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From: [redacted]
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To: EO-PresubmissionConsultation
Subject: Comments Ombudsman Inquiry on EMA pre-submission activities

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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

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?

   EMA should ensure that staff who were involved in the provision of scientific advice are not involved in the subsequent evaluation of the product for marketing authorisation. For a reason, driving instructors are not the examiners. This is a major conflict of interest. Individuals who have given advice are likely to be reluctant to admit at the licensing stage that a study was not good enough for approval and they will be more likely to approve the product to save the face and to save potential provocation from the industry. Most of the time advice is sound but… the landscape of drug development changes, people's knowledge and experience change, it might very much be possible that the drug approval based on the advice given a few years in the past is no longer possible. Making sure the assessors are not emotionally conflicted, different teams should be assigned to the tasks.

   EMA very proudly shows that out of successful marketing authorisations ~85% of companies sought scientific advice. There is a chance there might be no link but it is hard to believe when advice is a fee-for-service exercise. Highlighting such statistics is a good marketing strategy, it is in the interest of EMA to achieve such a high number to lure more clients. Such number is easier achieved when the same people are involved in advice and the evaluation. Even if malice is non-existent and we assume that EMA staff have the highest levels of integrity and professionalism, there is still a great benefit of separating the advice and evaluation functions as when a new person looks at a trial programme, he or she will not be influenced by previous knowledge and experience and is likely to be more objective.

   Another issue is that many EMA employees worked for the industry in the past or contemplate getting a job in the industry after leaving the EMA. Some assessors and advisers maybe more lenient towards the companies they wish to work for one day. I have been at many meetings where the agency was not critical enough of the company's plans. By ensuring that different people are involved in the advice and evaluation stage will help (partially) to manage this hypothetical conflict of interest as well.

   For example, at NICE this system works: scientific advice is provided by a separate group and external experts who cannot be representatives of the decision-making NICE committee. A NICE

committee making the decision on the product is not even aware that the scientific advice was obtained by the company in the past.

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?

   As per above, better if not

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 fact that advice is non-binding should be stated in the contract (or a confirmation of project booking) documents between the EMA and the company and added as disclaimers to any written advice/company's minutes and at the face-to-face meeting with the company.

   It is important to make sure that the advice is not binding so EMA is not seen as a co-developer of the product, plus clinical landscape may change and the study may need to be halted, expanded, or adjusted. The companies also need to take into consideration advice from other agencies and align the expectations of different stakeholders.

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

   It is definitely not transparent and it is a shame. These activities should be transparent. If not specific details of advice (at the time of advice), public has the right to know what companies approached agencies for advice. It is a disgrace that EMA (as well as FDA) are funded by the industry. I have co-chaired many scientific advice meetings alongside EMA and on many occasions I observed how pro-industry (rather than standing by the interest of public health and patients) EMA has acted, how EMA staff were not critical enough of the industry plans (which were scientifically and ethically questionable), how often patient engagement in these meetings were 'for show' only and how EMA chairs of advice meetings even forgot that the patients were in the room. Patient testimonies are not taken into consideration in the EMA advice letters. On many occasions, EMA puts interests of the industry and speed of their approvals above patients' interests. As a result, the market is flooded with expensive 'me too' products for which clinical effectiveness was never established. Research community and patients have the right to see how the regulator ensures (via scientific advice) that trial design plans are robust for the company to answer clinically relevant questions.

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?

EMAs responsibility should be towards patients and not shareholders of the industry. EMA must increase transparency and provide brief summaries online of all SA meetings. Freedom of Information requests should allow people access to all advice letters and minutes of the meetings at least at the stage of marketing authorisation. This practice will let researches and the public see if EMA holds the industry to the relevant scientific standards and whether the industry complies.

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;

Absolutely, the names of the people should be public. If staff are afraid to put their names forward and stand by the advice they offer, this is a huge worry to the society and scientific integrity.

- disclosed the questions posed in scientific advice procedures; and/or

It would be very useful. If not possible to release this information at the stage of scientific advice, this information should be released at Marketing authorisation. For products that do not reach MA, this information should be available no later than 3 years (if possible, sooner) after the receipt of the advice letter by the company. Making this information public is extremely important for transparency and efficiency of scientific research. Scientists and companies working in this field can save resources and avoid making similar mistakes.

- made public comprehensive information on the advice given.

Yes, this information should be public including advice given in parallel with health technology assessment agencies.

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.

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

   If scientific advice was transparent and public, this would improve the quality and speed of medicines' development. Many companies make the same mistakes in parallel and this is a huge waste of time and resources! They can learn from each other. Transparency will also help discontinuation of many development plans and these resources can be reallocated to other initiatives.

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

   No, EMA should be free to highlight any concerns to the company to ensure the protection of patients in the trials and later in clinical practice.

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

All EMA advice letters and minutes should be available under FoI requests at any time for research purposes and decision-making (e.g. HTA bodies can request it at any time as well as independent researchers). For this, the issues of fees for EMA SA should be reconsidered. If industry pays for the advice, it has the right to demand confidentiality. If advice is provided using public funds, then advice should be publicly available. It is EU's responsibility to ensure that the regulator is not funded by the pharmaceutical industry, not for advice, not for any evaluations. Fees are not the only problem, as

developers of orphan products or SMEs are not charged or charged at 90% discount, it is the policy of transparency that needs to be prioritised. There is no pricing information in advice letters and the fact that industry demands confidentiality is utter non-sense. The only reason to keep hidden the plans for clinical trials is shamefully poor methodology (and rather unimpressive products for the most part) which is the hallmark of many development programmes.

Patients and the public should be able to trust the regulator and rely on the regulator to protect public health.

Thank you for your consideration of my responses.
I was the head of scientific advice at NICE UK between 2014 and 2018 and I have co-chaired about 40 scientific advice meetings with EMA
Please feel free to contact me if you have further questions.

Kind regards,

Leeza Osipenko
Senior Lecturer in Practice
London School of Economics