

Accountability of the European Medicines Agency in Marketing Authorisation of New Medicines

Qualitative and literature analysis of accountability within the European medicine evaluation

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Executive summary

Introduction

Due to the ability of medicines to evoke biological responses, medicines are subjected to strict regulation and must be authorised by an appropriate regulatory authority to enter the European market. Central in the 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. 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 operation. 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. Moreover, the recent inquiry by the European Ombudsman showed the need for greater transparency on the EMA's interaction with medicine developers in the pre-assessment phase and a better separation of the advisory activities from medicine assessment. These cases raise the question on how the EMA copes with accountability and how the stakeholders involved in medicine evaluation perceive accountability to eventually identify the areas for improvement. Therefore, the objective of this research project is to provide policy recommendations to the European regulatory authorities in medicines to improve EMA's accountability in the scientific assessment by investigating how accountability is incorporated in the current policies of the EMA and how accountability is understood by the stakeholders involved in the medicine evaluation.

Theoretical background and conceptual framework

Accountability is often seen as a desirable and important feature of organisations and public officials. However, accountability lacks consensus as it can mean different things to different people. The ambiguity and fuzziness on the definition of accountability demands, therefore, a robust conceptual framework. In this study, Bovens (2007) definition of accountability was used in which accountability is seen as a relationship between an actor and a forum that is bound by the actor's obligation to justify its conduct to the forum and the forum's ability to pass judgement on the actor. Moreover, the conceptual frameworks of Koppell (2004) and Joshi (2017) were integrated to categorise accountability of the EMA according to three types; performance, political/democratic and social accountability. Thereby, three general purposes of accountability were distinguished, which are control, assurance and improvement/learning.

Methodology

A qualitative research was conducted using two data collection methods; a document review and semi-structured interviews. Thereby, 13 documents concerning the policies, regulation and standards of the EMA were systematically reviewed according to the types of accountability and purposes of the arrangements. Moreover, 10 semi-structured interviews were performed to explore the stakeholders' view on EMA's accountability, corresponding regulation and accountability related challenges in medicine evaluation. The study population comprised of three categories of stakeholders involved in the assessment; assessors, applicants and ad-hoc experts. The interviews were transcribed and coded using the coding program ATLAS.ti 8.

Key findings

The key findings can be summarised as follows:

- A general consensus exists among the stakeholders on how accountability is understood. The majority of stakeholders defined accountability in terms of responsibility or transparency and referred thereby mostly to the performance and political/democratic aspect of accountability as the context often related to the quality of the assessment, conformity to the EU law and

public trust. Also, the stakeholders generally agreed that the EMA/CHMP is accountable for the assessment outcomes while the EC and citizens were considered the formal and informal forums to which the EMA needed to be accountable.

- Current policies and standards cover all three types of accountability. The efforts made by the EMA to improve its accountability were acknowledged by the majority of the stakeholders. However, many of them perceived some degree of challenges that may compromise accountability of the EMA. Whilst these challenges differed greatly among the stakeholders, common views were identified.
- The ad-hoc experts perceived the challenges mostly in the area of political/democratic accountability, mentioning the insufficient transparency and the inadequate involvement of experts with practical knowledge as the main obstacles.
- The challenges perceived by the assessors mainly related to performance aspect of accountability such as the consistency and scientific justification of the assessment and the different contribution from the individual member states.

Discussion

The limited inclusion of stakeholders with actual experience in medicine evaluation and the select number of literature used for the document review that may have resulted in a distorted representation of reality. Despite these limitations, the study findings show that the stakeholders' understanding on the meaning of accountability and the expectation of the EMA were generally in line with each other.

Policy recommendations

Based on the findings, three main areas for improvement are identified. Policy recommendations are formulated to help the EMA to improve accountability in these areas.

1. Investing in knowledge retrieval systems

Findings from the interviews revealed the difficulties experienced by the assessors in recovering the knowledge from the previous assessment. Although the relevant information is stored and made accessible through electronic data systems, much effort is needed to find and extract the useful knowledge from those data, at the expense of efficiency and perhaps, consistency of the assessment. Thus, recommendation is made to the EMA to invest in knowledge retrieval systems for the betterment of performance accountability.

2. Increasing involvement of external advisors

From the interview findings it was apparent that criticisms on the assessment outcomes often related to different views on clinical endpoints and perceived lack of practical knowledge. Involving more ad-hoc experts in the begin phase of medicine evaluation is therefore recommended to address this knowledge gap, ultimately improving the overall performance of the assessment. Inputs from external experts may also lead to better designed clinical studies and subsequently, more robust data.

3. Increasing transparency of selection criteria for experts

EMA's criteria to select the experts in medicine evaluation are still unclear among the external stakeholders. Increasing transparency on how the EMA approaches and selects suitable experts will help the agency to increase the political/democratic accountability and, potentially, performance accountability by gaining public trust and finding better ways to engage external experts in medicine evaluation.

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Abbreviations

BoT – Breach of Trust
CHMP - Committee for Medicinal Products for Human Use
Col – Conflict of interest
CV – Curriculum vitae
DMT - Disease-modifying therapy
DoI – Declaration of interest
EC – European Commission
EEA - European Economic Area
EMA - European Medicines Agency
EPAR – European public assessment report
EU – European Union
GxP – Good practice
MA – Marketing authorisation
MAA – Marketing authorisation application
MS - Multiple sclerosis
PRAC – Pharmacovigilance Risk Assessment Committee
RMP - Risk management plan
SAWP - Scientific Advice Working Party
VU – Vrije Universiteit Amsterdam

1. Introduction

The inherent ability of drugs to exert far-reaching effects on human physiologies makes the pharmaceutical industry one of the most strictly regulated industries in the world (Handoo, Arora, Khera, Nandi, & Sahu, 2012). To ensure efficacy and safety of drugs when reaching the market, drugs are subjected to a rigorous process of testing and regulation controlled by international agreements and (inter)national regulatory bodies. In the European Union (EU), the medicine regulatory system operates through a partnership between the European Commission (EC), the national medicines regulatory authorities in the EU and the European Economic Area (EEA) and the European Medicines Agency (EMA) (EMA, 2019d). Central in this system is the EMA, a decentralised scientific agency that is in charge of the evaluation and post-authorisation pharmacovigilance of medicinal products for human and veterinary use (EMA, 2019d).

The EMA is responsible for coordinating the standards for medicine evaluation at the EU level and provides guidance and support to pharmaceutical companies on regulation and clinical study design among others (EMA, 2019d). Through a centralised procedure, companies can apply for a license that is valid in all EU member states and the EEA. Based on EMA's recommendations, MA is formally issued by the EC (Saurer, 2009). Although EMA has only an advisory role, the EC relies heavily on its scientific expertise in their decision-making (Parliament & Council Regulation 726/2004, *supra* note 95, 2004; Saurer, 2009). Given the importance of the EMA in authorising medicines in the EU, it is only natural to expect the highest standards in the agency's practice. Recommendations for medicine approval should, therefore, be based on sound science away from external influence involving outside interest or private gain. To achieve this, EMA has set a vast number of policies and guidelines to ensure that the agency works independently while maintaining high quality in its science-based recommendations (EMA, 2019d).

Despite the EMA's efforts to increase the agency's legitimacy and integrity, several health advocates still argued that the policies are not extensive enough (Garattini, 2016; Prescrire International, 2019; Quintano, 2014). The agency's practice of providing scientific advice to the companies for the preparation of clinical studies of which the results are judged by its own committee, along with the EMA's task of monitoring and sometimes even withdrawing the same medicine that it has authorised led to questioning the agency's integrity (Garattini, 2016). Others were concerned about the 'closed-door' meetings offered by the EMA to the applicants in the pre-submission stage of the MA (Natsis, 2018). Although the EMA argues that these meetings lead to better designed clinical studies, the lack of public information during this stage raises the concern that the agency's decision-making may be potentially influenced by the pharmaceutical industry (Garattini, 2016; Natsis, 2018). This concern was shared by the European Ombudsman who after its assessment recently advised the EMA to provide greater transparency to this matter to sustain public trust (European Ombudsman, 2019).

Another case in which the EMA's decision-making was questioned is daclizumab, a treatment against multiple sclerosis (MS) that was withdrawn from the market in 2018 (Avasarala, 2018; Prescrire International, 2018). Daclizumab was authorised in 2016 by the EC and introduced to the market as a new, alternative drug for the treatment of relapsing MS. However, the EMA suspended the license for daclizumab due to severe and sometimes even fatal adverse effects associated with the drug. In the aftermath of daclizumab withdrawal, a few researchers questioned how some of the clinical data could be overlooked that may have given the clue for the severity of these reactions (Avasarala, 2018; Chisari et al., 2019). One particular medical journal even argued that the drug should have never been authorised and criticised the standards held by the agency (Prescrire International, 2018, 2019).

While it is difficult to conclude who is right and who is wrong in this case without a deep understanding of the research and processes involved, the various controversies surrounding the EMA's mode of

operation makes one question how the agency copes with accountability. Accountability is a term that has been widely used in the public and political discourse due to the positive image of accountability as an epitome of trust, integrity and transparency (Bovens, 2007). However, despite its popular use, accountability is a term that lacks consensus as it can mean different things to different people (Koppell, 2005). Therefore, it is important to understand how accountability is understood by different stakeholders of the EMA and how accountability is incorporated into the agency's policies. This will help to better understand the systems and procedures adopted by the agency to ensure reliable and impartial medicine assessment and to hold individuals, committees and the agency accountable for their performance. It will also provide insights into stakeholders' views on accountability and what they perceive as accountability related challenges.

Based on these findings, areas can be identified to improve the EMA's accountability in the medicine assessment. Therefore, the objective of this research project is to provide policy recommendations to the European regulatory authorities in medicines to improve EMA's accountability in the scientific assessment by investigating how accountability is incorporated in the current policies of the EMA and how accountability is understood by the stakeholders involved in the medicine evaluation. This is formulated into the following research question:

“How is accountability understood by stakeholders of medicine evaluation and how is accountability incorporated into the policies and guidelines of the EMA to ensure impartial and reliable evaluation of new medicines for marketing authorisation?”

The following chapters will provide information on the contextual background of the topic, the relevant theories and the conceptual framework used in the study. Thereafter, the methodology of the study will be presented followed by an overview of the main results. In the last chapter, the main findings will be discussed along with the strengths and limitations of the study, and a final conclusion will be given. Based on the main findings, policy recommendations for the improvement of EMA's accountability are formulated.

2. Contextual background

2.1 Marketing authorisation of medicines

For a medicinal product to enter the European market, it must be authorised by an appropriate regulatory authority (European Commission, 2019). There are currently four different types of MA in Europe that differ in the scope of authorisation, procedures and eligibility (EMA, 2016e). This study focuses on the centralised MA that is carried out by the EMA.

2.1.1 Centralised MA procedure

The EMA is a decentralised scientific EU agency that provides evidence-based advice to the European institutions and medicine developers (EMA, 2016e). Scientific assessment of new medicines is thereby one of its key tasks. This centrally regulated EU-wide drug assessment allow medicine developers to apply for a MA license that is valid throughout the whole EU and EEA territory (EMA, 2016e). The MA is formally granted by the EC that based its opinion on the assessment carried out by the EMA's Committee for Medicinal Products for Human Use (CHMP)(European Commission, 2019). As the executive body of EU, the EC oversees compliance to EU law on pharmaceuticals, initiates new or amended pharmaceutical legislation and is responsible for its implementation (EMA, 2016e). The role of the EMA in this whole process can be considered as those of a quasi-regulatory agency as it does not have the formal authority to grant the permission yet the “strong recommendatory power” to the EC (Busuioc, 2010; Craig, 2006, p. 155).

The eligibility for the centralised procedure differs per type of products. For some products (e.g. cancer treatments, orphan drugs, biopharmaceuticals), the centralised procedure is compulsory while it is optional for others (CHMP, 2007). The procedure is initiated by the medicine developer upon submitting the MA application (MAA)(EMA, 2019d). The timeline of the procedure is shown in **Figure 1**. Among the required information are the target patient population, physicochemical properties, mechanism of action, the administration route and metabolic profile of the drug (EMA, 2019d). Additionally, a risk management plan (RMP) need to be submitted which discloses information on the safety profile of the medicine and how the risks will be minimised, monitored and studied after authorisation (EMA, 2019d). The evaluation of RMP is delegated to the Pharmacovigilance Risk Assessment Committee (PRAC) who provide their opinion to the CHMP.

Each MAA is assessed by two different teams led by a rapporteur and co-rapporteur, who are appointed CHMP members from different member states that assess the medicine independently from each other (EMA, 2019d). Teams consisting of experts from the national medicines agencies who support the (co-)rapporteurs in the assessment. Similar to the CHMP, the PRAC also appoints a rapporteur and a co-rapporteur to assess the RMP. The outcomes of the initial assessments are discussed with all CHMP and PRAC members and together, additional issues are identified that need to be addressed by the applicant. The (co-)rapporteurs' assessment reports are also subjected to peer review by other CHMP members to check the robustness of the scientific arguments. After the initial assessment, the assessment is brought to halt while the applicant prepares the materials on the issues raised during what is called a clock-stop (EMA, 2019d).

The assessment continues upon receiving new, additional information from the applicants. A second clock-stop may be requested when there are still noticeable issues that need to be clarified. Thereby, the CHMP can consult additional experts, such as patients and healthcare professionals in ad-hoc expert group sessions for more insights into the disease, patients' needs, risks associated with the medicine and practicality issues faced by the healthcare professionals (EMA, 2019d). After the second assessment, a final discussion takes place in which the CHMP takes a formal stance on the medicine (EMA, 2019d). Usually, the CHMP develops a final opinion by reaching consensus but occasionally, when the consensus cannot be reached, a formal vote will take place (EMA, 2019d).

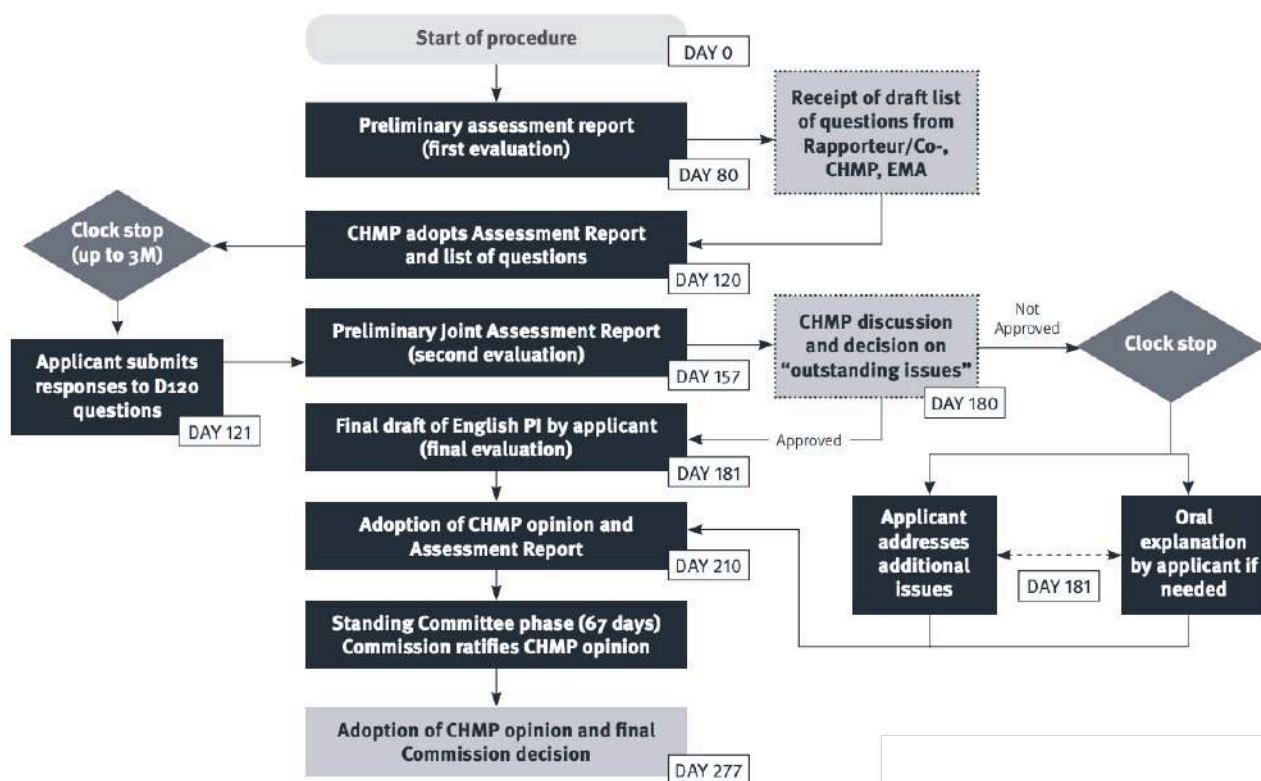


Figure 1. Timeline of the MAA procedure. Adopted from Sardo (2019, p. 3).

Overall, the assessment of each application takes about a year, comprising of a 210-day period of evaluation by the EMA and one or two clock-stops, which generally takes 3-6 months and 1-3 months respectively (EMA, 2019d). All of the gatherings are documented in meeting minutes, including the names of the involved members, their opinions and declarations of interests. Together with the MAA assessment report, the so called European Public Assessment Report (EPAR), and the submitted clinical data, these meeting minutes are made publicly available (European Commission, 2019). When the opinion is unfavourable, the applicant can request for a re-examination with a new rapporteur and co-rapporteur. However, these rapporteurs only look at the issues brought up by the applicants based on the data that was available during the initial opinion (EMA, 2019d). Once the EMA's recommendation is set, the EC decides within 67 days on whether to grant or not to grant the medicine an authorisation in the EU.

2.2 Concerns related to EMA's accountability

Although the EMA puts great effort to ensure reliable scientific judgement through a joint decision-making system, there are still some voices of concerns related to EMA's accountability. The following sections will discuss two specific cases in which the EMA's accountability was questioned.

2.2.1 Withdrawal of daclizumab for multiple sclerosis

The first case is about a MS treatment named daclizumab. Daclizumab belongs to a group of disease-modifying therapies (DMTs) which reduce the frequency of MS relapses. In 2016, daclizumab entered the European market and was recommended by the EMA as a first-line treatment for relapsing MS (EMA, 2016b). Daclizumab had several advantages over other DMTs as it was the first MS treatment whose mechanism involves Interleukin-2 signalling pathway and the first in monthly subcutaneous injection regimen (EMA, 2016b). However, despite the promising outlook, a fatal case of daclizumab-induced hepatitis occurred in 2017 and the EMA had to adapt the use of daclizumab to only patients whose treatments with other DMTs had failed to reduce the risk of serious liver damage (Prescribe

International, 2018). Shortly afterwards, multiple cases of serious inflammatory brain diseases and rare but severe immune reactions were reported that were also linked to the use of daclizumab, and as a result, the EMA strongly recommended the EC to suspend the MA of daclizumab (EMA, 2018a). Eventually, daclizumab was voluntarily withdrawn from the market by its manufacturers in 2018 (Prescrire International, 2018).

Although the clinical data did not show any cases of inflammatory brain diseases, some side-effects were later linked to a severe idiosyncratic drug reaction with high mortality rate (Chisari et al., 2019). However, these symptoms were initially misclassified as a worsening condition of MS and were only identified later during post-marketing surveillance (Avasarala, 2018). This led some researchers into questioning how these symptoms could have been overlooked (Avasarala, 2018; Chisari et al., 2019). One journal criticised the EMA for not having stricter standards and argued that daclizumab should not have been authorised given the disproportionate harms (Prescrire International, 2018). Though the authors did not always explicitly address, their criticisms appear to derive from their want for clarity and justification on the decisions made by the EMA and hence, the agency's accountability. Also, a certain degree of alleged culpability towards the EMA could be observed.

2.2.2 Inquiry of the European Ombudsman on the EMA

The second case is related to the EMA's engagement with the medicine developers before MAA assessment in what is called the pre-submission activities. Medicine developers can request a meeting with the EMA to receive guidance on the application requirements (EMA, 2019d). Additionally, medicine developers can seek 'scientific advice' from the EMA on drug development, product safety and the design of clinical studies (EMA, 2019d). As these meetings are held behind closed doors, some raised concerns about transparency and potential influence of pharmaceutical industry on the EMA (Garattini, 2016; Natsis, 2018).

Recently, the European Ombudsman carried out an inquiry on these activities (European Ombudsman, 2019). Thereby, the Ombudsman pointed out one aspect of the scientific advice that was especially worrisome. Scientific advice falls under the formal responsibility of the CHMP, but its groundwork is assigned to two members ("coordinators") of the Scientific Advice Working Party (SAWP) who are appointed by the CHMP based on their specific knowledge. However, SAWP and CHMP have a significant number of overlapping members; according to the EMA (2019, p. 7), *"about one-fifth of SAWP members are also CHMP members"*. Remarkably, being appointed as a coordinator in the past does not necessarily restrain that person from being appointed as the rapporteur for the same medicine. Although the nature of both assessments is different; scientific advice focusses on how the clinical studies should be carried out whereas the MAA assessment relates to the robustness of the actual data, the ombudsman decided that the risks of bias and partiality cannot be fully ruled out (European Ombudsman, 2019). Even if the risks are somehow mitigated, the public perception that the risks are still present can be detrimental to the EMA's legitimacy (European Ombudsman, 2019). Therefore, the Ombudsman urged the EMA to increase the transparency in the agency's pre-submission activities and to better separate the scientific advice from medicine evaluation (European Ombudsman, 2019).

Both of the aforementioned cases show the concerns raised by external parties on EMA's accountability. While the daclizumab case is more concerned with the accountability in EMA's decision making and the subsequent outcomes, the European Ombudsman case emphasises more on transparency and potential bias in medicine evaluation. As medicine evaluation is a complex process, involving a vast number of clinical data, steps and experts, it is beyond the scope of this research to investigate the allegation of daclizumab or any other cases. However, as a European agency whose main purpose is to serve the European citizens, it is important to investigate how the EMA incorporates accountability in its system to ensure reliable and impartial evaluation of new medicines.

2.3 Stakeholders involved in medicine evaluation

To investigate how accountability is understood and incorporated in the MAA assessment, it is important to determine the relevant stakeholders. Stakeholder analysis is thereby a useful tool to identify the involved parties, their role and their interest in the MAA assessment (Schmeer, 2000). It provides a clear overview of the key players that will be used to select the participants for qualitative research. Stakeholders that are directly involved with the MAA assessment are; the CHMP, PRAC, pharmaceutical industry, healthcare professionals, patients and national medicines agencies (**Table 1**). Stakeholders that are not directly involved in the assessment but are important to the MA and the EMA are the EC and the EU citizens. Although the EC is responsible for the actual authorisation of a medicine, the task of medicine evaluation is delegated to the EMA and thus, conducted in the absence of the EC. Moreover, the EU citizens referred to the people from the EU to whom the EMA's mission, safeguarding the public health, is directed. Technically, patients can be considered as a subcategory of the EU citizens but as the patients are more directly involved in the MAA assessment, a distinction is made to better display each role.

Table 1. Overview of the relevant stakeholders of the MAA.

Stakeholders	Role	Engagement	Interests
Committee for Medicinal Products for Human Use	- Lead assessor of the MAA	- Bears the final responsibility for the MAA assessment (incl. risk management plan) - Formulates the final recommendation to the European Commission	- Primarily focused on the health of the EU citizens - Ensuring that MAA assessment is scientifically sound and following the EU guidelines
Pharmacovigilance Risk Assessment Committee	- Risk management plan assessor	- Provides scientific assistance in the MAA assessment as the assessor of the Risk management plan	- Ensuring that Risk management plan is scientifically sound and following the EU guidelines
Pharmaceutical industry	- MA applicant - Medicine developer - Holder of the intellectual property rights for the particular medicine	- Gathers and submits the information needed for the MAA assessment - Provides clarifications on the issues raised by the rapporteurs - Bears the cost of the MAA assessment *	- Providing new medicines to patients - Launching new medicines in the EU market - Earn revenues from the sales of medicines
Health care professionals	- Ad-hoc experts	- Provides first-hand insider knowledge on unmet health needs, workability and practicality issues related to the drug administration and the risk measures proposed	- Focused on patients' health, workability and practicability of the medicine in question
Patients	- Ad-hoc experts - Targeted patient group	- Target patient group of the particular drug - Provides first-hand insights on their needs, experiences of the disease and benefit-risk ratio of the medicine	- Industry responsiveness to the patients' needs and demands for a particular medicine
National medicines agencies	- Assessor of the MAA	- Supporting the rapporteur or co-rapporteur in their assessment	- Ensuring that MAA assessment is scientifically sound and following the EU guidelines
European Commission	- MA authority	- Formal authority to grant permission based on EMA's recommendation	- Primarily focused on the health of the EU citizens
EU citizens	- General recipients of the EMA's services	- Not actively engaged in the MA application assessment	- Expect EMA to act accordingly to the highest standards for the benefit of EU citizens' health

*Depending on the type of medicinal product and the size of the enterprise, medicine developers can benefit from fee reductions from the EMA.

3. Theoretical background

To have a proper understanding of this study, it is critical that the concepts that are used are well defined and understood in their meaning, theories and relations to each other. This chapter will provide an overview of the concepts that are relevant to the research question and the conceptual framework.

3.1. Multiple definitions of accountability

Accountability is a term that has been widely used within political and public discourse due to the implicit connotation of trustworthiness, righteousness and transparency (Bovens, 2007). Accountability is often seen as a desirable and important feature of organisations and public officials. As Koppell (2005, p. 94) phrases: *“Accountability is good—there is little disagreement on this point. Seldom is an organization branded “too accountable””*. One broadly adopted definition of accountability is the one by Bovens (2007, p. 450) where accountability is defined as *“a relationship between an actor and a forum, in which the actor has an obligation to explain and to justify his or her conduct, the forum can pose questions and pass judgement, and the actor may face consequences”*. Relationship refers to the social interaction and the notion of exchange that take place between the actor and the forum (Bovens, 2007). The actor and forum can be an individual or an organisation and the obligation imposed on the actor and the potential consequences either be informal or formal in nature (Brinkerhoff, 2005; Bovens, 2007).

From the EMA context, the accountability relationship between an actor and a forum can be understood as a formal relationship. In that sense, the CHMP, or the EMA as an organisation, can be considered the formal actor that is accountable for the evaluation of MAA as the CHMP bears the final responsibility for the assessment. (EMA, 2019d). Subsequently, the formal forum to which the CHMP needs to be accountable is the EC, the authority that grants the MA based on the CHMP's assessment (EMA, 2019d). The EC can be regarded then as the authority that is formally accountable for the marketing authorisation. Therefore, a subtle difference between accountability for the MAA assessment (or in other words medicine evaluation) and accountability for the marketing authorisation should be noticed. Moreover, the CHMP (or the EMA) can also be considered accountable to the European citizens. Accountability relationship in this larger sense can be perceived as more ambiguous since it is less straightforward and formalised as with the EC and more embedded in the organisational values and mission of the agency (EMA, 2019d). Among the stakeholders, however, different views may exist on who is accountable to whom in the medicine evaluation. As the stakeholders' view on accountability can have an influence on their expectations regarding the EMA, evaluating the stakeholders' opinions on accountability relationships is essential in the accountability discussion.

3.1.1. Accountability in health systems

Although Bovens' (2007, p. 450) definition of accountability is generally agreed upon, he acknowledges the ambiguity and fuzziness that still surround accountability. Koppell (2005) made an effort to distinguish the multiple aspects of accountability through his framework 'the five dimensions of accountability'. Here, Koppell (2005) attempted to facilitate the discussions of accountability in an orderly manner without imposing a single, comprehensive definition of accountability. However, none of the aforementioned scholars provide the context in which their definition/framework of accountability is applied. It is unclear from Bovens' (2007) and Koppell's (2005) work alone for which aspects of his or her conduct the actor is expected to be accountable.

Brinkerhoff (2004) has sought to address this matter by specifying accountability within the context of health systems. Health system represents an intertwined network of ministries, legislatures, regulatory agencies and companies that are connected to each other through different types of accountability relationships. Brinkerhoff (2004) proposed a conceptual framework in which these accountability

relationships are classified into three categories: financial, performance and political/democratic accountability. In the following section, each type of accountability will be described. However, financial accountability will not be elaborated as this study does not cover EMA's accountability regarding the agency's finance.

Performance accountability

Performance accountability refers to the answerability of one's performance in the view of the predetermined performance targets (Brinkerhoff, 2004). The focus thereby is on the services and outputs delivered at the organisational and programme level and thus, on overall achievement and efficiency. It is, therefore, not applied in the individual context. In the context of the market authorisation of the EMA, performance can relate to maximising the efficiency of the process or increasing the quality of the services delivered by the EMA. Moreover, performance accountability also relates to conformity to different regulation that are in place to deliver certain performance. This includes legal, regulatory and professional standards/policies but also quality standards, monitoring and evaluation tools.

Political/democratic accountability

Political/democratic accountability refers to the responsibility of the government to deliver on the election promises and to be receptive to the public's needs and demands (Brinkerhoff, 2004). This also means gaining public trust and representing the public that it serves. Therefore, political/democratic accountability is linked to performance accountability in that the elected officials and legislatures are expected to fulfil their campaign promises and thus, to deliver on the agreed-upon targets (Brinkerhoff, 2004). As an EU agency, EMA is expected to deliver on similar promises, namely safeguarding and promoting public (and animal) health in a science-based manner (EMA, 2019d). The corresponding accountability mechanisms are more of philosophical nature concerning the relationship between the EMA and the public, although conformity to law and regulations is also applicable. The philosophic aspect refers to the various standards of integrity, honesty, ethics and professional responsibility that reflect the EU values and culture (Brinkerhoff, 2004).

3.1.2. Social accountability

The framework of Brinkerhoff (2004) provide a good overview of the accountability in the health systems context. However, none of the accountability types include the aspects of social accountability, the notion of citizen engagement and participation in order to hold the government and organisations accountable (Fox, 2015; Joshi, 2017). Social accountability is important since the EMA/CHMP needs to be accountable to the EU citizens as well in addition to the EC. Here, social accountability is understood as "*citizens' efforts at ongoing meaningful collective engagement with public institutions for accountability in the provision of public goods*" as defined by Joshi (2017, p. 161). In the health context, public goods can refer to healthcare services, regulatory standards or access to information (Boydell, McMullen, Cordero, Steyn, & Kiare, 2019). Social accountability mechanisms thereby support the public voice and their rights, and hold the government, public organisations and officials accountable for their actions and performance (Fox, 2015). Examples of accountability mechanisms are systems in which the citizens can collectively address complaints, conventional media or monitoring through surveys and interviews, of which the found information can be demonstrated to healthcare officials and policy makers (Fox, 2015; Joshi, 2017). However, for these mechanisms to succeed, it requires an active, mobilised community that is well-informed and willing to collectively engage in the public discourse (Joshi, 2017). Therefore, social accountability does not focus on individual issues but rather on collective problems through unified action. Collective actions can occur through alliance building, legal intermediaries or policy advocacy (Fox, 2015; Joshi, 2017).

3.2. Purposes of accountability

According to Brinkerhoff (2004), three general purposes of accountability can be defined. These are *control*, *assurance* and *improvement/learning*. Control helps to prevent corruption and reduce concentrations of power while assurance is to ensure compliance with regulation, social values and laws when exercising authority or using (public) resources (Brinkerhoff, 2004). Improvement/learning is to enhance the performance through feedback and learning. Although purposes can overlap with each other, control is the predominantly purpose of political/democratic accountability whereas improvement/learning purpose is mainly pursued by performance accountability (Brinkerhoff, 2004). Assurance purpose is applicable to both performance and political/democratic accountability (Brinkerhoff, 2004). Although social accountability is not included in Brinkerhoff's framework, social accountability purposes can be formulated in similar manner as they are intended to reduce corruption, increase public engagement (both related to control) and ultimately, to improve the performances of health services (related to improvement/learning)(Joshi, 2017)

4. Conceptual framework

To better understand the connection and relations between the concept of accountability and the current context of the EMA, it is important to construct a conceptual framework. Thereby, Brinkerhoff's (2004) framework is used as the basis for the proposed conceptual framework. Although the focus of this project is solely on the MAA assessment and not the health system as a whole, the MAA procedure and the involvement of various stakeholders are dynamic and complex, and therefore, the framework was also used in the context of this study. Thereby, Yoshi's definition of social accountability is added as the third type of accountability (Yoshi, 2017). This results in a comprehensive framework of three different types of accountability within the health system context, each with different purposes (**Table 3**). Moreover, Bovens' (2007) definition of accountability was used to describe the actor(s) and forum(s) in medicine evaluation.

The topic of accountability was assessed at two levels; organisational level and individual level. Assessment at organisational level deals with the policies, regulations and strategic plans that are currently in place whereas individual level is concerned with the way that individual stakeholders interpret and experience accountability in the MAA assessment. Thereby, the proposed conceptual framework was used as a guiding analytical tool to explore and map the accountability concept according to the accountability types and purposes.

4.1. Sub-questions

In order to answer the main question '*How is accountability understood by stakeholders of medicine evaluation and how is accountability incorporated into the policies and guidelines of the EMA to ensure impartial and reliable evaluation of new medicines for marketing authorisation?*', the following sub-questions are formulated:

1. What are the policies, standards and protocols adopted by the EMA to ensure the agency's accountability in medicine evaluation?
2. How is accountability understood by the different stakeholders in medicine evaluation?
3. What (if any) are the accountability related challenges in medicine evaluation that are perceived by the stakeholders?

Table 2. Proposed conceptual framework of accountability based on Brinkerhoff (2004, p. 375) and Yoshi (2017, p. 161).

Type of accountability	Context	Dominant purposes of accountability
Performance	<ul style="list-style-type: none"> - Predetermined performance targets - Quality of care/ services - Professional behaviour - Regulation by professional bodies 	<p>Dominant: Assurance and improvement/learning.</p> <ul style="list-style-type: none"> - Assurance purpose emphasises on conformity to legal, regulatory, and policy framework, professional and quality standards. - Improvement/learning purpose focuses on standard setting, quality management, client satisfaction, operations research, monitoring and evaluation.
Political/democratic	<ul style="list-style-type: none"> - Service delivery - Transparency - Responsiveness to citizens - Service user trust - Dispute resolution 	<p>Dominant: Control and assurance.</p> <ul style="list-style-type: none"> - Control relates to citizen/voter satisfaction, use of taxpayer funds, addressing market failure and distribution of services. - Assurance purpose focuses on principal-agent dynamics for oversight; availability and dissemination of relevant information; adherence to quality standards, professional norms, and societal values.
Social	<ul style="list-style-type: none"> - Oversight electoral promises - Improve institutional performance - Citizen engagement and participation 	<p>Dominant: Control and improvement/ learning.</p> <ul style="list-style-type: none"> - Control relates to reducing corruption, overseeing electoral promises through citizen engagement and participation - Improvement/ learning relates to improving health care services, better policies and governance.

5. Methodology

To provide recommendations to European regulatory authorities to improve EMA's accountability in medicine evaluation, qualitative research was conducted using two data collection methods; a document review and semi-structured interviews. A concise document review was performed by systematically reviewing the policies, regulations and standards of the EMA that are in place to ensure scientifically sound MAA assessment and to hold the individuals and the EMA accountable for the outcomes. Semi-structured interviews were conducted to explore the stakeholders' view on EMA's accountability and accountability related challenges. The study took place over 5 months, between March and July 2020. The following section will provide more details on the study design.

5.1 Document review

The aim of the document review was to answer the **sub-question 1**. The predominant source of data were internal documents published by the EMA. The types of data included professional standards, different policies, reports on policy management etc. These materials are labelled grey literature as the data are not published from traditional publishing and distributing channels (Adams et al., 2016). Data were collected through the EMA website (www.ema.europa.eu).

5.1.1 Search strategy and data extraction

An initial exploratory search on the EMA website on relevant data revealed a tremendous amount of policies, work instructions, rules and guidelines etc. The maze-like website structure of the EMA made it difficult to locate all potentially relevant documents as most were scattered throughout the website. It was, therefore, beyond the scope of this study to identify every relevant document and review them on the accountability aspect. Thus, a deliberate selection had to be made on the to-be-used materials. Three documents were selected as a starting point for the document review namely, Anti-Fraud strategy, Annual Reports on Independence and Procedural Advice to CHMP members (EMA, 2008, 2017, 2019). Information on Anti-fraud strategy and Annual reports on Independence were obtained from the EMA website under the main category 'About us' and sub-category 'How we work' whereas the document Procedural Advice to CHMP members was found under the main category 'Committees' and sub-category 'CHMP'.

The document 'Anti-fraud strategy' was selected as it described the agency's effort to combat fraud to ensure agency's (scientific) integrity (EMA, 2017a). The Anti-fraud strategy also described the policies and procedures that were in place to identify and mitigate the fraud-risks, such as policy on whistleblowing and breach of trust procedure. These were further investigated according to the accountability types and purposes. The Annual Reports on Independence provided information on the status of policies related to the agency's independence. Many of them were also described in the Anti-Fraud strategy (EMA, 2017, 2019). These reports also presented the different controls that were performed by the agency to check policy compliance and their outcomes. Moreover, the Procedural Advice to CHMP members described the responsibilities of the CHMP members along with guidelines for a consistent approach in MAA assessment (EMA, 2008). In the document, references were made to other related materials which were subjected to further investigation. Additionally, EMA's response to the recommendations of the European Ombudsman was evaluated as it corresponded to the agency's democratic/political accountability. The relevant materials were found on the website of European Ombudsman (www.ombudsman.europa.eu), using the case number (CASE OI/7/2017/KR) as the search term.

5.1.2 Data analysis

In total, 13 documents were reviewed. The list of literature used, and the type of documents are displayed in **Annex 1**. For the data analysis, a deductive approach was used in which the findings were

mapped according to the pre-determined categories of the conceptual framework (**Table 3**). Each document was analysed according to the accountability types and purpose by using the conceptual framework as a guiding analytical tool.

5.2 Semi-structured interviews

Following the document review, semi-structured interviews were conducted to answer the **sub-questions 2 and 3**. This was to complement the findings from the document review on the existing accountability policies and their implementation and to gain more insights into the stakeholders' perspectives of accountability. Interviewing is a qualitative research method that provides a deeper understanding of the stakeholders' perspectives on accountability (Gray, 2018). Semi-structured interviewing was chosen over other types of interviewing as it allows the researcher to prepare the interview questions beforehand while it still offers the flexibility to ask follow-up questions and to steer the conversation (Gray, 2018).

5.2.1 Study population and sampling strategy

The study population consists of different stakeholders of the MAA assessment based on three categories: assessors, applicants and ad-hoc panel of experts. Assessors consist of the EMA and national competent medicines authorities. Applicants refer to the medicine developers and ad-hoc panel of experts to the healthcare professionals and patient/consumer organisations. Of each category, three to four participants were interviewed. Participants were categorised based on the organisation that the participants represented. For instance, a participant that worked for a pharmaceutical company was categorised as an applicant. Participants were selected through convenience sampling by using the network of Wemos as the primary source of recruitment. In addition to that, snowball sampling was used in which the participants were asked to refer the researcher to potential respondents from their professional network. The ideal participant was a stakeholder that had been involved in the MAA assessment but as that was not always feasible, the selection criteria were broadened to participants that were not directly involved in the assessment but familiar with the process.

5.2.2 Data collection and analysis

The interview guide was constructed based on the conceptual framework and sub-questions (**Annex 2**). Interview topics concerned stakeholders' definition of accountability, accountability related challenges and their knowledge on policies and policy implementation to ensure EMA's accountability in medicine evaluation. Relevant findings from the document review were incorporated into the interview guide to allow discussion on the MAA assessment and the EMA's pre-submission activities. The interview guide was adjusted and fine-tuned after initial interviews. Moreover, questions were slightly adjusted to each stakeholder type to better align with their perspectives. The interviews were held one-on-one in either Dutch or English and took around 40-60 minutes. Due to the COVID-19 pandemic, interviews were conducted either via telephone or video calls (Zoom) according to the participants' preference. In one interview, the participant provided her responses in written form. However, telephone interviews had a significant disadvantage over video calls that the behaviour and body language of the participants could not be observed. Additionally, the sound quality of telephone interviews was often very poor and made the transcribing more difficult. The interviews were transcribed and coded upon completion. Based on the document review and the conceptual framework, an initial coding guide was developed. The codes were corrected and adjusted as the coding progressed. The final coding guide is displayed in **Annex 3**. Coding was conducted using the ATLAS.ti 8 (ATLAS.ti Scientific Software Development GmbH, Berlin).

5.3 Ethical considerations

The online self-check tool by the Ethics review committee of the Vrije Universiteit Amsterdam concluded that no significant risks were associated with this study as the collected data were either

publicly available or related to the professional views of the participants (**Vrije Universiteit Amsterdam, 2018**). Thus, an ethical approval was not required. Interview participation was voluntarily, and the participant received an information sheet with the study aim and an informed consent form (**Annex 4**). Before the start of the interview, the participants were informed again on the study objective, the interview procedure and the participants' rights. The interview started only after receiving the signed informed consent and audio-recording was performed upon agreement. Participants had the right to refuse to answer any particular question and to withdraw from the study at any time. To guarantee anonymity, all personal details that can be traced back to the participant were deleted. More details on data management can be found in the data management plan in **Annex 5**.

5.4 Research quality

To increase the research reliability, two different data collections methods were used, namely document review and interviews. By using different research methods to collect data from different sources on the same topic, triangulation can occur (Easterby-Smith, Thorpe, & Lowe, 2002). Triangulation enables comparison of the findings, to even out the potential weakness in each research method and to increase the reliability of the results (Gray, 2018). Moreover, by recruiting participants that have been directly involved in the MAA assessment or are at least familiar with the assessment process, increased data validity is assured. Guaranteeing participant anonymity in the study and subsequent publications may have also contributed to more honest responses.

6. Results

The following chapter displays the relevant findings derived from both research methods and are structured according to the following themes; the definition of accountability, accountability role division, EMA's policies, and perceived accountability challenges and proposed solutions.

In total, 10 respondents were interviewed. The sample population of this study was extremely heterogeneous due to the small number of interviewees for each type of stakeholders and differences in their area of expertise and involvement in the MAA assessment. Some of the participants were involved in other EMA activities while others were more engaged with national medicine or reimbursement authorities. The extent of knowledge about the assessment procedure also differed greatly among the participants. Therefore, efforts were made to provide more context on the participants' responses. The characteristics of the study population are displayed in **table 4**. The main findings from the interviews are discussed in **section 6.1-6.5**.

Table 3. The characteristics of the participants.

Respondents number (n=10)	Type of stakeholders	Involvement in the MAA assessment	Area of expertise
01	Assessor	No	Reimbursement and pricings of pharmaceuticals
02	Assessor	Yes	Clinical assessor
03	Assessor	Yes	Clinical assessor
04	Ad-hoc expert	No	Policy, consumer organisation
05	Ad-hoc expert	No	Patient organisation
06	Ad-hoc expert	Yes	Medical specialist
07	Ad-hoc expert	No	Policy, consumer organisation
08	Applicant	No	Pharmaceutical market access
09	Applicant	No	Regulatory affairs
10	Applicant	No	Regulatory affairs

The document review (n=13) consists of four documents on policies and one on strategy, five instructions on particular procedures and three reports, including the Anti-Fraud strategy, Annual Reports on Independence and Procedural Advice to CHMP members (EMA, 2008, 2017, 2019). The latter three documents were used as a base to find the remaining literature, as they provided a comprehensive overview of related policies and standards (see **section 5.1.1** and **Annex 1**). The main findings are displayed in **section 6.3**. Moreover, two reports on the inquiry of the European Ombudsman were reviewed and discussed in **section 6.4.4**.

6.1 Accountability definition

The first step in comprehending the perspectives of different stakeholders on accountability was by evaluating how accountability was defined by these stakeholders. Unsurprisingly, accountability was described in various ways by the participants. However, most of the participants referred accountability in terms of responsibility. For instance, the 'assessor' stakeholder group addressed accountability in medicine evaluation mainly as the responsibility of the EMA to comply with the EU legislation and to justify the decisions that are made. For the 'applicant' stakeholder group, accountability meant the responsibility of medicine developers to submit in the best possible way a comprehensible file with correct, complete data of the clinical studies and being certain about the data submitted. This also meant that the applicant group expected medicine developers to be transparent and honest in their way of presenting the data and providing answers to the CHMP's questions. For the 'ad-hoc expert' stakeholder group, accountability was mainly defined in terms of responsibility and transparency that were expected from the EMA. Similar to the assessor group, they referred

accountability to as EMA being responsible for the decision-making in the MAA assessment and compliant with the European legislation. However, transparency was emphasised as a crucial element of accountability as transparency around the EMA's decision-making processes, people involved, and implementation of policies are needed to allow external scrutiny and to hold the EMA accountable for the subsequent outcomes:

"Transparency around decision making processes thereby allowing external scrutiny of actions and accountability for those actions and intended/unintended outcomes of those actions. Transparency about who is involved so that all can be held accountable. Honesty and humility about when things go wrong and accepting blame." – (ad-hoc expert representing consumer interests)

6.2 Accountability in medicine evaluation

This section elaborates further on participants' understanding of accountability by outlining their perception of stakeholders in medicine evaluation and the participants' opinions on who is accountable for the subsequent outcomes.

Although not always explicitly mentioned, most of the participants made a distinction between stakeholders that deal with the actual decision-making and stakeholders that are affected by the consequences of it. The majority of the participants considered the EMA, national authorities and the EC as the stakeholders of the decision-making process. Naturally, these stakeholders were also perceived as the ones that are directly involved in the MAA assessment. Stakeholders that are not directly involved in this but are affected by their outcomes were regarded patients, taxpayers, health professionals, insurance and pharmaceutical companies. Remarkably, the majority of the assessor group did not consider ad-hoc experts (i.e. patients and health professionals) as direct stakeholders as they are only consulted during certain phases of the assessment and thus, are not engaged in the decision-making process.

Moreover, the participants generally agreed that the EMA, or more specifically the CHMP, is accountable for the MAA assessment as the CHMP is formally responsible for the scientific evaluation and ultimately, the agency's formal stance on a particular medicine. However, an assessor with substantial experience in medicine evaluation explained that in practice, carrying out of the assessment is seen as a joint responsibility among the assessors of the EMA and national authorities. According to her, each assessor considers themselves equally accountable for the assessment and acted accordingly. She also explained that as representatives of each EU member states, CHMP members are appointed in a personal capacity, which greatly enhances their involvement in the evaluation. Similar to that, assessors within the national agencies act in good conscience from their professionalism.

Furthermore, the participants generally appointed the EC as the formal authority to which the CHMP needs to be accountable. An assessor pointed out that a delegate of the EC is always present as an observer in the meetings of the EMA committees for accountability purposes. Naturally, patients and the society at large were also mentioned as stakeholders to which the EMA needs to be accountable, albeit more in an informal sense, as a goal to aspire towards. For the assessor stakeholders, however, accountability of the CHMP went even further and was directed towards all the stakeholders that are involved or affected by their decisions:

"To all inhabitants of Europe, to all people who experience consequences of that decision; patient but also non-patients as they pay for it. Also companies. We are kind of arbitrators; we determine whether a file is of good quality to let a product on the market. So, you have to be able to explain when you are negative about something. You need to be able to explain why and also, when you are positive about it, to make sure you employ an equal treatment." – (Clinical assessor)

6.3 Accountability policies in MAA assessment

This section discusses the study findings on the internal arrangements of the EMA to ensure reliable and impartial medicine evaluation and accountability for the outcomes. First, the findings from the document review (n=11, see **section 5.1.1**) are discussed, which are grouped under four main topics. The interview findings are elaborated in **section 6.3.5**.

6.3.1 Conflict of interest

Conflict of interest (Col) may occur when assessors or experts involved in the MAA assessment are financially or in other way affiliated with the pharmaceutical industry. The assessors' affiliation with the industry could potentially influence their impartiality in the assessment, hence weakening the reliability of the outcomes (EMA, 2016d). Consequently, the EU legislation states that Col is undesirable and needs to be prevented (EMA, 2016d). Whether the interest actually influences the assessors' partiality is thereby irrelevant as the mere presence of the interest can be detrimental to the EMA's integrity and credibility of the assessment. Avoiding Col is, therefore, beneficial from both performance and political/democratic accountability perspectives. As a result, the EMA adopted a policy that requires committees' members and expert to annually submit a declaration of interests (DoI)(EMA, 2016d).

The assessment of Col consists of a 2-step procedure in which the level of interest is defined and the type of decision making that the person in question is planning to partake (Dias & Guido, 2007). The type of interest levels is automatically assigned and determines the length of restrictions applied. For the decision-making, five categories exist ranging from the highest type of decision making (e.g. Directors) to lowest (e.g. regulatory assistants). The restrictions that apply are based on the nature of the declared interest and the role and responsibilities to be assigned (Dias & Guido, 2007). To achieve transparency, the EMA publishes these materials, including Dols, CVs of the experts and assignment of the interest levels, on their website (EMA, 2016d). Moreover, since 2016, the EMA publishes clinical data submitted by medicine developers as supporting evidence for their MA application, making the EMA the first major regulatory authority in providing access to clinical data (EMA, 2019c).

When policies are violated, for instance, through incomplete and/or incorrect DoI, Breach of Trust (BoT) procedure can be initiated (EMA, 2018b). This relates to the liability aspect of accountability, where individuals within the agency face consequences for their actions. When intentional or serious negligence is suspected, the BoT procedure is started, leading to temporary suspension from EMA activities and appearing in a hearing (EMA, 2018b). In addition to that, all scientific outputs provided by the person in question are reviewed on scientific integrity. When a BoT is confirmed, sanctions may be applied such as exclusion from any memberships and activities of the EMA, handover to European anti-fraud office in case of suspected fraud and possibly, public exposure (EMA, 2018b).

6.3.2 Anti-fraud strategy

Moreover, the EMA maintains an active anti-fraud strategy to combat any forms of unlawful activities that undermine the agency's reputation and scientific integrity and works thereby closely with the European anti-fraud office (EMA, 2017a). The strategy consists of an action plan based on four objectives; creating an anti-fraud culture within the agency, managing an efficient reporting system, strengthening the current detection measurements and identifying and mitigating fraud-risks. Some of the anti-fraud arrangements are already mentioned, such as BoT procedure and policies on COI and transparency (e.g. publishing CVs and Dols) but others include policy on whistleblowing for the staff and a policy on alleged improprieties by the EMA from external sources (EMA, 2017b, 2017c, 2017a). The latter two policies help to promote proactive reporting on alleged concerns on fraudulent behaviour through an environment of trust and a low-threshold reporting system. The policy on alleged improprieties from external sources also enhances social accountability of the EMA as it allows external sources to call out on the agency's improprieties (Joshi, 2017).

6.3.3 EMA Annual reports on Independence

Since 2015, the EMA started publishing an annual report on Independence in which various agency-wide policies regarding independence are reviewed (EMA, 2016a). The report provides information on the status of these policies, their implementation and the outcomes of check-ups. It also elaborates on actions that were taken and focus areas for improvement. Majority of the independence policies are related to Col and DoI of EMA employees and the control mechanisms that are performed are both *ex ante* and *ex post* of nature. *Ex ante* controls checks the new experts on correct filling of the DoI form and conformity of the information given in DoI with those in CV while in *Ex post* controls, experts are randomly selected for evaluation (EMA, 2019a). According to the most recent report, around 21% of CHMP members and 23% of experts had either a direct or indirect interest with the pharmaceutical industry in 2019 (EMA, 2019a). Moreover, seven BoT procedures had been initiated over the years 2018 and 2019 leading to one condemnation, where the person in question was excluded for 12-months from all EMA activities (EMA, 2019a).

6.3.4 Procedural Advice to CHMP members

The foundation for the operational system of CHMP is based on the EU legal framework for medicinal products for human use, that is integrated into the CHMP Rules of Procedure (EMA, 2007). In this CHMP Rules of Procedure, the responsibilities and composition of the CHMP, the appointment of the (co)rapporteurs, and the data to be published are defined among others (EMA, 2007). More details are described in Procedural Advice to CHMP members that are prepared to maintain a consistent approach for the assessment and to efficiently operate the procedure, which contribute to the performance accountability (EMA, 2008). It provides thereby guidelines for each action to be taken from the CHMP members, (co-)rapporteurs and peer-reviewers for each phase of the assessment along with guidance on interactions with EMA staff, external experts or applicants on different topics.

6.3.5 Qualitative data on accountability policies in MAA assessment

To complement the findings from the document review, semi-structured interviews were conducted to obtain more insights into the current policies/standards of the EMA to ensure accountability and their implementation. However, this proved to be difficult as most participants were not directly involved in the assessment. Even for those that were closely engaged with the MAA assessment such as the assessors, it was difficult to provide specifics on the policies and the way they are realised. Most often, this was due to the tremendous number of policies/guidelines, their extensive details and the numerous organisational levels within the EMA. For instance, participants could not say with certainty who controlled and monitored a particular policy. Majority of those participants, therefore, referred to the EMA website, where all the documents on policies and regulation are published. However, this resulted in another challenge or as one assessor puts it:

“But try to find it. It is an insanely large website. There are even training courses on how to find my way on the EMA's website. Internal people grab Google to search their own website, which is still difficult. On the one hand they are very transparent, on the other hand it is also so much. You have been browsing the website yourself. It is quite a bit, it is quite a lot.” – (Assessor with expertise in reimbursement and pricings)

Instead of informing on specific policies and their implementation, some participants spoke of how the EMA engages different stakeholders to improve its accountability. For instance, patient/consumer organisations participate through EMA's working parties in discussions to advocate for policies and issues that are of interest of patients and consumers. One assessor also mentioned the EMA network strategy for 2020-2025 that was open for public consultation. All types of stakeholders were allowed to provide input and thereby, contribute to the future direction of the agency. Both can be considered as a form of social accountability as they allow citizens to raise awareness on the patients' needs and address (systemic) problems (Joshi, 2017). The main purpose is improvement/learning, which is the dominant purpose of social accountability. However, these examples can also be seen as a form of

political/democratic accountability as they enable the EMA to be responsive to citizens and gain their trust (Brinkerhoff, 2004). According to another assessor, the EMA regularly holds public hearings to engage citizens in the medicine discussion. He referred to a public hearing on safety concerns of valproate in 2017, where everyone could sign up and provide input on the questions discussed. As these hearings are not intended to hold the agency or officials accountable but rather to engage the public in the EMA's decision-making, they can be considered as political/democratic accountability. In medicine evaluation, stakeholder engagement related mostly to EMA's effort to increase the reliability of the MAA assessment and hence, the performance accountability (Brinkerhoff, 2004). The assessors considered thereby, scientific insights and expertise as most important. According to them, the EMA works together with experts from all over Europe through the agency's working parties and related groups. The rapporteurs, however, also have the authority to include external experts or patient groups when more perspectives are needed. The assessors also mentioned that relevant stakeholders are regularly invited to CHMP meetings to provide inputs which help the CHMP in strengthening the scientific justification and eventually, in forming an opinion on a drug.

6.4 Accountability challenges in medicine evaluation

The following section elaborates on accountability related challenges in medicine evaluation perceived by the participants and the solutions proposed by them. Here, the challenges refer to any risks and difficulties faced by the EMA that may compromise the reliability and impartiality of the assessment. Most participants perceived some degree of challenges and differences existed in the extent to which the participants were satisfied with current interventions and execution. However, participants were generally of the opinion that the EMA was doing its best to meet the expectations of all stakeholders and was continuously striving for excellence and improvement. Moreover, the challenges mentioned by the participants were often so different from each other that it was difficult to reach a consensus. The stakeholders also sometimes had different views on certain issues. Despite these differences, four common themes could be identified. The following section will elaborate on the main findings under each theme. Thereby, more emphasis is laid on the narrative and context of the challenges addressed.

6.4.1 Stakeholder engagement in medicine evaluation

According to a medical specialist that had been previously involved in the assessment, the EMA fails to meet the patients' needs due to the lack of practical knowledge. The participant pointed out the insufficient involvement of experts (including medical specialists) with practical experiences in the assessment as the main problem. To her, the role of ad-hoc experts feels quite limited as they are consulted only in the last phase of the assessment when most of the matters seems already decided. The medical specialist stated that this lack of early involvement can lead to issues such as clinical studies with questionable endpoints due to inadequate knowledge of a particular disease and its complications. As the outcomes of the assessment may be affected by this, the problem corresponds to the performance accountability (Brinkerhoff, 2004).

Two underlying causes were mentioned for this whole problem. According to the medical specialist, the EMA is willing to change but are restrained by its system which she called *"bureaucratic"*, *"top-down"* and *"incredibly inflexible system"*. She criticised the EMA's way of holding meetings over and over again to come up with new procedures and frameworks with *"nice-sounding names"*. The medical specialist was sceptical, however, whether these new procedures actually lead to better effectiveness and more efficient use of medicines. According to her, the EMA functions in a too narrow circle of experts to adequately visualise the problems and their relation to each other. However, the participant believed that the EMA is not blameable for operating in a flawed system, although the EMA could try or enforce the system to change. She believed that ad-hoc experts also have a shared responsibility, which leads to the second cause of the problem.

In the normal course of events, the EMA approaches experts from its own database. However, according to the medical specialist, those that are actively involved with the regulatory activities are also often affiliated with the pharmaceutical industry, leading to Col. According to her, other experts with practical knowledge are either unaware of the EMA activities or are not interested in being involved.

“They must be included early in the process, but in such a way that they are independent from the pharmaceutical industry. And that’s a hell of a problem because the real experts are often deeply intertwined in conflict of interest with the industry.” – (Medical specialist)

Therefore, she proposed two-sided recommendations for improvement: Firstly, the EMA should try harder to include the ad-hoc experts much earlier in the assessment and should thereby actively approach experts not listed in their system. Secondly, external experts also need to proactively engage in medicine evaluation and be willing to provide their expertise separate from the industry. This problem of Col among the experts was also mentioned by another ad-hoc expert that represents consumers’ interests. However, this participant approached the issue from the political/democratic accountability perspective. According to her, more transparency is needed from the EMA on selection criteria as it is currently unclear why certain experts with Col are allowed to participate in certain discussions while others are not. Therefore, transparency is needed on the efforts made to find other experts without Col and when Col is inevitable, a justification for the situation. Therefore, this ad-hoc expert emphasised the need for transparency in the EMA’s decision-making to sustain public trust and subsequently, political/democratic accountability (Brinkerhoff, 2004).

Most of the assessors acknowledged the limited role of ad-hoc experts in the decision making of the CHMP whose exclusive right to form opinions is defined by the EU legislation. A highly experienced assessor stated that ad-hoc experts are only invited to provide additional perspectives on a specific file. Excluding external experts from decision-making was considered important to keep the assessment consistent because otherwise, a system is introduced that can take a certain direction depending on who is invited. Thus, the CHMP’s way of decision-making corresponds to both performance and politic accountability as it is related to the quality of the assessment but also to consistent service delivery. However, he acknowledged the criticism on the EMA for not engaging more different experts although, more efforts are made in recent years to include experts from all corners of Europe. Nonetheless, this assessor believed that more engagement was needed from the stakeholders as firms are usually the ones that proactively participate. He does recognise that this is a matter of capacity, such as people and time. He also stated that the different nature of PRAC and CHMP might play a role in this: The PRAC deals with the safety profile of a medicine, which is easier to understand and directly affects patients and citizens while the CHMP is more concerned with the scientific assessment.

6.4.2 Scientific assessment

The following section elaborates on the challenges related to the scientific justification of the assessment. In the contextual background, the daclizumab case functioned as an example in which the CHMP’s decisions were criticised. Although this study does not focus on specific cases, the daclizumab case provided a glimpse on accountability issues related to the outcomes of the assessment. This section attempted to provide insights into the difficulties faced by the assessors during the assessment.

The challenges that were mainly addressed by assessors related to the consistency of the assessment and scientific argumentation and therefore, corresponded to performance accountability as they concerned the quality of the assessment (Brinkerhoff, 2004). Many assessors called the uncertainty in decision-making a challenge, that of finding the right balance between scientific evidence and forming an opinion on a product. They all stated that no decision can be made without a certain degree of uncertainty as otherwise, no medicines will be authorised. According to them, finding the right cut-off

point needs to be continuously worked on as the benefit-risk ratio of medicines are different for each disease. According to one assessor, medicines are authorised on the condition that their safety profile is acceptable, and the potential benefits are known. The assessor explained that benefits and risks are clearly communicated to the doctors and patients and it is then often up to them to determine whether the medicine is suitable for the patient.

“What can happen is that you say: This is the benefit, most of the patients will experience this side effect. However, for the patients who can tolerate this side effect, there is clearly an advantage. And that can be a reason to be positive and by that, a product becomes an option for a patient without saying that it is suitable for everyone.” – (Clinical assessor)

Another challenge that was mentioned was acquiring ‘knowledge’ from past decisions. According to an assessor, the ability to reflect on past judgments is extremely important for consistency and fair treatment of each assessment. She argued that questions such as *“Why did we approve it then and don't we approve it now?”* and *“Can we explain that or is there really no difference at all and should we do the same as last time?”* must be answered with high certainty. This also serves accountability purposes as the assessors need to be able to justify their decisions to both EC, patients and medicine developers. Although the data and files are stored in electrical systems and thus, readily available, the process of finding and analysing the relevant information to obtain the right knowledge is extremely time-consuming. According to her, most of this knowledge is *“contained”* in individuals and retrieving this knowledge depended on individuals’ memories. She believed that the extent to which this knowledge is accessible determines the efficiency of the assessment. She emphasised, therefore, the need for better organisation of information.

“Those people, at least that's how it works, those people can look it up because they remember “Oh yes, that was in 1995 in the summer. We discussed that matter in this way”. This is how it is found and taken along, while actually, you should have that knowledge system all over Europe and it should not be dependent on organisation at a national level or its cooperation with the EMA.” – (Clinical assessor)

Moreover, according to another experienced assessor, criticisms on authorised medicines often results from differences in the endpoints adopted by critics and the subsequent reimbursement discussion. Clinical endpoints define how the outcomes of clinical studies are measured and subsequently, when medicine is considered to be effective. The assessor took oncology as an example, where life extension can be taken as an endpoint but also relief of symptoms. These are not necessarily correlated to each other thus different opinions may exist on the suitability of the endpoint taken. For instance, insurances can refuse to reimburse a certain cancer treatment as it only results in 3 months life extension.

6.4.3 Skewed balance between national competent authorities

The assessors also mentioned the current EMA system that is highly dependent on the contribution of individual member states a challenge. According to them, a huge variable exists in the way that national agencies of the member states are organised. Consequently, not every member state has the financial means or expertise to equally contribute to the MAA assessment. Additionally, the reference frameworks between the states are often different which may create variability in the assessment. Thus, these issues seem to correspond with performance accountability as they relate to standard setting and operationalisation of the assessment (Brinkerhoff, 2004). One assessor stated that the EMA's annual report shows that five member states, including the Netherlands, accounted for approximately 55% of the rapporteur appointments in 2019 (EMA, 2020a). Though the member states are equally represented in the CHMP, only a small part are involved in the major work. Multiple assessors pointed out the primary cause for this skewed balance to the capacity of each member states such as financial resources but also work efficiency and innovation gaps. However, according to them, a clear-cut approach is difficult to acquire as finances of national agencies are regulated at national

level. The assessors did emphasise that the quality of overall assessment is not necessarily comprised as all CHMP members provide inputs during the meetings and steer the assessment in right direction when needed. Moreover, the assessors stated that the EMA tries to allocate the (co-)rapporteur roles to a member state with a well-established system together with a member state with a less advanced system when possible. Also, the EMA encourages the member states to form a multinational assessment teams, an initiative that has been launched in 2013 (EMA, 2017d). Here, the assessment teams are formed by more than one member states, thus, allowing the role of (co-)rapporteurs to be shared by multiple states instead of two.

6.4.4 EMA's engagement with medicine developers prior to submission

This section discusses the findings from the document review (n=2, **section 5.1.1**) and interviews on pre-submission activities of the EMA. Based on the inquiry in 2019, the European Ombudsman recommended the EMA to better separate the scientific advice from the MAA assessment and to provide more transparency on the pre-submission activities (European Ombudsman, 2019). The Ombudsman also recommended that at least one of the two rapporteurs is not involved in the scientific advice for that same medicine and if this is not feasible, that the EMA should provide justification in EPARs (European Ombudsman, 2019). The EMA promised to work on these recommendations and provides now a summary of scientific advice in EPARs (EMA, 2019b).

The participants were asked to give their opinion on this matter. All participants agreed about the necessity of scientific advice for the improvement of clinical study designs. However, the ad-hoc experts were concerned on potential bias and inconsistent treatment. Though there was not a direct cause for concerns, these participants considered important to remove even the illusion of partiality/bias to improve the agency's political/democratic accountability (Brinkerhoff, 2004). Multiple ad-hoc experts considered transparency thereby as an important factor in fostering the EMA's accountability. A participant representing consumers' interests stated that more transparency is needed on scientific advice and appointment of rapporteurs. Not only allows transparency for external scrutiny but it was also believed that transparency could benefit all parties, including pharmaceutical companies, from information sharing. The EMA's promise to review the Ombudsman's recommendations was, therefore, highly encouraging although it ultimately depended on the implementation. As a control mechanism, she suggested an independent committee or board that evaluate how the agency is run and how policies are being implemented. But transparency alone without a preconceived plan was considered not enough. A follow-up and open dialogue with the relevant stakeholders are needed to learn and improve the policies.

Conversely, the majority of the assessor and applicant groups considered current policies sufficient to provide adequate advice and reliable assessment. They argued that decisions and meetings are held with multiple people and that there is a high degree of integrity and professionalism among the stakeholders. Some of the participants were also favourable towards the idea of appointing a coordinator with previous experience in scientific advice to a rapporteur role to increase the efficiency. According to them, coordinators who initially had contact with medicine developers are already familiarised with the product and its development. It is, therefore, easier for those assessors to evaluate whether the studies are properly executed and resulted in more robust data.

"It is really nice that a rapporteur member state already knows what else has been done and they know very well what is going on with your product, what the product stands for and why you may have made certain choices." – (applicant from regulatory affairs)

Moreover, the assessors related the lack of transparency in the scientific advice primary to commercially confidential information of the companies rather than the unwillingness of EMA to disclose any information. According to an assessor, the phase in which scientific advice is requested is during the development stage where new ideas are created and tested. Publishing information during

this phase of development means that these ideas become available to competitors. Thus, even though the EMA puts efforts to maximise its transparency and takes precautionary measures, forcing complete transparency can have the negative effect that medicine developers become reluctant to seek advice. This was considered to be even more harmful to public health and innovation than the current concerns on transparency. This presents the dilemma the EMA finds itself as it is constrained by two opposing stakes; public and private interests.

6.5 Other remarks

The applicants did not perceive many accountability related challenges in medicine evaluation. Certainly, medicine developers encounter difficulties in collecting enough accurate data for the submission but the evaluation itself was experienced as a standardised process. One participant working in regulatory affairs stated that application file is filled according to a fixed template with, for instance, guidelines on standard phrases to be included in certain situations. She considered the procedure timeline and the standards to which the file must comply to be very clear. Moreover, the EMA always gives justification when a certain product earns a negative opinion. Therefore, from applicants' perspectives, no challenges were perceived related to accountability.

Moreover, some of the participants also mentioned the challenge of pricing and medicine reimbursement after the medicine is authorised. Patients access to medicines depends as much on pricings and reimbursement as on authorisation. However, pricing and reimbursement are regulated on a national level according to national legislation and are, therefore, not part of the EMA's tasks. Some of the interviewees wished for greater involvement of the EMA and other authorities in the reimbursement discussions and thus, expanding the EMA's accountability to other areas but as this subject was beyond the scope of medicine evaluation, it was not included in this study.

7. Discussion and conclusion

This research aims to provide policy recommendations to the European regulatory authorities in medicines on EMA's accountability in medicine evaluation by investigating how accountability is incorporated in the current policies of the EMA and how accountability is understood by the stakeholders involved in medicine evaluation. In the following chapter, the interpretations and potential implications of the main findings will be discussed, along with their link to the conceptual framework. It will also elaborate on the limitations of the study and provide suggestions for future research. Finally, policy recommendations for the improvement of EMA's accountability are given, followed by conclusion.

7.1. Discussion of main results

7.1.1 Accountability according to the stakeholders of medicine evaluation

The majority of the participants identified the CHMP/EMA as the actor that is formally accountable for the outcomes of the MAA assessment. Consequently, the formal and informal forums to which the CHMP needs to be accountable were considered the EC and EU citizens, respectively. Moreover, the majority of the participants defined accountability in terms of responsibility. For instance, assessors defined accountability mostly as the EMA's responsibility to adhere to the EU legislation and to take ownership of the decisions made. They also associated responsibility (and thus, accountability) with a personal sense of obligation coming from professional norms and values. Thus, the assessors' definition of accountability corresponded largely to Brinkerhoff's (2004) performance accountability as it related to the answerability to the outcomes and professional behaviour. However, political/democratic accountability could also be noticed from the EMA's responsibility to conform to the EU law. The applicants' understanding of accountability also related to performance accountability although they defined accountability as the responsibility of medicine developers to submit a correct file according to the EMA's standards, to be certain about the submitted data and to answer honestly to the questions of the assessors. Furthermore, ad-hoc experts expressed accountability from their expectation of the EMA to be responsible for the outcomes of the medicine evaluation and compliant with the EU legislation. The ad-hoc experts also related accountability to transparency in EMA's decision-making processes that is necessary to allow external scrutiny so that the EMA can be held accountable. Thus, the ad-hoc experts addressed accountability mostly in the political/democratic context; the need for transparency to control the EMA of any wrongdoing and the importance of maintaining public trust.

Although none of the applicants considered medicine developers to be accountable for the assessment, based on their definition of accountability, it seemed that their role as applicant still demanded some form of answerability. The relationship between the applicants and the EMA were similar to those between an actor and a forum and fitted well to Bovens' (2007, p. 450) definition of accountability (**section 3.1**). Here, the MA applicant (i.e. medicine developer) is the actor that is obliged to explain and justify their data to the CHMP, the forum. As medicine regulatory authority, the CHMP can ask questions to the applicant and pass judgement on the provided information. The well-known consequences are receiving positive or negative opinion on their product. Therefore, this example suggests the presence of different layers within the assessment procedure and the possibilities of various accountability relationships between multiple actors and forums.

7.1.2 Accountability policies in medicine evaluation

From the document review, different types of accountability arrangements were found that are adopted by the EMA to ensure reliable and impartial MAA assessment and accountability for the outcomes. However, information on the current accountability policies and their implementation could not be obtained from the participants as the majority of them were not directly involved in the

MAA assessment. Same was true for stakeholders that were closely engaged due to the vast number and the extensive nature of the policies. The participants often suggested looking upon on the EMA website where all policies are published. Nonetheless, some participants were able to explain how the EMA tries to improve accountability by engaging with different stakeholders. Based on the findings from the document review and interviews, the accountability policies and modus operandi of the EMA were evaluated using the conceptual framework (**Table 3**).

Accountability measures related to the performance are the CHMP's guidelines and rules in which the CHMP's responsibilities are outlined to ensure a more consistent approach in medicine evaluation and policies on DoI and CoI that help to reduce potential bias and impartiality in the assessment. Moreover, engaging different stakeholders (ex. ad-hoc experts) during the assessment and the CHMP's way of collectively making decisions also contribute to strengthening performance accountability as the decisions are made by multiple people based on multiple insights. The main purposes of these measures are assurance since they help to safeguard the scientific integrity of the assessment while also ensuring compliance with the quality/professional standards (Brinkerhoff, 2004). The BoT procedure, whistleblowing policy and *ex ante* and *ex post* check-ups are thereby the control mechanisms that oversee compliance with the regulation. The presence of an EC delegate in the committees' meetings also contributes to that objective.

Political/democratic accountability is achieved through public hearings where citizens can engage in the medicine discussion and transparency policies on clinical data, meeting minutes, EPARs, DoI etc. Policies on DoI and CoI also contributes to the EMA's political/democratic accountability by protecting the agency's legitimacy and reducing corruption. Also apparent from the anti-fraud strategy, the EMA actively works on creating a culture of integrity. The aim of these measures is to increase the EMA's responsiveness towards the citizens and to maintain their trust. However, transparency policies are also related to social accountability as the public needs to have clear insights into the EMA's performance in order to hold the agency accountable. The EMA's reporting system that allows external sources to report on alleged wrongdoings of the agency is another form of social accountability measure and relates to the control aspect of accountability. Other examples are public consultation and different working parties where patient/consumer organisations can participate in the discussions to raise awareness on the patients' needs and new policies. Thus, the main purpose here is improvement/learning.

7.1.3 Perceived accountability challenges and solutions

Although differences exist in the extent to which the participants were satisfied with current interventions, the majority of the participants acknowledged that, given the situation, the EMA does its best to conduct the scientific assessments as objectively as possible. However, there was little consensus among the participants on accountability challenges in medicine evaluation. Some participants were very outspoken while others were more nuanced or neutral. Participants also often had different views on certain issues. Still, this section attempted to provide insights into the main issues identified.

The challenges addressed by the ad-hoc experts mostly related to political/democratic accountability, concerning the responsiveness and transparency of the EMA. The ad-hoc experts considered insufficient transparency and the lack of practical knowledge as the main challenges in medicine evaluation. They stated that more transparency is needed on EMA's decision-making (ex. scientific advice, selection criteria for experts) and the implementation of policies. For instance, an independent committee or board could be established that evaluate the implementation of policies. Additionally, experts with practical knowledge should be involved in a much earlier phase of the assessment as this could help to reduce the number of clinical studies with questionable endpoints. Moreover, more efforts should be made by the EMA to include experts outside its database.

However, the ad-hoc experts' views were not always agreed on by other stakeholders. Many assessors and applicants considered the current policy system sufficient and some were even favourable towards having the scientific advice and medicine evaluated by the same assessors as it would increase the efficiency. Moreover, the lack of transparency on certain processes were often related to the commercially confidential information of companies rather than the unwillingness of the agency to be transparent. Additionally, excluding the ad-hoc experts from the decision-making was considered important for the consistency of the assessment though it was admitted that most criticisms on the assessment outcomes related from different views on clinical endpoints.

The challenges perceived by the assessor group were mostly related to consistency and scientific justification and thus, performance accountability. Difficulties in retrieving knowledge from past judgements and uncertainty in decision-making were considered the main challenges. Better organisation of information was thought to increase the accessibility to relevant knowledge and subsequently, efficiency. However, uncertainty in the assessment will always remain as no universal solution exist. Another challenge mentioned was the capacity imbalance between the member states that leads to unequal contribution and variety in the assessment. Here too, finding a univocal solution is difficult since the member states are regulated at national level. Nevertheless, the overall quality of the assessment was not compromised as the CHMP decisions are collectively made. Also, member states with smaller capacity can still contribute by joining into multinational assessment teams.

7.2 Strengths and limitations

To evaluate and validate the findings of this study, it is important to understand the strengths and limitations of the research design. This section provides an overview of the strengths and limitations of this study. The main limitations of the study are the small size of the sample population and the limited inclusion of stakeholders with experience in the MAA assessment. For each stakeholder type, three to four interviews were conducted. Moreover, only three participants had been involved in the MAA assessment. Some of the participants were active in other areas of the EMA, while others worked only with national regulatory authorities. The participants were, therefore, not always able to answer the interview questions. Difficulties were experienced in finding and recruiting participants with this specific experience. Recruiting ad-hoc experts and applicants was especially challenging as their involvement in medicine evaluation was less apparent than for example, the CHMP members. Also, many professionals declined the interview invitation because of the increased workload related to COVID-19. Therefore, the criteria for selection had to be adjusted to participants that were familiar with the MAA assessment.

Moreover, the select number of literature used for the document review may have resulted in a limited representation of reality. As a full elaboration on all relevant regulations was beyond the scope of this research, the document review mainly focused on accountability policies based on three EMA documents (see **section 5.1.1**). Originally, the results from the document review should have been complemented by the findings from the interviews. However, due to the limited contribution of the participants, triangulation could not be achieved to validate the obtained data (see **section 7.1.1** for explanation). These factors likely have contributed to the heterogeneity of the data. The study focuses, therefore, on the context and narratives of each participants. By doing so, more detailed information could be obtained on the participant's opinions and experiences in the setting of the EMA and medicine evaluation. Many participants had years of experience in their field and had an excellent overall understanding of the (European) regulatory system for medicines. Interviewing different types of stakeholders on accountability also provided insights into the complexity of the issues.

7.3 Further research

To strengthen the findings of this study, two suggestions are given for further research. Firstly, a follow-up study on the implementation of policies should be performed to obtain a more in-depth

understanding of how accountability is realised by the EMA. This study provided little information on policy implementation and investigated only a fraction of the existing policies. Therefore, interviews with, for example, experts in the field of pharmaceutical regulation and a more extensive document review will provide a more comprehensive understanding of the EMA's accountability arrangements. Secondly, the study may be expanded to other areas of accountability or medicine evaluation such as EMA's financial accountability, conditional MA and accelerated assessment. For instance, the industry's contribution to the EMA amounted ~€306.8 million in 2020, which is around 86% of the agency's whole yearly budget (EMA, 2020b; Garattini, 2016). Subsequently, some concerns have arisen on the EMA's financial dependence on the pharmaceutical industry. Moreover, under certain conditions, the EMA can grant a positive opinion for a drug with less comprehensive evidence in case of immediate health risk situations (EMA, 2016c). Accountability in conditional MA and accelerated assessment seem especially relevant in the current outbreak of COVID-19 due to the urgent need of vaccines.

7.4 Policy recommendations

Based on the main findings, policy recommendations are formulated that could help the EMA to improve accountability in medicine evaluation.

Policy recommendation 1: *Investing in knowledge retrieval systems*

With the continuously growing amount of data and information, it becomes increasingly important to retrieve the right knowledge for application (Yao, Zeng, Zhong, & Huang, 2007). The traditional data system that makes the information accessible becomes thereby less relevant as the focus shift to the extraction of relevant knowledge and the context of information (Yao et al., 2007). From the interviews with the assessor group, it was apparent that much of the knowledge about previous assessments comes from individuals' personal experiences. Retrieving this knowledge of the past decisions, therefore, relied heavily on individuals' memories rather than on data systems. Although the relevant documents and information are stored in data systems, much effort is needed to find and extract the useful knowledge from those data, at the expense of efficiency and perhaps, consistency of the assessment. Therefore, investing in systems that enable knowledge retrieval is highly recommended to the EMA to maintain consistency in medicine evaluation and to increase performance accountability (Sheng, Fan, Thomas, & Ng, 2001; Yao et al., 2007).

Policy recommendation 2: *Increasing involvement of external advisors*

The authority of the CHMP to lead the assessment and to provide advice to the EC is derived from the EU legislation and was considered important for the consistency of the assessment. Thus, inputs from external experts were only sought when additional insights were needed. However, involving more experts in the begin phase of the evaluation may help to reduce criticisms on the assessment outcomes, which are often related to clinical endpoints. Moreover, inputs of 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 may be improved and thereby, the agency's accountability on performance.

Policy recommendation 3: *Increasing transparency of selection criteria for experts*

In addition to recommendation 2, a policy recommendation is made to increase the transparency on the selection criteria for experts. Although increasing efforts are made by the EMA to engage experts from outside the agency, there was still unclarity among the external stakeholders on which criteria the EMA bases its selection. Transparency is, therefore, needed on the efforts made by the EMA to approach suitable and independent experts along with justification when Col of a particular expert is inevitable. Not only will this increase the agency's political/democratic accountability, by being responsive to the public and gaining their trust, but it will also benefit the agency's performance

accountability as transparency on selection criteria may help to find better ways to approach and engage external experts in medicine evaluation.

7.5 Conclusion

This research aimed to provide insights into accountability policies of the EMA and stakeholders' perception of accountability and accountability related challenges in medicine evaluation to provide policy recommendations to EU regulatory authorities. This study showed that a general consensus exists among the different stakeholders on how accountability is understood and who is considered accountable for the outcomes of the MAA assessment. Moreover, the EMA's efforts to enhance accountability was recognised from the numerous policies and standards that were in place to ensure reliable assessment and accountability for the outcomes. However, many stakeholders perceived some degree of challenges in medicine evaluation that may compromise accountability of the EMA. In general, the ad-hoc experts mostly experienced challenges related to political/democratic accountability, while assessors were more concerned with performance accountability. Based on these findings, three policy recommendations are formulated to improve EMA's political/democratic and performance accountability in medicine evaluation: Investing in knowledge retrieval systems, increasing involvement of external advisors and Increasing transparency of selection criteria for experts.

8. References

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Annex 1: Literature used for document review

Number	Title and reference	Type of document
1	CHMP Rules of Procedure - (EMA, 2007)	Instructions on the procedure
2	Procedural Advice to CHMP Members - (EMA, 2008)	Instructions on the procedure
3	SOP Assessment of competing interests of Agency employees - (Dias & Guido, 2007)	Instructions on the procedure
4	2018-2019 Annual reports independence - (EMA, 2019a)	Report
5	Anti-Fraud Strategy Revised December 2017 - (EMA, 2019a)	Strategy
6	Breach of trust procedure for DoI and confidential information - (EMA, 2019a)	Instructions on the procedure
7	Fraud Reporting Process - (EMA, 2017c)	Instructions on the procedure
8	Reply from the European Medicines Agency (EMA) to the Ombudsman's suggestions for improvement in strategic inquiry OI/7/2017/KR into EMA's pre-submission activities - (EMA, 2019b)	E-mail correspondance
9	Decision in strategic inquiry OI / 7 / 2017 / KR on how the European Medicines Agency engages with medicine developers in the period leading up to applications for authorisations to market new medicines in the EU. - (European Ombudsman, 2019)	Report
10	Policy Handling allegations of improper act - (EMA, 2017b)	Policy
11	Policy on the handling of competing interests of scientific committees' members and experts - (EMA, 2016d)	Policy
12	European Medicines Agency policy on access to documents - (EMA, 2018c)	Policy
13	European Medicines Agency policy on publication of clinical data for medicinal products for human use - (EMA, 2019c)	Policy

Annex 2: Interview guides

A. Interview guide - English

Topics	Questions
Introduction	<p>Introduction</p> <p>Good morning/ afternoon, (thank you for participating in this interview).</p> <p>My name is Eunjin and I am a graduate intern at the Wemos foundation. As you know, I am interested in finding out about your professional views on accountability in the EMA's evaluation of new medicines. Participation is completely voluntary so you can always choose to not answer particular questions. Please just let me know if that is the case, then I will move to another question. If you wish to stop your participation in the study, you can inform me at any point and all your data will be deleted and removed from the study.</p> <p>The conversation will be recorded so that I can make a transcript later. The data is for research purposes only and is only accessible to me and my direct supervisors. The audio recordings will be deleted once the study is completed. The transcript will be anonymised, and your identity and other personal details will not be disclosed any time during or after the study.</p> <p>Do you give permission for audio recording the interview? Do you have any other questions?</p> <p>Then, if you are ready, I will start recording now (when indicated) and start with the interview.</p> <p>(Start audio recording)</p>
Background	<p>I would first like to start with general questions about your professional experiences.</p> <ol style="list-style-type: none"> 1. What is your current occupation and what is your role in your organisation? 2. To what extent are you familiar with the EMA's marketing authorisation (MA) assessment of new medicines? <ol style="list-style-type: none"> a. If familiar, have you been previously involved in the assessment? What was your role? 3. Have you been involved in other activities of the EMA?
Accountability - general	<ol style="list-style-type: none"> 4. What does the term accountability mean to you? 5. According to you, who are the stakeholders that are involved in the MA assessment? <ol style="list-style-type: none"> a. According to you, who is accountable for the MA assessment? b. To whom do you think is that party accountable to? 6. Accountability can mean different things to different stakeholders. What do you think that the EMA should do to manage the expectations of the stakeholders?
Accountability - challenges	<ol style="list-style-type: none"> 7. What do you think are the accountability related challenges that EMA faces during the MA assessment if there are any? <ol style="list-style-type: none"> a. What can the EMA do to overcome these challenges? b. What do you consider as important factors in fostering accountability in the MA assessment? <p>Each EU member state has two representatives in CHMP who can be selected as rapporteur or co-rapporteur.</p> <ol style="list-style-type: none"> 8. To what extent do you think that the differences between the national medicines authorities (if any) affect the quality of the medicine assessments, if at all?

	<p>Sometimes, it can happen that EMA scientific members and experts that were previously involved in the pre-submission activities are also involved in the MA assessment for the same medicine. (Examples of pre-submission activities: scientific advice on clinical study design or a private meeting to receive guidance on regulatory requirements)</p> <p>9. What is your view on the EMA's engagement with medicine developers prior to the assessment?</p> <p>A few months ago, the European Ombudsman released a report on EMA's transparency and pre-submission activities. EMA pledged to adopt the Ombudsman's recommendations that followed, concerning a better separation between scientific advice and MAA assessment and more transparency about what is discussed during scientific advice.</p> <p>10. How do you view this?</p> <p>An important part of the MA assessment is weighing the benefit-risk ratio, where the desired effects (or benefits) of a medicine is balanced against its undesired effects (or risks). This is a difficult and complex task that involves qualitative judgement of the assessors.</p> <p>a. In what way does the EMA ensure that the benefit-risk assessment is carried out in a reliable and consistent way?</p>
Accountability – Policies	<p>11. (As far as you are aware) How does the EMA manage to stay accountable on their decision making?</p> <p>a. Could you describe the policies and tools that are adopted by the EMA to ensure that?</p> <p>12. Are these policies that are currently adopted by the EMA sufficient in your opinion?</p> <p>a. Why or why not?</p> <p>b. In what way can the EMA improve to enhance its accountability?</p> <p>13. How does the EMA assure that the stakeholders adhere to these policies and standards?</p>
Closing	<p>Are there any important issues that you think I have missed?</p> <p>Do you have any other comments/ questions?</p> <p>Would you like to receive the abstract of the report after completion?</p> <p>Do maybe you know more people on this topic that I can potentially approach for the interview?</p> <p>You can always reach me by e-mail or telephone if you have questions.</p> <p>I would like to wrap up the interview then. Thank you again for your time.</p> <p>Have a nice day.</p>

B. Interview guide – Dutch

Onderwerpen	Vragen
Introductie	<p>Introductie Goedemorgen/ middag,</p> <p>Bedankt dat u heeft ingestemd dit interview.</p> <p>Mijn naam is Eunjin Jang en ik ben een scriptie stagiair bij Stichting Wemos. Zoals u weet, ben ik geïnteresseerd in uw professionele mening over EMA's verantwoording bij de evaluatie van nieuwe geneesmiddelen. Er zijn in dit interview geen goede of foute antwoorden en uw antwoorden zullen anoniem worden behandeld in mijn onderzoek. U kunt er altijd voor kiezen om bepaalde vragen niet te beantwoorden. Ook kunt u zich op elk gewenst moment terugtrekken uit het onderzoek, dit geldt ook voor na het interview. In dat geval, worden alle data en gegevens van u verwijderd.</p> <p>Het gesprek wordt opgenomen zodat ik later kan omzetten in tekst.</p> <p>Heeft u nog andere vragen?</p> <p>Als u er klaar voor bent, begin ik nu met opnemen (indien aangegeven).</p> <p>(Start audio-opname)</p>
Achtergrond	<p>Ik zou eerst wat meer willen weten over uw professionele achtergrond.</p> <ol style="list-style-type: none"> Wat is uw huidige functie en wat is uw rol binnen uw organisatie? <ol style="list-style-type: none"> Bent u wel eens bij de EMA's beoordeling betrokken geweest? Wat was uw rol daarin? Bent u betrokken geweest bij andere activiteiten van het EMA?
Verantwoording - Algemeen	<ol style="list-style-type: none"> In de context van EMA's medicijnen beoordeling wat betekent de term accountability voor u? Wie zijn volgens u de stakeholders die betrokken zijn bij de EMA's medicijnen beoordeling? <ol style="list-style-type: none"> Wie is volgens u accountable voor de beoordeling van de nieuwe geneesmiddelen? Aan wie moet die partij verantwoording afleggen? Accountability kan verschillende betekenissen hebben bij verschillende stakeholders. Wat vindt u dat de EMA eraan moet doen om deze verwachtingen te managen?
Verantwoording - Uitdagingen	<ol style="list-style-type: none"> Wat zijn volgens u de uitdagingen waarmee het EMA wordt geconfronteerd tijdens de medicijnen beoordeling (als die er zijn)? <ol style="list-style-type: none"> Wat beschouwt u als belangrijke factoren voor de bevordering van accountability bij de medicijnen beoordeling? Wat kan het EMA eraan doen om deze uitdagingen te overwinnen? <p>Elk lidstaat heeft twee vertegenwoordigers in CHMP die kunnen worden uitgekozen als rapporteurs of co-rapporteurs.</p> <ol style="list-style-type: none"> In hoeverre denkt u dat de onderlinge verschillen tussen de nationale medicijnen autoriteiten (als die er zijn) de kwaliteit van de medicijnen beoordelingen beïnvloedt of denkt u dat het helemaal geen invloed heeft? <p>Soms kan het voorkomen dat leden van het wetenschappelijk comité en experts die eerder betrokken waren bij de pre-submission activiteiten, ook betrokken zijn bij de beoordeling voor hetzelfde geneesmiddel. (Voorbeelden hiervan: wetenschappelijk advies over het ontwerp van</p>

	<p>klinische studies of een privévergadering om advies te winnen over wettelijke vereisten bij de vergunningaanvraag)</p> <p>8. Wat is uw mening over het contact tussen het EMA en medicijnontwikkelaars voorafgaand aan de medicijnen beoordeling?</p> <p>Een aantal maanden geleden heeft de Europese Ombudsman een rapport uitgebracht over transparantie en pre-submission activiteiten van EMA. Het EMA heeft beloofd de aanbevelingen van de Ombudsman die daarop volgden aan te nemen. Dat ging over betere scheiding tussen scientific advice en medicijnen beoordeling, maar ook meer transparantie over wat er wordt besproken tijdens scientific advice.</p> <p>13. Hoe kijkt u hier tegenaan?</p> <p>Een belangrijk onderdeel van de EMA's medicijnen beoordeling is het afwegen van de baten-risicoverhouding, waarbij de gewenste effecten van een geneesmiddel worden afgewogen tegen de ongewenste effecten. Dit is een moeilijke en complexe taak dat sterk afhankelijk is van kwalitatieve beoordeling van de experts.</p> <p>1. Op welke manier zorgt de EMA ervoor dat de beoordeling op een consistente manier verloopt?</p>
Verantwoording - Beleid	<p>2. (Voor zover u op de hoogte bent) hoe slaagt het EMA erin accountable te blijven voor hun besluitvorming?</p> <p>a. Kunt u de beleidsmaatregelen en tools beschrijven die door het EMA zijn aangenomen om dat te waarborgen?</p> <p>3. Voldoen de huidige beleidsmaatregelen naar uw mening?</p> <p>a. Op welke manieren kan het EMA volgens u zich verbeteren?</p> <p>4. Hoe verzekert het EMA ervan dat stakeholders zich houden aan dit beleid?</p>
Afsluiting	<p>Zijn er belangrijke zaken waarvan u denkt dat ik ze heb gemist?</p> <p>Heeft u nog andere opmerkingen/ vragen?</p> <p>Kent u misschien meer mensen over dit onderwerp die ik kan benaderen voor interview?</p> <p>Wilt u aan het eind samenvatting van het verslag ontvangen?</p> <p>U kunt me altijd bereiken via e-mail of telefoon als u vragen heeft.</p> <p>Ik wil het interview dan graag afronden. Nogmaals bedankt voor uw tijd.</p>

Annex 3: Coding guide

Themes	Codes	Definition	Comments
Professional background	Type of stakeholder	Types of stakeholders in terms of assessor, medicine developer or ad-hoc expert	
	Area of expertise	In general terms, the expertise area of the interviewees related to the EMA, medicine evaluation or marketing authorisation	
	Involvement in the medicine evaluation process of the EMA	The way in which the stakeholders are involved in the medicine evaluation of the EMA or national medicine regulatory authority	
Definition of accountability		Accountability in the context of EMA and medicine evaluation as defined by the interviewees	
Accountability role division	Stakeholders	The relevant stakeholders in the medicine evaluation according to the interviewee	
	Role division	Interviewees perception on who is accountable to whom in the medicine evaluation.	
Policies of the EMA	Existing policies, guidelines, standards etc.	Policies, guidelines etc. that are adopted by the EMA to ensure reliable and impartial evaluation of the medicines	
	EMA's engagement	How the EMA engages with different stakeholders to increase accountability in the MAA assessment	
	Judgement	Interviewee judgement on the current policies and the way that EMA manage them.	
Opinion on specific topics	EMA's engagement with medicine developers prior to submission of the application	EMA's engagement with the medicine developers in the pre-submission phase that has led to European Ombudsman's inquiry	
	National authorities	(potential) Differences among the national authorities (who are appointed as the rapporteurs for the medicine evaluation) and its effect on the medicine evaluation	
	Risk benefit assessment	The impact of the complexity of weighing the benefit-risk ratio on EMA's accountability	
	Conflict of interest	Conflicting interests among the assessors and experts during the medicine evaluation.	
Areas for improvement	Perceived challenges	The challenges that the EMA faces relating to accountability as perceived by the interviewee	
	Proposed solutions	The solutions proposed by the interviewee to overcome the aforementioned challenges and the factors that foster the accountability of the EMA	

Annex 4: Informed Consent form

A. Participant information sheet - English

Research project

Accountability of the European Medicines Agency in Marketing Authorisation of New Medicines

Researcher: Eun Jin Jang

University: Vrije Universiteit Amsterdam

Commissioner: Wemos Foundation

Introduction

My name is Eun Jin Jang and I am a Master student of Drug, Discovery and Safety at Vrije Universiteit Amsterdam. I am currently doing a thesis internship at the Wemos foundation on the subject accountability in the context of the EMA. For this research project, I am looking for professionals and experts who are familiar with the medicine evaluation process of the European Medicines Agency (EMA). You have been given this informed consent form because you are being invited to take part in this research study. The informed consent form exists in two parts:

1. an information sheet with the description of the study and the interview procedure
2. and a consent form in which you can indicate to participate

Purpose of this study

The aim of this project is to understand how accountability is understood and incorporated into EMA's policies to ensure reliable and impartial evaluation of new medicines for marketing approval (also known as Marketing Authorisation assessment). By interviewing different stakeholders involved in this process, I want to explore the stakeholders' views on accountability.

Voluntary participation

Participation in the interview is voluntary and it is completely up to you whether or not to participate in the study. You can always refuse to answer any particular question during the interview, and you are always free to withdraw from the study at any time without giving me a reason.

Interview procedure

When you decide to participate in this project, you will be invited to take part in an interview. The interview will be conducted by me, Eun Jin Jang. The interview will be about your professional views on accountability within the EMA's marketing authorisation process and the challenges that come with it. Due to the current situation with COVID-19 outbreak, the interview will be held via Skype or Zoom at a time convenient to you. The interview is expected to take between 40 to 60 minutes. With your permission, I would like to audio record our interview so that I can convert our conversation later into text. This is very helpful for me as I do not have to take a lot of notes during the interview. The audio record is for research purpose only and will be deleted as soon as the project is finalised. If you do not want the interview to be audio recorded, the interview will proceed by taking notes instead.

Confidentiality

Personal information about you and information shared during the interview will be kept confidential. The data is for research purpose only and will be only accessible to me and my direct supervisors. Any summary of the interview content or direct quotations from the interview that are published in the report will be anonymised. To ensure anonymity, your identity and contact details will be kept separately from the transcript and any details that can be traced back to you will be removed from the transcript. Details disclosed in the study will be limited to the general area of your expertise and the type of stakeholders to which you belong (e.g. pharmaceutical company). All of the data will be stored on a secure, password-protected server and audio records of the interview will be immediately destroyed after the study is completed. Other data from the study are retained for 3 years on the secured server of Wemos foundation.

Benefits/ risks

There will be no direct benefits for you, but your participation in this study will help me to better understand the role that accountability plays in the EMA's marketing authorisation assessment and how accountability is understood by different stakeholders. There is no known risk associated with your participation, but you have the right to stop the interview or withdraw from the research at any time.

Contact details

I am the main contact for the study. If you have any questions about the project, please feel free to contact me. My contact details are: eunjin.jang@wemos.nl, T: +316 1026 1711.

Thank you for considering taking part in this study and taking the time to read this information. If you are willing to take part in an interview for this research project, please complete the consent form on the next page.

Consent form

Project title: Accountability of the European Medicines Agency in Marketing Authorisation of New Medicines

By signing this form	Yes	No
I confirm that I have read and understand the information sheet provided for this study. I have had the opportunity to ask questions and have had these answered satisfactorily	<input type="checkbox"/>	<input type="checkbox"/>
I understand that my participation in this study is voluntary. I understand that I can refuse to answer questions and that I am free to withdraw at any time, without giving a reason.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that the interview will be audio recorded and then transcribed into text for analysis.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that personal information that may identify me will be removed from the transcript of my interview and that I will not be identified in any publications, reports or presentations following this study.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that the accessibility of the data will be limited to the researcher (Eun Jin Jang) and her direct supervisors only.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that the actual recording will be destroyed after the completion of the project and that the other (anonymised) data from the study will be retained for 3 years on the secured server of Wemos foundation.	<input type="checkbox"/>	<input type="checkbox"/>

A copy of the signed Informed Consent Form will be given to the participant.

Signature:

Name:

Date:

Researcher I have provided verbal explanation about the nature, method and purpose of the research. I declare that I am prepared to answer any upcoming question about the research to the best ability.

Signature:

Name:

Date:

**Thank you for agreeing to take part in this study.
Your contribution is very much appreciated.**

B. Participant informatieblad - Nederlands

Onderzoeksproject

Accountability of the European Medicines Agency in Marketing Authorisation of New Medicines

Onderzoeker: Eun Jin Jang

Universiteit: Vrije Universiteit Amsterdam

Opdrachtgever: Wemos Foundation

Introductie

Mijn naam is Eun Jin Jang en ik ben een masterstudent Drug, Discovery, and Safety aan de Vrije Universiteit Amsterdam. Als onderdeel van mijn studie loop ik stage bij Stichting Wemos waar ik onderzoek doe naar het onderwerp verantwoording in de context van het Europees Medicijn Agentschap (EMA). Voor dit onderzoeksproject ben ik op zoek naar professionals en experts die bekend zijn met het medicijnevaluatieproces van het EMA. U heeft dit formulier gekregen omdat u wordt uitgenodigd om deel te nemen aan dit onderzoek. Het toestemmingsformulier bestaat uit twee delen:

1. een informatieblad met de beschrijving van de studie en de interviewprocedure
2. en een toestemmingsformulier waarin u kunt aangeven deel te nemen aan het onderzoek

Doel van het onderzoek

Het doel van dit project is om te onderzoeken hoe verantwoording is opgenomen in het beleid van EMA om ervoor te zorgen dat nieuwe geneesmiddelen op een betrouwbare en onpartijdige manier worden beoordeeld voor de Europese markt (ook wel bekend als marketing autorisatie beoordeling). Ook kijk ik daarbij hoe verantwoording wordt begrepen door verschillende stakeholders die betrokken zijn bij dit proces. Met behulp van interviews hoop ik een beter beeld te krijgen van de verschillende percepties over verantwoording.

Vrijwillige deelname

Deelname aan dit onderzoek is geheel vrijwillig. Het is volledig aan u of u mee doet of niet. Tijdens het interview kunt u altijd weigeren een vraag te beantwoorden. Ook staat u vrij om te stoppen met uw deelname op elk gewenst moment zonder opgaaf van redenen.

Interview procedure

Wanneer u besluit deel te nemen aan dit project, wordt u uitgenodigd voor een interview. De interviews worden door mij, Eun Jin Jang, afgenomen. Het interview gaat over uw professionele kijk op verantwoording binnen het EMA-proces voor marketing autorisatie en de uitdagingen die daarmee gepaard gaan. Vanwege de huidige situatie met COVID-19-uitbraak zal het interview via Skype of Zoom worden gehouden op een tijdstip dat u uitkomt. Het interview duurt naar verwachting tussen 40 en 60 minuten. Bij het interview zal ik u vragen of ik het gesprek mag opnemen om het later om te zetten in tekst. Hiervoor ga ik u toestemming vragen. De interviews worden achteraf geanonimiseerd. De audio-opname is alleen bedoeld voor onderzoeksdoeleinden en wordt direct verwijderd zodra het project is afgerond. Als u niet wilt dat het interview op audio wordt opgenomen kunt u dat aangeven.

Vertrouwelijkheid

Persoonlijke informatie over u en informatie die tijdens het interview wordt gedeeld, worden vertrouwelijk behandeld. Uw data zijn alleen toegankelijk voor mij en mijn directe begeleiders. Om de anonimiteit te waarborgen, worden uw identiteit en contactgegevens gescheiden van het transcript bewaard en worden alle gegevens die naar u kunnen worden herleid, verwijderd uit het transcript. Details die in de studie worden onthuld, zijn beperkt tot het algemene gebied van uw expertise en het type stakeholder waartoe u behoort (bijv. farmaceutisch bedrijf). Alle gegevens worden opgeslagen op een veilige, met een wachtwoord beveiligde server en audio-records van het interview zal onmiddellijk worden vernietigd nadat het onderzoek is afgerond. Overige (geanonimiseerde) gegevens uit het onderzoek worden 3 jaar bewaard op de beveiligde server van Stichting Wemos.

Voordelen/ risico's

Er is geen direct voordeel verbonden aan de deelname van het onderzoek, maar uw deelname zal mij erg helpen om te begrijpen welke rol verantwoording speelt bij de medicijnen beoordeling van het EMA en hoe verantwoording wordt begrepen door verschillende stakeholders. Voor zover bekend is er geen risico verbonden aan uw deelname, maar u kunt altijd een vraag weigeren te beantwoorden als u van mening bent dat de vraag te persoonlijk, ongepast of ongemakkelijk is.

Contactgegevens

Voor vragen of opmerkingen kunt u mij bereiken via e-mail of telefoon. Mijn contactgegevens zijn als volgt: eunjin.jang@wemos.nl, T: +316 1026 1711.

Toestemmingsformulier

Project titel: Accountability of the European Medicines Agency in Marketing Authorisation of New Medicines

Kruis aan wat van toepassing is	Ja	Nee
Ik bevestig dat ik het informatieblad heb gelezen en begrepen. Ik heb de gelegenheid gehad om vragen te stellen en deze zijn naar tevredenheid beantwoord.	<input type="checkbox"/>	<input type="checkbox"/>
Ik begrijp dat mijn deelname aan deze studie geheel vrijwillig is. Vragen die ik niet wil beantwoorden kan ik weigeren en ik kan me te allen tijde terugtrekken uit het onderzoek zonder opgaaf van redenen.	<input type="checkbox"/>	<input type="checkbox"/>
Ik begrijp dat het interview met audio zal worden opgenomen en om vervolgens te worden omgezet in tekst voor analyse.	<input type="checkbox"/>	<input type="checkbox"/>
Ik begrijp dat persoonlijke informatie die naar mij kunnen worden herleid uit het interview transcript zal worden verwijderd en dat er alleen zal worden gewerkt met geanonimiseerde data.	<input type="checkbox"/>	<input type="checkbox"/>
Ik begrijp dat de toegang van de gegevens beperkt is tot de hoofdonderzoeker (Eun Jin Jang) en haar directe begeleiders.	<input type="checkbox"/>	<input type="checkbox"/>
Ik begrijp dat de audio opname van het interview zal worden vernietigd na de voltooiing van het project en dat de andere (geanonimiseerde) gegevens van de studie 3 jaar zal worden bewaard op de beveiligde server van Stichting Wemos.	<input type="checkbox"/>	<input type="checkbox"/>

Een kopie van het ondertekende formulier wordt aan de deelnemer verstrekt.

Naam deelnemer:

Handtekening:

Datum:

Onderzoeker: Ik heb schriftelijk uitleg gegeven over de aard, methode en doel van het onderzoek. Ik heb deze naar waarheid verteld en de deelnemer heeft voldoende tijd en gelegenheid gehad om het informatieblad te lezen en vragen te stellen.

Naam onderzoeker:

Handtekening:

Datum:

Annex 5: Data Management Plan

1. Project description

The project aims to provide policy recommendations to the European regulatory authorities in medicines on accountability to better ensure impartial and reliable MAA assessment. In doing so, the research investigates how the concept of accountability is understood and incorporated into the policies of the EMA through the case study of two MS treatments. The assessment will take place on two levels; organisational level that deals with the current EMA policies and individual level that addressed the way the stakeholders interpret and experience accountability in the MAA assessment.

2. Data collection

The data collection methods used in this study are a document review and semi-structured interviews. The document review comprises of reviewing the existing documents on the current EMA policies and standards. The primary source of data is internal documents published by the EMA on the subject professional code of conduct, MAA evaluation guidelines, policies on conflicting interests, data management etc. Data will be collected mainly using the EMA website. The relevance of the data will be determined based on its link to the MAA assessment. Semi-structure interviews will be held with different types of stakeholders of the MAA assessment. Three types of stakeholders can be distinguished: assessors (EMA & MEB), applicant (medicine developer) and ad-hoc panel of experts (patients and healthcare professionals). Recruitment of the interviewees will be done convenience sampling, using the existing network of Wemos. Stakeholders will be interviewed either by telephone or telecommunication application such as Zoom or Skype.

3. Planning

The total duration of the project is 24 weeks, starting from 2nd March 2020 until 14 August 2020 (Table 5). The first seven weeks were dedicated to writing the extended research design, of which the go/ no-go evaluation took place in week 9. The data management plan and the document review started in week 8. The document review took three weeks in total and one week was reserved for the construction of the interview guide. Towards the end of week 11, the recruitment of interview participants was started followed by the interview itself. Data processing and analysis were performed parallel to the interviews, including transcription and coding. The last few weeks were committed to writing the conclusions and the report.

Table 5. General planning of the research project.

	Months/ Weeks																							
	March					April					May				June				July				August	
Assignments	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Scanning literature/ formulating RQ																								
Extended Research Design																								
Data management plan																								
Desk research & Writing interview guide																								
Recruitment interviewees																								
Qualitative data collection																								

will be informed on their rights; the right to refuse to answer any particular question and to withdraw from the study at any time. The participants get the option to receive the abstract of the report at the end of the project. The whole report will be sent only upon request.

Post-interview process

The audio file is transferred to the secured cloud storage of Sync right after the interview and removed from the recording device (see **Annex 2.7. Data storage**). Field notes taken during the interview are transferred into a Microsoft Word file as soon as the interview is finished. Before transcribing, member checking will be performed. In doing so, a summary of the interview is made and sent to the participant to check for the accuracy and alignment with their experiences. Soon after the interview, the audio recording is transcribed and analysed using the thematic analysis method. Coding is conducted in the following order: open, axial and selective coding.

Data anonymisation

Data derived from the interviews are anonymised. In case of verbal informed consent, the consent is recorded separately from the interview and stored in a separate file. To guarantee anonymity, personal information and details that can be traced back to the participants are excluded from the report. Participant details disclosed in the study is limited to the area of the participant's expertise and the type of stakeholders (assessors, applicants and ad-hoc experts). Identity and personal information of the participant (e.g. signed/ verbal informed consent, name, e-mail address and function) are kept confidential and only accessible by the project executer and the project supervisors.

7. Data management

Data storage and access

All data are stored on the secured cloud storage platform named Sync. The use of Sync is approved by the on-site supervisor and VU supervisor. Separate folders are made for:

- Audio files of the interview
- Member checked summaries, field notes and transcripts
- Signed forms or verbally given informed consents and key files with the contact details and personal information of the participants.
- Data from the document review
- Coded and analysed data
- Draft and final report and poster presentation file

The Sync platform is password protected and is only accessible by the project executer, on-site supervisor and VU supervisor. The folders will be updated regularly by the project executer. For practical reasons, the daily operational version of the report will be stored on the computer of the project executer. For academic grading, the final report will be submitted on the Canvas page of the VU and shared with the appointed second VU-assessor.

Data retention

Audio files of the interviews will be deleted after completion of the project. Key files and signed and verbal informed consent forms are deleted from Sync platform after the final report is approved and graded. The final report will be stored on the server of Wemos and VU and the computer of the project executer. The remaining data (both from the document review and the interviews) are kept for 3 years on the server of Wemos and then removed. Data stored on the Sync platform will be deleted after the report is graded.

8. Folder structure and file names

Folder structure and file names on the Sync platform:

Internship project accountability 2020 > general folder

- Research proposal >
 - Extended Research Design (draft and final version)
 - Data Management Plan
- Interviews >
 - Data collection >
 - Interview guide
 - Raw data: audio recordings of the interview and field notes
 - Transcripts
 - Informed consent and key files
 - Data analysis >
 - Coded transcripts, coding frame, tables and spreadsheets.
- Document review >
 - Documents and literature used for the analysis
- Output >
 - Analysed data (Figures, Publications, Communicative means, Tools, Deliverables)
- Final product
 - Final report
 - Poster presentation file
- Others

Folder structure and file names on the computer of the project executor:

Stage Wemos > general folder

- Logbook
- Final report
- Report >
 - Extended Research Design (draft and final version)
 - Data Management Plan
- Document review >
 - analysed data
 - Literature/ documents

Files are named as followed:

Literature/ articles:

Surname author/ organization – Title article

Others:

ProjectName(Accountability)_FileName(e.g. ExtendedResearchDesign)_ DateLastEdit(2020_12_04)