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Follow Up Flag: Follow up
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Dear Ms O'Reilly,

Thank you for the opportunity to comment on the inquiry on EMA pre-submission activities. Please find IQWiG's comments in the attachment.

Please do not hesitate to contact us in case of any further questions.

With kind regards
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European Ombudsman's inquiry OI/7/2017/KR
Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany
28 January 2019

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

IQWiG appreciates the opportunity to provide comments on this inquiry. IQWiG is responsible for health technology assessments of new drugs to inform decision making in the German health care system. IQWiG has been involved in HTA and EMA/HTA scientific advice procedures and would like to share the experience from these procedures.

From our experience we do not see why scientific advice needs to be performed behind closed doors. Most of the questions discussed consider general study design issues. Making this information publicly available has the potential to improve general drug development and thus benefit patients. A different model of scientific advice could also save limited resources of experts both at the regulators and the medicine producers. At the same time having this discussion in the public would allow for public scrutiny and would protect regulatory decision making from perceived or actual undue influence.

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?**

- An involvement of a person in both pre-submission activities and evaluation of the same product should be avoided because this might jeopardize the independent evaluation of a new drug at the point of marketing authorisation.
- The evaluation of a medicine should be based on the evidence submitted for this evaluation as well as on state of the art methodologies and context (e.g. available therapies) at the point of evaluation. It should not be influenced by any decisions made at an earlier time point. Furthermore, due to an inherent conflict of interest the evaluation should be independent from the medicine producers, i.e. the applicant for the regulatory decision.
- Any notion of being bound to earlier suggestions or interpretation of information from an advice procedure would put the independent evaluation and decision making at the point of marketing authorisation at risk.
- This risk could be managed by a clear separation between persons advising medicine producers on studies and development programs and persons evaluation these trials and development programs and deciding on marketing authorisation. IQWiG has laid down this separation in it's methods paper.[1]

[1] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (2018, 10.07.2017). "General methods: version 5.0." Retrieved 06.06.2018, from https://www.iqwig.de/download/General-Methods_Version-5-0.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?**

- The involvement of experts having provided scientific advice at national level in international scientific evaluation is problematic for the same reasons as described in Question 1.

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 seems difficult to ensure that persons involved in scientific advice consider their own advice and interpretation of information at the point of advice as absolutely non-binding. Therefore, there should be a separation between persons involved in advice and evaluation (please see Question 1).
- We would like to point out that even a report on EMA/HTA parallel scientific advice suggests that in a future concept of this activity the advice should indeed not be legally binding but should be considered "scientifically binding".[2] This has been the outcome of a workshop at EMA on the topic and highlights possible pressures put not only on persons involved in both advice and evaluation but also on the regulators generally. This is specifically critical because according to our experience medicine producers use scientific advice procedures to "negotiate" the level of evidence to be generated in a drug development programme.

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?

- EMA's engagement with medicine developers is not sufficiently transparent. So far only very limited information (like the number of procedures) is available. There is no information on the content of the advice available in the public domain.
- The lack of transparency of EMA scientific advice has been problematic in German HTA procedures. There have been a number of cases, where medicine developers stated that specific study design features criticised in the discussion during the HTA, had been based

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[2] EMA Human Medicines Research and Development Support Division; 23 March 2016; EMA/695874/2015; Report of the pilot on parallel regulatory-health technology assessment scientific advice; https://www.ema.europa.eu/documents/report/report-pilot-parallel-regulatory-health-technology-assessment-scientific-advice_en.pdf

on recommendations from regulatory scientific advice. Without transparent information on the regulatory scientific advice in the public domain, the participants of the HTA discussion do not have the possibility to assess this information.

- We cannot see how EMA's operations would be negatively affected by greater transparency. On the contrary, we feel that increased transparency would support EMA's position as an independent regulator.
- We also do not think that medicine producers would be negatively affected because of the mostly generic nature of the advice and the fact that most of the information on planned study programmes is available elsewhere. On the contrary, in general medicine producers could benefit from public information on EMA recommendations from scientific advice due to resource savings and timely information (please see Question 6). From our point of view, medicine developers could feel disadvantaged only when they would hope the advice procedure could result in decreased requirements or could somehow bind the 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.

- There is a need to enhance the transparency of scientific advice to medicine developers.
- Due to the lack of public information on the content of scientific advice, it is not possible to analyse if the aims of the procedure are met or if any disadvantages to regulatory decision making result from the procedure.
- From our point of view, the questions and comprehensive information on the advice given should be made publicly available. This might not only overcome the disadvantages of the current lack of transparency but would potentially even improve drug development as described in our answers to Question 6.
- Concerning the development of information on scientific advice content in a Q&A format as described in our answer to Question 7, this should be made publicly available continuously because this advice would then inform general drug development as timely as possible. This is specifically important in rapidly evolving areas. Any remaining individual scientific advice to medicine developers should be made publicly available at the point of marketing authorisation because once the drug is used by patients the complete basis of it's approval should be publicly available.

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

- The advantage would be that the outcomes of scientific advice would inform all medicine developers and therefore the overall drug development environment rather than individual companies. This would have a positive impact on the quality of drug development by supporting appropriate clinical trials not only by individual medicine developers but generally. It could result in clinical trial programs using sufficiently comparable (high quality) study designs and study outcomes to allow for the generation of additional knowledge by data synthesis across development programs for individual drugs.
- From the point of view of resources required for the scientific advice both at regulators and medicine developers, the public availability of advice outcomes should reduce the resources needed on both sides by avoiding repetitive discussion of similar questions. Our experience from both international and national HTA (/regulatory) scientific advice is that there is a repeated discussion of the same questions in advice procedures for different or even the same medicine developers. Avoiding this waste of resources might then also allow for better use of limited resources of experts.
- Public availability of scientific advice could also foster a general scientific debate about the best approaches to drug development in individual therapeutic areas.
- We do not see any disadvantages in making the outcomes (questions and answers) of scientific advice publicly available.

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

- There might be questions that are more specific than the content of clinical efficacy and safety guidelines. However, that does not mean that these questions can only be answered in individual confidential scientific advice procedures. Answers to more specific questions could be made publicly available in a Q&A format. This would be more transparent and would benefit a wider audience than an individual medicine producer. Any requests for scientific advice could be checked against the available Q&A content for a given indication and would only require new answers if not already covered. Such a procedure would require substantially less resources than the repeated individual scientific advice.
- According to our experience medicine producers repeatedly put forward the same questions (e.g. on the relevance of a specific endpoint in a given clinical indication). This gives the impression that these requests are not primarily aiming at solving open questions but possibly at building up pressure on regulatory decision making.

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

- From our point of view the processes of PRIME are specifically critical. According to EMA "Through PRIME, the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications." Specifically, EMA "appoints a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy to provide continuous support and help to build knowledge ahead of a marketing-authorisation application."
- The process results in close interaction of the rapporteur with the medicine producers throughout the development of the new drug. In such a situation, it seems unrealistic to ensure an independent evaluation at the point of marketing authorisation.