[redacted]

**From:** [redacted]
**Sent:** 30 January 2019 17:58
**To:** EO-PresubmissionConsultation
**Subject:** Comments Ombudsman Inquiry on EMA pre-submission activities
**Attachments:** Comments to inquiry of the European Ombudsman.docx

**Follow Up Flag:** ema6
**Flag Status:** Flagged

Please find attached comments to the questions raised in the European Ombudsman's inquiry OI/7/2017/KR from Anja Schiel and Rune Kjeken, Norwegian Medicines Agency and members of the Scientific Advice Working Party, EMA.

Best regards
**Anja Schiel, PhD**
Senior Adviser / Statistician, Unit for HTA and reimbursement
Department for Pharmacoeconomics

www.noma.no

Norwegian Medicines Agency

# Questions

Please give reasons for your answers.

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?

*In our experience, involvement of EMA staff members and national experts in pre-submission activities is a necessity to ensures timely, consistent and efficient advice to the industry. Pre-submission activities such as pre-submission meetings or scientific advice are legally non-binding scientific discussion that allow the early detection of shortcomings and evidence gaps in drug development programs.*

*These activities are based on the scientific knowledge at the time of the advice, and therefore opinions evolve in time based on the accumulating knowledge. Reflecting such scientific developments in the centralised assessment process is improved by having staff members or national experts being involved in different phases of a drug passing through the regulatory system. Passing on details of the scientific discussion requires more than just minutes of pre-submission meetings or Final advice letters (the output of a Scientific Advice procedure). Such documents communicate the consensus reached but can never fully reflect the full scientific discussion that lead to this consensus. The involvement of EMA staff and/or experts in pre-submission activities should therefore be considered a strength rather than raise concerns.*

*It should also be emphasized that any decisions regarding Market access are based on the input and scientific exchange of all national agencies at the CHMP and never are solely based on single agencies opinion. As such having continuity in the form of either EMA staff members and/ or national agencies/experts being involved in multiple steps of the interaction with an applicant ensures consistency, a better in depth understanding, regulatory consistency and a more efficient assessment as involved staff and assessors are already familiar with the details of that particular drug development program at the time of an application for Marketing Authorisation.*

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?

*In principle, scientific advice provided by national agencies should be based on the same available current scientific knowledge and therefore national advice deviates most likely only in such aspects that are regional specific from advice given on the same subjects if central advice would be given.*

*Not allowing experts, who have previously provided scientific advice at the national level on a particular medicine to be involved in EMA's scientific evaluation of the same medicine, may limit access to experts in a particular field and impact the quality of the assessment being performed.*

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?

*Based on our experience from being involved in various regulatory stages of product development, we believe current practice as outlined by EMA guidelines is sufficient to ensure that all participants understand the non-binding nature of pre-submission activities. At the beginning of pre-submission meetings, discussion meetings that are part of a scientific advice procedures and also on the EMA website providing general information on the scientific advice procedure it is clearly stated that advice given is not considered legally binding. Data clearly shows that applicants do not blindly follow advice given. Moreover, it is evident from current practice that in the absence of compliance with previous regulatory guidance, CHMP will still approve a MAA when convincing data on efficacy and safety is provided.*

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?

*Yes, in our opinion the way in which EMA engages with medicine developers in pre-submission activities is sufficiently transparent. Many of the details regarding drug development shared with regulators during pre-assessment meetings and scientific advices involve business sensitive information considered confidential by the applicant. Failure to ensure confidentiality by regulatory authorities would potentially result in reluctance of drug developers to seek regulatory advice or to hold back on information considered business sensitive. To provide meaningful scientific advice regulators must have access to detailed information provided by the applicant. A requirement for greater transparency could result in less specific, more general, high level submissions lacking relevant details and as a result, less useful feedback to developers.*

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 stated previously, we consider the current level of transparency adequate and that further enhancing the transparency of scientific advice EMA provides to medicine developers e.g by disclosing names of assessors and experts involved in the procedure may be counterproductive. The names of all national experts are available on the EMA website. To disclose which individual assessors/experts is involved in each procedure to the public may put an unnecessary strain on these persons, as they may perceived as "responsible" for decisions which are taken not by them but by the CHMP. In addition, as pointed out in Q1, decisions are never made by individual national agencies or experts alone but at all times are the result of a broader discussion in the plenaries of SAWP and CHMP. As pointed out in response to Q4, the information provided by applicants must be considered confidential. The entire process of regulatory interactions is based on the clear understanding that there is a certain need for confidentiality from the drug developers side. Therefore, neither questions asked in specific procedures, nor details of advice given should be made public unless the applicant would agree. Yet, as already reflected on in the answer to Q4, the risk of jeopardizing the established trust between the industry and regulators by requesting more transparency should be carefully weighed against the benefit of current practice.*

*It is current practice that at the time of MAA published EPAR's refer to the fact that scientific advice was part of the procedure, albeit without providing specific details. It is difficult to see what purpose disclosure of such information at an earlier time point / or to provide more details regarding the specific advice, would serve. Today the applicant is free to disclose at any time, that they have applied for, or received scientific advice, at either EMA or national level. Again, from an industry perspective this is information the applicant may not want to be available in the public.*

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

*Each drug development program is different, sometimes different approaches can be considered valuable and complement drug developments in the same area. There is a higher risk that the industry would perceive advice to be 'absolutely binding' than wanted and this could result in a higher degree of submissions following the same blueprint instead of development programs that help to answer relevant scientific questions. As such, a requirement for more transparency might eventually lead to less tailored development programs and more 'copycat' programs based on previously successful developments instead of planning an optimised development program for the specific product at hand.*

*One could argue that companies could benefit from reading advices but it should be pointed out that advices is tailored to the specific product and the final document is (as mentioned in Q1) a consensus and can never fully reflect the scientific discussion it was based on. It is one of the tasks of the regulatory system to ensure that learnings from previous procedures are incorporated into later advices continuously to provide advice at the highest quality possible based on the concurrent knowledge.*

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

*No, guidelines can only provide overarching instructions. Each development program has specific details that might not be addresses in such guidelines or are open to interpretation. As pointed out previously, pre-submission meetings and scientific advices are tailored processes, focusing primarily on the issues that are not covered by sufficient detail in existing guidelines or to clarify to what extend existing Guidelines are applicable (or not) to the specific drug development program.*

*Furthermore, SME's and academic developers are often less experienced with the regulatory requirements and may therefore tend to pose questions which are in fact covered by existing guidelines but might either be worded slightly ambiguous and/or be open to interpretation. To restrict the possibility for regulatory guidance would be a disservice to these groups.*

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

*While, based on our experience the current system works fairly well, there is certainly room for improvement. Most importantly, we believe that the current system is underutilised, particularly by academic developers and SME's. These may in fact be the groups, which would benefit the most from early interactions and continuous regulatory support.*

*There is a noticeable increase in submissions for drugs developed for orphan diseases, small populations and personalized medicines. The number of available experts that can potentially contribute to the assessment of such submissions is often a limiting factor, not the least for the smaller EU member states. It might therefore be important to assess the demands in terms of absence of conflict of interests. If requirements are unjustly high, this might prohibit the recruitment of in particular external experts with clinical and academic backgrounds.*

*While we acknowledge the Ombudsman concerns, we do believe the continuous involvement of regulatory experts at several stages in the development process an advantage and a reasonable trade off. Continuity improves quality and allows transfer of knowledge across the different phases of interactions with greater efficiency and less use of recourses.*

*Anja Schiel and Rune Kjeken, Norwegian Medicines Agency and EMA Scientific Advice Working Party*