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From: [redacted]
Sent: 31 January 2019 09:09
To: EO-PresubmissionConsultation
Cc: [redacted]
Subject: RE: Comments Ombudsman Inquiry on EMA pre-submission activities
Attachments: MEB Draft response to the EU ombudsman Public Consultation MEB.docx

Importance: High

Follow Up Flag: ema7
Flag Status: Flagged

Dear European Ombudsman,

Please disregards the previous version and find attached **the response of the Medicines Evaluation Board of the Netherlands** on the public consultation.

Best regards,

Birte van Elk
Senior Advisor International Governance and Regulatory Affairs

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Van: [redacted]
Verzonden: donderdag 31 januari 2019 8:47
Aan: [redacted]
CC: [redacted]
Onderwerp: Comments Ombudsman Inquiry on EMA pre-submission activities

Dear European Ombudsman,

Please find attached the response of the Medicines Evaluation Board of the Netherlands on the public consultation.

Best regards,

Birte van Elk
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Draft response from HMA to the EU Ombudsman - Public Consultation on EMA pre-submission activities

Questions posed by the Ombudsman

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 and the experts of the National Competent Authorities can provide scientific advice or protocol assistance during various phases of the medicinal product's lifecycle. The advise during the development phase of the medicinal product intends to assure that developers use test procedures, endpoints and clinical trial designs that will allow a proper evaluation of product quality and drug effects in the intended target population at time of a marketing application. The aim of early dialogue is to optimize the development plan (not to evaluate data) through advice on the methodological direction to take. Such that at time of a marketing approval application (MAA) the expected quality tests, non clinical evaluations and clinical trials have been performed and that the data generated with these tests and trials allows a thorough assessment of a drug's quality, and its benefits and harms by the national competent authority experts . Therefore, these experts assessing drugs at time of a MAA are best placed to advice on the expected tests and study designs that should be used in a drug development program. Procedures such as scientific advice or protocol assistance are in place to foster the development of safe and effective products for patients in a timely manner by fine-tuning drug development plans at an early stage.

It may thus happen that the same NCAs and its experts are involved in both the pre-submission activities and the assessment for the marketing authorisation procedure and is not considered problematic. For the above described reasons it is actually even desired. In our opinion this is a matter of no-concern:

- pre-marketing interactions are focused on the methodology and completely separated from the (assessment of) the MAA dossier that contains all data; the way medicines are regulated in the European Union provides a counterbalance, by the legally and procedural embedded appointment of a rapporteurship and a co-rapporteur for each assessment. These appointed rapporteurs from the 2 NCAs are responsible (with the team of their NCA) for an independent parallel assessment, which is then discussed plenary with representatives of all other NCA's; their role as concerned member states contributes to a well balanced system of advice/decision making that can't possibly be dominated by one or two experts. At the same time the involvement of all other NCAs during the discussion rounds as Concerned Member States during the review of the assessment reports further contribute to that. The reviews/input of the Concerned Member States are important for both maintaining the expertise up to date and at the same time will improve the quality of decision making.

- another type of counterbalance is included in the system: in the advisory procedure several Committees in different phases are involved (first of all the Committee on Orphan Medical

Products (COMP), the Scientific Advice Working Party (SAWP) and the Committee for Medicinal Products for Human Use (CHMP)). In case of scientific advice several other committees can also be involved, such as the Committee on Advanced Therapies (CAT) and/or Paediatric Committee (PDCO). Their specific expertise contributes to the outcomes of the SAWP and the CHMP.

Distinction between initial scientific advice (SA) and assessment of the marketing authorisation application (MAA)

Scientific advice

At a European level pre-submission activities cover the full range of meetings and procedures that facilitate interaction between medicine developers, EMA and experts during the development phase, prior to the assessment of a medicine developer's application for marketing authorisation. The EMA appoints 2 coordinators within the SAWP to provide each an assessment in parallel. A coordinator provides an assessment with a team of experts from their NCA to advise on the development program, what kind of guidelines should be taken into account and specific studies that should be performed. Providing scientific advice by regulators is an incentive for innovators to take into consideration the regulatory guidelines to optimize the development plan and to reflect on the methodological direction. Protocol assistance is scientific advice to stimulate the development of orphan designations.

Assessment of a MAA dossier

As already mentioned a counterbalance is legally and procedurally embedded in the appointment of a rapporteur and a co-rapporteur of the CHMP. The rapporteur and co-rapporteur are appointed from 2 different NCAs.

In the process of assessment of a MAA, NCAs and EMA rely on each other's work to avoid duplication and share workloads and scientific competences. The expertise of the NCAs form the backbone of the European regulatory system for medicines.

The EMA is responsible to keep oversight and implement processes for the Committees, Scientific Advisory Groups (SAG) and SAWP to cooperate, peer review and involve independent experts and ensure the system of checks and balances. The Network of EMA and NCAs brings together scientific expertise rooted in all Member States and the resources of the whole EU to ensure that medicines are regulated to the appropriate highest scientific standards.

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?

At a national level pre-submission activities, such as providing scientific advice is a statutory task of the Medicines Evaluation Board (MEB) in The Netherlands. MEB staff contributes to the assessments of Centralised Procedures, MRPs, DCPs, and/or to scientific advices at EU level or at the national level. This is needed to keep track of current scientific developments and discussions both in the advisory pre-authorisation interactions as well as at the time of MAA evaluation and decision-making. This ensures the quality of assessments and maintains a high level of efficiency and knowledge within our agency, within The Netherlands and within the Network. The MEB would like to underline that all those experts from the NCAs being part of the Committees or Working Groups (such as the SAWP) are appointed and nominated based on their expertise. The experts from the NCAs always work as part of a team and have to declare their conflicts of interests outside the agency's work before each meeting. We would like to emphasize that the final conclusion on the approvability of an application will be based on the assessment of the results included in the dossier at the time of MAA.

In principle experts may thus be involved in both the pre-submission activities and (often years later) in the assessment of the MAA. In The Netherlands independence is guaranteed by the discussion of reports in the Board of the MEB that consists of 17 independent members, appointed by the Minister of Health. This national governance procedure provides an additional measure to ensure quality, consistency and independence in advice and decision-making.

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 is responsible to make sure that applicants requesting scientific advice or protocol assistance are aware and must note that any scientific advice or protocol assistance given is not legally binding. Advice letters contain the following statement; "The response given by the CHMP is based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state of the art in the relevant scientific fields."
Thus at time of the MAA, the actual data will be assessed considering the scientific standards that are valid at the time of the application which are not necessarily the same as those when the advice was given.

If you believe that greater transparency in pre-submission activities is necessary, how might greater transparency affect: EMA's operations (for example the efficiency of its procedures, or its ability to engage with medicine developers) and ii. medicine developers?

There is transparency on the website clinicaltrial.gov which shows all clinical trial protocols performed in humans. During the development phase of a medicinal product, however, the commercially sensitive nature limits full transparency of pre-submission activities due to the fact that the clinical development evolves, potentially on the basis of the scientific advice given.

If full transparency would be aspired, companies may be less likely to seek alignment with European regulators and seek input from regulators elsewhere or worse, develop programs more independently with the risk that they will be less aligned with the needs of the EU population.

4. 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.

We would underline that, due to the commercially sensitive nature, full transparency of pre-submission activities during drug development will be detrimental. Greater transparency would have a negative impact on the development of medicines and therefore we do not see the added value of more transparency. The MEB does therefore also not favor to disclose the names of the national experts giving advice or performing the MAA assessment.

The MEB would like to stress that experts involved in the procedures (rapporteurs etc) are working as part of a team and not as individuals. The scientific advice has been concluded by the two named coordinators (in the advice letter to the companies), and an anonymous peer reviewer for each Scientific Advice Working Party case. The names of the team members working within both agencies of the coordinators who have also worked on the advice are not disclosed outside the regulatory system.

Importantly, as part of the European Public Assessment Report (EPAR) the main details of the development program and the names of the members of the CHMP are made public.

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

See answers above.

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

Guidelines reflect a harmonised approach of the NCAs and the EMA on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy. In reality often it is needed that deviations from these guidelines are needed due to the specific nature of a product or specific disease or because of specific patient issues not included in a guideline. As regulators we are seeing increasing trends where products in the pipeline may not fit into standard or traditional designs. Similarly, regulatory frameworks must adapt and evolve to serve the assessment process for medicines meant for curing rare diseases and involving smaller patient populations. This necessitates novel clinical trial designs, use of real world evidence and convergence of products/technologies. In this context, but also in standard drug development, scientific advice is related to the interpretation of the clinical efficacy or safety guidelines. We don't think that limiting EMA in the way as formulated in the question will help the quality and effectiveness of the process of scientific advice in any possible way, to the contrary.

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

The mechanisms of checks and balances embedded in the pre-submission activities and in assessment procedures are considered sufficient to safeguard a balanced benefit-risk assessment at the time of a MAA.
To improve pre-submission activities further, involvement of HTA bodies, interaction with patient representatives and horizon-scanning could be strengthened. In this respect, early encounters with HTA bodies, patient organsiations and innovators from academia also function as horizon scanning, will help to prepare NCAs and their experts to anticipate on new technologies and prevent spending amounts of money in developing medicines that finaly fail to reach the patients.