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POLICY PERSPECTIVES

Improving the Contribution of Regulatory Assessment Reports to Health Technology Assessments—A Collaboration between the European Medicines Agency and the European network for Health Technology Assessment

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ABSTRACT

In response to a recommendation from the Pharmaceutical Forum, the European Medicines Agency and the European network for Health Technology Assessment initiated a collaboration with the aim to improve the contribution regulatory assessment reports can make to the assessment of relative effectiveness of medicinal products by health technology assessment bodies. This collaboration on improving European Public Assessment Reports (EPARs) started in February 2010 and was performed over 2 years. As a result, the templates for preparing EPARs were revised to better address the needs of heath technology organizations. The better understanding of information needs was a key outcome of the collaboration. To ascertain whether these template changes led to the inclusion of relevant information, a review of a small set of EPARs for recently approved medicinal products was carried out in parallel by both the European network for Health Technology Assessment and the European Medicines Agency. This report provides an account of this project on improving EPARs, which is part of the ongoing dialogue between regulators and health technology assessment bodies on a European level to support policymaker decisions in the future.

Keywords: European Medicines Agency (EMA), European network for Health Technology Assessment (EUnetHTA), European Public Assessment Reports (EPARs), relative effectiveness assessment.

Introduction

Scientific evaluation of the clinical data produced during drug development can be intended to estimate the benefit/risk ratio of the product (recently in some jurisdictions also referred to as benefit/harm/uncertainty), for the purpose of marketing authorization, or to estimate the effectiveness of the new product as compared with existing therapies, as part of the health technology assessment (HTA) process to support decision making on price and reimbursement.

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications for European Union (EU) marketing authorizations for medicinal products in the so-called centralized procedure. Under this procedure, a single marketing-authorization application is submitted to the EMA and once authorization is granted by the European Commission on the basis of a pan-European scientific assessment of quality, efficacy, and safety by EMA committees, a centralized marketing authorization is valid in all EU member states.

The subsequent evaluation and decision-making process leading to decisions on the pricing and reimbursement of medicinal products lie with the national bodies. HTA is a multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value [1]. Criteria for HTA vary between countries, but generally HTA bodies in Europe use relative effectiveness assessment (REA), a European equivalent to comparative effectiveness research in the United States, as part of the HTA process [2].

The European network for Health Technology Assessment (EUnetHTA) is a network of organizations appointed by EU member states that produce or contribute to HTA to facilitate efficient use of resources available for HTA, to create a sustainable system of HTA knowledge sharing, and to promote good practice in HTA methods and processes [1,3]. Originally started as

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a project in 2006, EUnetHTA was established to create an effective and sustainable network for HTA across Europe [4].

In October 2008, the Pharmaceutical Forum, a high-level ministerial platform for discussion between member states, EU institutions, industry, health care professionals, patients, and insurance funds, agreed on conclusions and recommendations to find relevant solutions to public health considerations regarding pharmaceuticals, while ensuring the competitiveness of the industry and the sustainability of the national health care systems [5]. One of these recommendations provided a political mandate to initiate collaboration between the EMA and EUnetHTA with the aim to improve the availability and best use of data relevant to HTA. Specifically, the objective of this joint project of regulators and HTA bodies was to "consider how information in the European Public Assessment Report /…/ can further contribute to relative effectiveness assessment" [5].

The regulatory assessment reports, which are the basis for central marketing authorizations, are publicly available as so-called European Public Assessment Reports (EPARs). EPARs reflect the scientific conclusions reached by the EMA's Committee for Medicinal Products for Human Use (CHMP) at the end of the regulatory review process after deletion of commercially confidential information. These are published on the EMA's Web site for every medicine authorized through the centralized procedure in the EU. Because these contain the CHMP's judgment on the methodological quality of the studies and the relevance and significance of results, in the perspective of the estimate of the balance between favorable and unfavorable effects for the medicinal product, they may also be used as source documents for REAs from the HTA perspective. In particular, such assessment reports are used in the context of rapid REA of pharmaceuticals [6].

The collaboration between the EMA and EUnetHTA on EPARs started in February 2010 and was performed over 2 years. It has been subject to a wider consultation within EUnetHTA as part of the Work Package 5 on REA of Pharmaceuticals of EUnetHTA Joint Action 1. This report provides an account of various activities as part of the project to address the recommendation on improving the EPAR.

Methods

In the first phase, EUnetHTA provided input on the usefulness of published EPARs and Summary of Product Characteristics (SmPC) in the context of REA of medicinal products based on the initial work performed in 2009 by some partners (which are also EUnetHTA partners) of the Medicine Evaluation Committee (MEDEV), a standing working group of the European Social Health Insurance Forum. This input was reviewed by the EMA and an action plan was established, which was mutually agreed between the EMA and EUnetHTA. Subsequently, the templates and guidance documents for the assessment of initial marketing authorization applications were amended by the EMA to implement the agreed improvements through either specific sections or supportive guidance. The revised templates and guidance documents were presented to the CHMP for adoption and subsequently published on the EMA's Web site (www.ema.europa.eu) for use by assessors in the centralized procedure (>Home >Regulatory >Human medicines >Pre-authorisation >Templates for assessors).

The second phase was the critical review of EPARs to establish compliance with revised templates. For this purpose, EPARs of the first 10 products, for which the assessment report has been prepared after the revised templates came into operation, were analyzed for compliance with specific aspects amended in the template. The following EPARs were reviewed: Esbriet (pirfenidone), Gilenya (fingolimod), Halaven (eribulin), Jevtana (cabazitaxel), Pravafenix (fenofibrate/pravastatin), Pumarix (pandemic influenza vaccine [H5N1]), Teysuno (tegafur/gimeracil/oteracil), Trobalt (retigabine), Xeplion (paliperidone), and Xiapex (collagenase clostridium histolyticum). The review took place in second and third quarters of 2011 on the basis of the publicly available EPARs. A questionnaire with 36 questions was developed by the EMA targeting the identified areas for improvement. Two types of answers were attributed depending on the nature of the question: either the option "yes/no/not applicable" (13 questions) if the underlying question was simply whether an item is included or the grading "excellent/good/could be improved/no/not applicable" (23 questions) if a more differentiated review was considered more meaningful. Table 1 indicates for each review item the type of question. Numerical values were assigned against the answers ("1/0" and "3/2/1/0" for binary and graded answers, respectively) to allow for statistical analysis of compliance of the EPARs for each individual question. The review of the 10 EPARs was performed in parallel by the EMA and by EUnetHTA, always involving two reviewers per organization and using the same questionnaire and numerical scales. In case of divergent views between the two reviewers, consensus was formed. One additional question on the benefit-risk assessment was added by HTA organizations at the time of EUnetHTA review. As regards EUnetHTA review, each EPAR was evaluated by two HTA organizations from EUnetHTA. Ten HTA organizations (see Acknowledgment) participated in this exercise coordinated by the French National Authority for Health (HAS). The results were calculated as mean values in terms of the overall compliance rate across all 10 EPARs and reviewers for each of the two organizations (i.e., if the answer for a binary question was "yes" ["1"] in 6 out of 10 EPARs, a 60% overall compliance rate was attributed). For descriptive purpose, the compliance rates are clustered in three distinct categories: more than 80% compliance (mean), 50% to 80% compliance (mean), and less than 50% compliance (mean).

Results

As a result of the project, the templates for preparing EPARs were revised to address the comments received. Furthermore, a review of a small set of EPARs was carried out in parallel by both EUnetHTA and the EMA to ascertain whether these template changes led to the inclusion of relevant information. The following sections present these results separately.

Revision of Templates for Preparing EPARs

Figure 1 displays the development of revisions to templates for regulatory assessments with the aim to improve the contribution such reports can make to the assessment of relative effectiveness of medicinal products. The initial analysis of a compilation of comments from EUnetHTA/MEDEV identified 34 topic areas for further discussion. These topics areas concerned the format and structure, the scientific content, the evaluation criteria, and other aspects of the assessment report. A detailed discussion of each item revealed opportunities for improvement of template and guidance as well as areas in which adherence to existing template and guidance might need to be improved. Certain items concerned the methodology for conducting an assessment rather than data presentation, such as the acceptability of certain surrogate parameters or the conduct of a wider literature search; these items were excluded from the exercise. Most of the items, which were addressed through revisions to the templates, concerned the scientific content of the assessment report, particularly, the clinical aspects. In most instances, the agreed items are related to a more detailed data presentation or more explicit reasoning of considerations for the regulatory decision making. In addition, specific sections of the SmPC have been identified in