EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ms Emily O'Reilly
European Ombudsman
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29 August 2017
EMA/566402/2017
European Medicines Agency

Dear Ms O'Reilly,

Subject: Strategic inquiry into pre-submission activities organised by the European Medicines Agency (OI/7/2017/KR)

I would like to thank you for your letter of 11th July 2017 notifying the Agency of your decision to conduct an own-initiative strategic enquiry into the arrangements that are in place for early engagement with individual medicine developers before they apply for marketing authorisations applications.

I welcome any opportunity to further clarify and foster public trust on these important operations, which have contributed so positively to public health by helping to bring new, safe and effective medicines to patients and the public at large.

As a general principle, early interaction with developers and provision of scientific advice are well-established processes in medicines regulation not only in Europe but worldwide. While we acknowledge the need to avoid and manage any risk of bias, experience over the years shows that such risk can be managed by having in place the necessary safeguards and I can assure you that the Agency guarantees adequate implementation of such safeguards. These include a strong policy for managing conflict of interests, a rigorous and independent process for evaluation of medicines and an unparalleled level of transparency of the Agency's operations.

Furthermore, in order to manage any potential perception of bias, which you mention in your letter, it is important that patients and the public are properly informed and can understand the benefits that these processes bring. These benefits include:

- Helping to providing patients with the timely access that they rightly demand to new, safe and effective medicines, with specific focus on areas of unmet medical needs where no treatments are available.
- Protecting patients and maximising the value of their involvement by ensuring that the clinical trials in which they take part are appropriately designed to provide robust and useful data as part of an optimised development plan, enabling us to identify the risks and the benefits of new drugs sooner, and avoiding exposing patients to useless or less useful clinical trials.

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- Helping developers (especially newer and smaller companies as well as academia) understand regulatory requirements and select the most appropriate regulatory pathway, thus minimising the administrative burden and resulting in faster and more efficient procedures. PRIME is an example of a recent initiative in this direction.
- Increasingly, providing a platform to include other parties involved in the approval process, particularly HTA bodies and payers; through collaboration with EUnetHTA, for example, developers are aware at an early stage what kind of data these other bodies will require, so that their data requirements can be built into the development plan, preventing delays at later stage. Similarly, incorporating post-marketing data requirements into the development plan at an early stage allows more rapid acquisition of the safety and efficacy data needed once a medicine is on the market, improving the overall safety of patients taking new medicines.

The potential public perception of bias is a concern which the Agency has always taken extremely seriously. The Agency has strong links with civil society, embedded in its day-to-day functioning and its governing structure. EMA has been at the forefront in Europe in developing interactions with patients, consumers and healthcare professionals in a way that allows them to engage in the work of the Agency at all levels of its operations, from the Management Board, to fully participating in the scientific evaluation through its Scientific Committees, Working Parties and Scientific Advisory Groups. This engagement allows civil society and the public to contribute and gain understanding of the Agency's activities and how these serve public health.

In addition, the Agency has long embraced the fundamental principles of openness and transparency as laid down in EU law for public bodies, and has been at the forefront of transparency in medicines regulation by publishing minutes, agendas, declaration of interests of experts and a huge volume of scientific information concerning medicinal products. Most recently its clinical data publication policy has been welcomed by patients and NGO communities.

With regard to pre-submission-activities, EMA is fulfilling a legal obligation; these activities are required by and conducted in accordance with the legal framework establishing the Agency[1]. They exist in strict fulfilment of the Agency's primary public health priorities, namely to facilitate timely access by patients and healthcare professionals to promising innovative medicines whilst maintaining their quality and safety in use.

Early dialogue with medicine developers, scientific advice, protocol assistance and paediatric investigation planning optimise the medicine's development plan, provide methodological direction and discourage the production of irrelevant or substandard data. This increases the likelihood that a medicine will be developed in a way that generates the evidence we need to properly evaluate its benefits and risks. In addition, subsequent pre-submission interactions enable the assessors/experts/scientific secretariat who are to be involved in the evaluation to gain an overview of

[1] Article 57 (1) n of Regulation (EC) No 726/2004 (EMA's Founding Regulation) provides that EMA shall, among others, 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*". Recital 25 states, inter alia: "*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*". As per Article 66 of our Founding Regulation, one of EMA's tasks is to "*adopt provisions for providing assistance to pharmaceutical companies*". At present it is not clear whether the inquiry is only about pre-submission activities in the human medicines field or also in the veterinary medicines field. Article 79 of our Founding Regulation states: "*The Management Board shall, in the case of veterinary medicinal products which have limited markets, or in the case of veterinary medicinal products intended for diseases with a regional distribution, adopt the necessary measures to provide assistance to companies at the time of submission of their applications*". In addition, there is explicit reference to scientific advice in the orphans, paediatric, advanced therapies medicinal products legislation.

the product and its development so that their assessment can be performed more efficiently and minimise any unnecessary administrative delay.

Finally, as stated above, it is important to stress that the Agency has robust and rigorous assessment processes in place, which separate the advice function from the final decision. No single person has the final say on a medicine's approval. Our Committees issue scientific recommendations based on extensive peer-review and discussions amongst approximately 30 committee members. The assessment is also supported by a wide range of independent experts, including patients, from around the EU; all of these bring their knowledge, experience and views into the decision-making process. Upon the medicine's approval, details of the assessment together with the complete clinical data of the medicine are published on the EMA website, leading to the highest level of transparency ever seen worldwide for any medicines regulator.

For further reference, a comprehensive list of EMA pre-submission-activities, together with links to information available on the EMA website for each activity, is provided as an annex to this letter.

The proposed scope of your enquiry is extremely broad-ranging as 'pre-submission activities' touch upon all the major operational processes of the Agency. Some of the questions you are raising may find an initial answer in the various documents already published on our external website. Some others would instead require a careful analysis as to their scope and purpose. We anticipate that the preparation of detailed statistical overviews of pre-submission activities in the last 5 years would be a challenging exercise, potentially covering thousands of such exchanges.

As you well know, the Agency is facing an exceptional situation and will be extremely busy in the next 18-24 months in connection with its necessary relocation as a consequence of the decision of the UK to withdraw from the EU. To be able to prepare for the move and work on necessary operational changes, we have already had to free up staff by reducing or temporarily suspending certain, less essential tasks. It is obvious that we need to limit what we undertake and plan our activities with extreme care to ensure that the huge disruptions linked to Brexit, affecting both the Agency as a whole and our staff individually, do not have an adverse impact on public health.

With this in mind, we fully agree with your suggestion to have, as a first step, a meeting in the last week of September with your services so as to have an initial exchange on the concrete scope of your initiative and agree on a reasonable timeline for the provision of further information potentially helpful for your enquiry.

My secretariat will contact your services for the organisation of such meeting.

Many thanks once again for your attention to EMA activities.

Yours sincerely,

[Signature on File]

Guido Rasi
EMA Executive Director

Annex

Pre-submission activities organised by the European Medicines Agency

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&mid=WC0b01ac0580b18a3a	
Scientific advice for human medicines	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9
Paediatric development	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000603.jsp&mid=WC0b01ac058002d4ea
Orphan drug designation	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001778.jsp&mid=WC0b01ac0580b18c74
Innovation task force (ITF)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9
PRIME scheme (PRIority MEdicines)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439
Qualification of novel methodologies	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0
Micro-, small- and medium-sized enterprises (SMEs) support	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&mid=WC0b01ac05800240cc
Adaptive pathways	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
Additional support for advanced therapies medicinal products (ATMPs)	
Classification of ATMPs	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp&mid=WC0b01ac058007f4bc
Certification procedure for ATMPs under development by SMEs	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&mid=WC0b01ac058095e6d5
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&mid=WC0b01ac0580b18196#section2