How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers’ views

G. Tafuri1,2*, P. Stolk2, F. Trotta1, M. Putzeist2, H. G. Leufkens2,3, R. O. Laing4 & M. De Allegri5

1Italian Medicines Agency (AIFA), Rome, Italy; 2Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; 3Medicines Evaluation Board, Utrecht, The Netherlands; 4World Health Organization, Geneva, Switzerland; 5Institute of Public Health, Heidelberg University, Heidelberg, Germany

Received 22 July 2013; revised 3 September 2013; accepted 14 October 2013

Background: The process leading to a regulatory outcome is guided by factors both related and unrelated to the data package, defined in this analysis as ‘formal and informal factors’, respectively. The aim of this qualitative study was to analyse which formal and informal factors drive the decision-making process of the European Medicines Agency (EMA) and Food and Drug Administration (FDA) regulators with regard to anticancer drugs, using in-depth semi-structured interviews with regulators of the two agencies.

Methods: In line with the theory and practice of qualitative research, no set sample size was defined a priori. Respondent enrolment continued until saturation and redundancy were reached. Data were collected through means of in-depth semi-structured interviews conducted either in a face-to-face setting or via Skype® with each regulator. The interviews were audio-recorded and verbatim transcribed. The analysis was manually carried out on the transcribed text. Data were independently coded and categorized by two researchers. Interpretation of the findings emerged through a process of triangulation between the two.

Results: Seven EMA and six FDA regulators, who had extensive experience with making decisions about anticancer medicines, were interviewed between April and June 2012. There is an open dialogue between the FDA and EMA, with the two moving closer and exchanging information, not opinions. Differences in decision-making between the agencies may be due to a different evaluation of end points. Different interaction modalities with industry and patients represent an additional source of divergence with a potential impact on decision-making. The key message of our respondents was that the agencies manage uncertainty in a different way: unlike the EMA, the FDA has a prevailing attitude to take risks in order to guarantee quicker access to new treatments.

Conclusions: Although formal factors are the main drivers for regulatory decisions, the influence of informal factors plays an important role in the drug evaluation process.

Key words: regulatory, EMA, FDA, interview study, qualitative research, anticancer medicines

introduction

The decision-making process for the evaluation of drug applications is complex. Based on the assessment of non-clinical, clinical, and quality data submitted by the pharmaceutical industry, regulators have to make sure that only products with a positive benefit–risk balance are brought to the public.

The importance of analysing and understanding the regulatory decision-making processes from a public health perspective has been recognized by both the two world leading agencies, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), who have set up projects to define a structured framework for regulatory decisions [1, 2].

Our previous analysis highlighted substantive differences between the EMA and the FDA in managing uncertainty when reaching decisions on anticancer drugs. Although such analysis showed clinically relevant differences in the EMA and FDA’s decisions, it could not identify the causes of such heterogeneity [3].

The present research is based on the assumption that the process leading to a regulatory outcome is guided by factors both related and unrelated to the data package, defined in this analysis as ‘formal and informal factors’, respectively (see supplementary Material S1, available at Annals of Oncology online). In fact, we assumed that, over the course of an application review, a regulator’s assessment of the data package is likely to be mediated by informal factors, such as the interaction with external stakeholders (e.g. pharmaceutical companies, patients, or other regulatory agencies), and influenced by socio-cultural and behavioural aspects.
The aim of this qualitative study was to analyse and to understand which formal and informal factors drive the decision-making process of the EMA and FDA regulators with regard to anticancer drugs, using in-depth semi-structured interviews with regulators of the two agencies.

**Methods**

The study was conducted between April and December 2012 and was designed as a cross-sectional, qualitative study, gathering information from selected respondents at one single point in time. Data collection stretched from April to June 2012, whereas analysis took place between August and December 2012.

The sampling process took into consideration the structural differences between the two agencies (see supplementary Material S2, available at *Annals of Oncology* online). Therefore, EMA respondents were purposely selected among the members of the Committee for Medicinal Products for Human Use (CHMP), of the Oncology Working Party (OWP) and of the Scientific Advisory Group on Oncology (SAG-O). FDA respondents were selected on the basis of their seniority and longstanding experience with the assessment of drug applications for anticancer medicinal products to represent all levels of decision making within the FDA Center for Drug Evaluation and Research (CDER). In line with the theory and practice of qualitative research, no set sample size was defined a priori, although the research team expected to conduct between 10 and 15 interviews. Respondent enrolment continued until saturation and redundancy were reached [4]. Data were collected through means of individual in-depth semi-structured interviews conducted either in a face-to-face setting or via Skype®. The interviewers made use of a semi-structured interview guide (see supplementary Material S3, available at *Annals of Oncology* online). All interviews were audio-recorded and verbatim transcribed.

Content analysis was manually carried out on the transcribed text by two researchers, GT and MDA, who subsequently coded and categorized the data independently from one another. GT relied on a deductive approach based on the themes and questions addressed by the interview guide, whereas MDA relied on a fully inductive approach, letting codes and categories emerge as she proceeded through the reading. Both analysts relied on a ‘contrast and compare’ method rooted in grounded theory [5]. Finally, GT and MDA confronted the two analyses, the respective emerging interpretations, and returned to the material to resolve divergent interpretations. This process of triangulation continued until the two analysts could agree on a common interpretation of the findings and on the relative importance of the various elements communicated by the respondents (see supplementary Material S4, available at *Annals of Oncology* online for an extensive description of the methods).

**Results**

Seven regulators of the EMA and six of the FDA’s CDER (see Table 1) were interviewed. Twelve regulators were interviewed in a face-to-face setting, while only one via Skype®. Interviews lasted between 45 and 60 min. Based on the three core questions asked to each respondent (i.e. formal and informal factors guiding the decision-making process as well as the causes of regulatory divergence between EMA and FDA), study findings are summarized in the three following sections and corroborated by relevant quotes (see supplementary Material S5, available at *Annals of Oncology* online for additional quotes).

**Formal factors guiding the decision-making process**

Most FDA and EMA respondents considered efficacy as a priority, with only two (one FDA and one EMA) respondents giving priority to safety.

If they (the products) really (do) not give me the benefit I can live with that, but if they harm me then I am concerned about that (FDA respondent 14).

Most EMA and FDA respondents agreed that when no alternative drugs are available on the market, decisions to approve a product may be made even if clinical evidence is not complete or if toxicity is higher. FDA respondents, however, were concerned with the risk of deviating from regulatory requirements in cases when no alternative therapeutic option is available.

Respondents from both agencies insisted on the need to ensure external validity, i.e. checking that study results are valid and applicable to the real world scenario. Respondents agreed on the importance of developing biomarkers, although they commented on how companies are not often interested in developing and validating new markers for commercial reasons.

They (companies) say that they have no validated marker for use, which of course they do not have because they have not done the investigations (…) They are not telling me: “The upper management board wants us to go into confirmatory trials as fast as possible because they have other competitors with a similar compound. We must be first on the market, that’s important”. They don’t say that (EMA respondent 3).

Most respondents defined a clinical benefit in cancer as an improvement in the overall survival (OS), a substantial improvement in progression-free survival (PFS), or in the quality of life.

A single EMA respondent held patients’ perspective as central to the definition of clinical benefit, implying that there is a benefit only provided that this can be simply explained and

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<tr>
<th>Characteristics of study respondents</th>
<th>EMA</th>
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<tbody>
<tr>
<td>Three CHMP members</td>
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<td>Staff members of the ‘CDER Office of Hematology and Oncology Products’ with specific expertise.</td>
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<td>Two OWP members</td>
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<td>One SAG-O member</td>
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<td>One in Clinical Oncology</td>
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<td>One staff member with expertise in Regulatory Affairs.</td>
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*CHMP, Committee for Medicinal Products for Human Use; OWP, Oncology Working Party; SAG-O, Scientific Advisory Group on Oncology; CDER, Center for Drug Evaluation and Research.*
understood by patients, such as a longer survival or symptom relief.

If I find something which is an interesting drug (but) I cannot explain to the patient (something) that could convince him or her of taking the drug. I do not see the clinical benefit (EMA respondent 2).

Two respondents, one from EMA and the other from FDA, described an experience of interaction with patients which changed their perspective in the assessment (see supplementary Material S6, available at Annals of Oncology online).

**the influence of the informal factors on decision making**

EMA respondents described the interactions with companies as regularly scheduled and structured during the entire review process, with the industry complaining about the limited contacts with the agency. The EMA wished to have more interactions with the companies in the early stages of clinical development.

FDA reported working in a ‘mutual understanding environment’ with the companies and to have frequent dialogues with them, especially given the short time lines for the application reviews. FDA respondents explained that their interactions with companies can be very useful, since sometimes these can bring to light aspects that had not been considered by the agency. FDA also described a mindset shift, since patients and not companies are now considered FDA most important ‘customers’. FDA and EMA respondents were aligned on the value of the inputs from clinical opinion leaders. All respondents considered their influence as minimal on decision making. Respondents showed caution about their interactions with pharmaceutical companies. Apart from potential conflict of interest, both EMA and FDA regulators felt that opinion leaders may have a different perspective in their own judgement of a new product: unlike regulators, they may focus more on the benefit for a single patient and may be keener to have a new therapeutic option, regardless of a robust benefit–risk balance in the overall population. Furthermore, most regulators said that opinion leaders involved in the development of a specific product may provide a biased opinion, tending to overestimate the clinical benefit and to underestimate the risks of a new drug.

They (clinical opinion leaders) are just annoying. (…) What they (clinical opinion leaders) say is influenced a lot, but in fact since they are paid in part by the companies, it just means that they have a tendency to be biased. It doesn’t mean everything they say is wrong. But you know, we often have key opinion leaders attending meetings with the companies. And sometimes I’m just embarrassed for them (FDA respondent 10).

Both EMA and FDA respondents appeared keen to disseminate the rationale of regulatory decisions, joining conferences and meetings with the oncology scientific community. However, during these interactions, EMA regulators felt that their agency is often the object of criticism for its decisions.

When I go to conferences, and I talk about the affairs and approval of drugs in a broad audience of oncologists, I have the distinct impression that Europe is being more and more criticized for having the standards a little bit too low. (…) We are considered to be a little bit more lenient, more relaxed (EMA respondent 1).

All the FDA respondents considered the inputs coming from patients as highly valuable, although they still thought that FDA ought to make regulatory decisions based on independent scientific grounds. FDA respondents stressed that their agency has been increasing its transparency and interaction with the outside world over time, integrating the perspectives of patients, physicians, and health care system specialists at all levels. FDA respondents defined public hearings as an important instrument to guarantee transparency, especially in case of borderline applications or in case of rejected drug applications, because they give the opportunity to the agency to explain their position directly to the public. FDA respondents thought that the inputs provided by the public hearings may be a factor leading to differences between EMA and FDA decision making.

Any advice we have, like that from the advisory committee, is open to the public, so people are pretty much put on the spot, when they are discussing this among their peers. I think it is a good system, that could be a major difference in the ultimate outcome of the decision making (FDA respondent 8).

More than half of the EMA respondents (four of seven) showed scepticism about the added value that patient advocacy groups could bring to the evaluation process and concern about their potential conflict of interest, and in general, did not seem to agree about establishing public hearings in the EU. In addition, they explained that an emotional involvement may ‘distract’ the assessor from the data of the application and affect the objectivity of the review process, which should only be science and evidence-driven.

I have never seen that a patient organization came up with arguments or issues that we had not thought of ourselves already, or weighted these arguments in a different way. (…). In my view their contribution is really of limited value (EMA respondent 7).

However, the other half of EMA respondents (three of seven) thought that public hearings could be potentially useful for different reasons: they may bring a ‘fresh eye’ to the process; they may introduce further transparency into the regulatory system; and they may be instrumental in explaining complicated situations to the patients, such as revoking or suspending a marketing authorization. Even respondents who agreed in principle to the establishment of public hearings in Europe, however, were afraid that including additional steps into the decision-making process could further slow down the approval of new anticancer medicines.

**why EMA and FDA reach different conclusions**

Respondents recognized the existence of an open dialogue between the FDA and EMA, with the two moving closer and exchanging information more frequently than in the past. Still, respondents unanimously reported that the FDA and EMA reach decisions independently, in spite of the monthly teleconferences...
between the two. They revealed that the exchange is driven by the need to check on the completeness of the documentation submitted by the pharmaceutical companies rather than by a wish to harmonize regulatory decisions across agencies.

I haven’t had an experience that they did something and that changed my mind. (…) (FDA respondent 11).

Both FDA and EMA respondents were aware that the two agencies may reach different decisions based on the same set of data. FDA respondents, however, were not concerned by this difference and expressed little interest in the decisions made by other agencies.

I don’t usually have the time to read what their opinion was. (FDA respondent 10).

FDA respondents further reported that since FDA has capacity to analyze the raw data of each application, other agencies rely on its analysis, but not on its decisions.

I think, definitely the other countries look to what we have done. Simply because we have more in-depth analysis (FDA respondent 9).

When discussing the independent statistical analysis of raw data submitted by companies, EMA respondents confirmed that they rely on FDA for the quality assurance of data analysis.

When asked about the causes of the differences in decision making between the EMA and the FDA, most EMA and FDA respondents attributed divergence to a different evaluation of clinical end points. EMA respondents tended to identify the end point of PFS as a clinical benefit per se, whereas FDA respondents considered it as a surrogate end point that has to be confirmed by an OS benefit. EMA and FDA agreed that unlike EMA regulators, FDA regulators are more open to base regulatory approval on activity data and phase II single-arm trials.

In the US as soon as a drug established an activity, an effect, not a benefit, but an effect, which is promising and provided that the drug is not obviously dangerous, it could get marketing authorization. (…) In Europe we want to be sure that the benefit-risk ratio is positive which (…) must be based on the strong evidence of a direct benefit for the patient. Not on hopes, on facts (EMA respondent 2).

Both EMA and FDA respondents noticed that another factor may be that the US regulatory system has traditionally been based on a close collaboration with the companies starting from the early stages of drug development. This was wished for by the EMA and only partly achieved in the EU through the increased use of scientific advice provided to the companies. The time lag between the EU and US approvals was seen by both EMA and FDA as an additional factor, since more data may become available in the meantime and consequently have an impact on the decisions of the agency that comes second in the assessment of the new product. Only according to one FDA and one EMA respondent, different regulatory guidelines and requirements may play a role. EMA respondents thought that regulatory divergence may also have cultural roots. They said that unlike the EU, the USA has a prevailing attitude to take risks in order to guarantee quick access to new anticancer treatments and at the same time withdraw products from the market more easily than the EU.

In Europe we build trust from zero to one hundred, in America they remove trust from one hundred to zero. (…) In Europe we want to be sure because we do not want to take the risks, maybe we are more into ‘let’s avoid risks’ in Europe and in the United States they are more ‘let’s take the benefits even if uncertain’ (EMA respondent 6).

FDA respondents thought that their agency tends to approve broader therapeutic indications than the EMA, whereas EMA respondents thought to be more restrictive, limiting the indication to very specific patient populations. Several FDA respondents thought that the assessment at the EMA level also takes costs into consideration with an impact on the different decisions between the two agencies.

My impression is, at least from the EU point of view, costs are probably more of a factor, so that may impact in some of their decisions (FDA respondent 10).

Most EMA respondents denied the impact of costs on the decision-making process, although they were concerned about the different access to new therapies across EU countries, depending on national resources and reimbursement systems. It also emerged that, in the EU, the more frequent use of therapeutic indications tailored on very specific patient populations may be related to country-specific reimbursement policies with only the selected patient population reported in the label being covered by the national health system.

FDA respondents also explained that they feel distant from the EMA in terms of organization, since, in the USA, both assessment teams and advisory committees are extremely specialized in specific therapeutic areas. The EU system based on rapporteurs, who vote for the approval of a drug in an area for which they do not necessarily hold an expertise, was described by US colleagues as ‘funny to watch’.

The bureaucracy involved in the EU process and the different levels of participation to the decision-making process among the member states were reported as concerns for a system that, according to most EMA respondents, should be more open to change and innovation.

You know, we have in Europe, 27 agencies, a system that is very bureaucratic. Very expensive, people do the same things, but don’t go into the details. (…) I would personally prefer having a European FDA and not all these national agencies (…) Assessment reports are much too lengthy (…) and one of the main problems with too lengthy reports is that they are not read, and if they are not read, it is a quality problem (EMA respondent 3).

FDA regulators tended to appreciate their own agency for its transparency, for providing an international and stimulating environment, and for giving voice to all people involved in the evaluation of drug applications.
discussion

This study represents the first systematic attempt to look into the actual decision-making process at both EMA and FDA through a comparative qualitative study reporting directly the views, opinions, and experiences of regulators themselves. The policy relevance of the findings has to be assessed in relation to the limited sample size of 13 respondents, typical of qualitative studies seeking depth rather than breadth in coverage [4]. This limited size, however, does by no means threaten the validity of the study.

The evidence emerging from this study is that the ongoing harmonization process has increased cooperation and exchange of information between the two agencies [6–8], but still it has not fostered the exchange of opinions.

The FDA is based on ad hoc discipline-specific working groups who base their judgments on re-analyses of the raw data provided by the company. The decision is then reached through a complex and inclusive process, which involves all stakeholders. On the other hand, regulatory decisions at the EU level are taken by the CHMP, whose members vote on the approval or refusal of a product, regardless of their expertise in a specific therapeutic area or their actual contribution to the review process. Different interaction modalities with both industry and patients represent an additional source of divergence between the two agencies with a potential impact on decision making. The FDA is characterized by both a closer collaboration with the industry from the early stages of drug development and the establishment of public hearings within the FDA advisory committees, where patient representatives, who can be voting members, offer their experiences in an effort to provide a realistic look at a new product. In contrast, EMA regulators do not seem to support patients’ involvement in the decision-making process and generally dislike the idea of establishing public hearings in the EU. However, public hearings have recently been authorized (but not yet implemented) in the new EU pharmacovigilance legislation, applicable as of July 2012 [9]. Interestingly, in a time when a deeper patient’s involvement in decision making seems to be ‘formally’ advocated, there is no consensus among EMA regulators about what benefit patients may actually bring to the process.

Respondents provided various explanations for divergent regulatory opinions between EMA and FDA, but the different interpretation of the end points such as the PFS as a measure of the clinical benefit prevailed. EMA regulators have moved away from the concept that PFS might be used for approval with expectation that relevant benefits in terms of OS would later materialize.

The key message of our respondents was that the EMA and the FDA manage uncertainty in a different way. According to the study respondents, the FDA is more open to take risks and base approval on less robust data in order to guarantee quicker access to anticancer medicines, although it allows product withdrawals from the market more easily than the EMA.

Future research in regulatory science may wish to build on the results of this study to construct a quantitative tool, aimed at measuring the relative importance of various decision-making criteria among a larger sample of regulators. In conclusion, this study has showed that although formal factors are the main drivers for regulatory decisions, the influence of informal factors plays an important role in the drug evaluation process.

acknowledgements

The authors thank the EMA and the FDA regulators who accepted to participate to this research as respondents, and the agencies’ staff for their valuable support in the organization of the interviews. The views expressed in this article are the personal views of the study respondents and the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency, the US Food and Drug Administration, the Italian Medicines Agency, the Medicines Evaluation Board, or the World Health Organization.

funding

Financial support for the conduct of the study was received from the Escher project (T6-202), a project of the Dutch Top Institute Pharma.

disclosure

The authors have declared no conflicts of interest.

references