[redacted]

From: [redacted]
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Attachments: Ombudsman public enquiry EMA presubmission activities Oct2018 final.docx

Follow Up Flag: ema20
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Dear Sir/Madam,
Apologies for the small delay. I was ravelling at the end of last week so this escaped my mind.

Please find attached the comments from AnimalhealthEurope to this public enquiry.

Kind regards
Rick Clayton

Rick Clayton
Technical Director

AnimalhealthEurope a.i.s.b.l.
Avenue de Tervueren 168, box 8
1150 Brussels, Belgium

T : +32 2 543 [redacted]

Transparency Register: 63322037415-37

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How the European Medicines Agency engages with medicine producers before they apply for authorisations to market their medicines in the EU

- Invitation to comment within the European Ombudsman's inquiry OI/7/2017/KR

Public consultation - **DATE** Monday | 08 October 2018

The Ombudsman invites all interested parties, be it individuals or organisations from the public, private or voluntary sectors, to put forward their views on this issue by replying to the questions below.

Background

In 2017, the European Ombudsman opened[1] an inquiry (OI/7/2017/KR) into the arrangements that the European Medicines Agency (EMA) has in place for engaging with individual medicine developers before they submit applications for authorisations to market their medicines in the EU (so-called 'pre-submission activities' or 'pre-authorisation activities'). Essentially, these 'activities' involve EMA providing advice, opportunities for dialogue and consultation, and regulatory and scientific support for medicine developers on different aspects of the authorisation process[2].

EMA's reply to the letter opening the inquiry[3], and a follow-up meeting, have given the Ombudsman a better understanding of the different types of pre-submission activities that exist. In so far as these activities facilitate the development and availability of high-quality, effective and safe medicines, they benefit patients and serve the public interest. Nonetheless, such meetings and preliminary discussions may pose some risks, including to the objectivity of how authorisation applications are subsequently assessed, particularly where the process is not sufficiently transparent.

Questions

Please give reasons for your answers.

Draft response from AnimalhealthEurope, 22 January 2019

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?

This is not a concern related to any pre-submission activities, in fact quite the reverse, it is a positive aspect (noting that the right controls are in place). Through earlier engagement the individuals are more familiar with the product and its technology and are better able to identify critical issues and so ensure the benefit:risk assessment is correctly focused. This preview opportunity allows the reviewer to have early access to information on the molecule and the product development path the sponsor is trying to take. It allows agency personnel to make more informed decisions but does not compromise their ability to make an impartial and objective assessment.

It also helps to bring consistency between the delivered Scientific Advice and the scientific evaluation of the final product dossier during the marketing authorisation process.

Are there specific pre-submission activities of particular concern in this regard?

'Pre-submission activities' relate to two very different procedures with different purposes:

1. **Pre-submission meetings**: only allow for procedural/administrative questions and scientific questions or discussions are not allowed in these meetings. These meetings only involve EMA-staff members and no scientific experts. EMA staff themselves do not conduct the assessment of applications nor do they get involved in decisions on product authorisation. For reasons of

efficiency, one project manager should be assigned from the EMA staff for a new product application, and that person should be involved as an administrator/manager in every step of the procedure, from pre-submission to the final decision on authorisation.

2. The request for **scientific advice** is a written procedure resulting in written feedback. This scientific advice is not binding to either the EMA or the medicine developer.

   Appointments to a scientific advice team (pre-submission) and to the scientific assessment team (post-submission) happen separately and are managed by the EMA with no input from medicine developers.

   Since expert selection is mainly driven by the availability of appropriate expertise, it is not unusual for some experts to serve in both teams. As a benefit, this brings consistency, which is important in the case of innovative products for which sound scientific guidance has not yet been established.

How should EMA manage such situations?

The EMA has procedures and measures to manage this situation, which are already sufficient. The EMA records all such activities and who is engaged in them. There is a system for disclosing and managing potential conflicts of interest for experts.

A single expert has some influence, but is part of a team covering the different disciplines of quality, safety and efficacy, and the final recommendations of the rapporteur must bring together an over-all benefit-risk assessment taking all information into account. The work of the rapporteur is scrutinized by a co-rapporteur from a different national agency. The final outcome and decision is then taken by the Committee as a whole, with all members having the opportunity to input.

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?

Yes.

EMA should allow experts (assessors) from national authorities, who have previously provided scientific advice at national level on a particular medicine, to be involved in the scientific evaluation of the same medicine. It is an advantage for an 'expert' to bring prior knowledge and exposure to the scientific questions behind the product development. It is particularly useful for new scientific areas if the assessor has had the opportunity to develop some background knowledge.

It is important that the EMA operates in an efficient manner so using the same expert for both pre- and post-submission activities makes sense. There is no conflict or risk to the integrity of the evaluation if experts from national authorities, who have previously provided scientific advice at national level on a particular medicine, are involved in EMA's scientific evaluation of the same medicine. It brings the benefit of consistency of scientific approach and it decreases the risk of contradictory advice. At the end of the day *science should prevail*, i.e. if that expert is the best to evaluate a specific application it would be wrong not to involve him/her in the assessment. Preventing such national experts taking part in EMA's scientific assessment could be detrimental for the whole assessment procedure.

Experts from national authorities are an integral part of the European Regulatory Network, and are indispensable for the scientific assessment procedure at EMA level. This approach gives EMA access to experts from across the EU, allowing it to bring together the best-available scientific expertise in the EU for the regulation of medicines. It also ensures a strong EU regulatory network by involving national experts in European scientific evaluation procedures, furthering their development and experience as regulatory scientists. It encourages the exchange of knowledge, ideas and best practices between scientists across the EU MSs.

The EMA maintains a list of national experts in a database; the list is publicly available upon request to EMA. To guarantee impartiality, each expert must declare annually any potential competing interests, and the EMA has strict procedures for handling any conflict of interest.

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?

The non-binding aspect of the scientific advice procedure is explained on the EMA website and is sufficiently disclosed in EMA guidance documents*. Before every pre-submission meeting EMA explains that the opinion given therein does not preempt the opinion of the CVMP. This is again stated in the meeting minutes and again it is stated in each scientific advice letter cover letter**. Thus, these precautionary measures are thorough through repetition at every point of contact and are more than sufficient.

* Applicants seeking advice under Article 56 of Council Regulation (EC) 726/2004, as amended, must note that any advice given is not binding on the Agency with regard to any future marketing authorisation application of the product concerned but will be taken into account in the evaluation of marketing authorisation application.

**"The SA agreed during the SAWP-V meeting was finalised during the CVMP plenary meeting held on….and is enclosed for your attention. It should be noted that the advice provided is without prejudice to applicable legislation relating to the particulars and documents, which must be submitted in support of any future application. Moreover, it is without prejudice to any future scientific assessment of an application for the granting of a marketing authorisation and appraisal of the data package in entirety and to any intellectual property rights of third parties…."

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

Yes.

The way in which EMA engages with medicine developers in pre-submission activities is sufficiently transparent through the publicly available guidelines and templates which provide exact guidance on the procedure and the topics that can and cannot be raised during (a) pre-submission or (b) scientific advice meetings.

Thus, greater transparency is not needed. Greater transparency in *the way in which EMA engages* with medicine developers in pre-submission activities is unlikely to have negative consequences for EMA's operations or for medicine developers. However, what must not be disclosed is any information prior to the completion of an application for a marketing authorisation.

If greater transparency leads to information on future applications being made public before the application is lodged and approved this will mean companies won't use these pre-submission support activities. This will have a negative impact on applicants as it will be harder for them to bring forward new applications with an appropriate data set at the time of the initial application.

Companies would continue to seek such advice just from other countries/regions where confidentiality is fully respected. EMA would then be less influential going forward in product developments, particularly with novel technologies.

It will also have a negative impact on the assessor, as the data dossier may be of lower quality compared to one that had benefitted from scientific advice pre-submission. The outcome might be a delay in the marketing authorisation, due to increased number of questions from the assessor and potentially more requests for additional data.

Finally, there will be a potential negative impact for the customer through delays in bringing the benefits of new medicines to animal health and welfare (and even potential public health benefits for certain medicines).

The meeting documents, including meeting minutes are kept by the agency and do provide sufficient transparency for the regulator-community, including the EMA secretariat, rapporteur and co-rapporteur and the CVMP. This ensures complete transparency to those directly involved in subsequent scientific evaluations and ensures a proper basis for the formal regulatory and scientific assessment.

5. Is there a need, in particular, to enhance the transparency of scientific advice EMA provides to medicine developers?

No, for the reasons given above in answer to the previous questions.

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.

Names of the officials and experts involved can be provided however the procedures should only be identified with a procedure number, not with any further details, such as the type of product (as this would disclose highly commercially confidential information). Details of the product are published at the end of the marketing authorisation procedure in the European Public Assessment Report (EPAR).

Questions raised during a scientific advice procedure and the advice given are highly commercially confidential. Publicly disclosing this information before the close of the marketing authorisation (MA) procedure and the publication of the EPAR will stop all applicants using the scientific advice procedure. Disclosure would provide a significant competitive disadvantage not only in terms of market access information but also with intellectual property transfer to direct competitors.

If companies do not seek scientific advice prior to MA applications then a lot of scientific questions may be raised which could otherwise have been avoided or already addressed. This may also lead to longer MA procedures (extended clock stops to answer questions) and potentially to an increase in MA refusals. Due to the intensity of resource use in medicine development and registration, any loss in efficiency is highly detrimental to all parties involved.

The introduction in the European market of innovative animal health products would be negatively affected as medicine developers will not want to disclose confidential information or know-how to their competitors. Moreover, the scientific advice procedure bears significant costs in terms of fees to be paid by the medicine developer, and making the advice publicly available will enable competitors to obtain intelligence on competitor development pipelines and strategies at no cost.

It must be noted that EMA's policy on access to documents is defined by EU regulations, namely Regulation (EC) No 1049/2001, which reflects the principles of openness and transparency of EU institutions by preserving at the same time the integrity of key public and private interests.

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.

None

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

We have considered the possible advantages of making scientific advice, given to one medicine developer, available to all medicine developers, and we have concluded that there are no advantages beyond those accrued by individual competitors. This is in fact a competitive disadvantage to the original company investing in the research and development and would be a strong disincentive to using the procedure.

Since scientific advice is granted several years before a product authorisation, the immediate disclosure thereof could reveal the commercial strategies and company-specific technical knowledge. Competitors would learn the development programs and products of others very early on, and would be able to adapt or refine their own strategy or interfere with potential distribution contracts that are not yet signed.

As stated in the previous question, it would also mean that industry would not ask for scientific advice in order to protect their intellectual property. This would be a significant step back with potential impact on availability of medicines which is not in the interest of regulators, the industry or the public.

Scientific advice is always specific to a product. Advice for one product may not be pertinent to another similar product. In case advice has wider and general applicability then this can be managed through the development and issue of CVMP Guidelines. Or, in the case of novel products, as an earlier step, through the question and answer documents prepared by ADVENT.

When authorisation has been obtained, the European public assessment report (EPAR) for the product will disclose a summary of the entire development program to the public: i.e., which studies were conducted, which results were obtained, how these were assessed and which conclusions could be drawn. The EPAR would also disclose whether pre-submission scientific advice was requested. All EPARs are available on the Agency's website.

The current system allows sharing of development solutions across medicine developers without negative impact to investment in innovative products and competition.

7. Should EMA be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines[4]?

No.

The absence of specific information in guidelines on a precise scientific question is actually the main reason why medicine developers request scientific advice.

Guidelines are just for guidance. They also permit alternative approaches to be used if scientifically sound and justified by the applicant. It is exactly such approaches that should be open to scientific advice. Furthermore, no matter how well-written, guidelines can be subject to different interpretations and it is important to understand the Authorities' interpretation *in the context of a specific product* before designing studies involving animals (to avoid running unnecessary studies in animals or needing to repeat studies involving animals).

Without scientific advice, a company may only find out too late that their scientific approach is not aligned to the expectations of the regulatory assessor. Consequently, MA procedures may take longer, more studies may have to be conducted or repeated and the number of MA application refusals may increase. This all translates into a massive waste of resources for both the company and the regulator.

As the purpose of scientific advice is to increase the quality of submissions, making the job of the assessor easier, it would seem self-defeating to overly restrict its scope.

It should be noted that scientific advice is not limited to safety and efficacy, but it is also open to questions related to manufacturing and control of product quality.

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

i. The scientific advice procedure is very formalised: questions are submitted, and answers are provided; a follow-up question, to clarify the advice received, is permitted.

   It would increase efficiency if an optional step for dialogue was included. After the questions have been submitted, a discussion between the company and the EMA representative and experts should be possible before the procedure starts. If the purpose and context of the questions can be discussed, the questions could be refined and the resulting scientific advice would be of greater value.

   This may reduce the need for the follow-up clarification of scientific advice which sometimes results from the current approach. The US CVM already operates in this way i.e. a request for a scientific advice is handed in, followed by a meeting where questions are discussed face to face and after that the advice is given to the company in a formalized and written way.

The time of the expert/assessor would be used more efficiently. It avoids the risk that the time of the expert is wasted in answering an incorrectly phrased question, so that the answer does not actually address the scientific issue of the applicant.

ii. As there are different types of pre-submission activities available it would be helpful to the industry if there was greater clarity on which of these activities are available and considered most appropriate along each stage of the product development cycle. There is high level pictorial guidance on this on the EMA website (https://www.ema.europa.eu/en/veterinary-regulatory/research-development/innovation-medicines) but additional guidance would be helpful.

iii. Involvement of Rapporteur and Co-rapporteur during pre-submission meetings would help the industry to better meet dossier requirements and allow a smooth procedure. This is especially important as sometimes questions have administrative as well as some scientific aspects but are not worth a lengthy scientific advice procedure.

iv. The development of parallel scientific advice procedures between the EMA and the FDA should be further encouraged as regulatory authority alignment on scientific approach is extremely helpful to companies developing new technologies and novel therapies.

Additional information

AnimalhealthEurope would like to provide some context in which these responses are provided. The regulatory environment in the EU is generally regarded as a world leading. This brings many benefits to medicines developers, but it also has downsides. For example, it also means the cost of product development is the highest in the EU.

Of direct relevance to this public enquiry, the EU is also a 'world leader' in transparency. The downside of this is that patients in the EU are less and less likely to be the first to benefit from new medicines. Medicines developers will submit their data dossier to other 'primary' markets first, and will delay submissions to the EU knowing that their competitors will then gain access to their intellectual property.

This reality was starkly illustrated in the findings of a recent Global Benchmarking Survey, conducted by the global industry association HealthforAnimals. The survey is repeated every five years, and aims to benchmark the competitiveness of global markets through the impact of regulatory environments on the industry's ability to innovate and be competitive.

A core finding of the 2015 survey is that the EU is regarded very negatively in this context compared to USA, China, Japan and Canada (see figure).

While there will be multiple reasons for this, a key factor is the impact of transparency on competitiveness and willingness to innovate.

Of the seven countries (/regions) included in the survey, only Brazil and Australia were seen as less favourable than the EU. However, at the time of the survey, the regulatory agencies in Brazil and Australia were close to non-functional due to crises in governance and funding.