the need for antimicrobial treatment within the EU."*

The new veterinary Regulation (EU) 2019/6[iv] that will apply from 28 January 2022, considers AMR to medicinal products for human use and veterinary medicinal products a growing health problem in the European Union and worldwide requiring urgent and coordinated intersectorial action in accordance with the One Health approach. The main aim of the new legislation is to increase availability of veterinary medicinal products in the EU, to tackle AMR, to reduce administrative burden and to strengthen innovation. In this context, stimulating the development of new, alternative medicines to prevent or treat resistant infections is one of the pillars of fighting against the AMR threat and a high priority for EMA and the European medicines regulatory network.

2. Aim

This reflection paper performs a gap analysis by reviewing the measures currently in place to support the authorisation 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.

Potential gaps in the area of authorisation of ATAm were identified through reflection on previous experience with such products at the European Medicines Agency (EMA), discussion with regulators from other regions such as USA, feedback from stakeholders, and review of the outcome of conferences on the subject jointly organised by OIE and the U.S. Department of Agriculture (USDA)[v].

EMA and 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)[vi] . 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 derived from the 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 (RONAFA) to illustrate the range of products and technologies covered within this discussion topic.

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[i]. In line with the conclusion in the CVMP Strategy on Antimicrobials 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. 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 antibiotics as a mean of reducing the use of antimicrobials in veterinary medicines and adopting a pro-active approach to promoting their authorisation;
- ensuring that the EU has the appropriate legal framework and the necessary guidance in place for authorisation of those categories of veterinary medicinal products 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 aligning the approach to authorisation where possible;
- providing advice and support to developers and applicants seeking to authorise ATAm within the EU.

3.1. Definition of terms

The terms 'antimicrobial' and 'antibiotic' are defined in the new Regulation 2019/6 as follows:

> *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 approach to the use of antimicrobials in animals or that reduces the need for their use'.*

The definition limits the scope of this document to veterinary medicinal products in line with the mandate of the CVMP. However, any consideration of ATAm will inevitably consider other types of products as the same substances may be used as medicinal products or for another purpose (e.g. as a biocide or feed additive) depending on the way it is presented and the claims that are made.

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 authorisation and use of effective vaccines are therefore included within the scope of this document.

It is recognised that some of the alternatives that are being developed will themselves fall within this definition of an antimicrobial. Nevertheless, it is appropriate to include such products within the scope of this paper as they represent an alternative to the use of conventional antibiotics which are the main focus of measures to reduce use. Furthermore, the availability of such products has the potential to broaden the choice of active substances that can be used to manage infectious disease in animals.

3.2. Current measures

In general, the same range of support measures is available for applicants seeking to authorise ATAm as for any other new veterinary medicinal product[vii], 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 to address the lack of veterinary medicines for the treatment of minor animal species and uncommon diseases in major animal species. Where applicants consider that ATAm are intended for a limited market they can seek classification by CVMP of their intended product as MUMS/limited market with the benefits in terms of reduction in data requirements and financial incentives that this may imply.
- The SME (micro, small and medium-sized enterprise) Scheme provides financial incentives and other benefits to companies designated as 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 be often innovative products that represent novel veterinary therapies, the following groups already generate 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 is facilitating early engagement with medicine developers working on therapeutic approaches for the treatment and prevention of bacterial and fungal infections.
- The Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) providing advice on the requirements for authorisation of therapies that are new to the veterinary domain.

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

AMR is a global phenomenon, as recognised by the WHO in the Global Action Plan[viii] and by OIE[iX] in their corresponding strategy. In terms of meeting the need for new products to meet 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 FDA Centre for Veterinary Medicines and the USDA Centre for Veterinary Biologics. More recently, the topic of ATAm in veterinary medicine has been included as specific action item 3.7 in the work plan of the Trans- Atlantic Task Force on AMR (TATFAR).

3.3. Gaps identified and possible additional measures

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

4. 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 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. Possible activities are proposed for the EMA secretariat, CVMP and its working parties, Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary, Heads of Medicines Agencies, the European Commission, the animal health industry and national competent authorities. This initial gap analysis clearly shows that making progress on this topic will require considerable engagement of resources across the Network and by industry. A long term approach is therefore supported.

5. Next steps

Following informal consultation within the regulatory network, CVMP considered the responses to the consultation on the draft discussion document and produced this CVMP reflection paper which is released for public consultation. Additional proposals on how to facilitate and incentivise the development and authorisation of ATAm are sought.

6. 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 major 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)	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 recommendation as to whether a product falls within the definition of a veterinary medicinal product. CMDv readiness and capability to classify ATAm to be confirmed. Possibility of developing guidance with other EU Agencies exists (e.g. EFSA, ECA). Would require mandate from EC and not clear that proactive approach would be better than rapid response to specific queries from applicants. 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 establishing appropriate requirements in legislation and providing guidance on the technical requirements that need to be fulfilled	3.	Explore how the new veterinary regulation (NVR) provides framework for authorisation of appropriate ATAm as veterinary medicines and reflect on need for additional guidance	CVMP	Current-Medium term	Within work on NVR	Requirements for VMPs are specified in technical annexes to the NVR, therefore need to ensure that requirements for ATAm are reflected in content of annexes. Reflection necessary on need for additional guidance.
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. Consider need for guidance on GMP requirements for specific ATAm products (e.g. bacteriophages, gene-editing products).

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		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. OIE list of vaccines that could reduce need for antibiotics may be a useful reference. Attention should be given to providing a regulatory framework for adjunct therapies that are not effective when administered alone but are effective when administered in association with another product (e.g. non-specific immunostimulant that boosts the effect of a vaccine). Likewise the possibility should be evaluated of developing an approach to assess efficacy of ATAm products as their efficacy levels may be lower compared to conventional antimicrobials authorised for the same disease but still show an overall positive benefit:risk balance and a beneficial effect in reducing the need to use conventional antimicrobials.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		Regulatory requirements for bacteriophages	EMA CVMP	Short term	Initial reflection already on work programme for ADVENT	Similar regulatory and scientific challenges exist for authorisation of bacteriophages as human medicines. Need to consider if specific guidance for bacteriophage products, in line with the new Annex II of Regulation (EU) 2019/6, are required.
		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 requirement related to MRLs	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs Relevant topic for ADVENT	ADVENT is working on this topic.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		Regulatory requirements for non-specific immuno-stimulants	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs. Possible relevant topic for ADVENT	To date advice has been given on a case-by-case basis on products/ substances that stimulate innate immunity to enhance 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. Immuno-stimulants are most likely not suitable for extended use. A framework is required to evaluate the impact of ATA 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 ADVENT	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).

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		Regulatory requirements for herbals, phytochemicals and other non-biological active substances presented as alternatives to antimicrobials including establishment of MRLs	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs	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. Consideration of the MRL requirements for these substances should be given. The efficacy of such substances is not directly comparable to existing antimicrobials and they are frequently presented as reducing the need for antimicrobials without replacing them. The feasibility of developing a framework for evaluation of such substances in support of a claim to reduce use of antimicrobials should be evaluated with a view to reducing the regulatory burden on applicants without compromising on safety, possibly in the context of the new veterinary regulation.
Internationally aligned requirements are needed to promote global development programmes for ATAm	5.	Dedicated exchange of information in the context of TATFAR Action 3. 7 on current activities in the area of ATAm to identify opportunities for further cooperation Harmonisation of requirements for ATAm	EMA (TATFAR) USA Canada Norway VICH	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. Long-term objective to harmonise requirements for ATAm products across regions.

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
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 the EU Innovations Network on the specific topic of ATAm to engage national innovation offices.
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.

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 on development of ATAm	EMA, CVMP,HMA	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. ATAm should be included as a priority topic for the veterinary domain within the EMA Regulatory Science Strategy in terms of both promoting ATAm technologies and the development of new regulatory tools.
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 reducing use of antimicrobials and monitoring their progress to authorisation could be an objective measure of success. This would require a substantial investment of resources to achieve.

7. Appendix 1

Examples of alternatives to antimicrobials*:

- Vaccines
- Antibodies
- Immunomodulators
- Bacteriophages (wild-type, engineered)
- Lysins
- Antimicrobial peptides (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
- Organic acids
- Biocides
- Teat sealants

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

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