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From: [redacted]
Sent: 30 January 2019 15:44
To: EO-PresubmissionConsultation
Cc: President; [redacted]
Subject: Comments Ombudsman Inquiry on EMA pre-submission activities: ISDB- Prescrire joint response
Attachments: 30_01_2019 ISDB & Prescrire joint response EU Ombudsman consultation on scientific advice.pdf

Follow Up Flag: ema2
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Dear Madam,
Dear Sir,

Please find attached the joint response from ISDB (International Society of Drug Bulletins) and Prescrire to the European Ombudsman public consultation on EMA pre-submission activities.

With kind regards,

Rita Kessler

Prescrire

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European Ombudsman's consultation on how the European Medicines Agency engages with medicine producers before they apply for authorisations to market their medicines in the European Union[i]

ISDB's and Prescrire's joint response

30-01-2019

We would like to thank the European Ombudsman for organising this public consultation on the pre-submission "scientific advice" provided by EMA to pharmaceutical companies. EMA was assigned the task of providing scientific advice to companies by the European legislator, notably in European Regulation No. 726/2004 (Recital 25 and Articles 56 and 57)[ii]. For several years, civil society organisations have been trying to draw the relevant authorities' attention to how this confidential practice creates an institutionalised conflict of interest for EMA. In a joint declaration, civil society organisations pointed out the weaknesses of and problems with this opaque system, and proposed a list of recommendations in favour of a new model for the provision of scientific advice, rooted in the principle of "open science"[iii]. To protect public health and foster trust in the regulatory process, it is important to bring transparency to scientific advice, to enable independent analysis of its impact and verification of its scientific basis.

Questions

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?**

EMA's confidential pre-submission "scientific advice" to companies jeopardises its ability to make independent decisions. Pre-submission activities effectively make EMA a co-developer of the medicine, yet it is subsequently called upon to issue its opinion on whether or not the medicine should be granted marketing authorisation. In practice, by providing such "advice", EMA puts itself in a position where it assists companies, for a fee (unless a waiver applies), by telling them the level of clinical evaluation it is likely to consider adequate to issue a positive opinion on a marketing authorisation application.

In all its dealings, EMA should keep direct interaction with companies to a minimum, by establishing an interface, and should avoid creating conflicts of interest for its staff and experts. Its policy for managing conflicts of interest should include measures that enable the public to freely and easily verify that nobody who provided pre-submission scientific advice

on a medicine is involved in assessing any subsequent marketing authorisation applications 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?**

In Europe, companies can request pre-submission scientific advice from national drug regulatory agencies, EMA, and health technology assessment bodies.
"Shopping" for scientific advice from national and European regulators for the same medicine is a questionable practice in itself.

The concern is that companies that request pre-submission scientific advice could exert control from an early stage over everybody involved in the assessment of marketing authorisation applications at both national and European level.

As we indicated in our response to question 1, to avoid advisors and experts having conflicting roles and therefore conflicting interests, experts involved in providing national pre-submission scientific advice must not be involved in any subsequent evaluation of European marketing authorisation applications for the same medicine.

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?**

EMA guidance on scientific advice clearly states that pre-submission scientific advice provided by EMA is not binding (cf. point 23)[iv]. If the company decides not to follow the advice given, it is simply asked to clearly justify this decision in any future marketing authorisation applications.

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.

There is no transparency over the content of requests for pre-submission scientific advice and the answers provided.

EMA publishes statistics on the total number of requests it receives for scientific advice and on the types of substance and therapeutic indications concerned. However, EMA is not at all transparent about the content of the requests it receives or the advice it provides. In 2017, EMA received 630 requests for scientific advice and protocol assistance (8% more than in 2016, mainly due to an increase in requests for protocol assistance)[v]. In none of these cases was the content of the request published in detail[vi].

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)

It is regrettable that EMA provides no precise information to the public about the content of its scientific advice or whether its advice was followed. Such information would greatly facilitate research on the provision of scientific advice and evaluation of its impact. The information published in the EPAR is too sporadic and provides no meaningful insight into the questions asked or the answers given. It is insufficiently detailed and unusable as a basis for serious research into the quality and usefulness of EMA scientific advice.

Currently, **only pharmaceutical companies and EMA itself are in a position to evaluate the impact of EMA advice, yet patients and health professionals are directly affected**[vii]. EMA's 2017 annual report states that 62% of applicants who received a positive opinion for their medicine had received scientific advice (cf. p. 13). It also reports the average number of days EMA took to assess marketing authorisation applications for new active substances (196 days), for medicines qualifying for accelerated assessment (136 days), after provision of scientific advice (170 days), and where the applicant was an SME (209 days). This suggests that scientific advice speeds up the assessment of marketing authorisation applications, yet there is no way of knowing whether swift assessment benefits public health.

The existence of a registry or annual publication of a list of medicines for which scientific advice was sought, including the advice provided, and provision of detailed information in the EPAR of each medicine concerned would enable independent analysis of the quality of EMA's advice and its impact on clinical trial design.

It is surprising that none of the EMA documents we were able to access mention whether EMA can refuse requests for scientific advice. Nor do they mention whether EMA regularly evaluates how efficiently scientific advices are designed or the impact of its advices on applicants. **In the absence of transparency, European citizens are concerned about the quantity and scope of these activities, while having no means to assess their usefulness or check whether they expose EMA to the risk of regulatory capture**.

ii. medicine developers.

Lack of transparency over the early scientific advice provided by EMA is detrimental to public health and undermines trust in EMA.

Confidential scientific advice given to an individual company may give it an advantage over its competitors. Public access to the scientific advice provided by EMA would benefit all medicine developers. By publishing its advice, EMA would be acting in accordance with its remit to serve the public interest and with full transparency.

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 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 reason for your suggestions.

Greater transparency over the scientific advice provided by EMA is absolutely necessary (cf. our responses to the previous questions). Scientific advice provided secretly to individual medicine developers, with no accountability, is harmful, antithetical to EMA's remit, and undermines its impartiality and credibility.
EMA's work must be conducted in the public interest and with the greatest possible transparency.

- disclosed the names of officials and experts involved in the procedures?

We fail to understand why **EMA attaches so much importance to informing medicine developers who request scientific advice of the names of its staff and experts** who attend discussion meetings with the applicant. To avoid the potential for institutional capture and misuse of such information, we feel that, on the contrary, private meetings conducted behind closed doors should be avoided as far as possible.

The general public, on the other hand, is given no information about the identity of the outside experts involved in drafting scientific advice. Once the scientific advice team's opinion has been finalised and sent to the applicant, we feel that the names of outside experts should be publicly disclosed. In particular, this would make it possible to check that the rules on conflicts of interest are followed.

- disclosed the questions posed in scientific advice procedures?

Yes
Public access to the questions posed would enable independent scrutiny of their legitimacy and detection of any abuse or misuse (for example sham questions, repeated questions, requests to deviate from current guidelines or for waivers to these guidelines, etc.). Access to the questions would help clarify pharmaceutical companies' needs and concerns when designing research programmes. It would also facilitate the preparation of "Frequently Asked Questions" documents and help improve existing guidelines by specifying or clarifying exactly what assessors need from clinical research.

- made public comprehensive information on the advice given?

Yes
By giving the public access to EMA advice, the quality of the advice could be evaluated by independent teams, and any deviation from the current principles of clinical research could be detected. Access to this information would make it possible to prepare suggested improvements to existing guidelines or to propose new guidelines. Rather than promoting more intensive use of early confidential interactions with individual companies, **EMA should make greater efforts to produce detailed, transparent, public, written guidelines on clinical research.**

If you have other suggestions, for example regarding the timing of the publishing of information on scientific advice, please give details and the reason for your suggestions.

Questions and scientific advice should be published as soon as the advice has been finalised and sent to the applicant.

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

There are no disadvantages to transparency over scientific advice, including making it available to the public as well as other medicine developers.

In the interests of impartiality and neutrality, advice from the European regulator on how to interpret current rules and design high-quality preclinical and clinical studies should be made available to everyone. Scientific advice from a regulator with a remit to protect patients and work in the public interest belongs in the public domain and should not be censored on the grounds that it contains trade secrets or confidential commercial information.

In the interests of scientific rigour, EMA should make its scientific and procedural requirements clearer, in detailed, transparent, public, written guidelines on clinical research and notes for guidance. EMA should develop scientific standards for each therapeutic field, applicable to all medicine developers, thus putting an end to a tailor-made service and enabling independent scrutiny. The development of such guidelines would help EMA make more efficient use of its limited resources.

EMA could also hold more public workshops to explain issues that arise in specific therapeutic fields or on more general issues. If the outcome of these discussions is useful and well-founded, it could be used to update existing guidelines or develop new guidelines.

Over the years, EMA has had the opportunity to accumulate a wealth of information on the types of questions posed in each therapeutic field. Drafting "Questions & Answers" documents for each therapeutic field would be a useful step towards information sharing and greater transparency.

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

Yes.
EMA has limited financial and human resources that it must manage and develop in compliance with its remit to serve the public interest.
It is essential to limit situations that expose EMA staff and experts to the risk of psychological capture that could compromise their impartiality and objectivity.

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

Repeated contact between pharmaceutical companies and EMA representatives long before submission of a marketing authorisation application can lead to institutional capture and the potential for corporate influence that disserves the public interest. EMA should take a keener interest in the results of social sciences studies on sales techniques and the psychological mechanisms exploited by commercial companies to exert influence[viii].

We believe it is time to put an end to these opaque practices and to take resolute action to promote independence and transparency, by requiring EMA to disclose the questions posed by companies and the answers given, to analyse the impact of these activities, and to provide details of the financial and human resources and time it expends on these services.

About US

ISDB. The International Society of Drug Bulletins (ISDB), founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. More info: https://www.isdbweb.org. Contact [redacted]

Prescrire is a non-profit continuing education organisation, committed to better patient care. Prescrire provides independent, reliable information on treatments and therapeutic strategies, in order to support informed decisions. Prescrire is entirely financed by its subscribers, and accepts no advertising or other external financial support. For more information, please visit http://english.prescrire.org or http://prescrire.org. Contact [redacted]

[i] https://www.ombudsman.europa.eu/en/public-consultation/en/104905 b
[ii] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf
[iii] http://english.prescrire.org/en/79/207/46302/5436/5152/SubReportDetails.aspx
[iv] https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf
[v] https://www.ema.europa.eu/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf
[vi] 28 requests were for drugs included in the PRIME scheme, and 29 were for parallel advice from both EMA and health technology assessment (HTA) bodies. More than half of requests related to clinical issues, 27% to preclinical issues, and 21% to quality issues. 55% of requests related to medicines in phase III and 32% in phase II of their clinical development. Patient representatives were involved in 158 interactions.
[vii] A study conducted by EMA staff members, published in 2015, found a positive association between compliance with EMA scientific advice on clinical trial design and success in obtaining marketing authorisation. Only 33% of clinical development programmes were deemed to have an acceptable trial design at the time scientific advice was sought. For the 67% of programmes deemed of unacceptable quality ("deficient"), EMA recommended modifications to the trial design, and 63% of applicants complied with this advice.
[viii] Prescrire International "*The mechanisms behind influence and persuasion*" October 2018 Volume 27 N° 197 pp. 248-249