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From: [redacted]
Sent: 29 January 2019 14:13
To: EO-PresubmissionConsultation
Subject: MHRA Comments - Ombudsman Inquiry on EMA pre-submission activities - IU/7/2017/KR
Attachments: 29 January 2019 - MHRA response to public consultation on European Ombuidsma's inquiry OI-7-2017-KR.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Colleagues,

Please find attached letter from Dr Ian Hudson, MHRA CEO, for your attention. This contains the MHRA comments on the European Ombudsman (ref IU/7/2017/KR) inquiry on EMA pre-submission activities.

I would be grateful if you could confirm receipt?

Kind regards
[redacted]

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29 January 2019

Reference: IU/7/2017/KR

Dear Colleagues,

Comments Ombudsman Inquiry on EMA pre-submission activities

This letter is sent in response to the invitation from the European Ombudsman (reference number OI/7/2017/KR) to put forward views on how the European Medicines Agency engages with medicine producers before they apply for authorisations to market their medicines in the EU.

Please find MHRA comments on the consultation attached.

Yours sincerely

[redacted]

Dr Ian Hudson
Chief Executive, MHRA

MHRA Response to Public Consultation on European Ombudsman's inquiry OI/7/2017/KR

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?**

Pre-submission activities are crucial to the rational development of medicinal products and for the preparedness of regulators to receive applications for innovative products, or applications based on innovative approaches to development. It is incumbent on developers to understand not only the legal and procedural aspects of medicines development and authorisation, but also scientific standards and expectations. It is therefore incumbent on EMA to be able to provide guidance on these matters to developers. Whilst EMA scientific guidelines outline methodological and disease-area standards for licensing in certain more common therapeutic indications, other settings are not covered by guidelines. Where scientific guidelines are available, they are necessarily based on established good practice and are written at a high level not attempting to outline standards to the level of detail at which individual development programmes need to be planned. Developers require the opportunity to engage in more detailed discussions on issues that are specific to their product, the proposed target population and proposed methodological approach to the design of relevant tests and trials. In addition, developers are encouraged to explore the pros and cons of novel approaches to development both for new medicines with the potential to address a medical need and for generics or biosimilars that reduce costs for a healthcare system. These important activities are handled through pre-submission activities, which are captured as obligations on the EMA in the existing legislation relating to the regulation of medicinal products.

Reducing the extent or the quality of pre-submission activities risks developers conducting tests and trials that are unsuitable to support marketing authorisation. This, in turn, risks decreasing both the number of innovative medicines, where the pre-submission activities mitigate the absence of direct precedent or other defined standards for authorisation, and the use of innovative approaches to study design and regulatory strategy. To have completed development programmes that are unsuitable to support marketing authorisation would be highly undesirable. In terms of product quality, it should be avoided that a product having demonstrated favourable risk-benefit is unsuitable for the target population in terms of its formulation, or does not have the data required to support its quality. In terms of clinical development, using resources ineffectively, at high cost to developers, and exposing volunteers and patients to experimental medicinal products, with associated side-effects, in clinical trials that are unsuitable for support regulatory assessment would be unconscionable. This underlines the importance of pre-submission activities. Any restriction to the ability of EMA staff and experts to contribute risks a reduction in the extent or the quality of these activities.

It should be recognized that pre-submission activities are always limited in scope and are not always definitive in nature. These activities are limited in respect of giving advice to specific aspects of a development programme (e.g. the choice of a primary endpoint in a clinical trial, or its inclusion / exclusion criteria): definitive endorsement of the entire development programme is not in scope. In developing areas, or for use of novel approaches, advice to developers can be given in terms of the extent of risk inherent in adopting a particular approach to development, without stating whether it definitely would or would not be accepted. Even if not definitive, advice explaining the risks and requirements of a particular approach remains useful to developers, as can be seen in the number of repeat pre-submission interactions. Finally, even where more definitive advice is possible, e.g. to endorse an aspect of the **design** of a test or trial, it must be recognized that this represents only part of the assessment that will be conducted at the time of evaluation. At the time of evaluation, the **results** from the development programme are also assessed in terms of demonstration of therapeutic efficacy and risk-benefit.

Critically, it must be recognized that neither pre-submission activities nor evaluations are handled only by individuals. Key EMA pre-submission activities that advise on standards for authorisation are adopted at the relevant EMA Scientific Committee following rounds of discussion at relevant Working Parties (Scientific Advice Working Party (SAWP), Biologics Working Party (BWP) etc.). Similarly, for

evaluation, Opinions are adopted at the level of the EMA Scientific Committees following input from two rapporteur teams and a peer reviewer. Since the draft recommendations are critically appraised, and revised, by the relevant working parties and committees, the influence of the individual expert in either activity is limited.

For these reasons, MHRA concludes that pre-submission activities are essential and that it would be inappropriate to exclude EMA staff members and experts from participating in both pre-submission and marketing authorisation activities for the same medicine.

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?

Yes. Because of the rigorous process for evaluation, with two rapporteurs, a peer review, multiple rounds of committee discussion and finally adoption of a Scientific Opinion by an EMA Scientific Committee, MHRA has no concern on this point. As stated above, restrictions to the contributions of experts risks a reduction in quality of pre-submission activities and to preclude individual experts that have been involved in pre-submission activities from assessment at time of Marketing Authorisation Application would be wasteful, requiring more resource to be available to NCAs and to EMA. To the extent that reducing or compromising pre-submission activities would promote uncertainty in the suitability of completed development programme to support Marketing Authorisation, developers would be disincentivized from approaching EU early, and perhaps at all, risking adverse consequences for EU public health.

To note, similar to the EMA Scientific Advice, individual experts do not give scientific advice directly and in a personal capacity: all scientific advice is subject to peer review and adoption by an oversight group on behalf of the Agency. Also to note that NCA advice is not regarded by the EMA Scientific Committees at the same level as advice given through the SAWP, which is the preferred approach for medicinal products that will seek a centralised authorisation.

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?

Pre-submission activities do not pre-evaluate **data**, other than a high-level review of the tests and trials that have already been completed in order to give advice to companies on the tests and trials that are still to be conducted in advance of MAA. Advice on a particular approach to the **design** of tests and trials is not understood by developer or by regulator as being "binding" for the evaluation of the **data** generated, or even of the chosen development approach. It is recognized that scientific and clinical standards may change. If standards have not changed, there is likely to be little reason to deviate from appropriate advice given during pre-submission interactions and the focus of assessment can be to evaluate the results of those tests and trials against criteria for product quality, safety and efficacy. Where discussion of the pros and cons of a particular approach to development is given rather than definitive advice, it cannot be binding by definition. Ultimately it is the data demonstrating the efficacy and safety of the medicinal product that is important, and it is the medicinal product that is authorised, not the design of the tests and trials that supported its development. Applicants seeking scientific advice or protocol assistance are advised that the scientific advice or protocol assistance given is not legally binding with regard to any future marketing authorisation application of the product concerned. Indeed, advice is frequently given contingent on a full review of the data at the time of Marketing Authorisation Application. A pre-submission interaction would not indicate that completed tests and trials were adequate to receive a positive evaluation. MHRA consider it unnecessary to consider

precautionary measures beyond those already in place, e.g. the current EMA Conflict of Interest policy, the peer review, plenary discussion and committee adoption. Training on the role of pre-submission activities in the evaluation an application for authorisation might be considered for new staff members and experts.

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?

Transparency in pre-submission activities is inevitably traded against whether those same pre-submission activities are attractive to developers, specifically the risks that commercial confidentiality is compromised, or that their own pre-submission activities might shortcut the development of a competitor product. There is the risk of reducing innovation if pre-submission activities are considered by developers as being less attractive.

Medicines development is expensive and developers are understandably protective of commercially confidential information. Pre-submission interactions are conducted on the basis that this commercial confidentiality is protected. To do otherwise would be to reduce the number and scope of such interactions, transferring influence to other regulators who are competent in engaging in similar discussions (e.g. US FDA) who do work in a confidential manner.

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.

To the specific points proposed:

- It would be meaningless and misleading to disclose the names of the officials and experts involved in the procedures since the advice is given by EMA Scientific Committees not by individual experts. Conflicts of Interest submissions from all EMA experts and members of EMA Scientific Committees are available on the EMA website.
- Disclosing only the questions posed without the answers given might not be harmful but would not obviously serve any useful purpose, even in terms of enhancing transparency.
- Please refer to Q4. Making comprehensive information public pre-authorisation bears risks that would ultimately reduce the extent of pre-submission activities and risks adverse consequences for patients in the EU. It might be considered to make information public post-authorisation (for those products authorised), to a greater extent than is currently done in respective public assessment reports, however certain information remains commercially confidential and the risk remains that other developers assume that the advice applies directly to the development programme for their product.
  EMA and the network of experts should be given the necessary resource such that published methodological and therapeutic area guidelines can be updated in a timely manner, where new standards emerge that are broadly applicable.

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

The advantage would be other developers that are, in some instances, better informed. The disadvantages, however, outweigh this advantage. Companies would be disincentivised from undertaking pre-submission activities if they felt that commercial confidentiality might be compromised or that advice given would also be available to competitors. There is also the risk that another developer would incorrectly interpret advice given to one specific development programme as being equally relevant to theirs. Beyond scientific standards that are generally applicable, and are documented in EMA scientific guidelines, many aspects of scientific advice are specific to the individual product and / or the individual development programme, and might not be applicable to another product or development programme. If the relevance of advice given to another company was to be misjudged, resources and patients might be committed to a development programme that was not suitable to support a marketing authorisation.

7. Should EMA be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines[4]?

MHRA would not support this and it is anyway not clear how this could ever be operationalised. Scientific guidelines are not written to the level of detail to which development programmes need to be planned or to which assessments of marketing authorisation application are conducted. Pre-submission activities go into further detail than is available in EMA guidelines, into the detail of specific development programmes, considering the specific target population, the mechanism of action of the specific product and the proposed clinical trial designs.

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

EMA and the EU network of NCAs should be prepared to increase the extent of these crucial pre-submission activities, including interactions with other stakeholders such as HTAs and other parts of the medicines regulatory framework, such as NCA activities in Clinical Trial Authorisation, in order for EMA to give advice that can optimize medicines development programmes in the EU, facilitating timely access of medicines to EU patients. EMA might be asked to re-evaluate the level of detail that can be presented after marketing authorisation, e.g. in Public Assessment Reports, to the extent that the content does not compromise commercial confidentiality and does not disincentivize any company from future pre-submission activities.