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From: [redacted]
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To: EO-PresubmissionConsultation
Subject: Comments Ombudsman Inquiry on EMA pre-submission activities
Attachments: BfArM_Response to the EU ombudsman on EMA pre-submission acitivities_draft.docx

Dear Ms O'Reilly,

We would first like to thank you for the opportunity to comment on the European Ombudsman's inquiry OI/7/2017/KR on how the European Medicines Agency engages with medicine producers before they apply for marketing authorisations.
Please find enclosed our response to the Ombudsman Inquiry on EMA pre-submission activities.

Kind regards,
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Comments Ombudsman Inquiry on EMA pre-submission activities'

Response from the Federal Institute for Drugs and Medical Devices (BfArM), Germany

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?**

Medicines developers/sponsors can request scientific advice at any stage of development from either the EMA, its committees or national competent authorities.

Pre-submission activities cover the full range of meetings and procedures that facilitate interaction between medicine developers and the EMA (or national compentent authorities) during the development phase, prior to the assessment of a medicine developer's application for marketing authorisation. This spans facilitating early dialogue with medicine developers to consider scientific advice, protocol assistance and paediatric investigation planning to optimise the medicine's development plan, provide methodological direction and to ensure that the appropriate tests and studies are performed thereby discouraging the production/development of irrelevant or substandard data. In addition, subsequent pre-submission interactions enable those with technical regulatory expertise (assessors/experts/scientific secretariat) who are to be involved in the evaluation to gain an overview of the product and its development so that their assessment can be performed efficiently and minimise any unnecessary (administrative) delay.

In Germany, the national competent authorities - the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institut (PEI)) are obliged to provide advice according to Section 71c of the Administrative Procedure Act (VwVfG) in conjunction with Section 25 sentence 2 VwVfG. Under the existing legislation relating to the regulation of medicinal products there is an obligation on the EMA to provide support, too, including the provision of scientific advice, to future marketing authorisation applicants.

The primary purpose of such advice is to assist developers in getting safe and effective products of the appropriate quality to patients in a timely manner as well as to ensure that clinical studies are not conducted unnecessarily, and thus protecting citizens against clinical trials of low or even absent scientific value. This is achieved by facilitating, through the provision of advice, the generation of appropriate data to provide the necessary evidence for assessment procedures. Typically, applicants seek advice on approaches to comply with the safety and/or efficacy requirements in situations where guidance is either not available or the available guidance does not fully apply to the product in question.

Advice is also provided on the quality aspects involved in the development of a new medicine. In 2017, one in five scientific advice procedures involved patients. In almost every case (93 %), patients provided added value to the scientific advice. In more than one in four cases, the scientific advice recommended that the development plan should be modified to reflect patient advice [Stakeholder Engagement report 2017: Patients, consumers, healthcare professionals, academics and their organisations; https://www.ema.europa.eu/documents/report/stakeholder-engagement-report-2017_en.pdf].

Regulators are experts in regulatory guidelines and the interpretation of same. Scientific advice and broader pre-submission activities are key methodologies used to ensure that patients within Europe can have access to innovative medicines, which is particularly important where there is an unmet need or where there are few treatment options. It also ensures the highest standards of safety and public health protection remain the focus of the development programme and ensures this is not compromised through the efforts to provide timely access. The focus is on the approach to the development programme and not the evaluation of the data being generated, whether the results of the whole development program support positive benefit/risk evaluation or not.

We believe that there is no conflict between the same national competent authority (NCA) providing scientific advice and also acting as (Co-)Rapporteur for the MAA. The EMA sufficiently manages the distinctive roles of scientific advice experts and scientific evaluation experts by having two separate procedures in place to select individual experts from NCAs to conduct both tasks. This contribution is based on the expert's technical knowledge and qualifications, with support from additional experts in that competent authority. Scientific advice given is always institutional, not individual, and is subject to multiple layers of peer review. For scientific advice procedures the EMA appoints two coordinators to provide independent assessment in parallel and both assessment reports are discussed in an open forum at the Scientific Advice Working Party (SAWP) meeting at the EMA. These meetings occasionally involve patient representatives. The purpose of these meetings is to reach a consensus view on the assessments and the approaches that the coordinators have taken.
In the legislation for human medicines, the role of the different committees and groups are mandated or outlined:

- Pre-submission – Committee for Orphan Medicinal Products (COMP-with regards the orphan designation), Committee for Medicinal Products for Human Use (CHMP) and Scientific Advice Working Party (SAWP- Scientific advice protocol admissions), Paediatric Committee (PDCO -Paediatric Investigation Plans);
- Evaluation – CHMP, Pharmacovigilance Risk Assessment Committee (PRAC), Scientific Advisory Groups (SAG)

Similarly, for MAA assessments of centralised products, two Rapporteurs (a Rapp and Co-Rapp) from different NCAs from EU member states provide independent parallel assessments as well as a separate peer reviewer from a third member state. *All* member

states review the assessment reports for the purposes of providing further review and opinions. Outside of this, a separate independent assessment is conducted on the pharmacovigilance (safety monitoring) aspects of the dossier by the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur.

Furthermore, for any subsequent queries arising, a scientific advisory group (SAG) consisting of independent clinical and scientific experts can provide their views at a SAG meeting prior to the CHMP.

Conclusions on specific marketing authorisation applications are taken by Committee members with input from supporting experts: that is, decision making is not in the hands of those participating in pre-submission activities. Opinions are published on the EMA website and the basis for all decisions relating to a marketing authorisation application are clearly communicated in European public assessment reports (EPARs). In the EPAR the main details of a development program are made public e.g. for other innovators to follow.

The exclusion of experts from national competent authorities who provide scientific advice from subsequent EMA MAA evaluations may negatively impact on the quality of the assessment of the authorisation. It would be entirely inappropriate to exclude such assessors who provide advice from the assessment process. As it stands, the availability of expert resource is scarce. This is particularly the case for certain innovative products, where the pool of experts in the European network may be limited such that any restriction on experts from the network that can participate in EMA MAA assessment activities may have implications for the quality of the assessment of the product. In addition, it may cause unnecessary delays for complex applications to use a different NCA for the assessment of the product.

The question as phrased suggests that there is some conflict of interest in the NCA performing both the provision of SA and the assessment of the MAA. The robust processes in place for marketing authorisation assessment as described, involving separate independent assessments, peer review and committee based approaches, are designed to mitigate against any such risk. In summary, in no case one single person/NCA is responsible for any advice or decision made in respect of SA of a MAA.

In addition, both the BfArM and the EMA have procedures in place for submitting annual declarations of interest in order to identify potential conflicts of interest at an early stage, analyse them and take appropriate measures.

SA primarily is focused on optimised regulatory pathways and does not assess data supporting the authorisation of the product. Therefore, if an applicant follows the SA in generating data, that data must subsequently be subject to an independent review to consider whether it supports the authorisation. Scientific advice does not guarantee a marketing authorisation and this point is validated by the statistic which shows that 16 % of products which receive scientific advice receive a negative opinion when they seek a marketing authorization (MP Hofer, C Jakobsson, N Zafiropoulos, S Vamvakas, T Vetter, J Regnstrom, R J Hemmings: Nature Reviews Drug Discovery 14, 302–303,

2015). In addition, two out of three development programmes submitted for scientific advice were initially not suitable for a future assessment of the medicine's benefits and risks. Following scientific advice, 63 % of these trials were modified to include a better way to assess the medicine's effectiveness or selection of a more appropriate comparator.

For the reasons outlined the BfArM does not believe that there is a conflict and any risk from the pre-submission process is adequately mitigated against. On the contrary, we strongly consider it reasonable that most applications which intend to be authorised through the centralised route, should seek scientific advice through the EMA procedure.

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?**

   The exclusion of experts who provide scientific advice at national level from subsequent EMA evaluations may negatively impact on the quality of scientific advice. As outlined above, their contribution is based on the expert's independent technical knowledge and qualifications with support from additional experts in that competent authority. There are a number of subsequent additional balances in the process including the Rapp and Co-Rapp appointment and involvement of the relevant committees. In the case of certain innovative products, the pool of experts in the European network may be limited such that any restriction on experts from the network who can participate in EMA marketing authorisation application assessment activities may have implications for the quality of the scientific opinion. The provision of scientific advice by regulators is a well recognised and accepted way of ensuring innovators take into consideration the appropriate regulatory guidelines. In comparable authorities, such as the US FDA or PMDA in Japan, similar processes exist.

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?**

   The EMA already takes sufficient measures to ensure that pre-submission activities are non-binding. Applicants requesting scientific advice under Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, or protocol assistance under Article 6 of the Regulation on Orphan Medicinal Products (EC) 141/2000 must note that any scientific advice or protocol assistance given is not legally binding with regard to any future marketing authorisation application of the product concerned, either on the Agency/CHMP/COMP, or on the Applicant. In addition, while some data which will form part of the final application may be submitted as part of the SA query, the SA does not assess it as part of the application. The fact that the views transmitted in pre-submission activities are non-binding is clearly communicated. Furthermore, given the structure of the EU evaluation process, including member state scrutiny of rapporteur/co-rapporteur evaluations through the CHMP, PRAC and other committees, any views expressed in the pre-submission phase are reviewed by

multiple parties that were not directly engaged in providing this advice. Furthermore, decision-making within committees is generally collective and consensus based and therefore ensuring a system of checks and balance is in place.

The timing of the advisory procedure alone, which is usually long before the date of marketing authorisation application submission, cannot make the advice binding with regard to continuous scientific progress.

As noted above, the primary purpose of this type of engagement is to improve the quality of regulatory submissions which are then assessed for quality, safety and efficacy. The pre-submission activities focus on HOW the development program or part of it should be carried out, what kind of guidelines should be taken in to consideration, and what kind of specific studies (chemical-pharmaceutical, non-clinical and clinical) should be done. These activities do not pre-assess the authorisation, rather ensure that appropriate and robust data is submitted to enable the best assessment of the application. The assessment of marketing authorisation application focus on what are the results of those studies and if the results support a positive balance between the risks (e.g. adverse events) and therapeutic benefits and indicate efficacy.

4. ***a)*** **Is the way in which EMA engages with medicine developers in pre-submission activities sufficiently transparent?**

The BfArM considers that there is appropriate transparency throughout the regulatory process including pre-submission activities and SA. The EMA has a pre-authorisation guidance published to their website. Also published to the website is a guidance for applicants seeking scientific advice and protocol assistance which provides an overview of the procedure and preparation required by applicants.
All declarations and conflicts of interests are available in the public domain.

The commercially sensitive nature of discussions with industry limits the transparency of pre-submission interactions with individual applicant companies. In order for SA to take place, there must be sufficient balance between the need/call for transparency with applicant needs/expectation for confidentiality. It is likely that any move to publish SA opinions prior to product authorisation would impact on the uptake of SA, potentially stifling innovation as commercially confidential information would be available to the innovator's competitors. This will result in a negative impact on timely access to medicines.
Making commercial information available either before or after authorisation would significantly damage Europe's ability to attract new medicine and with the resulting impact on patient care. It is the BfArM´s view that ensuring the EU remains competitive for innovation is in the best interest of European patients.

b) **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 no need for further transparency regarding pre-submission activities; the appropriate balance between transparency and protecting confidentiality is being achieved. The authorities are updating guidelines as new questions emerge in pre-

submission interactions to add clarifications into existing guidelines or if needed, creating new ones.

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.

   BfArM considers the naming of individuals involved in SA unnecessary as the overall advice is issued from CHMP (or CVMP for human and veterinary medicines respectively). The advice has been concluded not only by the 2 named coordinators, and a peer reviewer for each Scientific Advice Working Party case, but also there may be a team working within both agencies also working on the advice. EMA also have input and in addition the advice is reviewed in advance by the SAWP. Therefore, there are many different layers of assessment, and a significant number of experts contributing to the report, which is finally endorsed by CHMP/CVMP.

   The EMA Committee's members and alternates list (including CHMP, CVMP, COMP, SAWP) is available on EMA website and conflicts of interest are published and assessed. National competent authorities are also obliged to review conflicts of interest of their delegated experts.

   The BfArM does not see any benefit of disclosing the questions posed in the SA as all commercial information would need to be removed and we would consider that what remains is unlikely to be meaningful and may raise more questions than it would answer. Especially at an early stage of development the fact that scientific advice from EMA/a national competent authority has been requested should be regarded as a trade secret, since knowledge of this fact could allow competitors to draw conclusions about the development status of a product.

   It must also be examined whether data protection concerns prevent the names from being published. The publication of expert names in scientifically very special areas in which only a few experts are available is problematic. In our experience, there is a high risk that these experts will refuse to cooperate on decisions taken when their names are being published and that it will then be difficult to find alternative experts.

   See also response to questions 4 above.

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

   This once again comes back to the issue of commercial sensitivity in relation to developing a new innovative medicinal product. BfArM considers that release of SA could not be done while legally maintaining data confidentiality. This question is also based on a presumption that advice for one product may be appropriate for another. General scientific guidelines for drug development are produced by the CHMP, and

these summarise advices given at a high level or describe other areas identified as requiring general scientific advice.

It should be noted that SA is open to all medicines developers, with substantial financial incentives for SMEs and those developing products for certain niche markets. Medicine developers are unlikely to want to share their development plans with other medicine developers which may impact on the uptake of SA. Furthermore, in our view the questions posed in scientific advice procedures have to be seen in context and in connection with the provided briefing material and considering increasing complexity of products/development programs, the answer to a question cannot always automatically be applied to similar questions for another product/development project.

As noted above, should there be frequent topics repeated during SA, this would lead to the development or update of guidelines to address issues arising.

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

The BfArM does not support limiting SA questions to issues not already addressed in clinical efficacy or safety guidelines as it is often through this type of process that complexities and gaps in guidance are identified. This is important for continually improving processes and guidelines to best serve stakeholders. There may be follow up situations where the company may need to clarify or deviate from guidance, with justification, due to the nature of the product and complexities in a specific patient population. In addition, there may be situations where EMA guidance does not fully capture the proposed approach of the product under development. In such cases, an applicant may need advice. The landscape is changing and the area of innovative medicines is forcing the regulatory system to adapt and evolve to guarantee preparedness. As regulators we are seeing increasing trends where products in the pipeline may not fit standard or traditional designs. Similarly, regulatory frameworks must adapt and evolve to serve rare diseases and smaller patient populations necessitating novel clinical trial designs, use of real world evidence and convergence of products/technology. Such complexities and innovation are driving us more towards flexible and adaptive approaches in light of increasing product complexity.

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

None. The BfArM supports the work the EMA has brought forward over the past number of years. It is considered that the European regulatory system lags behind other international counterparts in pre-submission supports and this may be negatively impacting European patients and their access to novel and innovative medicines and other healthcare products. We fully support the EMA in contributing to ensure 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. The EU must remain competitive and act in the best interests of patients and it is therefore imperative that the current EMA pre-submission work is supported and can continue to grow and evolve.

The BfArM agrees that there is a need to avoid and manage any risk of bias; our experience to date demonstrates that such risk can be managed by establishing and implementing appropriate safeguards, which we believe to be in place. Policy around conflicts of interest, a rigorous and independent medicines evaluation process, including the pre-submission aspects, and optimum transparency, support this risk management process. Through engagement with key stakeholders, particularly civil society groups, including patients and consumers' representatives, the EMA aims to address any potential public perception of bias. The mechanisms to receive input from patient representatives, consumers and healthcare professionals are incorporated at various levels within EMA's organisational structure, including in the EMA Management Board, in Scientific Committees, Working Parties, including the dedicated Patients and Consumers Working Party, and Scientific Advisory Groups.

Bonn, 10 January 2019