[redacted]

From: [redacted]
Sent: 31 January 2019 12:27
To: EO-PresubmissionConsultation
Cc: ROOVERS Koen
Subject: Comments Ombudsman Inquiry on EMA pre-submission activities
Attachments: EPF response January 2019.pdf

Follow Up Flag: ema8
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Dear Mrs O'Reilly,

Please find in attachment the comments of the European Patients' Forum on the inquiry on pre-submission activities of the EMA.
Kindly acknowledge receipt of this email.

Thank you for your consideration.
With best regards,

Dictated with my voice recognition software. Please excuse possible typos.

Kaisa Immonen
Director of Policy

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European Ombudsman
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CS 30403 F-67001 Strasbourg Cedex
By email only:
[redacted]

Dear Mrs O'Reilly,

Comments Ombudsman Inquiry on EMA pre-submission activities

The European Patients' Forum (EPF) is the EU-level umbrella organisation of 72 patient organisations across the EU – both disease-specific patient groups at European level, and national coalitions of patients. Our vision is for all patients in Europe to have access to high-quality, patient-centred health and related care. Our organisation's mission is to be the collective, influential patient voice in European health-related policies, and a driving force to advance patient empowerment and equitable patient access to care in Europe.

Having been involved in various strands of the work of the European Medicines Agency for many years, *inter alia* as a long-standing member of the Patients and Consumers Working Party (PCWP) and being represented on the Pharmacovigilance Risk Assessment Committee (PRAC) and the Management Board, EPF is both highly committed to the work of the Agency and familiar with its processes.

We are pleased the Ombudsman recognises that different pre-submission activities are organised with the purpose to enhance timely patients' access to new medicines which are effective and safe, focusing on areas where no treatments exist; to optimise the efficiency of the process including minimising less useful clinical trials and maximising the value of the data generated; help in particular smaller, new companies and academia navigate through the complex process; and – a goal that is becoming particularly important – ensuring the data requirements for regulatory approval and subsequent HTA assessment are better aligned. The report of the meeting between the offices of the Ombudsman and EMA stated that she "is not in any way questioning the existence of pre-submission activities … that are geared towards these objectives. On the contrary, to the extent that they achieve the goals outlined above, they are *encouraged*." (italics in original)

The Ombudsman focuses on two questions in particular: the level of transparency around pre-submission activities, i.e., "it should be clear what has happened before a medicine developer submits an application", and the extent to which there are appropriate "firewalls" in place to ensure the application of marketing authorisation applications is independent and not biased by the dialogues that may have taken place at a previous stage. Primarily, this issue centres around having separate experts involved in pre-submission and post-submission activities.

These are reasonable concerns. Through our long and close engagement with the EMA in different roles, we do recognise the Agency as being at the forefront of transparency and engagement with patients and the public. There is, of course, always room to improve, and we have witnessed the commitment and efforts of the Agency at the highest level to continually improve the way in which it operates.

It is important to stress that should the EMA be asked to add new procedures that will require additional staff or other resources, it must be provided with the necessary additional budget to do so.

Currently, the Agency's capacity is restricted due to the situation brought on by Brexit and its forced relocation to Amsterdam. Whilst this is not a permanent situation, it has highlighted more generally the limited resources compared to the increasing responsibilities the EMA is asked to undertake, such as the important question of improving the user-friendliness of the medicines package leaflet (COM(2017) 135 final).

The European Patients' Forum, representing a diverse range of patients for whom the EMA is a crucial interlocutor, remains committed to supporting and working closely with the Agency, including through the Patients and Consumers' Working Party, with the goal of further improving transparency and public engagement. We ask that our answers to the questions below be taken into consideration and regarded in the constructive spirit of continuing joint work towards our common objective: ensuring equitable and timely access to safe, effective medicines for European patients and safeguarding public health.

Yours faithfully,
On behalf of the EPF Governing Board

[redacted]

Marco Greco
President

Annex: Answers to the Ombudsman's questionnaire

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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?**

Pre-submission activities, as the Ombudsman and EMA make clear, cover a broad range of activities, from procedural advice to meetings, scientific advice, or early dialogues. From our point of view, the main activities where issues may arise would be in-person meetings and provision of scientific advice/protocol assistance.

In principle, to avoid conflicts of interest, we believe scientific evaluation, such as for the purposes of marketing authorisation, and scientific advice must be separate functions, and separate experts should be responsible for each. This principle is in line with EPF's position on Health Technology Assessment (2018).

However, practical experience shows that it is not always possible. To insist on a complete separation would therefore, in our view, risk impacting negatively on the quality of both activities. This may be particularly the case where expertise is scarce, such as in orphan conditions or advanced therapies. Secondly, the number of eligible European experts is scarce as they have to fulfil stringent requirements, so it is theoretically possible that the same experts may need to be involved in different parts of the process In any case, the EMA has explained that the Agency staff responsible do come from different parts of the agency, and secondly, that no single person has a final say in the evaluation as that is undertaken by a committee (and also includes patient input).

In conclusion, our view is that the EMA should strive to ensure that there is a separation as far as feasible, but recognising that this is not always possible. The Agency should, naturally, ensure that appropriate procedures are in place to avoid any personal conflicts that may have a bearing on the impartiality of the scientific assessment.

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?**

Please refer to our previous answer. In principle, this should be avoided; however, it may be unavoidable in practice. To manage potential conflicts of interest, such involvement should be declared and taken into account appropriately in the evaluation process.

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?**

In our view, pre-submission activities should absolutely not be considered as a "pre-approval" of the company's submission. Rather, the added value of pre-submission activities – in particular, *early dialogues* that ideally bring together the regulator, the developer, patients, medical professionals and

HTA/payers – lies in ensuring better alignment between the evidence needs for marketing approval and subsequent assessment of added value and cost-benefit as well as pricing and reimbursement decisions. The patients' role in such dialogue is vital for example to select the right outcome measures to ensure that the therapy demonstrates concrete improvements for their health and quality of life.

A review of existing procedures, guidance to companies, and ways in which information is communicated to the company, would be helpful to avoid any misconceptions.

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?**

EPF supports the principle of maximum transparency. Transparency is vital for generating and maintaining trust of patients and the wider public in the regulatory process on medicines in the EU.

We are not in a position to comment on the impact on EMA's ability to engage with medicine developers, but we do believe further enhancing the transparency of the process would enhance the EMA's *ability to engage with patients and the public*, demonstrate its accountability to the public, and support greater trust by the public. Proactive, lay-friendly communication about the processes and purposes of pre-submission activities would also enhance understanding and trust.

Transparency could be improved by more public reporting. We believe improvements could be achieved in this way without unduly disclosing information that can be legitimately claimed to be confidential. In line with the new EU Clinical Trials Regulation, redacting commercially confidential information must balance the legitimate economic interests of companies against the public interest; EPF considers that what is deemed as "commercially confidential" should be defined as narrowly as possible, in favour of public reporting. Reports should be available in lay-friendly language and formats to ensure accessibility to patients and the public. Please see also our response to question 5.

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.**

We believe it would be useful to have more transparency about and on the scientific advice given, without disclosing information that is legitimately considered confidential.

Regarding publication of the questions posed and advice given, currently the content of scientific advice or protocol assistance outcomes can be accessed by a submitting a "request for access to documents", after the completion of the assessment. We suggest that these documents should be published as a matter of course, after the completion of every assessment procedure. This could be done separately or incorporated into the European Public Assessment Report (EPAR), which currently includes only a mention of whether the developer requested scientific advice. Diverging views expressed during the assessment could also be considered for inclusion in the EPAR. The EMA has

already said it will reflect internally on what new transparency parameters it would set for the EPAR. We would support such a reflection and encourage a dialogue with the civil society representatives on the working parties representing patients, consumers and healthcare professionals.

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

We believe this could be helpful to avoid duplication of work and improving the design of clinical trials, thus making the process more efficient and avoiding trials that are unnecessary/badly designed. In addition, it would contribute to public trust and better understanding of the regulatory process.

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

We do not see this strictly, as some developers – which include also small, new companies and academic organisations unfamiliar with the regulatory process – may wish to clarify some issue even though it is covered in the guidelines. The EMA already states it refers to official guidance whenever relevant. Having said this, a review and possible updating / expansion of available guidelines to take into account emerging issues that are frequently addressed in scientific advice, would also be helpful, since the guidelines are available to all in the public domain.

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

We have no further comments. EPF will be pleased to engage further with EMA in its ongoing efforts towards greater transparency and embedding meaningful involvement of patients and the public in its processes.