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Cc: [redacted]

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Dear Sir/Madam,

Please find attached EFPIA/Vaccines Europe/EBE/AESGP comments to Ombudsman Inquiry on EMA pre-submission activities.

Best regards,

Pär

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Pär Tellner
Director, Regulatory, Drug development and Manufacturing
EFPIA - European Federation of Pharmaceutical Industries and Associations
Leopold Plaza Building, Rue du Trône 108, B-1050 Bruxelles
Tel: +32(2)626[redacted] (Direct Line), Tel: +32.[redacted] (Mobile)
E-mail:[redacted]

Strategic inquiry into pre-submission activities organised by the European Medicines Agency (OI/7/2017/KR) - Response to EU Ombudsman

Preamble to Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 36 national associations and 40 leading pharmaceutical companies, EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy. Our vision is for a healthier future for Europe. A future based on prevention, innovation, access to new treatments and better outcomes for patients.

The European Biopharmaceutical Enterprises (EBE) represents the voice of biopharmaceutical companies of all sizes in Europe and is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). Established in 2000, EBE is recognised as the leading biopharmaceutical association in Europe. To learn more about EBE, visit www.ebe-biopharma.eu.

Vaccines Europe (VE), is a specialized vaccines group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), the professional association of the pharmaceutical industry in Europe.

AESGP, the Association of the European Self-Medication Industry, is the representation of manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe. It is composed of national associations and the main multinational companies manufacturing self-care products. AESGP is the voice of more than 2000 companies operating in the consumer healthcare sector in Europe, affiliated with AESGP directly or indirectly through the national associations.

In this response we wish to offer our view on the EU Ombudsman's strategic inquiry into pre-submission activities organized by European Medicines Agency.

Introduction

Innovative companies of all sizes are committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world. Fulfilling this mission requires leading-edge research methodologies and sophisticated development plans – both of which are informed through inputs from multiple stakeholders including regulators. European patients rely on medicines developers to successfully and rapidly bring forward new medicines to meet the unmet medical needs of patients. They also rely on Health Authorities to apply scientific excellence in the evaluation and supervision of medicines, for the benefit of the public in the European Union.

This is clearly noted in the European Ombudsman's inquiry to the EMA stating "(i)n so far as these (pre-submission) activities help the development and availability of high-quality, effective and acceptably safe medicines, they benefit patients and serve the public interest".

Pre-submission and pre-authorisation guidance, including scientific advice is an essential part of medicines development to manage the complex regulatory procedures. It allows to advance science and technology and ensure that the research programme answers the appropriate research question, that the appropriate development plan is finalised and studies are conducted minimizing the risks to patients. A clinical protocol that has been challenged and discussed before the conduct of the study minimizes risk to study participants, facilitates the medicine developer identifying the most significant endpoints to various stakeholders (e.g. patients, regulators and health technology assessment bodies,) and helps to avoid redundant trials being conducted. This ultimately enables generation of relevant data to enable

regulators to assess the benefit:risk balance once the marketing authorisation application has been submitted.

Moreover, we consider that regulators directly benefit from pre-submission and pre-authorisation interactions. These interactions inform and strengthen understanding of the development of a given product, but more broadly ensure that our European regulators have the opportunity to be aware of products coming through the pipelines at the forefront of technological and clinical state of the art practices for medicines, engaging with and shaping these trajectories. For example, CAR-T cell based medicines, use of Real-World Evidence, continuous manufacturing and platform trials are all new paradigms which require close collaboration and collective learning, best achieved in the pre-submission space.

In particular for small innovative companies, including SMEs, who develop medicinal products at the forefront of medical science it is important to be guided by scientific advice and pre-submission dialogues as they have limited resources and due, to the smaller teams, limited access to regulatory experience.

Scientific advice and pre-submission dialogues are also instrumental to companies in need of additional guidance when seeking to change the legal status of a medicinal product (from prescription to non-prescription) in an innovative self-care indication notably in order to address unmet self-care needs.

Conversely, preventing this early scientific dialogue which is also a standard practice in other regions of the world - and which is distinct and separate from the evaluation process - would result in delays for patients and unnecessary costs and development work rather than acceleration of breakthrough medicines and technologies. Various pre-submission activities are a well-established process in other non-EU medicines agencies, including Swissmedic[1,2] (Switzerland), U.S. Food and Drug Administration[3] (USA), Health Canada[4], Therapeutic Goods Administration[5] (Australia) and Pharmaceutical and Medical Devices Agency[6] (Japan).

<u>None</u> of these presubmission interactions can make a poor medicine into a good medicine, suitable for approval. In other words, early dialogue and scientific advice can ensure that trials are designed to provide the data necessary for an application; but these early interactions cannot guarantee success. The full evidence of the benefits and risks of a medicine will be provided to the regulators and shared publicly through EMA publications.

[1]https://www.swissmedic.ch/dam/swissmedic/en/dokumente/stab/networking/scientific_advicemeetingsmaghpprocedure.pdf.download.pdf/scientific_advicemeetingsmaghpprocedure.pdf

[2]https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl/zl105_00_001d_wlfirmenmeetingsimzulassungsverfahrenimbereichzl.pdf.download.pdf/ZL105_00_001e_WL Guidance document Meetings for applicants held with the Authorisation sector.pdf

[3] https://www.fda.gov/downloads/drugs/guidances/ucm079744.pdf

[4] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html#a5.1

[5] https://www.tga.gov.au/publication/pre-submission-meetings-tga

[6] https://www.pmda.go.jp/english/review-services/consultations/0002.html

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?

It is not a matter of concern for the reasons stated above. The focus of scientific advice is on clarifying requirements and advising on study designs and not on pre-evaluating the results of such studies.

For the benefit of patients in the EU, it is essential that the people with the right scientific expertise, be they in regulatory agencies or within medicines developers, are available to provide their advice and guidance on how best to develop new innovative products, without undue risk or unnecessary exposure of patients, while ensuring that the evidence generated during the development phases is of the best quality to support the timely availability of new therapies.

For all developers of innovative medicines, pre-submission and pre-authorisation guidance, including scientific advice, given by a regulatory authority are an essential part of drug development to ensure that medicinal products are developed in such a manner to enable them to meet the stringent health authority requirements and to ensure the developers are able to deliver effective, safe and high-quality medicines to patients.

By having the right expertise present during all the development phases and at the time of scientific evaluation and/or marketing authorisation, European patients can rely on medicines developers to successfully and rapidly bring forward medicines to meet the unmet medical needs of patients.

We strongly believe the involvement of the same regulator staff and experts in presubmission and subsequent activities is not a matter of concern since appropriate safeguards are in place in the European Medicines Agency, including a strict policy on managing conflicts of interest and separation between advice and evaluation, as well as a high level of transparency of the Agency's operations. For example, there is no single expert or group of experts that would be solely involved in the interaction and decision-making process for a medicine as it proceeds from pre-submission activities through the application process.

While the assessment reports from the rapporteur and the co-rapporteur are of course essential, the CHMP Opinion is subject to a voting process involving all Member States (incl. a possibility to review dossier assessment and a possibility to express divergent positions), which provides additional guarantees for an appropriate decision-making process. This collective review process serves to protect against any potential conflict of interest.

Nevertheless, we agree that any assumption of bias by the public in these processes can be unhelpful, both for the Agency and the medicines developers. If such a public perception exists or arises, EMA might need to re-emphasise the importance of scientific advice and the relevant controls they have in place.

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?

Considering the collective review process as well as policies and procedures to manage conflict of interest that offer protection against potential bias, there are no reasons to why experts from national authorities that have been involved in national scientific advice should not subsequently be involved in the scientific evaluation of the same medicine. On the contrary, using the same expertise at both stages should be encouraged as it can lead to efficiencies.

Expertise from national authorities is crucial when they are specialized in certain disease areas and their teams are called upon in the evaluation either through Rapporteurship or through multi-national teams.

Following the increasing number of submissions (a positive trend) and as the new therapies and development programs become increasingly complex (either due to fast evolving science, the regulatory environment or rare diseases), it becomes challenging to find and develop experts with the right level of expertise. Multi-national teams are one avenue to address the need for very specialised expertise.

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 current measures taken by EMA are in our view sufficient and ensure that pre-submission dialogue is not implicitly or explicitly perceived as "binding" or regarded as a "pre-evaluation" of consequent applications for marketing authorisations:

- *The description of Scientific Advice (SA) on the EMA webpage clearly states "Scientific advice received from the Agency is not legally binding on the Agency or on the medicine developer with regard to any future marketing-authorisation applications for the medicine concerned"[7]. This is a noticeable reminder of a principle of SA. Additionally, as referenced on the webpage, SA is offered as an optional opportunity for a company to seek essential input on key research questions and the overall merits of its development plans.*
- *Scientific advice meetings are introduced by the chair with a reminder to all participants that the comments are considered as non-binding.*
- *Regarding data, the rules of procedure for the Scientific Advice provided by the CHMP[8] SA working party clearly state in point 31 that "The SAWP shall not be responsible for pre-assessment of data that will be used to support future marketing authorisation applications". The SA does not pre-evaluate the data but offers input on the overall development package and its completeness to support the assessment of the benefit risk balance of a product by the time of the marketing authorisation. From a timing point of view, it is materially not feasible to have confirmatory data to share with the regulators during the pre-submission interactions.*
- *Medicine developers can request scientific advice from the EMA at any stage of development of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not. Thus, scientific advice is not necessarily associated with a subsequent centralised authorisation procedure.*

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?

We strongly believe that the way in which EMA engages with medicine developers in pre-submission activities is sufficiently transparent. They are well described in detailed guidance on the Agency website. When a developer has engaged with the EMA and once the authorisation process is complete for the product on which early advice was sought, the details of this early engagement can be disclosed:

[7] Scientific advice and protocol assistance. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance [Accessed 19 October 2018].
[8] Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP) https://www.ema.europa.eu/documents/other/mandate-objectives-rules-procedure-scientific-advice-working-party-sawp_en.pdf

- *Elements of any SA given might be discussed in European Public Assessment Reports (EPARs) and/or in Module 2 documents published under the European Medicines Agency policy[9] on the publication of clinical data for medicinal products for human use (so-called policy 0070)*
- *Third parties can request access to such SA through European Medicines Agency policy[10] on access to documents (so-called POLICY/0043) and these documents can be released*

As stated earlier in this response, given that the development of medicines is a rapidly advancing field with a high level of innovation (e.g. cell and gene therapies and novel drug device combinations), reflecting advances in science and technology, it is sometimes necessary for medicine developers to meet with regulators to discuss and seek SA on various aspects of their plans for studying the efficacy and safety of a medicine; these [early] dialogues also provide an opportunity to engage other stakeholders e.g. health technology assessment bodies and patients' organisation representatives during the development process.

These SA meetings between an individual medicine developer and the Agency do not require further publicising or transparency. These discussions often deal with very specific technical product-related issues that pertain to the medicine being developed. Where recurring topics are discussed which could impact more generally on the development of a medicine in a specific disease area, there is the opportunity for the Agency to develop or revise publicly available scientific guidance documents to reflect these topics. Furthermore the existing rules on Clinical Trials data sharing guarantee that detailed information about study design and results are made publicly available.

Transparency of EMA activities must always be balanced and, in particular, as per Regulation 1049/2001, the Agency should not disclose information where 'disclosure would undermine the protection of commercial interests of a natural or legal person, including intellectual property' [Article 4(2)]. Pre-submission activities generally take place at an early stage in the development process where disclosure of the detail of the interactions between applicants and EMA could greatly undermine the intellectual property and commercial interests of companies. This may have the consequence that companies avoid seeking advice within Europe, and that drug development standards from other regulatory jurisdictions are applied instead. This would not be in the best interest of European patients.

In that regard it is important to note that various pre-submission activities with comparable levels of transparency are a well-established process in other non-EU medicines agencies, including Swissmedic[11,12] (Switzerland), U.S. Food and Drug Administration[13] (USA), Health Canada[14], Therapeutic Goods Administration[15] (Australia) and Pharmaceutical and Medical Devices Agency[16] (Japan).

[9] (EMA/240810/2013) European Medicines Agency policy on publication of clinical data for medicinal products for human use: https://www.ema.europa.eu/documents/other/european-medicines-agency-policy-publication-clinical-data-medicinal-products-human-use_en.pdf

[10] (EMA/729522/2016) European Medicines Agency policy on access to documents: https://www.ema.europa.eu/documents/other/policy/0043-european-medicines-agency-policy-access-documents_en.pdf

[11]https://www.swissmedic.ch/dam/swissmedic/en/dokumente/stab/networking/scientific_advicemeetingsmaghpprocedure.pdf.download.pdf/scientific_advicemeetingsmaghpprocedure.pdf

[12]https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl/zl105_00_001d_wlfirmenmeetingsimzulassungsverfahrenimbereichzl.pdf.download.pdf/ZL105_00_001e_WL Guidance document Meetings for applicants held with the Authorisation sector.pdf

[13] https://www.fda.gov/downloads/drugs/guidances/ucm079744.pdf

[14] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html#a5.1

[15] https://www.tga.gov.au/publication/pre-submission-meetings-tga

[16] https://www.pmda.go.jp/english/review-services/consultations/0002.html

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.

Scientific advice details, pertaining to the scientific discussion, are disclosed once a medicine is approved. This is relevant and appropriate.

- *Disclosing the names of the officials and experts involved in the procedures*

  The disclosure of names of experts/officials involved in specific pre-submission procedures would not be useful given the already high level of transparency that exists in the system (searchable list of experts on the EMA website) and the presence of sufficient other safeguards i.e. conflict of interest. We consider that the current approach of involving experts during the pre-submission stage to provide scientific and technical expertise, and then conducting the assessment at a committee level, where the names, details and curriculum vitae of all committee members are available is appropriate. This reflects the high level of transparency already present in the EU system e.g. the Rapporteurs and Co-Rapporteurs for a particular application are published and the details of all Committee members and Experts (names and curriculum vitae) are also available on EMA.

- *Disclosing the questions posed in scientific advice procedures; and/or*
- *made public comprehensive information on the advice given.*

  It would not be useful to:

  - *Disclose the questions posed, as these are directly about the development plans of the Applicant and are recognized appropriately as commercially confidential by EMA. If disclosed prior to approval of the medicine under consideration, developers would be deterred from seeking Scientific Advice from EMA which would be detrimental to patients.*
  - *Make the advice public, as this would give other developers, including those outside the EU, a blue print for developing a potentially similar product, therefore removing incentive for the medicines developers, including pharmaceutical industry, to engage with EMA.*

If more transparency is introduced, pre-authorisation, this should be limited to the publication of aggregated and general data on themes and topics explored in SA meetings and followed up in scientific workshops.

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

Scientific advice details, pertaining to the scientific discussion, are disclosed once a medicine is approved. This is relevant and appropriate.

We consider there are mainly disadvantages of making scientific advice, given to one medicine developer, available to all medicines developers. The considerations include:

- *SA involves detailed and targeted discussions around the clinical development programme for investigational compounds, and hence often includes commercially sensitive confidential information.*
- *Key information about the quality, non-clinical and clinical development for a molecule would be given away if scientific advice given to one medicine developer would be made available for other developers. Consequently, this could serve as a blueprint or serve as a competitive advantage for*

competitors and clearly put Europe in a disadvantage compared with other regions where such transparency measures are not in place.

- *In addition, as per our response to question 4, disclosing the details of the advice would greatly undermine the protection of commercial interests.*

However, the incorporation of developments and learnings from multiple SAs into consolidated feedback, through the mechanism of guidance documents is a much more effective way of ensuring advances in thinking are communicated. As stated earlier, we consider that the transparent mechanism for issuing revisions or new guidance, together with the opportunity for discussion in public forums is the optimal approach that could be potentially optimised further.

Guidance based on collective experience is welcomed and is effective, as also exemplified by Innovative Medicines Initiative (IMI) and its opportunity to work together in a precompetitive space, but disclosure of identifiable development programmes is to be avoided.

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

We believe that the EMA should not be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines.

Published guidance provides a framework for scientific advice discussions, and the outcome of SA is the meeting point between the reality of product development and what would be expected by the regulators in an ideal situation (often envisaged through a guideline) for several reasons:

- *EMA scientific guidelines represent a harmonised Community position, which if followed by relevant parties will facilitate regulatory assessment. Nevertheless, given the complexity of drug development, and fast-evolving scientific environment, alternative approaches may be taken in specific situations provided that these are appropriately justified. Advances in science and techniques may also be available that were not foreseen by the guidance. An important benefit of scientific advice is therefore to allow proactive discussions between regulators and medicine developers of proposed deviations from guidelines and their potential regulatory acceptability given the specific characteristics of the compound. Limiting provision of scientific advice to questions not already addressed in EMA guidelines would prevent these important discussions leading to potential inefficiencies in drug development.*
- *Specifically, the EMA guidance on SA recognises the need for this: "Scientific advice may be given on issues relating to interpretation and implementation of (draft) EU guidelines."*
    - *As an example, the Advanced Therapy Medicinal Products (ATMPs) (eg. CAR-T cell based therapies) regulatory guidance is being developed alongside the evaluation of relevant technologies as all regulatory challenges cannot be anticipated.*
- *In addition, guidelines are developed based on the state of art at the time of their writing, and therefore there might be areas of advice from the guideline which may no longer be relevant. Indeed, during SA, a stakeholder discussion might not only identify gaps in the guideline, but also highlight changes in medical practice and/or State of Art (e.g. imaging tools) that may require an update of the guideline. As partially covered above, a written guideline is static and as medical practice changes, new treatment advances are added and technology evolves, hence the written guideline will become outdated and less relevant. SA discussion driven by these medical practice changes is required to ensure guidelines are maintained as current as possible to facilitate appropriate development of new treatments for patients. Furthermore, clinical safety and efficacy guidelines cover therapy area, clinical and/ or scientific principles. It is not feasible for every eventuality or aspect of clinical development to be covered in a formal development guideline.*

Further examples why EMA should not be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines include:

- ***Trial design:*** *trials are unique and designed according to the treatment being investigated, target patient population, and characteristics of the disease and the medicinal product's mechanism of action. This is too granular to be captured in a guidance for all development programmes. EMA and Sponsor discussion and agreement on this aspect is very important. For example, a conventional randomised, controlled trial may not be possible if administration of a treatment leads to a skin reaction which would nullify any effort at blinding the trial, or if the disease is considered rare. In addition, combination products with medical devices or gene therapy are rapid developing versus small molecule (chemical) medicinal products.*
- ***Comparator choice:*** *the choice of comparator in a trial is also too specific for a guideline e.g. in oncology where the landscape is complex and fast moving.*
- ***Minimal Residual Disease (MRD):*** *there is EMA guidance on how to measure MRD for different diseases but the technology used to measure this is fast moving and evolves faster than a published guidance can keep up. EMA agreement on how this will be measured is crucial before a trial can begin.*
- ***Statistical aspects:*** *consistent with the bullet on trial design, statistical analysis plans, interim analyses and additional statistical questions are unique to a treatment, disease and patient population. Guidelines provide useful advice but not at the required level of granularity for every trial.*
- ***Timing of deliverables:*** *important discussions take place regarding trial timings, endpoints/ surrogate endpoints etc. Clarity on milestones and timings are crucial for EMA and Sponsor planning and a mutual understanding on these aspects is preferred before a trial proceeds.*
- ***Joint EMA-Health Technology Assessment (HTA) body SA:*** *EMA and HTA bodies often have different expectations eg on comparator choice; guidelines alone will not be sufficient to support these discussions.*

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

The EMA response to the Strategic Inquiry into pre-submission activities organised by the European Medicines Agency (EMA/566402/2017) outlined the key benefits of pre-submission activities with medicines developers. Primarily (in summary):

- *Facilitates the elaboration of product developments plans that address regulatory requirements which can ultimately lead to more efficient development of products and provide patients with timely access to new, safe effective medicines.*
- *Protect patients and maximise the value of their involvement in clinical trials.*
- *Gain an overview of the product and development and understand what is coming through the pipelines.*

It is crucial that these activities continue to ensure that companies of all sizes receive the necessary advice to achieve the above.