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To: EO-PresubmissionConsultation
Cc: ROOVERS Koen
Subject: Response to consultation-Comments Ombudsman Inquiry on EMA pre-submission activities
Attachments: EPHA response to EO public consultation on EMA pre-submission activities.pdf
Follow Up Flag: ema10
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Dear E.O. Team,

Thank you very much for your investigation into the EMA's pre-submission activities. Your work will hopefully contribute to the top EU regulator becoming (more) transparent.

Please find attached EPHA's submission to your [public consultation](#). Feel free to publish the attached on your website. We will upload it to our website shortly as well.

I am at your disposal for any further information. Kind regards,

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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

EPHA Response to the Public Consultation

- 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?**

The EMA should change its current practice in order to ensure there is a clear and complete distinction between the experts involved in the two processes for the same product. The provision of Scientific Advice (henceforth SA) behind closed doors is of particular concern since there is very limited publicly available information on the exchanges between the regulator and the pharmaceutical companies. This raises questions about the transparency of this particular process, one the EMA's "black boxes", so to speak. Confidential SA to individual companies poses a number of potential problems:

- Neither the questions raised nor comprehensive information on the advice given are made public: therefore, neither the purpose of the SA nor its utility can be assessed publicly.
- Individual confidential SA to companies inherently bears the risk of regulatory capture. Current arrangements might allow for a bargaining process which may be a way to negotiate confidential waivers to existing guidelines. As a consequence, individual confidential SA could be used as a driver towards lowering the regulatory bar.
- Confidential SA does not allow a public debate on the scientific requirements of drug development and approval.
- Confidential SA could undermine trust in the impartiality of the regulatory decision-making process.
- Confidential SA including contact between drug assessors and the regulated pharmaceutical company has the potential to compromise the overall independence of the regulatory agency. This is particularly critical under the current fee-for-service model and in the context of possible "revolving door" effects.

In relation to the specific question:

- Provision of SA on the development of a drug by the same person who later in the process assesses the drug leads to a potential conflict of interest, which may influence the decisions on drug approval.



- Provision of SA on drug development by the same organisation which later assesses the drug leads to a potential conflict of function of the organisation, which may influence decisions on drug approval.

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 answer is "No" for the same reasons outlined in the answer to question number one.

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?

It should be clearly stated and understood by all parties involved that the advice provided during the pre-submission activities is not binding (possibly through legal disclaimers and provisions). The EMA must ensure that the currently opaque interactions with pharmaceutical companies do not signal that the regulator is becoming a co-developer of medicines.

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: i. EMA's operations (for example the efficiency of its procedures, or its ability to engage with medicine developers) and ii. medicine developers?

It is unfortunate that the European Ombudsman has had to intervene to shed some much-needed light into this critical phase of drug development. The EMA ought to have proactively taken measures to promote transparency and public accountability of its activities.

Although 90% of its budget is financed by private sources (charges and fees) the EMA is a public authority. As such, patients and consumers have a right to know what the regulated i.e. pharmaceutical companies are asking the Agency and what the Agency's answers are.

It is critical that citizens maintain their faith in the marketing authorisation system in Europe. To this end, the perception of the Agency's independence and integrity are as important as the reality itself. Hence, it is the Agency's task to proactively dispel any fears about regulatory capture.

The pharmaceutical sector is a highly secretive business but the industry should not be fearful of greater transparency at the EMA, unless they feel that the pre-submission activities yields them greater access and influence over the final decisions of the top EU regulator.

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.



As explained above, the current model for the provision of Scientific Advice by the EMA to the developers of medicines is in dire need of reforms to ensure there is much needed transparency and scrutiny of its processes. To this end, the EMA should disclose the names of the officials and experts involved in the procedures as well the questions and answers/advice given.

To avoid any detrimental effects of confidential SA and simultaneously ensure clarification of scientific and procedural requirements, SA should be conducted in a transparent way. As such, SA should include:

- General guidelines on scientific principles for conducting randomised clinical studies, including comparative trials against standard treatments using patient-relevant endpoints, assessing efficacy as well as harms. Indeed, current EU regulation does not rule out marketing applications containing such comparative trials, which are essential to help patients and professionals choose the best options.
- Disease-specific guidelines to clarify disease-specific requirements (e.g. on patient populations, interventions and comparators, outcomes and study duration). These guidelines are partly already available.
- General or disease-specific public workshops to clarify upcoming questions at shorter notice. Guidance developed by means of these workshops could then be used to update existing or develop new guidelines. To avoid any inappropriate influence on the workshop outcomes, clear guidance on how to conduct these workshops should be developed.
- Written questions by individual companies to EMA (and/or HTA bodies or payers), and their written answers (without confidential meetings), should be made publicly available at the time the answers are issued. The EMA services should prepare publicly available frequently asked question and answer documents. New requests for SA should be limited to questions which are not yet covered in the available question and answer documents. This procedure would substantially reduce the number of questions to be answered. In this context, EMA should refrain from collecting fees for SA.
- SA processes should be public to avoid confidential waiver negotiations to existing guidelines.
- SA should be given by independent advisors, outside of the marketing approval nor the pharmacovigilance process as well as being independent from industry (as emphasized in question 1).

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

- Confidential SA to individual companies represents an increasing burden and an inappropriate use of the sparse resources of regulatory agencies and other scientific experts. Additionally, individual SA misses the opportunity to set transparent, uniform standards for therapeutic areas which could be applied to all companies and publicly scrutinised. In this way, a level-playing field would also be guaranteed for medicines' developers since the regulator would not favour one developer over others. Another advantage of transparency would be that companies could learn from each other thus preventing the duplication of mistakes, which can cost billions.



Moreover, these uniform standards would contribute to a more efficient management of limited resources for both companies and the regulators and would improve the comparability of evidence available for different treatment options.

Overall, transparency is of real added value for the improvement of the drug development process and conducive to ensuring robust scientific debate.

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

Yes.

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

The industry fees that most of the Agency's revenue comes from are insignificant amounts of money for the pharmaceutical companies. Nevertheless, the EMA's dependency on this source of income creates yet another possible opportunity for regulatory capture. Therefore, the Agency, the European Commission and EU member states should revisit this dependency including the fees charged for the provision of Scientific Advice in the context of the pre-submission activities. This dependency also paves the way for the industry to demand confidentiality. Had Scientific Advice been provided using public funds, the information would not have been kept secret. This is one of the reasons why companies have no problem paying for this sort of services. Last but not least, it should be noted the absence of industry fees is no guarantee against regulatory capture – further safeguards are needed as regulatory capture is multi-layered.