ACCOUNTABILITY AT THE EMA AND RISK OF BIAS IN PRE-SUBMISSION ACTIVITIES AT THE EMA

INTRODUCTION

The inherent ability of medicines to exert far-reaching effects on human physiologies makes the pharmaceutical industry one of the most strictly regulated industries in the world. To ensure quality, efficacy and safety when medicines reach the market, they are subjected to a rigorous process of testing and regulation. Central in the EU regulatory landscape is the European Medicines Agency (EMA), that is in charge of the scientific assessment of new medicines. Based on the EMA's recommendations, the European Commission grants marketing approval that is valid in the whole EU. The significant role of the EMA in the marketing authorisation of new medicines requires the agency to work independently according to the highest standards of quality and accountability. Despite the countless policies and standards adopted by the EMA to ensure the quality of the assessment, some concerns were expressed regarding the agency's accountability and judgements. For instance, the late withdrawal of an MS treatment named daclizumab due to severe adverse effects, has led some to question why daclizumab was authorised in the first place[1,2]. Moreover, the recent inquiry by the European Ombudsman showed the need for greater transparency regarding EMA's interaction with medicine developers during the period of the Pre-Submission Activities (PSAs)[3]. The European Ombudsman recommended a better separation of experts who are involved in advisory activities, from those who are involved in medicine assessment. This argument was recently re-iterated in a letter that was sent out by the European Ombudsman towards the EMA. She argued that - even though different stakeholders exert high amounts of pressure on pharmaceutical regulatory authorities to approve COVID-19 related technologies:

"it is important to ensure that an appropriate balance is struck between providing the best possible advice and assistance, while guaranteeing the independence of any subsequent evaluations."[4]

Wemos set out to look into various questions that were raised by the beforementioned cases: How does the EMA deal with accountability? How do the stakeholders involved in medicine evaluation perceive accountability? And, eventually, which areas can be identified for improvement? Additionally, we sought to answer questions regarding the risk of bias during PSAs.

[1] https://journals.aboutscience.eu/index.php/dti/article/view/1401

[2] https://english.prescrire.org/en/81/168/55120/0/2018/ArchiveNewsDetails.aspx?page=1

[3] https://www.ombudsman.europa.eu/nl/decision/en/116683

[4] https://www.ombudsman.europa.eu/nl/correspondence/en/130852

Wemos' intern Eunjin Jang (student of the master programme *Drug, Discovery and Safety* at Vrije Universiteit Amsterdam) researched the accountability of the EMA, under supervision of Ella Weggen and Tom Buis. In addition to Eunjin's research, Tom Buis conducted research into the risk of bias in PSAs. Our objective was to provide policy recommendations to the European regulatory authorities in medicines on how to improve EMA's accountability in the scientific assessment and PSAs. Hence, we investigated how accountability is incorporated in the current policies of the EMA and how accountability is understood by the stakeholders involved in the medicine evaluation. We conducted semi-structured interviews with different stakeholders involved in Dutch and EU medicines evaluations and PSAs, such as policy experts, regulatory experts from industry and regulatory agencies and NGO representatives.

KEY FINDINGS

Our key findings can be summarised as follows:

- We used three forms of accountability in our theoretical framework: 1) performance, 2) social and 3) political/democratic accountability (as described by Anuradha Joshi[5] and Jonathan Koppel[6]). A general consensus exists among the stakeholders on how accountability is understood. The majority of stakeholders defined accountability in terms of responsibility or transparency. Additionally, the stakeholders generally agreed that the EMA is accountable for the assessment outcomes and that the regulatory body is accountable to the European Commission and its citizens.
- The majority of the stakeholders acknowledged EMA's efforts to improve its accountability. However, many of them perceived some challenges that could compromise the agency's accountability. While the mentioned challenges differed greatly among the stakeholders, common views were identified.
    - The ad-hoc experts perceived challenges mostly in the area of political/democratic accountability. They mentioned insufficient transparency and inadequate involvement of experts with practical knowledge as the main obstacles.
    - The assessors mainly noted challenges related to the performance aspect of accountability, such as the consistency and scientific justification of the assessment and the different contributions from individual Member States.
    - Different interviewees mentioned the risk of bias when there is no clear separation between EMA experts involved in PSAs from those conducting the medicine assessment. During interviews with experts in the Dutch context, it remained unclear if similar risks also occur in the Dutch national regulatory authorities.
    - It remains unclear what criteria the EMA uses to select experts that are involved in PSAs (coordinators) and experts involved in medicine assessment (rapporteurs). Although interviewees did not question the expertise of the

[5] https://www.sciencedirect.com/science/article/pii/S0305750X17302425

[6] https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1540-6210.2005.00434.x

individuals involved in these specific activities, it was not always clear why the agency chose a certain expert over others.

POLICY RECOMMENDATIONS TO THE EMA

POLICY RECOMMENDATION 1: INCREASE TRANSPARENCY OF SELECTION CRITERIA FOR EXPERTS

Although increasing efforts are made by the EMA to engage experts from outside the agency, the criteria it uses to select *rapporteurs, coordinators* and *external experts* was not clear for many of the interviewees. The way in which the EMA approaches suitable and independent experts should, therefore, be more transparent. If the EMA increases transparency of selection criteria for (external) experts, it will likely positively affect the agencies accountability.

POLICY RECOMMENDATION 2: INCREASE SEPARATION BETWEEN EMA EXPERTS INVOLVED IN PSAS AND EXPERTS INVOLVED IN ASSESSING THE MARKET APPLICATION

According to a previous inquiry by the EU Ombudsman, there is a current overlap in EMA experts who conduct PSAs and EMA experts who are responsible for the medicine evaluation. A clear separation between these two roles decreases the risk of bias. When there is no suitable external expert for PSAs or medicine evaluation, for instance for orphan diseases, the EMA could potentially look for ad hoc experts outside of the European Union, to maintain this clear separation. In order to increase consistency of high quality and independent PSAs, the EMA could provide national regulatory authorities with guiding documents on how to make clear separations between EMA experts involved in PSAs and experts involved in medicine evaluation. Decreasing the risk of bias through this policy recommendation could be beneficial to the EMA's performance accountability and political/democratic accountability.

POLICY RECOMMENDATION 3: INCREASE INVOLVEMENT OF EXTERNAL ADVISORS

In line with EU legislation, the CHMP (EMA's committee responsible for assessing marketing applications) is authorised to lead the assessment and to provide advice to the European Commission. The interviewees considered this to be important for the consistency of the assessment. Currently, inputs from external experts are only sought when additional insights are needed. However, involving more experts in the early phase of the medicine evaluation may help to reduce criticisms on the assessment outcomes, which are often related to clinical endpoints. Moreover, inputs from external experts with practical knowledge of a particular disease or a patient group, can help to design better clinical studies and subsequently, generate more robust data. The decision-making still falls under the CHMP's duties, but by adding more practical expertise in the process, the overall quality of the assessment could be improved. And with that, the agency's accountability on performance and political/democratic accountability.

POLICY RECOMMENDATION 4: INVEST IN KNOWLEDGE RETRIEVAL SYSTEMS

With the continuously growing amount of data and information, it becomes increasingly important to retrieve the correct knowledge to make the right decision in the medicine approval process. Based on an interview with an EMA expert involved in the CHMP, it became apparent that much of the knowledge about previous assessments comes from individuals' personal experiences and is therefore not easily available for involved EMA employees. Retrieving knowledge around past decisions, therefore, relies heavily on individuals' memories, rather than on data systems. Although some relevant documents and information are stored in data systems, it takes much effort to find and extract useful knowledge, at the expense of efficiency and, possibly, the consistency of the assessment. Therefore, we recommend the EMA to further investigate how information on past decisions of market approvals can best be retrieved and to investigate whether our findings are in line with experiences of other EMA experts.