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To whom it may concern,

Please find attached the comments of the Danish Medicines Agency on the inquiry on pre-submission activities organised by the European Medicines Agency.

Kind regards
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LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

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The Danish Medicines Agency's comments on the public consultation in relation to the European Ombudsman's inquiry into pre-submission activities organised by the European Medicines Agency

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?

   The Danish Medicines Agency (DKMA) considers pre-submission support and scientific advice (SA) necessary tools to ensure not only regulatory efficiency but also safety for European patients.

   Medicines developers or sponsors may find it necessary to request scientific advice at any stage of development from the national competent authorities or EMA.

   Typically, applicants seek advice on how to comply with the safety and/or efficacy requirements in situations where guidance is either lacking or insufficient for the product in question. Scientific advice ensures that clinical studies are not conducted unnecessarily, which ultimately protects citizens from clinical trials where the scientific value is negligible or even nonexistent.

   Further, scientific advice ensures that resources are utilised efficiently and effectively. 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.

   Regulators are experts in regulatory guidelines. 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. 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. Thus, scientific advice contributes to avoiding unnecessary delay in bringing new medicines to market for the benefit of the patients without compromising quality and safety.

In our opinion, there is no conflict of interests if a national competent authority (NCA) or EMA providing scientific advice also acts as Rapporteur for the MAA. As the SA and MAA have very different purposes and the objects of scrutiny are different, an authority can sufficiently manage 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.

The exclusion of experts from national competent authorities (NCAs) who provide scientific advice from subsequent EMA MAA evaluations may negatively impact on the quality of the assessment of the authorisation and would be entirely counterproductive. As it stands, the availability of expert resource is scarce not the least 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 or NCA 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, no one NCA is responsible for any advice or decision made in respect of SA of a MAA.

Scientific advice is primarily focused on the best possible utilization of the regulatory system for the product in question and does not assess data supporting the authorisation of the product. As a result, 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. The authority that provides the scientific advice has not claimed a stake in the data generated and has no vested interest in the application. This should make it clear that scientific advice does not in any way guarantee a marketing authorisation and this point is validated by the statistic which shows that 15% of products which receive scientific advice receive a negative opinion when a marketing authorisation is sought for them.

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. The 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.

As outlined in the response to Q1 there is no vested interest for the authority as such nor for individual experts in the success of an application. However, using the experts from the initial scientific advice will ensure efficiency and ultimately be of benefit to the patients.

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?

This may be a misunderstanding of the nature of pre-submission activities. As noted above, the primary purpose of is to improve the quality of regulatory submissions not to preassess the authorisation. The pre-submission activities focus, 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. in order to ensure that appropriate and robust data is submitted to enable the best assessment of the application. The assessment of quality, safety and efficacy only takes place subsequent to the submission of the application. The EMA and NCAs are not rewarded separately for approving applications for which the applicant has previously seeked SA.

The DKMA finds that there are already sufficient safeguards to ensure that pre-submission activities are non-binding. Applicants seeking 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.

It is communicated clearly that the views transmitted in pre-submission activities are non-binding. 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.

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

The DKMA considers that there is appropriate transparency throughout the regulatory process including pre-submission activities and SA. The EMA and the NCAs have a pre-authorisation guidance published to their website as well as guidances for applicants seeking scientific advice and protocol assistance. This provides an overview of the procedure and clarity of the preparation required by applicants.

Further, declarations and conflicts of interests are declared and made in the public domain.

The commercially sensitive nature of discussions with industry limits the transparency of pre-submission interactions with individual applicant companies. As in all areas where great innovation takes place and development costs are high, there must be 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. Ultimately it would be European patients who would pay the price.

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?

Please refer to the reponse to Q4.

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.

The DKMA 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. 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 DKMA would consider little value in listing names of individuals publicly when it is such a broad assessment with input from a number of contributors. 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 DKMA 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.

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. The DKMA considers that release of SA could not be done while legally maintaining data confidentiality. This question is also based on a wrong presumption that advice for one product may be applicable for another. General scientific guidelines for drug development are produced by the CHMP, and these summarise at a high level advices given 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 and as a result jeopardise the benefits that SA provides to patient safety and development of novel medicinal products in the EU.

As noted above, should there be frequent topics repeated during SA, this would lead to the development 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 DKMA does not support limiting SA questions to issues not already addressed in clinical efficacy or safety guidelines and also finds it unclear what benefit would be achieved from such a restriction. 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 and does not damage the integrity of any subsequent MAA procedure. 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 published guidance does not fully capture the proposed approach of the product under development. In such cases, an applicant may need advice that the approach they are intending to pursue is scientifically valid. Furthermore, scientific advice is part of the public health mission of the EMA and of the NCAs, insofar as unnecessary or suboptimal designed clinical experiments may be avoided, thereby streamlining the process and ensuring best practice approaches.

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. There is a move away from situations where guidelines consider and address all aspects due to the pace of innovation. Relevant and appropriate regulation for stakeholders and crucially for patients requires a level flexibility, thereby ensuring a focus on faster and safer access to the market. In the end, all of this has the ultimate aim of benefitting the patients.

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

The DKMA is of the general opinion that any risk of bias is managed effectively by the existing safeguards and as a result SA and other pre-submission activities provide important benefits in terms of efficiency, innovation and patient treatment and safety.