European Ombudsman

Report on the second meeting with the European Medicines Agency in the European Ombudsman inquiry into pre-submission activities organised by the agency (OI//72017/KR)

Correspondence - 26/11/2019

Case OI/7/2017/KR - **Opened on** 17/07/2017 - **Decision on** 17/07/2019 - **Institution concerned** European Medicines Agency (No further inquiries justified) |

Case title: Strategic inquiry into pre-submission activities organised by the European Medicines Agency

Date: Wednesday, 15 May 2019, 10:00-15:00

Location: EMA (temporary 'Spark Building'), Orlyplein 24, Amsterdam

Present

The European Ombudsman

represented by:

Mr Fergal Ó Regan, Head of Coordination of Public Interest Inquiries;

Mr Koen Roovers, Case Handler, Strategic Inquiries Unit;

Mr Diesmer de Jonge, Trainee, Strategic Inquiries Unit.

The European Medicines Agency

represented by:

Head of Legal Department;

Head of Product Development Scientific Support;

Head of Public Engagement;

Head of Stakeholders and Communication;

Head of Scientific Committees Regulatory Science Strategy.

List of acronyms

CHMP

COMP

EMA

EPAR

MAA

PRIME

SAWP

Committee for Medicinal Products for Human Use

Committee for Orphan Medicinal Products

European Medicines Agency

1. Introduction and procedural aspects

The purpose of the meeting was for the European Ombudsman and the European Medicines Agency (EMA) to exchange views on the Ombudsman's inquiry into the arrangements that EMA has in place concerning pre-submission activities.

The inquiry

The strategic inquiry into this matter was opened by the Ombudsman on her own initiative on 17 July 2017 and concerns the ways in which EMA engages with individual medicine developers before receiving their applications for marketing authorisations. [1] The inquiry concerns the principles underpinning EMA's work during the early dialogue and evaluation phases of medicine development, such as the need for objectivity and transparency. It looks at systemic issues relating to the work of EMA and is not related to any particular file or case.

The Ombudsman acknowledges the important role of EMA's pre-submission activities in supporting the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. However, she has also noted certain risks relating to these pre-submission activities, for example that eventual decisions by EMA on the authorisation of medicines may be influenced - or be reasonably perceived to be influenced - by interactions with medicine developers prior to receiving their formal submission for evaluation.

In September 2017, a first meeting was held with EMA for the Ombudsman to learn more about EMA's approach to pre-submission activities. [2] In October 2018, the Ombudsman launched a consultation on EMA's engagement with medicine developers in pre-submission activities. The results of this consultation were shared with EMA.

The meeting

In addition to the responses to the consultation, the Ombudsman proposed the following three issues for discussion:

1. The participation of experts from EMA's Scientific Committees in the provision of advice to applicants, and the transparency thereof.

2. The participation of EMA staff in the provision of advice to applicants, and the transparency thereof.

3. Whether EMA can, once a medicine is approved, make public all documents related to pre-submission activities regarding that medicine.

The discussion during the meeting was based on these points.

The Ombudsman representatives outlined the legal framework applicable to the meeting, notably that the Ombudsman will not disclose any information identified by EMA as confidential without prior agreement [3] .

2. Exchange of views and clarifications provided by the European Medicines Agency

EMA's view on contributions to the Ombudsman's public consultation

EMA noted that the Ombudsman's consultation has resulted in a substantial number of valuable contributions from a variety of stakeholders and in an interesting mix of perspectives and views. The input is considered very important by EMA.

When analysing the results, EMA considered that the contributions from organisations and individuals that are not directly involved in pre-submission activities often called for significant changes. The contributions from organisations that are involved - national competent authorities and the pharmaceutical industry - were mostly aimed at finding a balance between ensuring that the benefits of the current system are kept, whilst assuaging any possible concerns.

EMA found the overall response to be constructive and found it reassuring that most contributors seemed to appreciate the value of the work done by the agency and the usefulness of pre-submission activities. The main conclusion EMA draws is that the contributors do not question the fact that EMA has pre-submission activities in the first place. Rather, questions are raised around *how* EMA is conducting pre-submission activities. EMA sees room for improvement in terms of communicating how it is conducting its work and about the safeguards it has in place.

Safeguards in place to ensure objectivity in the medicine evaluation

When asked about the safeguards that are in place to ensure objectivity with regard to a marketing authorisation application (MAA), EMA explained that different independent assessments are in place.

First, scientific advice is given by a Scientific Advice Working Party (SAWP), representing a variety of expertise provided by the national competent authorities with which EMA cooperates. Two coordinators are appointed within the SAWP who each prepare, possibly with their teams, and present a report. The allocation of coordinator roles is done on the basis of best available expertise and the specific characteristics of the medicine in question. Scientific advice is not

necessarily a holistic exercise; it might concern only clinical or non-clinical questions or questions relating to safety. The coordinators' reports are presented within the Working Party and any divergences are debated within the entire SAWP before the advice is finalised for adoption.

When a medicine developer applies for marketing authorisation, it is evaluated by the Committee for Medicinal Products for Human Use (CHMP). Two rapporteurs are appointed, the rapporteur and co-rapporteur, who both make independent, primary assessments of the data provided by the medicine developer which are discussed in the CHMP. The allocation of the role of rapporteur is based on best available expertise.

EMA pointed out that, when a medicine developer who obtained scientific advice for a medicine applies for marketing authorisation for that same medicine, the selection of rapporteurs is not necessarily influenced by the previous selection of scientific advice coordinators.

EMA stressed that the strength of its approach lies in the fact that decisions for both the scientific advice and marketing authorisation are adopted in committees. This decision-making consists of a collegial scientific discussion without any hierarchy between members. The decision is taken as a collective where all members vote. In this respect, the scientific advice given by EMA as well as a medicine evaluation is not the product of two experts, but is a decision that is peer-reviewed by a group of over thirty experts who, all together, ultimately adopt the final opinion.

Separation of roles of experts involved in scientific advice and marketing authorisation application

It is essential for regulatory agencies to give the best possible advice and use the best available experts in evaluating medicines. The question, however, is whether that goal can be achieved whilst ensuring safeguards are in place that eliminate perceptions of bias to the greatest extent possible. In this context, the Ombudsman's inquiry is examining whether any further measures can be put in place that guarantee the independence of experts involved in scientific advice and/or medicine evaluation.

EMA is confident that the system is sufficiently safeguarded from any bias. EMA argues that further changes in the methods run a risk of suboptimal scientific advice being given or a suboptimal medicine evaluation.

Because of the collegial nature of the decisions in the committees, EMA's view is that the role of the rapporteurs in shaping the decisions taken in the CHMP should not be overstated. In EMA's view, the role and value of the rapporteur and co-rapporteur in the final vote is the same as any other member of the CHMP.

EMA further pointed to the different nature of scientific advice and MAA evaluation. They are fundamentally two different concepts:

· the focus of scientific advice is on methodology and study design to obtain rigorous data that can support regulatory decision-making (i.e. how best to generate the evidence which demonstrates if the medicine works);

· the focus of the evaluation for MAA is to look at these results, independently of the advice previously given, and determine whether quality, safety and efficacy has been adequately demonstrated or not.

EMA provides scientific advice to medicine developers on the understanding that the advice is not binding, either on the medicine developer, or on EMA. During an MAA, primary assessments of the data provided are carried out. If a MAA is submitted which is in line with scientific advice given by EMA at an early stage, it will be rejected by the CHMP if, in the meantime, that advice has become outdated because of scientific developments that change the understanding of the disease. Importantly, the data submitted in MAA is considered in a wider context during the CHMP evaluation, where factors other than those that were covered by the scientific advice might come into play.

Regarding the separation of roles of experts involved in scientific advice and marketing authorisation, EMA provided some numbers to substantiate the discussion. In 2018, EMA issued 84 positive and five negative opinions on MAAs. Of these, two thirds received scientific advice before the MAA was submitted; on average, products received scientific advice (with changing coordinators) 2.5-3 times during development. In around ten percent of cases, one of the rapporteurs was involved in giving scientific advice. EMA stated that there was no case whereby both rapporteurs evaluating the MAA were involved as coordinators of all the scientific advice given on the same medicine development. [4]

Transparency of pre-submission activities

It is an absolute priority for EMA to reinforce its role as a trusted regulator. EMA aims to be a reference authority globally in terms of transparency and public outreach. EMA sees possibilities for improvement in the way it explains its decision-making to the public and how its various procedures differ in nature.

EMA has taken various steps to inform stakeholders about how it works. An example is the recently published EMA brochure ‘From laboratory to patient: the journey of a centrally authorised medicine’ [5] , informing the public about the procedures in place in relation to the authorisation of medicines. Other audio-visual informative publications are being prepared. A suggestion that EMA intends to take away from the Ombudsman’s consultation is not only to explain the safeguards in place, but also to justify better certain decisions it takes in selecting experts, for example to explain the necessity of experts having a role in both the scientific advice procedure and the evaluation of a MAA on the same medicine.

EMA has also recognised the need for more transparency as regards the pre-submission activities that take place prior to an MAA, and has started to include a list of subjects that were covered in scientific advice in the European Public Assessment Report (EPAR). The inquiry

team welcomed this step, and noted that publishing all documents, where necessary with redactions, could inform the public even more and limit the need for requests for public access to be made. EMA furthermore underlined that after marketing authorisation, the regular access to documents regime applies to documents held by EMA.

The inquiry team raised the possibility of making public the names of the coordinators involved in the scientific advice procedure. EMA noted the difficulty of publishing the names of experts involved in scientific advice, bearing in mind the General Data Protection Regulation, which has renewed the focus on protecting names. In general, EMA sees no problem in publishing the names of the coordinators involved in scientific advice, although it can be sensitive when the advice concerns a controversial area, such as non-clinical testing. EMA questioned whether publishing the names of EMA staff would be in the public's interest, and emphasised that, as for all its activities, it has a duty to protect its staff. EMA noted that the relevance of publishing names could be limited as the marketing authorisation might take place years after the scientific advice has been provided.

The PRIME scheme

EMA explained that the priority medicines scheme (PRIME) is a framework under which EMA identifies products from which society could benefit greatly. The development leading up to the MAA is carried out as smoothly as possible. The aim is to give the medicine the best possible chance to make it through to the MAA stage. One aspect is, for example, that a rapporteur is designated several years before what would be the case in a normal MAA.

The PRIME scheme is used in exceptional cases [6] , for medicines that target conditions for which there are no satisfactory treatments and that have shown promising initial results. This scheme is open to all medicine developers. One in two medicines accepted on the scheme so far are being developed by small- or medium-sized enterprises or academia, who are the main originators of innovative medicines but run a risk of not getting their product through marketing authorisation due to limited resources and lack of knowledge of the regulatory framework.

EMA noted that although a rapporteur is appointed early in the process, this does not mean that this rapporteur will also be appointed as coordinator in any scientific advice given to the developer. A key element of having the rapporteur involved early on is to provide guidance in working with assessment bodies to optimise and build knowledge ahead of the MAA. When asked whether the increased cooperation does not create too close of a link, EMA noted that all the normal guarantees remain in place. The difference is that the process is geared towards acceleration of the process leading to the medicine evaluation.

EMA noted that the safeguards it had referred to during the meeting are applied to the PRIME scheme as well.

3. Follow-up

EMA agreed that it would provide the Ombudsman with more information in writing after the

meeting [7] . This information includes:

· examples of EPARs with additional information on scientific advice,

· an analysis of possible overlap in the roles of SAWP coordinators and CHMP rapporteurs,

· examples of diverging opinions between the CHMP rapporteurs.

The inquiry team thanked EMA for their time and for receiving them to EMA's premises.

Fergal Ó REGAN, Head of Coordination of Public Interest Inquiries

Koen ROOVERS Case Handler, Strategic Inquiries

Brussels, 26/6/2019

[1] For the Ombudsman's letter opening the inquiry, see: https://www.ombudsman.europa.eu/en/cases/correspondence.faces/en/81555/html.bookmark

[2] For a report of this meeting, see: https://www.ombudsman.europa.eu/en/correspondence/en/87563

[3] Article 4(8) of the European Ombudsman's Implementing Provisions.

[4] These data were corroborated with the same analysis of MAA outcomes in 2017 and provided after the meeting (see "Follow-up").

[5] See: https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf [Link].

[6] Designation in the PRIME scheme does not automatically lead to medicine evaluation. Of the four products in PRIME since its inception, only one made it to market authorisation under an accelerated timetable. Two appeared too complex and were referred to the normal MAA timetable, and one withdrew.

[7] This was provided on 11 June 2019.