Report on the meeting with the European Medicines Agency in the European Ombudsman inquiry into pre-submission activities organised by the Agency (OI/7/2017/KR)

Correspondence - 19/12/2017
Case OI/7/2017/KR - **Opened on** 17/07/2017 - **Decision on** 17/07/2019 - **Institution concerned** European Medicines Agency (No further inquiries justified) |

Institution or body concerned: European Medicines Agency

Date and time: 28 September 2017, 8:30-11:00, 11:15 - 12:30

Location: 30 Churchill Place, Canary Wharf, London

The European Ombudsman represented by:
- Mr Fergal Ó Regan, Head of Coordination of Public Interest Inquiries;
- Mr Koen Roovers, Case Handler, Strategic Inquiries Unit.

The European Medicines Agency represented by:
- Stefano Marino, Head of Legal Department;
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- Michael Berntgen, Head of Product Development Scientific Support Department, Human Medicines Research and Development Support Division;
- Jordi Llinares, Head of Scientific and Regulatory Management;
- Tony Humphreys, Head of Division Regulatory Science Strategy.

List of acronyms

ATMP

CHMP

COMP

EEA

EFTA

EMA

EPAR

MAA

PDCO

PIP

PRIME

SAWP

Advanced Therapies Medicinal Products

Committee for Medicinal Products for Human Use

Committee for Orphan Medicinal Products

European Economic Area

European Free Trade Association

European Medicines Agency

European public assessment report

Marketing Authorisation Application

Paediatric Committee

Paediatric Investigation Plan

PRIority MEdicines

Scientific Advice Working Party

1. Introduction and procedural aspects

On 17 July 2017, the European Ombudsman opened an inquiry OI/7/2017/KR) into the arrangements that the European Medicines Agency (EMA) has in place for engaging with individual medicine developers before the Agency receives applications for marketing authorisations from them ('pre-submission activities').

In her opening letter, the Ombudsman made it clear she is aware that, in so far as pre-submission activities help the development and availability of high-quality, effective and acceptably safe medicines, they benefit patients and serve the public interest. [1]

The Ombudsman cautioned, however, that pre-submission activities may pose some risks.

For example, there is a risk that the eventual decisions by EMA on the authorisation of medicines may be influenced - or be reasonably perceived to be influenced - by what has been discussed during the meetings with medicine developers prior to receiving their formal submission for evaluation.

The Ombudsman feels these risks need to be managed carefully, and that one way of doing this is by ensuring that the process is sufficiently transparent.

In order to learn more about EMA's approach to pre-submission activities, the Ombudsman proposed a meeting. In his reply to the Ombudsman's opening letter, EMA's Executive Director, Guido Rasi, welcomed any opportunity to further clarify and foster public trust in the arrangements that are in place for early engagement with individual medicine developers before they apply for marketing authorisation. [2]

In relation to this inquiry, Mr Rasi pointed out that it would potentially be wide-ranging in scope. He also stated that EMA faces exceptional circumstances in light of its pending relocation due to the United Kingdom's withdrawal from the EU.

The Ombudsman carries out inquiries where she sees grounds to do so, as in this case. In conducting these inquiries, she aims to insure that the impact on the subject of the inquiry (EMA in this case) is proportionate. To this end, the questions in the opening letter that involve statistical analysis were discussed at the meeting. EMA indicated that producing overviews, along the lines suggested in the opening letter, would require significant resources. To accommodate this concern, the Ombudsman agreed to look at other sources with statistical information, such as EMA's Annual Reports.

The meeting that is described in this report allowed the Ombudsman and EMA to discuss the Ombudsman's opening letter and EMA's reply. The questions in annex I were proposed by the Ombudsman to serve as the basis for the meeting. However, the discussion that took place was more thematic in nature.

As a next step, the Ombudsman is considering holding a targeted public consultation in this complex subject matter. This consultation would seek responses from the numerous organisations - from the private, non-profit and academic sectors - that have expressed an interest in contributing to this inquiry.
2. Exchange of views and clarifications provided by the European Medicines Agency

As regards the purpose of the meeting

At the start, Ombudsman staff set out the thinking behind the inquiry. It is understood that different types of pre-submission activities are organised with an aim to:
- help patients with timely access to new, safe and effective medicines, especially in areas where no treatments are available;
- minimise the risks of exposing patients to useless or less useful clinical trials, and maximise the value of the data that clinical trials generate, by ensuring these trials are appropriately designed;

- help smaller and newer medicine developers and academia by explaining the applicable regulatory framework and options open to them;
- raise awareness of the data requirements of different parties involved in the approval process, and thereby allow medicine developers to take these into account from the start, preventing delays at a later stage; and
- minimise the administrative burden on both medicine developers and the Agency by avoiding misunderstandings in the assessment process.

The Ombudsman is not in any way questioning the *existence* of pre-submission activities (for an overview, see annex II) that are geared towards these objectives. On the contrary, to the extent that they achieve the goals outlined above, they are encouraged. It is *the way* in which they happen that needs to be carefully considered.

Two issues merit specific attention for the Ombudsman at this stage:

i. the level of transparency around pre-submission activities (it should be clear what has happened before a medicine developer submits an application); and

ii. the extent to which EMA ensures there is a separation between those persons responsible for activities that happen prior to submission of applications, including activities such as providing information and advice, and the persons responsible for the subsequent evaluation of medicine developers' applications. Such a separation between stages in a regulatory process is often referred to as a 'firewall'.

As regards the second issue, a firewall in this context could be understood as a mechanism that allows decision-makers to look at an application with fresh eyes once it has been submitted. Generally this would exclude them from any of the preparatory steps taken to get to the point of submission. This would avoid any risk of bias, or the perception - from the point of view of the public - thereof.

With her inquiry, the Ombudsman wants to make sure that the necessary safeguards are in place, so that a fully independent assessment of the facts is made after an application has been submitted.

As regards the environment in which EMA operates

EMA staff described the environment in which they operate in broad terms. To date, EMA has authorised approximately 1,000 products. EMA receives between 500 and 600 requests for scientific advice each year. Pharmaceutical products and their development process is generally complex. There is a lot of diversity and some uncertainty as to such development planning.

The development of new medicines is a global activity and, as such, EMA is being compared in its operations - its procedures and their efficacy - to the operations of regulators in other major markets, for example the US Food and Drug Administration and Japan's

Pharmaceuticals and Medical Devices Agency.

Based on such comparisons, EMA is of the opinion that pre-submission activities of regulatory bodies must be appreciated in a global context. EMA also believes that it is leading example in terms of its transparency and publication policy, which covers clinical data, scientific information concerning medicinal products and information related to its internal decision-making process, including agendas and minutes of committee meetings and declarations of interests of experts with whom EMA works.

EMA sees its decision-making process as robust, based on the independence of assessors involved, the strict conflict of interest management of experts, the collegial adoption of scientific opinions, the multiple scientific committee involvement in evaluations and peer review process applied to the Agency assessments. Given the collegial nature of the activities of scientific committees, no one individual has a final say on a medicine's approval. [3]

As regards the subject matter of the Ombudsman's inquiry

It is important to distinguish between 'pre-submission activities' in general, and 'pre-submission meetings' specifically. Pre-submission **activities** cover a range of possibilities for interaction between EMA and medicine developers in the development phase of a medicinal product. This could relate to opportunities for medicine developers to obtain procedural advice and guidance for developing their medicine from EMA.

Pre-submission meetings concern interactions with medicine developers, often in-person. These meetings look at the regulatory and scientific completeness of the submission package to allow for later assessment. In our discussion, EMA described such meetings as 'procedural, preparatory meetings'.

The Ombudsman's inquiry is aimed at the first category, which covers the full range of meetings and procedures that facilitate interaction between medicine developers and EMA during the development phase, prior to the assessment of a medicine developer's application for marketing authorisation. [4]

A general question the Ombudsman's team asked in relation to pre-submission activities concerned how EMA assesses if an activity requested by a medicine developer is likely to facilitate the achievement of EMA's own objectives and thus serve the public interest. For example, whether a question posed by a medicine developer for a pre-submission meeting is not addressed by existing guidance documentation. EMA answered that it does not distinguish between requests, as this could lead to discriminating between medicine developers; however if general guidance applies than this is being referred to during the review. Furthermore, it was noted that some pre-submission activities are compulsory.

The procedures that are in place for veterinary medicines were described by EMA as very similar to those that concern human medicines. The Ombudsman is interested in the way in

which EMA's procedures for pre-submission activities are designed, also in terms of the risks they might pose. This is important both for human and veterinary medicines.

As regards the legal basis of pre-submission activities

Pre-submission activities are based on EU legislation. EMA's Founding Regulation [5] sets out that EMA shall, among other things, fulfil the task of " *advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products* " (article 57 (1) n). The Founding Regulation also states that EMA shall " *adopt provisions for providing assistance to pharmaceutical companies* " (article 66).

It is also worth mentioning Recital 25 of the Founding Regulation, which relates to scientific advice. This states that: " *Scientific advice for future applicants seeking marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises, should be put in place* ".

The scientific advice EMA gives to a medicine developer generally relates to the appropriate tests and studies necessary for the development of a medicine. EMA stated that the scientific advice that it gives to medicine developers, concerns questions related to methodology, and not a pre-assessment of the results obtained during development. Scientific advice is provided in relation to an application for marketing authorisation. The methodological requirements that EMA adheres to evolve, and the standards may change as science evolves.

Medicine developers can request scientific advice from EMA at any stage of development of a medicine, whether the medicine is eligible for the centralised authorisation procedure [6] or not. [7]

In addition to this, there are explicit references to scientific advice in the applicable EU legislation on:
- orphan drug products [8] (which are designated medicines for rare diseases);
- paediatric medicine development [9] , which aims to ensure that the necessary information is obtained to support the authorisation of medicines for children (up to the age of 18), mainly through assessing the content of 'paediatric investigation plans' (PIPs), which determine the studies that medicine developers must carry out on the impacts on children when developing a medicine; and
- the classification of Advanced Therapies Medicinal Products (ATMP) [10] , which is aimed at establishing whether a medicine based on genes, cells or tissues, meets certain scientific criteria.

As regards the separation between interacting with medicine developers and evaluating their applications

EMA explained how the work in support of medicine development - through interactions

with medicine developers before evaluation activities (for example scientific advice) - is separated from the work in support of the later evaluation activities (for example in terms of the benefit/risk assessment and the 'labelling and standards'). EMA confirmed that the EMA staff involved at the pre-submission stage, and the EMA staff that assist the evaluation process belong to different EMA services.

In terms of interaction with medicine developers during the development stage, the different procedures for giving scientific advice are of importance. Of these, EMA identified the three main "opportunities" for medicine developers as being the procedures related to orphan drug products and paediatric medicine development, along with the procedure for scientific advice. [11]

The membership composition of the scientific committees that lead these procedures - respectively the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), and the Scientific Advice Working Party (SAWP) - is prescribed by EU legislation. In turn, they consist of:

COMP - one member nominated by each EU Member State, one member appointed by each of the European Economic Area (EEA)-European Free Trade Association (EFTA) states, three members nominated by the European Commission to represent patients' organisations, three members nominated by the Commission on the basis of a recommendation from the Agency, and a Chairperson. COMP members are appointed for a renewable three-year term.

PDCO - five members of the CHMP, appointed by the CHMP; one member appointed by each EU Member State whose national competent authority is not represented through the members appointed by the CHMP; three members who represent health professionals and three members who represent patient associations, all appointed by the Commission. [12] PDCO members serve on the committee for a renewable three-year term and have alternates, who substitute for members that are not available.

SAWP - Contrary to the scientific committees, the SAWP does not consist of representatives from the EU member states, but of members that are nominated based on their expertise. It consists of 24 members proposed and appointed by CHMP [13] and between one and three members nominated as representatives by each of the following committees: COMP, Committee for Advanced Therapies (CAT), PDCO and Pharmacovigilance Risk Assessment Committee (PRAC). SAWP members serve on the committee for a renewable three-year term and may have alternates.

Ombudsman staff asked whether the opinions of committee members with additional roles, such as of rapporteur and co-rapporteur [14] , or the peer reviewer, who provides a critique of the assessors, are given greater weight than those of other committee members. EMA answered that, generally, its scientific committees seek to work on a collective basis and are guided by collegiality, and not on individual performance. Differences of opinion between committee members, including with the rapporteur and the co-rapporteur, are not unheard of. **The Ombudsman's team expressed an interest in seeing documented cases of these types of differences of opinion, and EMA agreed to make this available** .

As regards what is published in terms of the various procedures that result in advice for medicine developers

During the meeting, the procedures related to orphan drug products, paediatric medicine development, and the procedure for scientific advice were given most attention, due to their prominence. Generally, the following information is published in relation to these procedures:

Orphan drug designation - The COMP discusses scientific elements on the rare diseases of interest and the data derived from the medicines development with a view to giving an opinion about requests for designation as an orphan medicine. Information regarding the adopted COMP opinions is published in the COMP's monthly reports. [15] Subsequently, the Commission takes the decision to designate orphan medicines. Such decisions are registered in the Community register of designated orphan medicinal products.

Paediatric medicine development - With the development plans, or 'paediatric investigation plans' (PIPs), PDCO aims to ensure that the necessary data is obtained through studies on the impacts on children, to support the authorisation of a medicine for children. EMA makes all opinions and decisions on PIPs public, after deletion of information of a commercially confidential nature.

Scientific advice - Following meetings of the CHMP, an overview of the number of final scientific advice or protocol assistance [16] letters adopted is published in the CHMP Monthly Report. This overview contains information regarding:
- broad details on the substance(s) concerned (including biological, chemical or other),
- the intended indication(s),
- the type of request (new request or follow-up), and
- the topic (pharmaceutical, non-clinical, clinical or significant benefit).

The content of the scientific advice or 'protocol assistance outcome' given by the CHMP for a medicinal product is considered confidential and will not be made public prior to, or during the assessment of, a submission of an MAA. Afterwards, it can be the subject of a request for access to documents under the EU's rules for public access to documents. [17]

The above procedures also allow for pre-submission meetings, prior to submitting the application to EMA. For the orphan drug designation procedure, the paediatric medicine development procedure and the scientific advice procedure, medicine developers are encouraged to request a pre-submission meeting particularly if they are not familiar with the process. This aims to ensure a smooth validation procedure, and subsequent procedure. Information on these technical pre-submission meetings is not pro-actively made public.

During the meeting, the Ombudsman's team asked to what extent pre-submission activities

could be reflected in greater detail in the European public assessment report (EPAR). EPARs are full scientific assessment reports of medicines that have been granted a central marketing authorisation and can therefore be marketed throughout the EU. [18] EPARs are prepared and published by EMA, and include details of the assessment as well as the complete clinical data of the medicine. EMA stated that the scope of EPARs includes all essential features of the scientific assessment that precede the marketing authorisation, in so far as they relate to the final results of the assessment and not the initial discussions. Where a medicine developer has requested scientific advice this will be indicated in the EPAR, but EPARs do not go into the content of such pre-submission activities.

The Ombudsman's team asked whether providing a detailed log on each of the pre-submission activities that have had relevance to the scientific assessment would help in terms of legitimising the final result, and allowing observers to better understand the way in which EMA conducts its work. The Ombudsman's team also asked if any diverging views expressed during the assessment could be mentioned in the EPAR. EMA noted that the EPAR already contains information in case scientific advice was obtained. **EMA said that it will reflect internally on additional transparency parameters it wishes to set for the EPAR.**

As regards the treatment of smaller and newer medicine developers

EMA has an office dedicated to assisting small and medium-sized enterprises (SMEs) by providing regulatory, financial and administrative assistance to smaller medicine developers. EMA maintains a Public SME Register with all the enterprises to which EMA has assigned SME status.

SME status is linked to EMA's fee incentives. For example, medicine developers with SME status get a 90% fee reduction for scientific advice for non-orphan medicinal products. Scientific advice for designated orphan medicinal products, paediatric medicine developments and medicines qualified through the PRIME scheme is free of charge. Fee incentives also apply to an MAA. [19]

The SME office offers SME briefing meetings, providing a platform for a medicine developer to discuss its planned regulatory strategy. EMA said the discussions that happen in such meeting aim to clarify the applicable regulatory framework, and are not scientific in nature.

Generally, SMEs are encouraged to approach the SME office to request a briefing meeting at any stage of their product development. Other ways in assisting smaller and newer medicine developers include the 'SME Info Days', and a dedicated SME user guide.

As regards mitigating the risk of the perception of bias

EMA sees its engagement with civil society groups - including patients and consumers' representatives - as an important measure for addressing the potential public perception of bias. EMA feels it has developed strong links with civil society groups and that input from patients, consumers and healthcare professionals are incorporated at various levels within EMA's organisational structure, including in the Management Board, in Scientific Committees, Working Parties and Scientific Advisory Groups. EMA also organises public hearings.

EMA also has a dedicated Patients and Consumers Working Party that meets 4 times a year, and is co-chaired by an EMA official and an elected civil society representative. The working party members review written information on medicines prepared by EMA, including precautionary statements and packaging of medicines, EPAR summaries and EMA's public safety communications. **During the meeting, the Ombudsman's inquiry team was given an article drafted by an EMA Management Board member who works for a European organisation that represents consumers, with an account of EMA's civil society engagement. [20]** Data for 2015 indicates that, out of 47 EPAR summaries reviewed by the Patients and Consumers Working Party, 33 were amended.

Brussels, 19/12/2017

Mr Fergal Ó Regan

Mr Koen Roovers

ANNEX I: Questions for the meeting with the European Medicines Agency in OI/7/2017/KR Concerning the overall framework that applies:

1. Which rules or regulations, including internal decisions, form the basis of EMA's current practice of organising pre-submission activities? Please provide copies (if available online, a link to the relevant page suffices).

2. When EMA receives a request for a pre-submission activity, how does it assess if the activity is likely to facilitate the achievement of EMA's own objectives and thus serve the public interest?

Regarding pre-submission activities themselves:

3. Please provide a list of key pre-submission activities EMA currently offers to medicine developers, briefly describing each activity and who, typically, participates in such pre-submission activities from EMA's side.

4. Please provide a statistical overview of pre-submission activities held from 2012-2016 with an indication of the type of pre-submission activity and the type of medicine developer involved (for example SMEs, large companies or applicants from the academic sector)? Please identify the 10 medicine developers EMA met with most frequently in the context of pre-submission activities during this period.

5. EMA's 'pre-authorisation procedural advice for users of the centralised procedure' [21] notes that medicine developers may meet with the relevant (co-)rapporteur [22] and assessment teams at the national level prior to submission. EMA further states that it wishes to stay informed about such activities. [23] Please provide a statistical overview of such activities from 2012-16 with an indication of the type of medicine developers that had such meetings (for example SMEs, large companies or applicants from the academic sector). Please identify the 10 medicine developers that (co-)rapporteurs met with most frequently in the context of pre-submission activities during this period.

6. Does EMA charge medicine developers to cover the costs of preparing for and attending pre-submission activities as well as the costs of any follow-up? If so, are there separate charging arrangements for first-timers, applicants from the academic sector, SMEs or large companies?

7. Does EMA allow persons (EMA staff, coordinators, rapporteurs and/or co-rapporteurs) to participate in pre-submission activities on a product if they will have a significant role in EMA's subsequent scientific evaluation and/or marketing authorisation procedure for the same product? If so, please explain for each relevant activity why EMA feels this is necessary and appropriate?

8. Does EMA take precautionary measures to ensure that information and views provided by EMA in the context of pre-submission activities do not constitute a pre-evaluation of data to support a marketing authorisation application? If so, could you please describe, for each relevant activity, these measures?

On the transparency of pre-submission activities:

9. There is no basic information publicly available on pre-submission activities organised by EMA, for example categorised in aggregate format about the type of pre-submission activity or the type of medicine developer. Would EMA be willing to publish this information? If not, could you please explain why not?

10. Does EMA publish the detailed minutes of pre-submission meetings, including the detailed advice provided in pre-submission activities, at any stage, for example as an integral part of the European public assessment report? If not, please explain why not?

On a general note, and not related solely to pre-submission activities:

11. Please describe the rules EMA has in place to govern contacts between, on the one hand, staff, coordinators and rapporteurs, and, on the other hand, medicine developers that apply for marketing authorisation?

ANNEX II: Pre-submission activities organised by the European Medicines Agency

[24]
Early development advice services

For a more detailed overview, please consult the Agency's Research and development webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001768.jsp&r

Scientific advice for human medicines

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&r

Paediatric development
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000603.jsp&r

Orphan drug designation
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001778.jsp&r

Innovation task force (ITF)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&r

PRIME scheme (PRIority MEdicines)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&r

Qualification of novel methodologies

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_00

Micro-, small- and medium-sized enterprises (SMEs) support

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&r

Adaptive pathways
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&r
support for advanced therapies med

Classification of ATMPs
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp&r

Certification procedure for ATMPs under development by SMEs

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&r

Interaction prior to marketing authorisation application

Pre-submission meeting (See section 2.9 of pre-authorisation guidance)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&m

[1] See: https://www.ombudsman.europa.eu/en/cases/correspondence.faces/en/81555/html.bookmark .

[2] See: https://www.ombudsman.europa.eu/en/cases/correspondence.faces/en/83875/html.bookmark .

[3] In carrying out its work, the CHMP is supported by the scientific evaluation and resources available to national marketing authorisations bodies.

[4] Some pre-submission activities - such as the scientific advice, paediatric medicine development and the 'orphan drug', which are medicines for rare diseases, designation procedures - can include pre-submission meetings (in other words procedural, preparatory meetings). A pre-submission meeting is also available to medicine developers that plan to submit a Marketing Authorisation Application (MAA). EMA's approach to all of these activities will be covered by the inquiry.

[5] Regulation (EC) No 726/2004 [..] laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004), p. 1–33.

[6] Medicine developers that successfully pass the centralised procedure are allowed to market the relevant medicine and make it available to patients and healthcare professionals, throughout the EU.

[7] EMA mentioned that 68% of initial clinical protocols are rejected, and that spotting these insufficiencies early on, allows further development to be improved.

[8] Regulation (EC) No 141/2000 on orphan medicinal products (OJ C 178, 29/07/2003), p. 2 - 8.

[9] Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending

Regulation (OJ L 378, 27.12.2006), p. 1–19.

[10] Regulation (EC) No 1394/2007 on advanced therapy medicinal products (OJ L 324, 10.12.2007), p. 121–137.

[11] The procedure on a classification of ATMPs, which also involves scientific advice, is an optional procedure. Applying for it is recommended before submission of a request for scientific advice, a Paediatric Investigation Plan evaluation, an orphan drug designation and a MAA.

[12] The Commission appoints these members on the basis of a public call for expressions of interest and after consulting the European Parliament.

[13] These members may be CHMP members or European experts from regulatory authorities or academia.

[14] A rapporteur, and if relevant a co-rapporteur, is appointed to coordinate and assess scientific evaluations that EMA carries out. Rapporteurs and co-rapporteurs are tasked to provide objective scientific opinions. For more information, see: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/1 .

[15] COMP opinions are published within a week of the end of the COMP meeting. See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_lis .

[16] Protocol assistance is the special form of scientific advice available for developers of designated orphan medicines for rare diseases. In addition to scientific advice, developers of orphan medicines can receive answers to questions relating to the criteria for authorisation of an orphan medicine.

[17] Regulation (EC) No 1049/2001 of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31.5.2001, p. 43–48.

[18] A central marketing authorisation is granted by the Commission following a CHMP assessment.

[19] See section 5.1.2 of the Explanatory note for fees payable to the European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/06/WC500228850.pdf .

[20] See: https://www.ncbi.nlm.nih.gov/books/NBK459045/

[21] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/1

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[22] A rapporteur, and if relevant a co-rapporteur, is appointed to coordinate and assess scientific evaluations that EMA carries out. Rapporteurs and co-rapporteurs are tasked to provide objective scientific opinions. For more information, see: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/1
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[23] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/1 , see page 48.

[24] As detailed in the annex of: https://www.ombudsman.europa.eu/en/cases/correspondence.faces/en/83875/html.bookmark
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