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**From:** [REDACTED]  
**Sent:** 31 January 2019 17:49  
**To:** EO-PresubmissionConsultation  
**Cc:** [REDACTED]  
**Subject:** RE: Comments Ombudsman Inquiry on EMA pre-submission activities- HAI  
**Attachments:** European Ombudsman Consultation Response - January 2019.pdf

**Follow Up Flag:** ema15  
**Flag Status:** Flagged

Dear all  
Apologies, my colleague from comms realised the lay out of the header changed when I saved the document in pdf.  
Please use this version for publication.  
Thanks  
Ancel.la

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**From:** Ancel.la Santos  
**Sent:** dijous, 31 de gener de 2019 17:06  
**To:** [REDACTED]  
**Cc:** [REDACTED]  
**Subject:** Comments Ombudsman Inquiry on EMA pre-submission activities- HAI

Dear all  
Please find attached Health Action International's reponse to the public consultation on pre-submission activities by the EMA.  
Many thanks for the opportunity to comment on this important issue.  
Kind regards  
Ancel.la



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31 January, 2019

## Response to the European Ombudsman's Consultation 'How the European Medicines Agency engages with medicine producers before they apply for authorisations to market their medicines in the EU'

1. It may happen that European Medicines Agency (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?

According to EMA's [website](#), scientific advice and protocol assistance are given by the Committee for Medicinal Products for Human Use (CHMP), on the recommendation of the Scientific Advice Working Party (SAWP). This means that the committee responsible for assessing applications for marketing authorisation is always involved in scientific advice procedures. CHMP members are elected for a term of three years, which may be renewed. Therefore, there is a likelihood that at least some CHMP members are involved in the two procedures: scientific advice procedure on a given drug and subsequent marketing authorisation evaluation. Irrespective of this question, however, at the time of assessing an application for marketing authorization, CHMP members might feel bound by the advice that the very same Committee they represent gave in the past to a company/marketing authorisation applicant.

In addition, Section 3 Article 2 of the document 'Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP)' says "*SAWP members may be CHMP members or European experts from regulatory authorities or academia.*"<sup>1</sup> The PRIME scheme goes a step further, by allowing selected products to benefit from "*support tailored to the stage of development, which will not only be provided through scientific advice, but, for products achieving proof of concept, through: early CHMP Rapporteur appointment or in case of advanced therapy medicinal products (ATMP), Committee for Advanced Therapies (CAT) Rapporteur and CHMP co-ordinator appointment (...).*"<sup>2</sup>

The involvement of CHMP members in the provision of tailored (and confidential) scientific advice and guidance to a specific company/applicant creates, at the very least, a perception of conflict of interest. Perhaps for this reason, other bodies have decided to separate the roles between scientific advice and appraisal committees (e.g., NICE) taking into account the potential for bias. Health Action International (HAI) considers that the EMA should err on the side of caution and draw a line between the roles of the two committees.

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<sup>1</sup> European Medicines Agency (2016). Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP). [https://www.ema.europa.eu/documents/other/mandate-objectives-rules-procedure-scientific-advice-working-party-sawp\\_en.pdf](https://www.ema.europa.eu/documents/other/mandate-objectives-rules-procedure-scientific-advice-working-party-sawp_en.pdf)

<sup>2</sup> European Medicines Agency (2018). Enhanced early dialogue to facilitate accelerated assessment of Priority Medicines (PRIME). [https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime\\_en.pdf](https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf)

- 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?**

See our previous response.

- 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?**

EMA's scientific advice is not formally binding. The separation of roles between those giving scientific advice and those assessing marketing authorisation applications could help reinforce the idea that scientific advice is not binding.

- 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?**

Scientific advice procedures are confidential. Therefore, it is impossible to know from the onset the advice a company has requested, and the EMA has subsequently provided, even though this would be relevant information to patients who are considering enrolling in a clinical trial, and to independent clinical trial reviewers. Open debate is essential to the advancement of science. Moreover, information on scientific advice would also be relevant to other clinical trial sponsors, be they commercial or non-commercial. In fact, by providing tailored and confidential advice to one company only, the EMA might be incurring in an anti-competitive practice.

While information on whether a company benefited from scientific advice can be found in the medicine EPAR, they do not report comprehensively on the content of the advice.

If, as the EMA claims, scientific advice contributes to improve clinical trial design, it would be in the public interest to make this information publicly available from the onset.

We do not see any disadvantage in making these procedures transparent. On the contrary, transparency can only help to enhance public accountability and trust in the marketing authorisation process.

People involved with EMA told the [BMJ](#) that manufacturers see pre-submission processes as a way to lobby the agency.<sup>3</sup> Transparency might dissuade companies from using these processes for lobbying purposes.

- 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.**

Scientific advice that is relevant to study design in a specific disease area or in general should immediately be made publicly available. A publicly available Q&A system should be developed

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<sup>3</sup> Cohen D (2017). Cancer drugs: high price, uncertain value. *BMJ*, 359:j4543. Available at <https://www.bmj.com/content/359/bmj.j4543>

and available to everyone. In addition, scientific guidelines should be amended on a regular basis to keep pace with scientific progress. Specific advice relevant to a particular drug development plan—but which cannot be extrapolated—should be, at the very minimum, made publicly available in a comprehensive way at the point of decision on marketing authorisation.

In this [joint letter](#), endorsed by HAI, we also proposed that regulators organise public general or disease-specific workshops on drug development. To avoid any inappropriate influence on the workshop outcomes, clear guidance about how to conduct these workshops should be developed.

We also believe that the names of experts involved in scientific advice should be publicly disclosed, together with their declarations of interest. Only personal details (identifiers) of patients involved could be anonymised upon their request. Patient representatives, however, shall be considered experts. Those experts/stakeholders involved in scientific advice procedures should not be involved in marketing authorisation procedures related to that medicine.

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

All drug developers would benefit equally from advice on study design. Transparency can also nurture debate within the scientific community about best approaches to drug development in general, or in specific disease areas. We believe all this is very important from a public health perspective—and is in line with good science.

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

Published scientific guidelines should be the primary resource drug developers consult for any questions they might have. In addition, they could check the publicly available Q&A system proposed above. Only if the information they seek is not there, should they ask for advice. The EMA should come up with criteria that helps justify the provision of advice.

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

As mentioned above, the close involvement of CHMP members in the PRIME scheme raises concerns. A clear separation of roles between advisors and marketing authorisation assessors should be established. We would also suggest greater transparency regarding the products accepted into the scheme. For an investigational drug to be selected, it should “*demonstrate the potential to address to a significant extent the unmet medical need for maintaining and improving the health of the Community, for example, by introducing new methods of therapy or improving existing ones.*”<sup>4</sup> At present, the EMA does not explain under which grounds it has been considered that a selected product meets the criteria based on the data submitted to support the request for eligibility. For example, see [here](#).

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<sup>4</sup> European Medicines Agency (2018). Enhanced early dialogue to facilitate accelerated assessment of PRiority Medicines (PRIME). [https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime\\_en.pdf](https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf)

