The European Medicines Agency: An Overview of Its Mission, Responsibilities, and Recent Initiatives in Cancer Drug Regulation

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Abstract

The European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union (EU). Since 2005, the agency has become responsible for the approval of all new oncology drugs in the EU. In this article we describe the mission, role, and responsibilities of the EMA, and provide a brief summary of recent initiatives related to cancer drug regulation. The EMA recently published its Road Map to 2015. Over the next 5 years, the agency aims to continue to stimulate drug development in areas of unmet medical needs. Concerning drug safety, one of the priorities over the next few years will be to establish a more proactive approach in ensuring patient safety. This is the result of new EU legislation coming into force in 2012 that will strengthen the way the safety of medicines for human use is monitored in the EU. In terms of its general operation, the agency is committed to increased openness and transparency, and to build on its interactions with stakeholders, including members of academia, health care professionals, patients, and health technology assessment bodies. The agency recently created an oncology working party to expand the current guideline for the development and evaluation of cancer drugs. The guideline focuses on both exploratory and confirmatory studies for different types of agents. The current revision will address a number of topics, including the use of biomarkers as an integrated part of drug development and the use of progression-free survival as a primary endpoint in registration trials. \textit{Clin Cancer Res; 17(16); 5220–5.} ©2011 AACR.

Introduction

Mission statement and legal role

The mission of the European Medicines Agency (EMA) is to foster scientific excellence in the evaluation and supervision of medicines for the benefit of public and animal health.

The EMA is the European Union (EU) body that is responsible for coordinating the existing scientific resources put at its disposal by member states for the evaluation, supervision, and pharmacovigilance of medicinal products. The agency provides the member states and institutions of the EU the best possible scientific advice on any question relating to the evaluation of the quality, safety, and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.

Principal activities

Working with the member states and the European Commission as partners in a European medicines network, the EMA

- provides independent, science-based recommendations on the quality, safety, and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines;
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorization granted by the European Commission;
- implements measures for continuously supervising the quality, safety, and efficacy of authorized medicines to ensure that their benefits outweigh their risks;
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines;
- recommends safe limits for residues of veterinary medicines used in food-producing animals for the establishment of maximum residue limits by the European Commission;

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• involves representatives of patients, health care professionals, and other stakeholders in its work to facilitate dialogue on issues of common interest;
• publishes information about medicines and their use; and
• develops best practices for the evaluation and supervision of medicines in the EU and contributes, alongside the member states and the European Commission, to the harmonization of regulatory standards at the international level.

Since 2005, the agency has become responsible for the approval of all new oncology drugs in the EU through its centralized procedure. The agency’s centralized procedure results in a single marketing authorization that is valid across the EU, as well as in Iceland, Liechtenstein, and Norway. The centralized procedure is compulsory for human medicines intended for the treatment of cancer and certain other conditions, including rare diseases.

**Functional organization**

The Committee for Medicinal Products for Human Use (CHMP) plays a vital role in the marketing procedures for medicines in the EU. The CHMP is responsible for preparing the agency’s opinions on all questions concerning medicines for human use, including marketing authorization, in accordance with regulation (EC) No. 726/2004. A summary of product characteristics is an integral part of the marketing authorization and includes the labeled indication.

The CHMP assessments are based on purely scientific criteria and determine whether the medicines concerned meet the necessary quality, safety, and efficacy requirements, and whether the benefit/risk balance is positive (in accordance with EU legislation, particularly directive 2001/83/EC). Once granted, a marketing authorization can be suspended or revoked in the case of lack of efficacy or when the benefit/risk balance is no longer considered to be positive.

The agency is not responsible for reviewing cost-effectiveness or pricing issues, or for making decisions on the availability of medicines in EU or European Economic Area (EEA)–European Free Trade Association (EFTA) countries through their national health systems. These issues are dealt with by the national government or health authorities of individual countries.

The members and alternates of the CHMP (a chairperson, 1 member, and an alternate nominated by each of the 27 member states, 1 member and an alternate nominated by Iceland and Norway, and up to 5 coopted members, chosen among experts nominated by member states or the agency and recruited, when necessary, to provide additional expertise in a particular scientific area) are chosen on the strength of their qualifications and expertise with regard to the different areas of evaluation of medicines. There are no members representing consumer or patient organizations. Appointed members may not have financial or other interests in the pharmaceutical industry that could affect their impartiality.

The CHMP may delegate certain tasks associated with scientific assessment or drafting guidelines to its working parties or scientific advisory groups. The CHMP meets monthly at the EMA. The meetings are not public, and currently no agendas or minutes of the meetings are published. After each CHMP meeting, a meeting report and a press release are published on the agency’s Web site. In addition, summaries of opinions adopted during each meeting with respect to specific medicines are published on the agency’s Web site.

Other important activities of the CHMP and its working parties include the provision of assistance to companies researching and developing new medicines, the preparation of scientific and regulatory guidelines for the pharmaceuticals industry, and cooperation with international partners on the harmonization of regulatory requirements for medicines. The guidelines are intended to provide a basis for practical harmonization of the manner in which the EU member states and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety, and efficacy contained in the European Union directives.

**International cooperation: the oncology cluster**

The EMA cooperates with many of the world’s largest regulatory bodies outside the EU in areas such as inspections, safety of medicines, and exchange of information on issues of mutual concern. Since 2003, confidentiality arrangements have been in place among the EMA, the European Commission, and the U.S. Food and Drug Administration (FDA), establishing a framework for cooperation between the two agencies. Mechanisms for information exchange include the exchange of assessment reports and review documents, regular teleconferences on oncology products and specific topics, ad hoc teleconferences between EU and U.S. experts, sharing of pharmacovigilance and inspection information, joint Good Manufacturing Practice (GMP)–Good Clinical Practice (GCP) inspections, involvement in training and education, hosting of workshops, agency liaison placements, and ad hoc agency staff visits, including participation in committee and working party meetings. Regular exchanges occur between EMA and FDA clusters (e.g., the oncology cluster) to share systematically relevant advice letters and FDA minutes or letters. The oncology cluster has been particularly active in this respect, resulting in increased dialogue between agencies and sponsors from early stages of development, in early exchange of views, in sharing of expertise, and in contributing to optimize and facilitate global development, thus meeting both agencies’ requirements. The topics discussed include requirements for approval, use of nonvalidated surrogate endpoints, use of pharmacokinetic data, early-approval strategies, the design of biomarker studies, and postmarketing studies. A similar confidentiality arrangement is in place with Health Canada, and the implementation plan also focuses on the exchange of information on oncology.
The EMA Road Map to 2015

The EMA Road Map to 2015 is a proposal for a longer-term strategy that takes due account of the changing environment in which the agency will have to operate over the next 5 years (1).

Special populations, areas of unmet medical needs

The availability of medicines for rare cancers and other currently unmet medical needs remains a challenge. The agency plans to continue to stimulate drug development in areas of unmet medical needs and for neglected and rare diseases. In this context, the term "unmet medical needs" includes those conditions for which no satisfactory method of diagnosis, prevention, or treatment has been authorized in the EU, as well as conditions for which such methods are available but major therapeutic improvements are possible. This builds on the 10-year experience with the EU orphan drug regulation, which has been widely applied to oncology products. Incentives include fee waivers for CHMP scientific advice throughout development and 10 years of market exclusivity for orphan medicinal products that are approved.

The availability of pediatric medicines, including pediatric oncology medicines, remains high on the public health agenda. Indeed, the success achieved in acute lymphoblastic leukemia is not a fair representation of the overall outcome in pediatric oncology. Even for targeted agents, pediatric development has been lagging behind. In 2007 the European regulation on medicines for pediatric use entered into force. This regulation aims to increase the availability of and information on pediatric medicines through high-quality, ethical research (2). A pediatric development plan has become obligatory for all new medicines. This regulation provides an opportunity to make further progress in achieving a cure and improving the quality of care for children with cancer, at a time when innovative and effective anticancer drugs are becoming available (3).

At the same time, pediatric development will require more collaborative approaches between academia and industry, and between pediatric and adult oncologists. It has to be proposed early, when there is preliminary evidence of potential benefit (4). Experience with EU pediatric legislation has shown that the mandatory engagement of regulatory authorities in early-phase development plans of the pharmaceutical industry can help to establish early dialogue with sponsors and to provide regulators with considerable knowledge of the data at an early stage, which in turn facilitates the scientific review process. This concept of early dialogue could be expected to develop beyond the field of pediatric medicines.

Demographic changes, in particular regarding population aging, are expected to drive the agency to undertake additional efforts to ensure that the needs of elderly people are taken into account in the development and evaluation of new medicines. There is a need to ensure that medicines used by geriatric patients are of high quality and have been appropriately researched and evaluated throughout the life cycle of the product for use in this population. Additionally, the availability of information on the use of medicines for older people should be improved, which would result in more-informed prescription. The agency will ensure that the best regulatory and scientific experts are available to provide advice to pharmaceutical companies during the development of medicines used by geriatric patients, particularly for innovative medicines and novel therapeutic approaches. The advice will include the appropriate number of geriatric patients to be included in clinical trials, the distinct needs of older people, consideration of age specific endpoints and any specific safety issues either pre- or post-authorization (5).

Increased contribution by academia

A visible trend is the increasing contribution by members of academia and learned societies to the agency’s work, supporting the development of regulatory science. One example is the extensive use of scientific advisory groups by the agency, particularly during the scientific assessment of oncology drugs. These advisory groups are composed of independent experts, mainly from academia, who are selected by the CHMP according to their specific expertise. Patient representatives may also be appointed. The agency has also established the Healthcare Professionals’ Organisations Working Group (HCP WG), which has identified as one of its priorities a debate on the level of involvement of prescribing physicians, academia, and learned societies in the scientific assessment process throughout a product’s life cycle.

Although the agency and its committees have issued guidelines on drug development for many years, it would seem timely to strengthen the involvement of stakeholders (in particular, academia, learned societies, and patients’ organizations) in this process, such as by organizing workshops at a very early stage of guideline development to which these stakeholders can actively contribute.

Interaction with health technology assessment bodies

A recent development in the pharmaceutical arena is the growing importance of health technology assessment (HTA) bodies in terms of the access to market of novel medicines, primarily due to increased pressure on health care budgets. The agency and representatives from the European network for Health Technology Assessment (EUnetHTA) Joint Action met in London on February 11, 2010, for the first of a series of workshops. This initiated a new collaboration, in which the agency and EUnetHTA are considering how the European Public Assessment Report can better contribute to the assessment of relative effectiveness by HTA bodies in the EU member states. Relative-effectiveness assessments are increasingly being used in the EU member states to help policy makers identify the most valuable medicines.

The agency and the EUnetHTA Joint Action also agreed to explore other areas of possible collaboration or exchange of information in the future, notably in the field of provision...
of scientific advice. In 2010, a new pilot process testing multi-stakeholder consultations in early-stage drug development was launched. The purpose of these consultations is to improve clarity and alignment among the stakeholders regarding what constitutes a medicine’s value and the evidence required to demonstrate that value most effectively. The agency participated in this activity through the CHMP’s scientific advice procedure and hosted the multi-stakeholder face-to-face meetings. This pilot initiative involves clinicians, health technology assessors, patient representatives, payers, regulators, and drug developers from France, Germany, Italy, the Netherlands, Sweden, the United Kingdom, and the EMA. Participating companies sought early advice regarding drugs under development for the treatment of breast cancer and type 2 diabetes, and multi-stakeholder face-to-face meetings have been held in recent months. It is envisaged that similar initiatives will continue to take place in the near future.

**Monitoring of the safety of authorized medicines**

Monitoring of the safety of authorized medicines is conducted through the EU network of national medicines agencies, in close cooperation with health care professionals and pharmaceutical companies. The CHMP closely monitors reports of potential safety concerns and, when necessary, makes recommendations to the European Commission regarding changes to a medicine’s marketing authorization or its suspension/withdrawal from the market.

For several years, the focus within the EU has been directed toward a more proactive approach in ensuring patient safety. Of note, a number of legislative changes in 2005 introduced new tools, such as the concept of risk management plans. Still, public opinion over time has become much more risk averse, resulting in increased demands for more-refined pharmacovigilance tools for medicines for human use. A new directive and regulation introducing a number of changes that will strengthen the monitoring of the safety of authorized medicines for human use.

The main EMA guideline for the development and evaluation of cancer drugs is the CHMP Guideline for the Evaluation of Anticancer Medicinal Products in Man (8). The latest revision came into operation in 2006 and was followed by an appendix covering methodological issues related to progression-free survival (PFS) and, in 2010, an appendix on hematological malignancies. The guideline focuses on both exploratory and confirmatory studies for different types of agents. The CHMP recently created an oncology working party, which is further revising the guideline to expand a number of topics, including the use of biomarkers as an integrated part of the drug development, the use of PFS, and the role of independent review of progression (9).

**Biomarkers as an integrated part of drug development**

There is a common understanding that for a treatment to be effective, whether it is “targeted” or not, the drug developer should aim to identify patients with an increased likelihood to respond favorably to treatment. Although this is generally the case (and has been so for a long time), in practice, medicinal compounds are still sometimes developed without this consideration being an integrated part of the drug development process from the time of drug discovery through nonclinical and clinical development.

Identifying a target and classifying patients according to the presence of that target can greatly speed up drug development and decrease the high attrition rate that is observed in late clinical stages of cancer drug development. For example, a trial of the use of trastuzumab (a HER-2 inhibitor) in a selected population of 469 HER-2(+) patients detected a 9.6% overall survival improvement at 1 year. A nontargeted trial would have required 23,586 patients to show a 2.4% overall survival improvement (10). On the other hand, failure to identify the correct target population early in development can lead to important delays in approval. Gefitinib (Iressa, an EGFR inhibitor) was rejected by the agency in 2005 when the claimed therapeutic indication was for an unselected population in non–small cell lung carcinoma, as the use of EGFR expression as a predictor of response failed to make any difference. Following a targeted development in patients with EGFR-activating mutations, gefitinib was approved in 2009. For situations in which the classifier for selecting responders is not known at the start of the confirmatory stage of clinical development, adaptive designs may offer the flexibility needed to incorporate learning about the population most likely to respond into an ongoing confirmatory trial (11).
There is an obvious and understood wish to use serum biomarkers to define the proper patients for therapy. However, investigators may need to obtain biopsies from tumors (primary and metastatic lesions) or, in some cases, normal tissues to obtain data on target saturation or downstream events when there are no other means to obtain information on the drug exposure–activity relationship (such as functional imaging or blood biomarkers) (8). Furthermore, due to the technical difficulties of collecting and handling samples, only rarely will it be possible to achieve complete sampling and valid analyses. Thus, further reflection is needed regarding the handling of missing data, use of data derived from several independent studies, the standards of laboratories performing the testing, and related technical and methodological issues.

PFS as a primary endpoint for registration

According to the current guideline, acceptable primary endpoints for confirmatory studies include overall survival and PFS. Other endpoints, such as symptom control, may also be acceptable in specific situations. Although overall survival remains the most clinically relevant and convincing endpoint in most situations, PFS has frequently been used as the primary endpoint in pivotal trials leading to approval, often based on single, randomized, controlled studies (as opposed to the 2 or more studies that are generally submitted in other therapeutic areas). Nevertheless, the general acceptance of PFS as a primary endpoint from a regulatory perspective remains controversial, and further guidance is needed on the use of this endpoint in registration trials. In particular, the clinical interpretation of this endpoint, which is based on radiological definitions intended for phase II trials, is often problematic in the context of the benefit/risk assessment at the time of approval. Unless the effect size in terms of PFS is substantial, the clinical relevance of this endpoint can be debated even in indications where conventional radiological response criteria are deemed appropriate. Thus, further reflection is needed on the clinical relevance of progression and how it can be adequately measured.

PFS is also a composite endpoint that includes new lesions, increased size of existing lesions, and death. The extent to which this pattern may differ by classes of compounds is not well understood and may have an impact in terms of clinical interpretation.

Furthermore, when PFS is the chosen primary endpoint, sufficient data on overall survival have to be available at the time of assessment to at least rule out a negative effect. Currently, there is no regulatory guidance as to what constitutes “sufficient” data in terms of overall survival. When a (one-way) crossover to the experimental arm after progression is considered appropriate, this is likely to hamper any subsequent comparisons in terms of overall survival. Thus, when PFS is the primary endpoint, there is a need to define situations and timing when this type of crossover is appropriate, keeping in mind that sufficient data should be available for an adequately powered treatment comparison to at least rule out a negative effect on overall survival.

The use of PFS also requires careful methodology and extensive resources to minimize the risk of bias. Complete blinded independent central radiological review (BICR) has been the regulatory standard for trials using PFS as the primary endpoint, although the systematic use of this complex review tool has been challenged (12–15). According to one proposal, for instance, the need for complete BICR could be reduced after assessing the risk of important bias in the treatment comparison based on an independent review of only a random sample of patients (14). Further reflection is needed on defining situations where complete and, if necessary, real-time BICR is needed, as opposed to situations where more efficient and risk-adapted approaches are possible. Also, regardless of the bias or efficiency of BICR, regulators face a dilemma of interpretation when the results of BICR and local evaluation differ significantly. Although BICR may estimate PFS in a less biased and more precise way, a local evaluation will reflect clinical practice and may be equally relevant under real conditions of use.

Conclusions

The EMA is the EU body that is responsible for coordinating the existing scientific resources put at its disposal by member states for the evaluation, supervision, and pharmacovigilance of medicinal products. Since 2005, the agency has become responsible for the approval of all new oncology drugs in the EU. A number of initiatives relevant for cancer drug development and evaluation have been started.

The Road Map to 2015 sets out the agency’s future challenges and vision from a high-level perspective. Over the next 5 years, the agency aims to continue to stimulate drug development in areas of unmet medical needs. We expect increasing interaction and collaboration between regulatory agencies and HTA bodies, particularly in the field of provision of scientific advice. Concerning drug safety, one of the priorities over the next few years will be to establish a more proactive approach in ensuring patient safety. This is the result of new legislation coming into force in 2012 that will strengthen the way the safety of medicines for human use is monitored in the EU.

The EMA recently created an oncology working party to expand the available guidance on a number of methodological issues in cancer drug development. Rational drug development based on the identification of pharmacodynamic targets and classification of patients by the presence of the target remains a priority because this can greatly increase the efficiency of clinical development and improve the benefit/risk profile of anticancer drugs. Identification of pharmacodynamic targets will require biopsies from tumors (primary and metastatic lesions) or, in some cases, normal tissues to obtain data on target saturation or downstream events. Although the practical difficulties of obtaining biopsies from metastatic lesions are acknowledged, we expect that patients and clinicians will want to meet this
challenge. One can anticipate that matching targeted drugs with better patient selection in the exploratory phases of development will lead to a wider use of early approval mechanisms, with drugs increasingly being approved initially for small subgroups of patients with great unmet needs (16). Further guidance is also expected about the choice of primary endpoint in registration trials and the clinical relevance of PFS, addressing some of the methodological issues related to measuring progression in an unbiased and more efficient way, and ensuring that sufficient data on overall survival are available to support a licensing decision.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its scientific committees or working parties.

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