EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2021
EMA/644209/2020
Committee for Medicinal Products for Veterinary Use (CVMP)

# Overview of comments received on 'Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU' (EMA/CVMP/461776/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
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| 1 | International Association for Veterinary Homeopathy (IAVH) |
| 2 | Association of European Manufacturers of Autogenous Vaccines and Sera (EMAV) |
| 3 | European College of Bovine Health Management (ECBHM) |
| 4 | Federation Europenne Des Fabricants D'aliments Composes (FEFAC) |
| 5 | Federation of Veterinarians of Europe (FVE) |
| 6 | Dog Trust 29.04.20 |
| 7 | Association of Veterinary Consultants |
| 8 | Réseau de phyto-aromathérapie de L'AFVAC, AVEF, SNGTV, France (RePAAS) |
| 9 | AnimalHealth Europe |
| 10 | European Board of Veterinary Specialisation (EBVS) |
| 11 | European Group for Generic Veterinary Products (EGGVP) |

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# 1. General comments – overview

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| 1. | The term 'alternatives' is insufficiently examined. Apart from vaccines and hygienic interventions, it appears that the term in the way the EMA understands it, relates mainly to finding other ways/products to eliminate infections in the sense of killing bacteria and other illness related organisms. The term should also include the understanding and the promotion that a patient can be helped in such a way that bacteria and other infection related agents disappear or are eliminated due to improved/normal defence or health balance of the patient(s). Such treatments are patient oriented and not bacteria (infection) oriented: the approach to the patient is based on the paradigm of salutogenesis rather than pathologenesis. It is the typical approach of many complementary medicines (CAM) and is different from vaccines it the way of helping patients. There is an increasing body of evidence relating to the efficacy and effectiveness of such approaches in human medicine. (See EUROCAM website: https://cam-europe.eu/research-on-cam ) | The comment is noted. Further clarification on the types/categories of alternatives to antimicrobials, in line with the scope of the document, has been added to the text. |
| 2. | In general, this document intends to promote the authorization of alternatives to antimicrobials (ATAm) in the EU. Potential gaps in the area of authorisation of ATAm were identified and considered here.<br><br>Although priority is given to the registration of vaccines, autogenous vaccines are significant tools in the prevention of antimicrobial resistances where gaps of authorisations of vaccines still exist and no registered vaccine is available.<br><br>Currently, the production and use of autogenous vaccines is regulated on a national level. For the future, a European wide GMP guidance on the manufacture and use of autogenous vaccines is planned as defined in paragraph 70 of the introduction to Regulation 2019/6 on Veterinary Medicinal Products. | The importance of autogenous vaccines as a tool to prevent/control infectious diseases in cases where gaps in authorised vaccines exists hence to contributing to reduce the need to use antimicrobials, is acknowledged.<br><br>However, autogenous vaccines are out of the scope of Reflection paper. A footnote with a reference to autogenous vaccines has been added on page 4 to clarify the point. |

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| | This reflection paper should support the use of autogenous vaccines where gaps of authorisations of registered vaccine are identified as they constitute individual and fast use as ATAm. | |
| 4. | We welcome the initiative taken by EMA to consider such measures. Many of the options considered in the CVMP document could also be relevant for the authorisation of feed additives.<br>A cooperation between EMA and EFSA should be promoted to ensure a consistent, complementary framework allowing to explore the full potential of any safe solution. | Thank you for your comments. |
| 5. | FVE welcomes CVMP's initiative to draft this reflection paper on promoting the authorisation of alternatives to antimicrobials in animal health in the EU and to give us the option to comment on it.<br><br>Due to urgent need to use less antimicrobials, alternatives to antimicrobials have become very popular. Many companies popped up, starting to sell many types of alternatives to antimicrobials, creating a totally unregulated and potentially harmful market. Trying to get a level of regulation in this market, would be extremely beneficial.<br><br>While the term "antimicrobial" is clearly defined in the European Regulation, this is not the case for "alternatives to antimicrobials". We welcome the effort made by EMA to make a definition for "alternatives to antimicrobials". However, while antimicrobials act directly against microbes either by killing them or by stopping their normal activity, most of the alternatives act in a totally different way mainly by supporting the organism e.g. by stimulating the local and systemic immunity system.<br>We therefore would rather speak of '**alternative treatment approach'**, but **not about alternatives to antibiotics**. Most are not real alternatives as they can't be used instead of antimicrobials when you have an infectious pathogenic disease outbreak to have a curative effect. In moderate to severe disease caused by pathogenic | Thank you for your comments. The point raised about issue of 'unregulated' products is noted.<br><br>Further clarification has been added to the definition and types/categories of alternative products considered in the context and scope of the Reflection Paper. The scope of the reflection paper is alternatives to antimicrobials that are or could be classified as veterinary medicinal products, as defined in Article 4.1 of Regulation (EU)2019/6 and these are the focus of EMA's attention. |

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| | bacteria, antimicrobials will most likely be the most effective, often live-saving option. Therefore, we strongly suggest to distinguishing between curative and preventive/ supportive approach of treatment.<br><br>The majority of products on the list EMA is considering have a preventive or supportive action such as by facilitating digestion and nutrients provision or by boosting the local and systemic immune system of the animals. They can be used alone or in combination with antimicrobials.<br><br>Additionally, prevention through implementation of non-medicinal best practices to strengthen health and well-being of animals, e.g. better internal and external biosecurity level, better feeding, following good production and good management and implementing integrated disease control programmes to both minimize the occurrence of diseases and eradicate endemic diseases - among others have also great contribution to prevention and control practices. We would like this being better recognised in the reflection paper.<br><br>The products EMA proposals are considering have a broad scope and will also impact other European legislation than the Regulation on veterinary medicinal products, e.g. the legislation on feed additives and biocides for veterinary hygiene. Therefore, to be effective, it would be good to make an overarching strategy between the different European agencies dealing with these products, to find ways at how alternatives to antimicrobials can be promoted in the both legislative fields of veterinary medicines, biocides and feed additives.<br><br>We note that this reflection paper only looks from the side of regulators. However, especially for this topic, it would be good to also include the challenges and opportunities experienced by the animal health industry, veterinarians, and farmers. As veterinarians, more evidence-based veterinary medicine information about the working and effectiveness and safety of these products would be extremely useful. | Acknowledged but aim of the document is to foster authorisation of alternatives to antimicrobial veterinary medicinal products.<br><br>Acknowledged. The importance of collaboration between relevant European Agencies is identified in the document. Recommendation of discussion/overarching strategy between EMA, EFSA and ECHA supported and reflected in the document. |

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| | Many of these products are now already on the animal nutrition/animal health market and are not inclined to go for authorisation as veterinary medicinal products. That raises many concerns for veterinarians and farmers looking for evidence-based information to ensure efficacy and safety of these products.<br><br>The reflection paper contains one list of alternative products to antimicrobials but does not contain the possible substances that can included in each group. We suggest including a list of possible substances including the target animal species and categories of animals for these categories of products.<br><br>Moreover, the FVE recognizes many of some category of these substances might be considered, as Generally Recognized as safe (GRAS) /Qualified presumption of safety (QPS) and that is not stated in the reflexion paper.<br><br>In respect to vaccination, we suggest differentiating even more in the paper between conventional and non-conventional (e.g. novel, autogenous, etc) vaccines. Conventional vaccines are already comprehensively described in EU regulation; therefore, it appears to be unnecessary to include more in detail conventional vaccines in the frame of this reflection paper.<br><br>Several EU research projects are looking specifically at alternatives to antibiotics such as the EU AVANT Project and the Healthy Livestock Project. FVE is partner in both of them. It would be good to closely interact with them to see the opportunities and challenges involved with these alternatives to antimicrobials.<br><br>AVANT is a multi-actor inter-sectorial project aimed at developing alternatives to antimicrobials for the management of bacterial infections in pigs, especially diarrhoea during the weaning period. The AVANT portfolio comprises a variety of alternatives for treatment or prevention of diarrhoea and/or respiratory infections, | |

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| | namely (i) gut-stabilizing interventions based on a symbiotic (pre- and probiotic) product and faecal microbiota transplantation; (ii) novel veterinary medicinal products containing bacteriophages and polymers for targeted treatment of enterotoxigenic *E. coli* infections; (iii) immuno-stimulating injectable and feed additive products, and (iv) alternative feeding strategies targeting sows and piglets. During pre-clinical studies, efficacy, toxicity, and mode of action of these interventions is tested, and their dosage and formulation optimized. The results and a survey for veterinarian-, farmer- and consumers perception of antimicrobial alternatives, will be used together with Legal and economic considerations to select three interventions for large-scale farm trials, assessing clinical efficacy and impact on antimicrobial use. All steps are supported by regulatory advice for quick market entry post-project.<br><br>The Healthy Livestock Project, an EU-China collaboration, studies the contributions of enhanced animal health and welfare on reducing the need to use antimicrobials in pigs and poultry. They look at non-medical and alternative medical in animal health (e.g., probiotics, Traditional Chinese Medicine as alternatives to antibiotics). www.healthylivestock.net<br><br>Finally, we note that the authorisation of veterinary medicinal products, requires a huge investment in time, personnel trained, finance, etc. to meet all the requirements described in the EU legislation. Therefore, a key issue for regulators will be to attract animal health companies to authorise these products, possibly via a 'light registration' providing the risk/benefit ratio remains favourable. It is important that alternatives to antibiotics available on the market are effective and safe for both animals and people. | Requirements for the authorisation of veterinary medicinal products are defined in legislation. In the context of the new veterinary medicines Regulation (EU) 2019/6 reduced data requirements at the time of submission will be possible for applications for limited markets and also for products considered as novel therapies. |
| 7. | AVC welcomes CVMP's initiative to provide this reflection paper on promoting the authorisation of alternatives to antimicrobials (ATAm) in the EU and to give us the option to comment on it. | |

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| | While the term "antimicrobial" is clearly defined in the European Regulation, alternatives to antimicrobials have a much wider scope and will also impact on European regulations other than the legislation on veterinary medicinal products. Predominantly, various measures can help reduce the use of antimicrobials, while in moderate to severe disease caused by pathogenic bacteria, antimicrobials will most likely be the most effective, often live-saving option. However, various other measures will also contribute to supporting the health and wellbeing of animals including hygiene, management, husbandry, but also feeding and exercise. Therefore, products falling within the definition of Feed and Feed Additives and Biocides may also play a significant role.<br><br>These are only general comments:<br><br>1 – Conventional vaccines are already comprehensively described in the new 2019/6 EU regulation. As this category of products will constitute the vast majority of alternatives to antimicrobials (as far as bacteria and viruses are concerned) it appears to be unnecessary to include conventional vaccines in the frame of this reflection paper; this category will be largely dominant and is thus likely to considerably minimise the importance of new alternatives such as those (except vaccines) listed in Annex 1. The rules applying to the registration of conventional vaccines have already been clearly established whereas incentives should now be given to promote the development of nascent or hitherto unapplied technologies to ATAm. New approaches for product development for novel therapies, and how to apply the concepts of the vaccine antigen master file and multi-strain dossier to products other than vaccines, should be opened. This should also take into consideration autologous vaccines which are described in Art.2 of Regulation (EU) 2019/6 as "inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in | The comment is acknowledged but not in the direct scope of this RP.<br><br>Not accepted. Vaccines are one of the most effective tools to prevent/control infectious disease, hence, to reduce the need to use antimicrobials. Nevertheless, as their regulatory framework are well established will not be the focus of the recommendations. |

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| | a unit having a confirmed epidemiological link" for which precise guidance is missing.<br><br>2 – The definition of veterinary medicines given in 2019/6 EU Regulation is unequivocal, in particular "any substance or combination of substances which is presented as having properties for treating or preventing disease in animals and/or whose 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."<br><br>This definition is clear enough for applicants to include their new product/technology as a veterinary medicinal product, a feed additive or a biocidal product if it enters into one of the relevant categories. Some categories of feed additives (Regulation (EC) No 1831/2003) such as those intended to (i) favourably affect the characteristics of feed, (ii) favourably affect the characteristics of animal products, (iii) favourably affect the colour of ornamental fish and birds, (iv) satisfy the nutritional needs of animals or (v) favourably affect the environmental consequences of animal production, are unlikely to concern authorisation of alternatives to antimicrobials (ATAm) (Novel Feed Additives) whereas some ATAm could be considered as reducing the use of antimicrobials by favourably affecting animal production, performance or welfare, particularly by affecting the gastro-intestinal flora or digestibility of feedstuffs. ATAm that reduce the use of antiprotozoals (which often also have antibacterial properties) could also be classified as having a coccidiostatic or histomonostatic effects. In this view, the concepts and approaches introduced by Regulation 2019/6 for VMPs are proposed to be added to the regulations for biocides and feed additive, defining specific fast track requirements for the registration of novel biocides and novel feed additives.<br><br>The requirements for assessing the quality, safety and efficacy of any new product are clearly described in the corresponding guidance, directives and regulation for any of the three categories (biocidal product, feed additive, VMP, including in particular | Not accepted. It is generally agreed that for so-called borderline products, the classification as veterinary medicinal product or, for example, as feed additive may not be that clear. Issue has been raised by industry - Lack of predictability on the applicable regulatory framework<br><br>Feed additives are outside EMA's remit and out of the scope of the Reflection Paper. |

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| | vaccines). Thus, a similar approach should be taken at the same time with the relevant organisations (ECHA for biocides, EFSA for feed additives).<br><br>It would appear that the assistance tools (e.g. scientific advice, assistance for SMEs, etc.) described in the position paper already exist for VMPs and thus do not need any particular or additional description as far as ATAm are concerned. However, for Feed additives, no such support is provided as is currently by EMA/CVMP for novel feed (no advantages for "Minor Species", limited markets, SMEs, no ITF or scientific advice procedure to support the fast registration of such alternatives for antimicrobials). It should also be added that the process within the EC after a positive opinion by FEEDAP should be as short and efficient as for VMPs.<br><br>3 – Full development to meet all the requirements described in 2019/6 EU Regulation corresponds to a huge investment in time, personnel, finance, etc.; a key issue for product/technology developers would therefore be an exemption from certain studies that are not deemed critical providing the risk:benefit ratio remains favourable (after considering that the reduction in use of antimicrobials would constitute a significant benefit that may be counterbalanced by additional controlled risks).<br><br>A separate approach than that adopted for MUMS should be considered for innovative products. ATAm will be truly innovative products/technologies for which no data are likely to be currently available for purposes of extrapolating from one species to another. Although for VMPs, MUMS guidelines are available, in many cases the effort required to develop a new product for MUMS is currently often not significantly different from developing a new product for a major species (only extrapolations from major to minor species are considered as providing some waivers in the dossier that needs to be provided); it is very important to include adapted procedures in a well-defined manner for ATAm as the rules for approval of conventional products are already available and perfectly well known by all developers. But new innovative products should reach the | The comments are noted. |

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| | market as soon as possible to allow for efficient treatment of animals, whether or not they belong to a major or minor species, or are considered VMPs, feed additives or biocides. | |
| 8. | **RePAAS Presentation**<br><br>RePAAS is a transversal French veterinary network created in 2018 by the three technical veterinary associations (animal production, small animals and equine, SNGTV*, AFVAC* and AVEF* respectively) to centralise veterinary information on herbal medicines and products.<br>The French Ministry of Agriculture financially supported this network through its eco-antibio project, in relation with its aim to develop new therapeutics and alternatives to antimicrobials, and help tackling antimicrobial resistance (AMR).<br>*SNVTV : Société Nationale des Groupements techniques Vétérinaires<br>AFVAC : Association Française des Vétérinaires pour Animaux de Compagnie<br>AVEF : Association Vétérinaire Equine Française<br><br>**Herbal products situation in France**<br><br>Herbal products (HPs) are potential candidates to prevent and treat infectious conditions. Their use has gained popularity and many French farmers and animal owners use nutraceuticals, complementary feed, or essential oils (EO), which can all be bought freely without veterinary professional advice. Although these products have nonofficial therapeutic claims, they are often given to promote health, immunity and sometimes to prevent or even treat infections with reduced veterinary expertise input.<br><br>The absence of legal veterinary categorisation for HPs, and the lack of evidence-based medicine studies in animals can partly explain the low implication of the veterinary profession in using plant-based products as potential alternatives to antimicrobials (ATAm). | Thanks for the information. |

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| | Considering the increasing use of HPs amongst livestock, French veterinary regulatory bodies and members of the veterinary profession are aiming to gather all the scientific information available in order to address traceability, safety, and maximal residue limits (MRLs) issues. | |
| 9. | AnimalhealthEurope welcomes the opportunity to comment on this draft reflection paper and appreciates the efforts by the CVMP to address this important topic.<br>ATAm is an important topic globally and we believe it would be beneficial if the regulatory authorities globally sought for regulatory convergence where possible in this area. | |
| 9. | A potential addition to the approaches explored would be the formulation of objectives, such as how many new authorisations for alternatives to antibiotics that would be seen as a measure for success. | The comment is acknowledged. Setting up objectives for monitoring success is covered in section on page 16 (Activity 10). See specific comment below. |
| 9. | In general, throughout the document, the words antimicrobial and antibiotic are used interchangeably, despite the section on definition of terms (see for instance the introduction to the discussion, lines 73-75). | Accepted. The document will be reviewed to ensure consistency. |
| 9. | It is critical to reduce the use of medically important antibiotics, also in veterinary medicine. In order to promote the development of non-medically important antibiotics, these should not be included in the requested reduction, as this does not incentivise the development of new, non-medically important veterinary antibiotics. Additionally, to improve clarity and predictability of which claims would be acceptable and viable and as to how to develop new appropriate and workable endpoints in line with new veterinary medicines regulation for treatment and control of infectious diseases. | The comment is not completely agreed.<br><br>Clarity on acceptable claims and definition of appropriate and workable endpoints are key aspects. The point is covered in the document. |

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| | Tools such as Scientific Advice, Innovation Task Force and ADVENT will have to maximise the options provided by the new legislation. | |
| 10. | EBVS welcomes CVMP's initiative to provide this reflection paper on promoting the authorisation of alternatives to antimicrobials (ATAm) in the EU and to give us the option to comment on it.<br><br>While the term "antimicrobial" is clearly defined in the European Regulation, alternatives to antimicrobials have a much wider scope and will also impact on European regulations other than the legislation on veterinary medicinal products. Predominantly, various measures can help reduce the use of antimicrobials, while in moderate to severe disease caused by pathogenic bacteria, antimicrobials will most likely be the most effective, often live-saving option. However, various other measures will also contribute to supporting the health and wellbeing of animals including hygiene, management, husbandry, but also feeding and exercise. Therefore, products falling within the definition of Feed and Feed Additives and Biocides may also play a significant role.<br><br>These are only general comments:<br><br>1 – Conventional vaccines are already comprehensively described in the new 2019/6 EU regulation. As this category of products will constitute the vast majority of alternatives to antimicrobials (as far as bacteria and viruses are concerned) it appears to be unnecessary to include conventional vaccines in the frame of this reflection paper; this category will be largely dominant and is thus likely to considerably minimise the importance of new alternatives such as those (except vaccines) listed in Annex 1. The rules applying to the registration of conventional vaccines have already been clearly established whereas incentives should now be given to promote the development of nascent or hitherto unapplied technologies to ATAm. New approaches for product development for novel therapies, and how to apply the concepts of the vaccine antigen master file and | These comments are exactly the same as for stakeholder no. 9. See comments above. |

| Stakeholder no. *(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| | multi-strain dossier to products other than vaccines, should be opened.<br><br>2 – The definition of veterinary medicines given in 2019/6 EU Regulation is unequivocal, in particular "any substance or combination of substances which is presented as having properties for treating or preventing disease in animals and/or whose 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."<br><br>This definition is clear enough for applicants to include their new product/technology as a veterinary medicinal product, a feed additive or a biocidal product if it enters into one of the relevant categories. Some categories of feed additives (Regulation (EC) No 1831/2003) such as those intended to (i) favourably affect the characteristics of feed, (ii) favourably affect the characteristics of animal products, (iii) favourably affect the colour of ornamental fish and birds, (iv) satisfy the nutritional needs of animals or (v) favourably affect the environmental consequences of animal production, are unlikely to concern authorisation of alternatives to antimicrobials (ATAm) (Novel Feed Additives) whereas some ATAm could be considered as reducing the use of antimicrobials by favourably affecting animal production, performance or welfare, particularly by affecting the gastro-intestinal flora or digestibility of feedstuffs. ATAm that reduce the use of antiprotozoals (which often also have antibacterial properties) could also be classified as having a coccidiostatic or histomonostatic effects. In this view, the concepts and approaches introduced by Regulation 2019/6 for VMPs are proposed to be added to the regulations for biocides and feed additive, defining specific fast track requirements for the registration of novel biocides and novel feed additives.<br><br>The requirements for assessing the quality, safety and efficacy of any new product are clearly described in the corresponding guidance, directives and regulation for any of the three categories (biocidal | |

| Stakeholder no.<br><br>*(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| | product, feed additive, VMP, including in particular vaccines). Thus, a similar approach should be taken at the same time with the relevant organisations (ECHA for biocides, EFSA for feed additives).<br><br>It would appear that the assistance tools (e.g. scientific advice, assistance for SMEs, etc.) described in the position paper already exist for VMPs and thus do not need any particular or additional description as far as ATAm are concerned. However, for Feed additives, no such support is provided as is currently by EMA/CVMP for novel feed (no advantages for "Minor Species", limited markets, SMEs, no ITF or scientific advice procedure to support the fast registration of such alternatives for antimicrobials). It should also be added that the process within the EC after a positive opinion by FEEDAP should be as short and efficient as for VMPs.<br><br>3 – Full development to meet all the requirements described in 2019/6 EU Regulation corresponds to a huge investment in time, personnel, finance, etc.; a key issue for product/technology developers would therefore be an exemption from certain studies that are not deemed critical providing the risk:benefit ratio remains favourable (after considering that the reduction in use of antimicrobials would constitute a significant benefit that may be counterbalanced by additional controlled risks).<br><br>A separate approach than that adopted for MUMS should be considered for innovative products. ATAm will be truly innovative products/technologies for which no data are likely to be currently available for purposes of extrapolating from one species to another. Although for VMPs, MUMS guidelines are available, in many cases the effort required to develop a new product for MUMS is currently often not significantly different from developing a new product for a major species (only extrapolations from major to minor species are considered as providing some waivers in the dossier that needs to be provided); it is very important to include adapted procedures in a well-defined manner for ATAm as the rules for approval of | |

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| | conventional products are already available and perfectly well known by all developers. But new innovative products should reach the market as soon as possible to allow for efficient treatment of animals, whether or not they belong to a major or minor species, or are considered VMPs, feed additives or biocides. | |
| 11. | Promotion of the authorisation of antibiotic alternatives is a highly important topic, and as such EGGVP totally welcomes and supports the ideas in the CVMP reflection paper of this topic. We found the paper comprehensive and well prepared, but we might add the following aspects for further consideration:<br>1. In connection to the definition of ATAm, EGGVP would recommend it to be worded in a way that will not exclude further potential alternatives, that might not be known yet. Therefore, in our opinion, wording should not be based on the properties of the currently known ATAm but should be general enough to involve substances that are not used/not well-known yet but might become possible ATAm in the future.<br>2. Currently it is a little bit unclear in the reflection paper if one, comprehensive regulation/guideline is advised to be prepared for all ATAm or if they should be regulated one by one. It seems slightly difficult to provide one regulation for all types of ATAm as they can be completely different.<br>At this point, EGGVP would also recommend preparing the regulation(s) or guideline(s) in a way that will not exclude further ATAm that are not known/used yet.<br>3. In connection with the requirements and risk-benefit assessment of ATAm, EGGVP would add the importance of preparing guidelines | Thank you for your comments.<br><br>The comment is not fully understood. It is considered that the definition proposed would not exclude any potential alternative product that could be developed in the future. |

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| | for the clinical studies of these substances and again taking into account possible further ATAm. | |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 4-5 | 2. | **Comment:** the title 'CVMP Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU' does not include the use of autogenous vaccines, that are by essence legally not authorised veterinary medicinal products<br><br>**Proposed change:** 'CVMP Reflection paper on promoting the authorisation **and use** of alternatives to antimicrobials in the EU' | The title has been revised to "CVMP Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products in the EU" |
| 8 and 11 | 6. | Comments:<br>The paper points out that current lack of guidance increases uncertainty in a number of areas and that the need for guidance on GMP requirements for specific ATAm products, such as gene-editing products, should be considered. Dogs Trust would add that the ethics around gene-editing products would need to be considered and that it would normally take a number of years to establish such a product.<br><br>Proposed change (if any): | No change is considered necessary.<br>Reference to gene-editing products is made in the in the context of products targeting bacterial pathogens or to restore antimicrobial efficacy by targeting bacterial extrachromosomal genetic elements only. It would appear that the comment has been raised in a different context and therefore not relevant. |
| 9 | 6. | Comments:<br>Dogs Trust welcomes the comment that attention should be given to providing a regulatory framework for adjunct therapies. It is important this framework includes safety and efficacy studies, and also whether there is an impact on the stability of the final VMP when an adjunct is combined with an active ingredient. | Any consideration to the regulatory framework for adjunct therapies will necessarily include discussion of safety and efficacy aspects. It is not of the RP to include specifics in this regard. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | Dogs Trust also questions whether the paper is suggesting creating something similar to a cascade system. In this case we would agree that framework for this would be beneficial.<br><br>We would have concerns about bypassing regulation for non-VMP. In order to be marketed VMP need to pass a regulatory framework that provides confidence in the efficacy of a product. Careful thought may need to go into how this is managed - within the details on Page 9 it is suggested that possible beneficial effects of a product could be placed in the product information in order to support it being passed as an ATAm.<br><br>Proposed change (if any): | It is not the intention of the RP to suggest the creation of a cascade system.<br><br>The scope of the RP, that has been further clarified in the RP, is veterinary medicinal products that can be used as ATAm, thus subject to the corresponding legislative requirements concerning quality, safety and efficacy.<br><br>No change is considered necessary. |
| 30-37 | 1. | Comment: from line 30 to 37 the text goes from the general of looking for 'new therapeutics and alternatives' to the more specific of finding ~~alternative~~ complementary and alternative medical products. (which is recognised in line 96). It is necessary to allow for the ~~alternative~~ complementary and alternative medical techniques to remain present in this document. ~~Alternative~~ Complementary and alternative medicinal techniques may lead to the commercialisation of products which require a different way of licencing. Such a possibility is already recognised in the new Veterinary Medicines Regulation which, for instance, recognises the specificity of homeopathic medicinal products.<br>Also, if the attention of the EU goes exclusively to the development of 'new products', the EU may miss out on | Not accepted.<br>The text included RP quotes literally the objectives specified in the EC European One Health Action Plan against AMR and in the CVMP strategy on antimicrobials, therefore it is not possible to introduce changes. |

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| | | research into other medical paradigms which already exist and come under the general terminology of CAM.<br>'Medicinal products' and 'medical techniques' are intrinsically linked: different medical techniques use medicines of a different kind. To widen the horizon research should not only be directed to find 'new products' but also to researching new and existing medical techniques. By concentrating on anti-microbial products and vaccines only the CVMP reduces its scope and the possibilities to find sufficient ~~alternative~~ complementary and alternative medical ways to preventing and treating infections.<br><br>**Proposed change (if any):** The European Commission has published a European One Health Action Plan against AMR which has as one of its objectives to develop new therapeutics and ~~alternatives~~ complementary and alternative ways of treatment. Correspondingly, the CVMP Strategy on Antimicrobials (EMA/CVMP/209189/2015) has as an objective to encourage and foster the development of complementary and alternative ways of treating animals and alternatives to antimicrobials with the specific action proposed:<br>"The CVMP will reflect further on measures that could be taken to promote the development and access to market of alternatives to antimicrobials, to promote the examination of ~~alternative~~ complementary and alternative ways of treating animals and give particular attention to vaccines (novel and improved) as part of the current initiative to promote availability of products and techniques that can reduce the need for antimicrobial treatment within the EU." | |

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| 43-45 | 1. | Comment: It is necessary to continue stimulating the interest in complementary and alternative ~~alternative~~medical techniques<br><br>Proposed change (if any): In this context, stimulating the development of new, ~~alternative~~ complementary and alternative medicines and medical techniques 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 | Not accepted. The scope of the RP is restricted to veterinary medicinal products that can be used as ATAm. |
| 55 | 3. | **Comment:** Suggestion not to limit to animal husbandry and livestock but to also include non-food producing animal species where the animal level of exposure to antimicrobials (ALEA) can be considerable as well. | Accepted. Reference added in line 55. |
| 72-83 | 3. | **Comment:** Would it be worthwhile emphasize / further extend the possibility of providing financial support under certain circumstances for applicants seeking to authorise ATAm? I run into discussions with product developers of smaller companies with a neutraceutical product in their portfolio for which they are inclined to suggest it may indeed be of therapeutic value. When asked why the product is not registered as ATA, prohibitive costs for trials and registration preventing them from embarking into the registration as medicinal product is a recurrent point | The comment is noted. Indeed, financial incentives have been identified in the gap analysis as one of the measures that could promote the development and authorisation of ATAm. The point is already covered in the reflection paper. No change is considered necessary. |
| 73-75 | 9. | **Comment:** Where it states "*recognising the importance of alternatives to antibiotics as a mean of reducing the use of antimicrobials in veterinary medicines and adopting a pro-active* | Partly accepted. The text has been n modified as follows: *recognising the importance of alternatives to antimicrobials as a mean of reducing the need* |

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| | | *approach to promoting their authorisation*;" surely a benefit of alternatives to antibiotics would be specifically reducing the need to use antibiotics.<br>**Proposed change:** "*recognising the importance of alternatives to antibiotics as a mean of reducing the* ***need to*** *use ~~of~~* ***antibiotics*** *in veterinary medicines and adopting a pro-active approach to promoting their authorisation;"* | *to use antimicrobials, in particular conventional antibiotics, in veterinary medicines and adopting a pro-active approach to promoting their authorisation".*<br>The revised text covers all antimicrobials and their alternatives with special focus on antibiotics and their alternatives. |
| 76-79 and 97-99 | 6. | Comments:<br>The text states that 'for some ATAm (e.g. vaccines) the legal framework is well established and adequate guidance is available currently'. Dogs Trust would add that the manufacturing process for vaccines is extremely rigid, with testing at every stage. We question whether, by expanding the parameters of ATAm, this could potentially include nutraceuticals which have far less checks. Indeed, the text later says that '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)'. Dogs Trust questions what quality assurance or safety net would be used for food supplements, compared to those for veterinary medicines.<br><br>Proposed change (if any): | Food supplements are not within the scope of the RP.<br>No change is necessary. |
| 76-79 | 9. | **Comment:** An appropriate legal framework as well as adequate guidance has to be ensured to support the development of ATAm. A review to establish if the current framework is | The need for a regulatory framework for evaluation of claims that relate to products reducing the need to use antimicrobials is already |

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| | | sufficient is appreciated. There may be room for improvement in areas on technical requirements. For example, claims related to public health and herd management and allowing non-conventional supporting efficacy data. | captured in the RP. Claims related to public health and her management need to be considered with caution as they may not fit with the definition of 'medicinal claim'. |
| 76-79 | 9. | **Comments:** Include in the legislation the possibility of conditional licenses allowing the use of the medicinal product while helping the applicant to collect data from the field to complete evidence for efficacy (field trials) provided other crucial sections of the application being submitted and considered aligned with EU regulatory requirements (Part II and Part III). Thus, the idea is to allow the conditional MA based on a full part II and part III and some justifications of the efficacy of the product.<br>Another option could be to agree on potentially lower efficacy rates or other efficacy considerations or benefits (at herd level) than those currently accepted but with the benefit of reducing antimicrobial uses/consumption. Thus, the corresponding specific guidelines could be revised in consequence. | No change is necessary.<br><br>Conditional authorisations are not foreseen in the new veterinary medicines regulation (EU) 2019/6. However, in specific cases such as applications for limited markets or applications for novel therapy VMPs, the possibility of providing post-authorisation studies to address data gaps in the original application dossier is contemplated.<br><br>The approach to evaluation of efficacy of ATAm products is already covered on page 9 (activity no. 4) of the document. |
| 78-79 | 2. | **Comment:** Please change:<br>Point 3 Discussion<br>"for some ATAm (e.g. vaccines) the legal framework is well established and adequate guidance is available currently;"<br><br>**Proposed change:**<br>"for some ATAm (e.g. vaccines, including autogenous vaccines) the legal framework is well established and adequate guidance is available currently or in the process of EU-wide harmonisation (e.g. for autogenous vaccines)"; | Not accepted.<br>Autogenous vaccines were not in the original scope of the RP. The gap analysis carried out and the activities proposed did not consider autogenous vaccines. Clarification that autogenous is not within the scope of the document has been added. |

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| 85-90 | 6. | Comment:<br>The terms antimicrobial and antibiotic are defined; however, it may be valuable to add context into this as well. Antimicrobial means 'any substance with a direct action on micro-organisms used for treatment or prevention of infections…' and in a broader sense this would include disinfectants. However, we feel that the essence of the paper is questioning medications that are applied orally or topically to an animal rather than to the environment and it may be useful to declare this here if that is the case.<br><br>Proposed change (if any): | Not accepted. The comment is not fully understood. The scope of this RP is VMPs that can be used as alternatives to conventional antimicrobial VMPs.<br><br>The scope of the RP has been further clarified. |
| 86-88 | 3. | With the definition of antimicrobial, "Alternatives to antiparasitic drugs" are explicitly not included (only to substitute antiprotozoal products). Is this on purpose? | The scope of the RP is based on the definition of antimicrobial in Regulation (EU) 2019/6. For this reason, alternatives to antiparasitic veterinary medicinal products (other than alternatives to antiprotozoal VMPs) are out of the scope. |
| 94-95 | 1. | Comment: This definition only opens the way for alternative **products** to treat infections not for complementary and alternative medical l **ways** of treating animals to avoid the use of antibiotics. By limiting this definition to products only, the EMA reduces avenues and diversity of research. (see previous comments)<br><br>Proposed change (if any): 'a veterinary medicinal product or a medical technique which provides a complementary and | Not accepted. Given the scope of the RP (i.e. veterinary medicinal products), the definition necessarily refers to products and cannot encompass medical techniques. A reference to the use of adjunct therapies is already included in the RP. No further change is considered necessary. |

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| | | alternative approach to the use of antimicrobials in animals or that reduces the need for their use' | |
| 94-95 | 3. | Comment: Some alternatives (eg herbals/homeopathy/phages...) are not specifically veterinary products. Suggestion thus to not limit this to "veterinary". | Not accepted. The scope of the Reflection Paper is veterinary medicinal products. |
| 94-95 | 3. | Considering vaccine as ATAm seems confusing. Vaccines aim to prevent disease. The use of antibiotics for the purpose of prevention is illegal (even if we know that it is still widely practiced). Although vaccines are certainly suitable to reduce antimicrobial use (like any strategy of prevention of infectious disease is) strictly speaking they should not be considered as alternative to antibiotics (that are supposed to be used exclusively for the purpose of treatment). We are thus in support of the RONAFA opinion. | Not accepted.<br>Further clarification of the definition of alternative to antimicrobials in the context and scope of the reflection paper has been given with the differentiation of the two different categories of ATAm:<br>i. VMPs that can be used as substitute treatment to antimicrobials i.e. used instead conventional antimicrobials for the treatment of infectious disease,<br>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.<br><br>It is important to keep vaccines within the scope of the Reflection Paper as vaccines are one of the most effective tools to prevent and control infectious diseases and therefore, hence in reducing the need for antimicrobial treatment. |
| 94-95 | 3. | Maybe modifying the sentence to "…of which provides an alternative TREATMENT approach…" would more specifically | Partially accepted.<br>The definition of ATAm has been modified to: |

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| | | point out the objective of providing treatment alternatives. In agreement with the RONAFA opinion vaccines should not be considered as treatment alternatives. | *'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'.*<br><br>However, vaccines will be kept in the scope of the Reflection Paper and they meet the second part of the proposed definition of ATAm. Please see the response to the previous comment. |
| 91-95 | 6. | Comment: Dogs Trust advocates the One Health concept and would like to see this paper note the importance of practices that act preventatively, including biosecurity e.g. common human practices such as drying a kennel floor thoroughly to help reduce the burden of giardia. The Bella Moss story being a good demonstration of this - https://www.thebellamossfoundation.com/<br><br>Proposed change (if any): | Noted. |
| 100-107 | 3. | Comment: To me there is a confusion between methods/practice/medicine to reduce the use of antibiotics (more resilient animals biosecurity, genetic, vaccine) on one hand and products/medicine to replace antibiotics (eg essential oils instead of antibiotic). In the first part you look for reducing morbidity and prevalence of disease/incidence, on the other hand you want to treat with products different from ATB and limit persistence. In practice, farmers use "alternative medicine" | Noted.<br>Clarification has been added in the text with the distinction of two categories of ATAm: ATAm that can substitute conventional antimicrobial VMPs and 2) ATAm that are not a substitute treatment but could help reducing the use of antimicrobials. |

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| | | such as homeopathy, osteopathy, essential oils primarily to treat. | |
| 100-107 | 3. | Comment: It is certainly appropriate to also aim at reducing disease prevalence (e.g. through vaccination). From a practical point of view the ATA – thus an alternative to antimicrobials is a product that can effectively and meaningfully reduce the need to recur to antimicrobials to treat disease. In my opinion vaccines receive too much emphasis is this paper (more so since registration of vaccines is rather well established already – here I see the least need for development) | The comment is noted. |
| 106 | 2. | **Comment:** Please change:<br>Point 3.1. Definition of terms<br><br>"… and use of effective vaccines are therefore …"<br><br>**Proposed change:**<br>"… and use of effective vaccines, including autogenous vaccines made from specific causative micro-organism'(s), are therefore …" | Not accepted. Autogenous vaccines are out of the scope of the RP. |
| 120-124 | 3. | Comment: Need to be cautious at least on MRL and safety part (for goats, sheep...) | Noted. No change is necessary. |
| 125-127 | 3. | Comment: Is this SME scheme adequately broadcasted in the industry and accessible the start-ups and smaller companies? Or might awareness of this be increased? | Noted. The lack of awareness of SMEs about SME scheme and the assistance provided by EMA has been identified in the gap analysis (table section 7) where a specific action is proposed. |
| 147 | 2. | **Comment:** Please change/add:<br>Point 3.2 Current measures | Not accepted. Autogenous vaccines are out of the scope of the RP. |

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| | | **Proposed change/addition:**<br>CMDv of the EMA has in addition published "Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within the EEA" that will be one of the sources for detailed guidelines of good manufacturing practice in accordance with the principles of good manufacturing practice (see paragraph 70 of the introduction to Regulation 2019/6 on Veterinary Medicinal Products). This will provide European-wide standards to autogenous vaccines as ATAm. | |
| Section 6 Table – General comment | 5. | Comment: Can you please indicate the number of for 'short time', 'medium term' and 'long term'<br><br>Proposed change (if any): define terms | The comment is acknowledged. It is difficult at this stage to define more accurately the terms. Decisions on priorities, actions and defined timelines will necessarily be part of the follow-up steps and discussions. |
| Section 6.a.1 | 3. | Comment: In agreement with the RONAFA opinion I would disagree with inclusion of vaccines as ATAm. If included, vaccines should probably receive less emphasis, simply because they do not present an alternative to antibiotics, they rather are suitable to prevent their use. | Partly accepted. The proposal to exclude vaccines of the scope of the Reflection Paper is not accepted. However, the definition of ATAm has been slightly amended and types/categories of ATAm products have been described in order to clarify further that vaccines are not considered a replacement for conventional antimicrobials but can hugely contribute to reduce the need of their use. |
| Section 6.a.2 | 4. | Comment: Guidance for the determination of the status of borderline products are essential considering that, if EMA is | Accepted. |

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| last column last line, | | mandated to provide advice to individual operators, this is not the case for EFSA.<br>Stakeholders should be involved in the drafting of such guidelines, as well as DG SANTE.<br><br>Proposed change (if any):<br>« Possibility of developing guidance with other EU Agencies exists (e.g. EFSA, ECA), in consultation with stakeholders and EU Commission. Would require mandate from EC ~~and not clear that proactive approach would be better than rapid response to specific queries from applicants.~~ » | |
| Section 6.a.2 | 8. | Borderline products containing EO and plant extracts already exist, and clear recommendations are needed to clarify type and concentration of EO or plant extracts authorized in their composition. | The comment is noted. No change is necessary. |
| Section 6.a.3 | 8. | For the French veterinary profession to take part in the development of herbal medicines, RéPAAS has edited a guide of recommendations for extemporaneous preparations of HPs recommending the use of MPUP (matières premières à usage pharmaceutique).<br>The use of standardised products, i.e. with a minimum of one constituent concentration known, is one of these recommendations. The use of HPs is limited to products with known MLR status. Only adapted new MLR regulations will warrant wider safer use.<br>Some publications have underlined the large quality variability of herbal products on the market [1]. | Comment noted. The text in the Reflection Paper is considered to be in line with the comment. No change is necessary. |

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| | | Developing European framework and clear rules regarding the use of herbal products therapeutically is the only way for the same rules to apply either side of European country borders. | |
| Section 6.a.4 | 3. | Treatment efficacy should be documented for every ATAm – as for any medicinal product on the market. Same applies to evaluation of safety and toxicity. It may be reasonable to accept lower treatment efficacy for the sake of reduction of antimicrobial use. The lower level of efficacy should however be quantified in order to make an informed decision. | Comment noted. The point raised is considered to be captured in section 6.a.4, last column where the need to develop an approach for the evaluation of efficacy of ATAm. No change is considered necessary. |
| Section 6.a.4 | 3. | Comment:" …could take into account that a product reduces the use of antimcirobials" This sentences highlights a "confounder" in this paper: The focus of this paper should be on the immediate objective of providing alternatives to antimicrobials. The reduction of the use of antimicrobials should be a consequence of these alternatives and are evidently the final objective. This paper should however specifically focus on the path of providing alternatives. | Not accepted. The purpose of the paper is to explore ways to promote the authorisation of alternatives to conventional antimicrobial veterinary medicinal products either by replacing them with substitute treatments or by reducing the need to use them by e.g. prevention of disease. The term alternatives to antimicrobials has to be interpreted as per the definition given in the document. No harmonised definition of alternatives to antimicrobials/antibiotics exist. Types or categories of ATAm have now been described in the text to increase clarity. |
| Section 6.a.4 | 3. | Once again confusing. Antimicrobial use can certainly be reduced by ATAm (which would be an important achievement). What is essential though are the consequences in terms of animal health and welfare. Also what about resistance of bacteria against these alternatives (eg resistance to essential oil active substance). Need to include surveillance of this resistance to ATAm | Accepted. It is agreed that the possible development of antimicrobial resistance against ATAm needs to be considered. A new paragraph in section 3 has been added. Also, a sentence addressing the point has been included in the table on page 9, activity 4: *"Where relevant, possible development of antimicrobial resistance* |

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| | | | *to ATAm needs to be considered during authorisation and monitored post-authorisation."* |
| Section 6.a.4 | 3. | Comment: "…beneficial effect on reducing the use of antimicrobials…reflect in the product information…" This seems a bit tricky. It is important to keep the balance in the benefit / risk analysis between reduction of antimicrobial use and treatment efficacy. As far as suitability to qualify as real ATA the confirmed efficacy for the treatment of a specific condition must be weighed at least as heavily as the capacity to reduce antimicrobial use. | The comment is acknowledged. The text in the RP refers to explore how the additional benefit of reducing the need to use conventional antimicrobials could be evaluated and taken into account in the benefit:risk analysis and, if relevant, reflected, in the product information. Of course, for authorisation the product, an overall positive benefit:risk for the intended disease will have to be shown. No change is necessary. |
| Section 6.a.4 | 3. | Comment: Also need to take into account animal welfare in the benefit / risk assessment (is poorer efficacy of an ATA compared to an antibiotic acceptable for the sake of reduction of antimicrobial use? what about mortality rate? | Noted. As per comment above, an overall positive benefit:risk for any ATAm product will have to be shown for authorisation. Considerations to animal welfare are indeed very important and part of the B:R evaluation. No change is necessary. |
| Section 6.a.4 | 3. | Concerning the use of bacteriophages: Maybe include reflection on possible consequences of introduction of such bacteriophages into the environment. | Noted. An environmental risk assessment is part of the requirements for authorisation. |
| Section 6.a.4 | 3. | For immunostimulants registered as ATAm, information should be available on the precise mechanism of action (type of immunity stimulated, cell clusters activated or stimulated) and for which medical conditions the would be most appropriate. | The comment is acknowledged. The points raised should be discussed in the context of the development of any specific guidance but are considered too specific/detailed to be included in the Reflection paper. |
| Section 6.a.4 | 3. | Comment: "Regulatory requirements for herbals…": also include essential oils here? | Essential oils (i.e. natural bioactive compounds derived from plant) are considered to be included with the category of herbals. No need to specify further. |

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| Section 6.a.4 | 9. | **Comment:** The proposal is to generate guidance on specific ATAm. For example, bacteriophage and non-specific immune stimulants. In determining the timeline to initiate such guidance it should be considered that premature guidance (i.e. before sufficient experience is gained by industry and regulators) can be very unhelpful. It is also important that any new guidance is not applied retrospectively. | The comment is acknowledged. No change is necessary. |
| Section 6.a.4 | 9. | **Comment:** The "OIE list of vaccines that could reduce need for antibiotics" is mentioned. However, the reference seems to be missing on page 17.<br><br>**Proposed change:** Please add the reference | Accepted. The reference has been added. |
| Section 6.a.4 page 4 | 11. | Comment: Guidance on GMP requirements for autogenous vaccines are also needed.<br><br>Proposed change (if any): | No accepted. Autogenous vaccines are out of the scope the gap analysis of the Reflection Paper. See responses to previous comments concerning autogenous vaccines above. |
| Section 6.a.4 last paragraph page 9 | 9. | **Comment:** AnimalhealthEurope supports this point. Nonetheless, it is clear that scientific advice and innovation task force tools should contribute to the development of appropriate and workable endpoints for such new types of claims.<br><br>**Proposal:** add at the end: "Scientific advice and innovation task force tools should contribute to the development of appropriate and workable endpoints for such new types of claims" | Accepted. |
| Section 6.a.4 page 9 | 5. | **Comment:** 'Explore how … a product reduces the use of antimicrobials.' Many of these alternatives you cannot compare with antimicrobials as they have not the same effect. In addition, calculating how much they reduce the use of | The comment is acknowledged. The demonstration of effect on reduction of the use of antimicrobials may be challenging. Nevertheless, it is one of the areas to be explored. |

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| | | antimicrobials will be extremely difficult as you are trying to prevent a disease you do not know would have incurred and prevention is multifactorial. | |
| Section 6.a.4 last paragraph page 10 | 9. | **Comment:** Again, also ADVENT should contribute to the development of appropriate and workable endpoints for such new types of claims and products<br><br>**Proposal**: add at the end "ADVENT should contribute to the development of appropriate and workable endpoints for such new types of claims and products." | Accepted. The reference to ADVENT has been replaced by reference to the new Novel Therapies and Technologies Working Party. |
| Section 6.a.4 last paragraph page 10 | 9. | **Proposal:** also add: Rather than inventing the new guidance in an abstract way, it would be more efficient and appropriate to develop such guidance using experience of actual projects. | The comment is noted. |
| Section 6.a.4 page 10 | 5. | **Comment:** Regulatory requirements for bacteriophage – you have different sorts of bacteriophages, suggest to detail.<br><br>**Proposed change:** define more clearly bacteriophages | Not accepted. Specific data requirements for phage therapy (listed as novel therapy) are given in the Annex to Regulation (EU) 2019/6 where a definition of bacteriophage is provided. No further definition in the context of this document is considered necessary. |
| Section 6.a.4 page 11 first row | 9. | **Comment:** The following statement is made re non-specific immunostimulants: "*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*." This is a very sweeping statement which would be better considered within any guidance. | Partly accepted.<br>The text has been modified as follows:<br>*"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~~.* |

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| | | Furthermore, when exploring the option to develop general guidance, it should be born in mind that it might be more appropriate and efficient to develop new guidance, based on actual new cases.<br><br>**Proposed change: "**~~Immuno-stimulants are most likely not suitable for extended use.~~" It should also be considered that developing new guidance, based on new actual cases, could be more efficient and appropriate.**"** | |
| Section 6.a.4 page 11 | 5. | **Comment:** In respect to immunostimulants, please explain what is meant with the sentence '*Immunostimulants are most likely not suitable for extended use*'.<br><br>Proposed change (if any): | The referred sentence has been removed (see previous comment). |
| Section 6.a.4 page 12 | 5. | **Comments:** Regulatory requirements for herbals, etc -) Botanical or herbal extracts, flavours, and etheric oils now fall within the scope of Regulation (EC) No. 1831/2003<br><br>**Proposed change (if any):** Refer to Regulation (EC) No. 1831/2003 | Not accepted. Additives for use in animal nutrition are out of the scope of the reflection paper. |
| Section 6.a.4, | 8. | ***Evaluation of claims that relate to products reducing the need to use antimicrobials***<br>This point seems crucial as HPs and more specifically EO are promoted and considered by some farmers as drug like products with potential antimicrobial activity. Even though a large number of studies have been conducted exploring the antimicrobial EO activity *in vitro,* the clinical efficacy has rarely been explored due | The comments are noted. |

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| | | to the lack of financial funding (as these products are not licensed or submitted to any type of patent), and of adapted regulatory recommendations for research. In the human medical field, a group of experts have edited a guide of recommendations for EO use in hospital settings and for French clinical research. [2] A similar guide could be edited at European level for the veterinary profession, taking in consideration the need of new MRL regulations.<br>Research studies have been conducted *in vitro* exploring the potential effect of concomitant use of antibiotics and EO [3], and clinical studies are needed to provide validation or non-validation of claims easily found on internet.<br><br>Conducting scientific research also relies on product quality, which mean defining strict standardisation processes for HPs harvest, storing and processing. A European quality label could be created.<br>Once research recommendations have been standardised it will then be possible to 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.<br><br>***Regulatory requirements for non-specific immuno-stimulants***<br>As herbal products are available on the market with immune-stimulation claims, including better response to vaccination, it is once again important for the veterinary profession to provide data relying on international cooperation research projects with standardised and quality labelled products.<br><br>***Regulatory requirements for herbals, phytochemicals, and other non-biological active substances presented as alternatives to antimicrobials including establishment of MRLs*** | |

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| | | ***"establishment of MRLs with a view to reducing the regulatory burden on applicants without compromising on safety"***<br>Considering creating a new regulatory framework for herbal products needs to be assessed at the European level as livestock are submitted to a large variety of plants with no evaluated MRLs.<br><br>One hundred twenty herbal substances are listed in table 1 of Commission Regulation (UE) 37/2010. But to allow the veterinary profession to work with some of the plant-based products currently used by farmers, the consumer safety issue needs to be addressed.<br><br>Due to the large variety of HPs constituents and in the absence of appropriate study material to evaluate their potential residues, **current rules are not adapted for herbal substances**.<br><br>For this reason, RePAAS has worked on the implementation of specific regulatory categories dedicated to HPs.<br><br>Data to be included in these new categories must be discussed at European level, but using new lists on the model of (EEC) 2377/90 regulation has been suggested, for example:<br>- Herbal substances present in table 1 of (UE) 37/2010 (ex-Annexe I)<br>- Herbal products with long term traditional use with no known toxicity (ex-Annexe II)<br>- Products for which toxicity and potential residues are unknown (ex-Annexe III)<br>- All plant products with known toxicity in humans or animals, which use should be avoided in farm animals (ex-Annexe IV). | |

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| | | Another option would be to establish a third table in regulation (CE) 37/2010, containing all herbal products allowed for use in food production.<br><br>A final option would be to gather safety information on long term used HPs and consider them as "Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) No. 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin".<br><br>Implementing new categories needs high level of collaboration of European regulatory bodies in order to compile safety data known to date. All data existing in different regulations (human medicine, biocide, food additives, ...) should be considered.<br><br>A European experts committee could be created to provide a framework for veterinary research projects on HPs including EO. Strict evaluation processes is the only way to validate their traditional use as anti-infectious products in view of reducing the use of antimicrobials.<br><br>**A more detailed contribution on this subject from the SNGTV drug commission is provided below.**<br>(Commission médicament SNGTV, Président : Dr O. Fortineau) | |
| Section 6.a.2, page 12, first line, last column | 4. | **Comment:** The formulation and /or the presentation of animal feed, including but not limited to the presence of phytochemicals, can reduce the need for antimicrobials. The EU Regulation (EC) No 767/2009 establishes a legal framework for claims and their substantiation. However, it fails to establish clear guidelines as regards claims linked to the reduction of the needs for antimicrobials? Likewise there is no guideline for the | Not accepted. Feed/feed additives are out of the scope of the reflection paper. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | assessment of the ability to reduce the need for antimicrobials in the risk/benefit assessment of feed additives.<br>A legal framework exists under the EU legislation on the marketing of feed for the assessment of claims related to feed meeting specific nutritional purposes ("meeting the specific nutritional needs of animals whose process of assimilation, absorption or metabolism is, or could be, temporarily or irreversibly impaired and who can therefore benefit from the ingestion of feed appropriate to their condition"). An extension of the scope to claims related to the reduction of the need for antimicrobials would be a pragmatic and efficient solution.<br><br>Proposed change (if any):<br>« 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, the future EU feed additives regulation and articles 9 and 10 of Regulation (EC) No 767/2009 on the placing on the market and use of feed. » | |
| Section 6.a.4 | 4. | Comment: Feed may also contribute to reduce the need for antimicrobials. There is no legal framework either for the assessment of claims on feed in relation to the reduction of the need for antimicrobials. | Not accepted. Feed additives are out of the scope of the reflection paper. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| page 9, last line, second column | | Proposed change (if any):<br>New Par.<br>« Explore how risk assessment for feed additives could take into account that a product contributes to reduce the need for antimicrobials." | |
| Section 6.a.4 and 6.a.5 | 8. | The RePAAS network would be happy to collaborate with any other European veterinary association or organism dedicated to HPs and promote exchanges amongst practitioners and researchers. | Noted. |
| Section 6.a.5 | 9. | **Comment:** The following remark is welcomed. "*Long-term objective to harmonise requirements for ATAm products across regions*". However, it should be noted the goal should be to avoid disharmonisation from the outset. Ideally Regulators from different Authorities develop the initial guidance together as far as possible. | Noted. |
| Section 6.b.6 p 13 | 9. | **Comment:** Challenges are mentioned (i) to identify experts available to the Network with knowledge of ATAm (ii) to identify companies working on ATAm and target communication to them. It would be beneficial to invite industry experts to lecture in "open colleges" for authority experts. Equally, it would be beneficial if the EMA could organize portfolio reviews with innovative companies to better understand upcoming developments, including those on alternatives to antimicrobials in general and specifically to antibiotics.<br><br>**Proposal**: Add to the first row, at the end: It would be beneficial to invite industry experts to lecture in "open colleges" for authority experts. Equally, it would be beneficial if the EMA could organize portfolio reviews with innovative companies to better understand upcoming developments, including those on | Partially accepted. The text has been revised to capture the point:<br>*'Explore organisation of portfolio reviews with innovative companies to better understand upcoming developments, including those on ATAm in general and specifically to antibiotics.'* |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | alternatives to antimicrobials in general and specifically to antibiotics. | |
| Section 6.b.8 | 8. | **Activity N°6 > cf activity N°5 and 6 above**<br><br>**Activity N°8 Financial or other incentives to authorisation of ATAm**<br>Financial independent support at national or European level seems the only way to promote research projects dedicated to the validation of ATAm claims, and data reproducibility, in order for the profession to be able to give sound advice on the various products sold freely without veterinary input. Creating European and national database gathering the available scientific information, providing detailed composition of herbal extracts (with tracers and concentrations) is an option worth considering, to stem the wide spread of non-scientifically proven anti-infectious and immunostimulant allegations. Only products in accordance with the new regulatory framework implemented could recommended for use amongst veterinary practitioners. This would help reduce self-medication, promote scientific-based use and increase veterinary input in livestock herbal medicine uses, especially with regards to organic farming. | The comment is noted. |
| Section 6.b.8 page 14 | 9. | **Comment:** it has been pointed out that any new technology, including (new) alternatives to antimicrobials, to be successful, needs to be communicated and explained early enough to end-users.<br>**Proposal**: it would be advisable that the European Commission would find ways to allow such communication to end-users and professional users. | The comment is noted. |
| Section 6.b.9, page 15, 3rd column | 4. | Comment: Animal nutrition contributes to reduce the need for antimicrobials.Therefore, EFSA should also be involved<br><br>Proposed change (if any): | Accepted. |

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>EMA, CVMP,HMA, EFSA</td><td></td></tr>
<tr><td>Section 6.a.9, page 15, last column</td><td>4.</td><td>Comment: Animal nutrition contributes to reduce the need for antimicrobials.<br><br>Proposed change (if any):</td><td>The comment is noted. Animal nutrition/feed is out of the scope of the reflection paper.</td></tr>
<tr><td>Section 6.b.10 page 15</td><td>9.</td><td>Comment: as an industry, animal health has not been able to secure funding though EU driven framework programs such as Horizon 2020. A specific call for projects on alternatives to antimicrobials (for veterinary use) could be an important incentive and stimulus.<br><br>Comment: this reflection paper does not formulate specific objectives for the Agency and National Competent Authorities in terms of number of alternatives they want to see authorised during the next (five or ten) years. Such an objective would stimulate the regulators to focus on innovation and new alternatives to antimicrobials, which would have a positive, incentivising effect on the develop of these projects.</td><td>Accepted. Point has been included activity no. 8.<br><br>Drafting a roadmap with targets for development of veterinary ATAm in the EU is one of the activities proposed in the Reflection Paper. Although the point is taken, it would appear to be premature to formulate objectives in terms of numbers at this stage.</td></tr>
<tr><td>Page 15</td><td>2.</td><td>Comment: Please change:<br>Point 6. Potential actions, Actors, Resource and Impact analysis<br>c) Gaps in strategic collaboration and communication with stakeholders
<table>
<tr><th>Gap</th><th>Activity No</th><th>Activity</th><th>Responsible (and others involved)</th><th>Timescale</th><th>Resource impact</th><th>Challenges, comments</th></tr>
</table></td><td>Not accepted. Outside the scope of the Reflection Paper.</td></tr>
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<table>
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<br>Proposed change/addition:<br>Point 6. Potential actions, Actors, Resource and Impact analysis<br>c) Gaps in strategic collaboration and communication with stakeholders
<table>
<tr><th>Gap</th><th>Activity No</th><th>Activity</th><th>Responsible (and others involved)</th><th>Timescale</th><th>Resource impact</th><th>Challenges, comments</th></tr>
<tr><td>No data-base for available autogenous vaccine authorisations</td><td>11.</td><td>Establish EU-data base</td><td>EMA, CVMP HMA, National authorities</td><td>Medium term</td><td>Would require including in the work programme of CVMP, WPs, EMA and possibly HMA?</td><td>Identifying ATAm with the greatest potential for reducing use of antimicrobials and monitoring their use</td></tr>
</table>
</td><td></td></tr>
<tr><td>Section 6.c.9</td><td>3.</td><td>Comment: “Create a platform of communication…”: Include a webpage where you can find what is authorized or not. Currently this information is not easy to retrieve</td><td>The comment is noted. No change is considered necessary in the context of the proposed activity. Union Product Database is being developed.</td></tr>
<tr><td>Section 6.c.9 page 15</td><td>5.</td><td>Comment: Communication with stakeholders – please define the stakeholders.<br><br>Proposed change (if any): define stakeholders</td><td>Accepted. Some examples of stakeholders have been added to increase clarity.</td></tr>
</table>

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
|---|---|---|---|
| Section 6.c.9 | 8. | **Activity n°9 Create a platform of communication and dialogue with industry on development of ATAm**<br>Once the regulatory and safety issues have been implemented, stakeholders involved in quality labelling and research should have easy access to available information in order to implement new production and marketing standards. | The meaning of the comment is not fully understood. |
| Section 6.c.10 | 3. | Comment: "Identifying ATAm with greatest […] measure of success": An "harmonized" system to collect antimicrobial usage should include all animal species not just livestock | The comment is noted but link or relevance in the context of the activity proposed is not understood. |
| Appendix 1 Page 16 | 2. | **Comment :** Please change:<br>Point 7. Appendix 1 - Vaccines<br><br>**Proposed change/addition:**<br>Point 7. Appendix 1- Vaccines (incl. autogenous vaccines) | Not accepted. See previous comments about autogenous vaccines. |
| Appendix 1 Page 16 | 5. | **Comment:** please insert polyunsaturated fatty acids (PUFA) and examples of substances such as oligosaccharides and fructans, short-chain fatty acids (SCFAs), microbial cell fractions, functional proteins, extracellular polysaccharides (EPS), cell lysates, teichoic acid, peptidoglycan-derived muropeptides and pili-type structures, flavonoid derivatives and tannins, essential oils, Phytochemicals or phytobiotics, etc and the animals for which they are used<br><br>**Proposed change (if any):** Include for the different classes examples of substances and target animals | The list is intended to provided examples of possible alternatives, but it is not an exhaustive list. |
| Appendix 1 Page 16 | 9. | **Comment:** Please add NSAIDs to Appendix 1 as an ATMa or at least add to comments (activity 4, page 9) as a beneficial effect in reducing the need to use conventional antimicrobials (e.g. in mild cases of mastitis) and in some cases synergistic effect/ increased efficacy of antimicrobials (e.g. in treatment of pneumonia)? | The list provides examples of possible alternatives, but it is not an exhaustive list. No change is considered necessary. |

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|---|---|---|---|
| Appendix 1<br>Page 16 | 9. | **Comment:** Please add injectable micronutrients to Appendix 1 since they can play a significant role in the preparation of the immune system of animals and allow a safe reduction in the use of antibiotics.<br>Antimicrobials have been widely used to help animals cope with episodes of infection caused by abrupt physiological or lifestyle changes. Strategic injectable micronutrient supplementation can play a significant role in the preparation of the immune system of animals and allow a safe reduction in the use of antibiotics. Indeed, injectable trace minerals and vitamins have been shown to influence the cow's resistance to mastitis and positively impact udder health and milk quality (Hogan et al, McDougall et al). They have been shown also to reduce the incidence of periparturient diseases, such as stillbirths, displaced abomasum and endometritis (2 papers from Machado et al). Trace mineral supplementation in newborn calves has been shown to decrease the incidence rate of neonatal diseases and mortality (Teixeira et al).<br><br>Hogan, J. S., Weiss, W. P. & Smith, K. L. Role of Vitamin E and Selenium in Host Defense Against Mastitis. J. Dairy Sci. 76, 2795–2803 (1993).<br>McDougall, S., Parker, K. I., Heuer, C. & Compton, C. W. R. A review of prevention and control of heifer mastitis via non-antibiotic strategies. Vet. Microbiol. 134, 177–85 (2009).<br>Machado, V. S. et al. Effect of an injectable trace mineral supplement containing selenium, copper, zinc, and manganese on the health and production of lactating Holstein cows. Vet. J. 197, 451–456 (2013). | Accepted. |
| Appendix 1 | 9. | **Comment:** Please broaden the concept of Herbals/Botanicals to Natural extracts | Accepted. |
| Page 17<br>Appendix 1 | 2. | **Comment:** Please change: Point 8. References | Not accepted. See previous comments on autogenous vaccines. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
|---|---|---|---|
| References | | **Proposed change/addition:**<br>Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within the EEA (2017): CMDv, London, 20 March 2017, EMA/CMDv/452656/2016, REC-002-01<br>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 | |