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Cc: [redacted]
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Attachments: Response from ANMV to the EU ombudsman Public Consultation for HMA MG consideration.pdf

Follow Up Flag: ema11
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Dear Sir,
Please find enclosed the comments from Anses-NAMV the French Agency for Veterinary Medicinal Products.

Best regards

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Draft response from ANMV to the EU Ombudsman - Public Consultation on EMA pre-submission activities

Introduction

The French Agency for Veterinary Medicinal Products (ANMV), within ANSES, is the Competent Authority in France for risk assessment and management with regard to veterinary medicinal products.
In this capacity, the Government was keen for the ANMV to strive for constant improvement of its services with a view to protecting public health as well as the health and welfare of animals.
To this end, the ANMV must enforce the current applicable legal provisions in an independent, competent and impartial manner.

With the aim of contributing to the protection of human and animal health by ensuring the safety of veterinary medicinal products from authorisation through to use, the ANMV:

- Evaluates National and European Marketing Authorisation Application dossiers for veterinary medicinal products and European dossiers on maximum acceptable limits for veterinary drug residues in food of animal origin
- Monitors the risk of adverse effects related to veterinary medicinal products, the quality of veterinary medicinal products, pharmaceutical establishments for veterinary medicinal products, advertising of veterinary medicinal products
- Authorises marketing of veterinary medicinal products, clinical trials on veterinary medicinal products, opening of pharmaceutical establishments for the manufacture, marketing, wholesale distribution and export of veterinary medicinal products, import, temporary use and export of veterinary medicinal products

The ANMV is an active member of the European network of Head Medicines Agency (HMA) and participates in discussions concerning veterinary medicines and contributes to the formulation of many regulatory texts.
The Agency, as an OIE collaborating Centre, is actively involved in many international organisations at the European and International levels.

Responses to questions posed by the Ombudsman

1. It may happen that EMA staff members and experts who participate in pre-submission activities will be involved in the subsequent scientific evaluation and/ or marketing authorisation procedure for the same medicine. To what extent is this a matter of concern, if at all? Are there specific pre-submission activities of particular concern in this regard? How should EMA manage such situations?

   Medicines developers/ sponsors can request scientific advice at any stage of development from either the EMA, its committees or national competent authorities. Pre-submission activities cover the full range of meetings and procedures that facilitate interaction between medicine developers and the EMA during the development phase, prior to the assessment of a medicine developer's application for marketing authorisation. This spans facilitating early dialogue with medicine developers to consider scientific advice, protocol assistance to optimise the medicine's development plan, provide methodological direction and to ensure

that the appropriate tests and studies are performed thereby discouraging the production/ development of irrelevant or substandard data. In addition, subsequent pre-submission interactions enable those with technical regulatory expertise (assessors/experts/scientific secretariat) who are to be involved in the evaluation to gain an overview of the product and its development so that their assessment can be performed more efficiently and minimise any unnecessary administrative delay.

Under the existing legislation relating to the regulation of medicinal products there is an obligation on the EMA to provide support, including the provision of scientific advice, to future marketing authorisation applicants. The primary purpose of such advice is to assist industry in getting safe and effective products of the appropriate quality to animals in a timely manner. This is achieved by facilitating, through the provision of advice, the generation of appropriate data to provide the necessary evidence for assessment procedures.

Typically, applicants seek advice on approaches to comply with the safety and/or efficacy requirements in situations where guidance is either not available or the available guidance does not apply to the product in question. A key aspect of scientific advice is the provision of strategic high quality advice so that studies are not conducted unnecessarily. It ensures resources are utilised efficiently and effectively. Advice is also provided on the quality aspects involved in the development of a new medicine, usually relating to manufacturing and controls. Ultimately the purpose is to protect and benefit welfare by avoiding unethical, unnecessary trials and avoiding unnecessary delay in bringing novel and new medicinal products to market. It should be noted that this is in line with the 3R rule.

Regulators are experts in regulatory guidelines and the interpretation of same. Scientific advice and broader pre-submission activities are key methodologies used to develop novel therapies or solve gap therapeutic in minor uses or minor species (MUMS), which is particularly important where there is an unmet need or where there are few treatment options. It also ensures the highest standards of safety and animal and human health protection remain the focus of the development programme and ensures this is not compromised through the efforts to provide timely access. The focus is on the approach to the development programme and not the evaluation of the data being generated, whether the results of the whole development program support positive benefit/risk evaluation or not.

Distinction between initial scientific advice (SA) and assessment of the marketing authorisation application (MAA)

We believe that there is no conflict between the same national competent authority (NCA) providing scientific advice and also acting as Rapporteur for the MAA. The EMA sufficiently manages the distinctive roles of scientific advice experts and scientific evaluation experts by having two separate procedures in place to select individual experts from NCAs to conduct both tasks. This contribution is based on the expert's technical knowledge and qualifications, with support from additional experts in that competent authority. Scientific advice given is always institutional and not individual. For scientific advice procedures, the EMA appoints one coordinator to provide independent assessment in parallel and both assessment reports are discussed in an open forum at the Scientific Advice Working Party (SAWP) meeting at the EMA. The purpose of these meetings is to reach a consensus view on the assessments and the approaches that the coordinators have taken.

In the legislation for veterinary medicines the role of the different committees and groups are mandated or outlined:

- Pre-submission – Committee for Medicinal Products for Veterinary Use (CVMP) and Scientific Advice Working Party (SAWP- Scientific advice protocol admissions)
- Evaluation – CVMP,

Similarly, for MAA assessments of centralised products, two Rapporteurs (a Rapp and Co-Rapp) from different NCAs from EU member states provide independent parallel assessments as well as a separate peer reviewer from a third member state. All member states review the assessment reports for the purposes of providing further review and opinions.

Furthermore, for any subsequent queries arising, a scientific advisory working party (SAWP) consisting of independent scientific experts can provide their views at a SAWP meeting prior to the Committee for Medicinal Products for Veterinary Use (CVMP) issuing their final opinion.

Conclusions on specific marketing authorisation applications are taken by Committee members with input from supporting experts: that is, decision making is not in the hands of those participating in pre-submission activities. Opinions are published on the EMA website and the basis for all decisions relating to a marketing authorisation application are clearly communicated in European public assessment reports (EPARs). In the EPAR the main details of a development program are made public for other innovators to follow.

The exclusion of experts from national competent authorities (NCAs) who provide scientific advice from subsequent EMA MAA evaluations may negatively impact on the quality of the assessment of the authorisation. It would be entirely inappropriate to exclude such assessors who provide advice from the assessment process. As it stands, the availability of expert resource is scarce. This is particularly the case for certain innovative products, where the pool of experts in the European network may be limited such that any restriction on experts from the network that can participate in EMA MAA assessment activities may have implications for the quality of the assessment of the product. In addition, it may cause unnecessary delays for complex applications to use a different NCA for the assessment of the product.

The question as phrased suggests that there is some conflict of interest in the NCA performing both the provision of SA and the assessment of the MAA. The robust processes in place for marketing authorisation assessment as described, involving separate independent assessments, peer review and committee based approaches, are designed to mitigate against any such risk. In summary, no one NCA is responsible for any advice or decision made in respect of SA of a MAA.

In addition, while NCAs are remunerated for their time, an independent review in 2018 by consultants appointed by the DG Santé European Commission, demonstrated that the cost for an NCA to act as rapporteur exceeds the income provided to them to execute that task. Therefore, it costs NCAs to provide this service and furthermore, their fee is not dependent on a positive assessment.

Finally, SA is primarily focused on optimised regulatory pathways and does not assess data supporting the authorisation of the product. Therefore, if an applicant follows the SA in generating data, that data must subsequently be subject to an independent review to consider whether it supports the authorisation.
We strongly believes and reiterates that there is no conflict of interest and any risk from the pre-submission process is adequately mitigated against.

2. Should EMA allow experts from national authorities, who have previously provided scientific advice at national level on a particular medicine, to be involved in EMA's scientific evaluation of the same medicine?

The exclusion of experts who provide scientific advice at national level from subsequent EMA evaluations may negatively impact on the quality of scientific advice. As outlined above, their contribution is based on the expert's independent technical knowledge and qualifications with support from additional experts in that competent authority. There are a number of subsequent additional balances in the process including the Rapp and Co-rapp appointment and involvemet of the relevant committees. In the case of certain innovative products or veterinary immunological products, the pool of experts in the European network may be limited such that any restriction on experts from the network who can participate in EMA marketing authorisation application assessment activities may have implications for the quality of the scientific opinion. The provision of scientific advice by regulators is a well-recognised and accepted way of ensuring innovators take into consideration the appropriate regulatory guidelines. In comparable authorities, such as the US FDA, similar processes exist.

For the reasons outlined in the response to Q1 we do not believe that there is a conflict. We also consider that most applications that intend to be authorised through the centralised route should seek scientific advice through the EMA procedure.

3. What precautionary measures should EMA take to ensure that information and views provided by its staff members and experts in the context of pre-submission activities are not, in practice, considered as a "binding" pre-evaluation of data used to support a subsequent application for authorisation?

We consider that the EMA already takes sufficient measures to ensure that pre-submission activities are non-binding. Applicants seeking scientific advice under Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, must note that any scientific advice given is not legally binding with regard to any future marketing authorisation application of the product concerned, either on the Agency/CVMP, or on the Applicant. In addition, while some data which will form part of the final application may be submitted as part of the SA query, the SA does not assess it as part of the application. The fact that the views transmitted in pre-submission activities are non-binding is clearly communicated. Furthermore, given the structure of the EU evaluation process, including member state scrutiny of rapporteur/co F rapporteur evaluations through the CVMP, multiple parties that were not directly engaged in providing this advice review any views expressed in the pre-submission phase. Furthermore, decision-making within committees is always collective, consensus based, and therefore ensuring a system of checks and balance is in place.

This question suggests a misunderstanding of the nature of pre-submission activities. As noted above the primary purpose of this type of engagement is to improve the quality of regulatory submissions which are then assessed for quality, safety and efficacy. The pre-submission activities focus on HOW the development program or part of it should be carried out, what kind of guidelines should be taken in to consideration, and what kind of specific studies (chemical-pharmaceutical, non-clinical and clinical) should be done. These activities do not pre-assess the authorisation, rather ensure that appropriate and robust data is submitted to enable the best assessment of the application. The assessment of marketing authorisation application focus on what are the results of those studies and if the results support a positive balance between the risks (e.g. adverse events) and therapeutic benefits and indicate efficacy.

4. Is the way in which EMA engages with medicine developers in pre-submission activities sufficiently transparent?

We consider that there is appropriate transparency throughout the regulatory process including pre-submission activities and SA. The EMA have a pre-authorisation guidance published to their website. Also published to the website is a guidance for applicants seeking scientific advice that provides an overview of the procedure and preparation required by applicants.

All declarations and conflicts of interests are declared and made in the public domain.

The commercially sensitive nature of discussions with industry limits the transparency of pre-submission interactions with individual applicant companies. In order for SA to take place, there must balance between the need/ call for transparency with applicant needs/ expectation for confidentiality. It is likely that any move to publish SA opinions prior to product authorisation would impact on the uptake of SA, potentially stifling innovation as commercially confidential information would be available to the innovator's competitors. This will result in a negative impact on timely access to medicines.

Companies have a significant commercial investment which they will want to protect. Making commercial information available either before or after authorisation would significantly damage Europe's ability to attract new medicine and with the resulting impact on animal care. It is the ANMV view that ensuring the EU remains competitive for innovation is in the best interest of European Human and Animal Health.

If you believe that greater transparency in pre-submission activities is necessary, how might greater transparency affect: EMA's operations (for example the efficiency of its procedures, or its ability to engage with medicine developers) and ii. medicine developers?

Appropriate balance between transparency and protecting confidentiality should be achieved. The authorities are updating guidelines as new questions emerge in pre-submission interactions to add clarifications into existing guidelines or if needed, creating new ones.

5. Is there a need, in particular, to enhance the transparency of scientific advice EMA provides to medicine developers? Would it, in your opinion, be useful or harmful, for example, if EMA:
- disclosed the names of the officials and experts involved in the procedures;
- disclosed the questions posed in scientific advice procedures; and/or
- made public comprehensive information on the advice given.

If you have other suggestions, for example regarding the timing of the publishing of information on scientific advice, please give details and the reasons for your suggestions.

We consider the naming of individuals involved in SA unnecessary as the overall advice is issued from CVMP for veterinary medicines. The advice has been concluded not only by the 2 named coordinators, and a peer reviewer for Scientific Advice Working Party case, but also there may be a team working within both agencies also working on the advice. EMA also have input and in addition the advice is reviewed in advance by the SAWP. Therefore, there are many different layers of assessment, and a significant number of experts contributing to the report, which is finally endorsed by CVMP.

We would consider little value in listing names of individuals publicly when it is such a broad assessment with input from a number of contributors. The CVMP members and alternates list is available on EMA website and conflicts of interest are published and assessed. National

competent authorities are also obliged to review conflicts of interest of their delegated experts.

We do not see any benefit of disclosing the questions posed in the SA as all commercial information would need to be removed and we would consider that what remains is unlikely to be meaningful and may raise more questions than it would answer.

See response 4 above.

6. What would the advantages and disadvantages be of making scientific advice, given to one medicine developer, available to all medicine developers?

This once again comes back to the issue of commercial sensitivity in relation to developing a new innovative or MUMS veterinary product. We consider that release of SA could not be done while legally maintaining data confidentiality. This question is also based on a presumption that advice for one product may be appropriate for another. General scientific guidelines for drug development are produced by the CVMP, and these summarise advices given at a high level or describe other areas identified as requiring general scientific advice.

It should be noted that SA is open to all medicines developers, with substantial financial incentives for SMEs and those developing products for MUMS markets. Medicine developers are unlikely to want to share their development plans with other medicine developers which may impact on the uptake of SA.

As noted above, should there be frequent topics repeated during SA, this would lead to the development of guidelines to address issues arising.

7. Should EMA be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines?

We do not support limiting SA questions to issues not already addressed in clinical efficacy or safety guidelines as it is often through this type of process that complexities and gaps in guidance are identified. This is important for continually improving processes and guidelines to best serve stakeholders. There may be follow up situations where the company may need to clarify or deviate from guidance, with justification, due to the nature of the product and complexities in specific cases. In addition, there may be situations where EMA guidance does not fully capture the proposed approach of the product under development. In such cases, an applicant may need advice that the approach they are intending to pursue is scientifically valid. Furthermore, scientific advice is part of the public health mission of the EMA and of our agency, insofar as unnecessary or suboptimal designed animal experiments may be avoided, thereby streamlining the process and ensuring best practice approaches. The landscape is changing and the area of innovative medicines is forcing the regulatory system to adapt and evolve to guarantee preparedness. As regulators we are seeing increasing trends where products in the pipeline may not fit standard or traditional designs. Similarly, regulatory frameworks must adapt and evolve to serve MUMS necessitating novel trial designs, use of real world evidence and convergence of products/technology. Such complexities and innovation are driving us more towards flexible and adaptive approaches in light of increasing product complexity. There is a move away from situations where guidelines consider and address all aspects due to the pace of innovation. Relevant and appropriate regulation for stakeholders and for animal requires a level flexibility, thereby ensuring a focus on faster and safer access to the market.

8. Any other suggestions on how EMA can improve its pre-submission activities? If so, please be as specific as possible.

We support the work and development that the EMA has brought forward over the past number of years. It is considered that the European regulatory system lags behind other international counterparts in pre-submission supports and this may be negatively impacting European animal and human health and access to novel and innovative medicines and other healthcare products. We fully support the EMA in contributing to ensure public trust on these important operations, which have contributed so positively to animal and human health by helping to bring new, safe and effective medicines to animals. The EU must remain competitive and act in the best interests of animals and it is therefore imperative that the current EMA pre-submission work is supported and can continue to grow and evolve.

We support the EMA responses to date and agree that while there is a need to avoid and manage any risk of bias, experience to date demonstrates that such risk can be managed by establishing and implementing appropriate safeguards, which we believe to be in place. Policy around conflicts of interest, a rigorous and independent medicines evaluation process, including the pre-submission aspects, and optimum transparency, support this risk management process. Through engagement with key stakeholders, the EMA aim to address any potential public perception of bias. The mechanisms to receive input from animal owners, consumers and healthcare professionals are incorporated at various levels within EMA's organisational structure, including in the EMA Management Board, in Scientific Committees, Working Parties, including Scientific Advisory Groups.

As HMA members , we are fully committed to partnering with the EMA in the operation of the European medicines regulatory network and it is a unique model for cooperation and work-sharing on statutory as well as voluntary regulatory activities, to best serve European citizen.