Journal of Epidemiology and Global Health (2015) 5, 385–395

http:// www.elsevier.com/locate/jegh

Role of patient-reported outcomes and other efficacy endpoints in the drug approval process in Europe (2008—2012)

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Received 1 August 2014; received in revised form 9 April 2015; accepted 10 April 2015
Available online 29 May 2015

KEYWORDS
European Medicines Agency;
European Public Assessment Report;
Patient reported outcomes;
Health related quality of health

Abstract The present study aimed at systematically reviewing the role and extent of patient-reported outcomes (PROs) usage within the package of scientific evidence considered for marketing authorization (MA). All regulatory information published by the European Medicines Agency (EMA) for products authorized between January 2008 and December 2012 and appearing in the European Public Assessment Report (EPAR) database was examined for efficacy endpoints. The endpoints here considered included: PROs, clinician reported outcomes (CROs), and laboratory reported outcomes (LROs). LROs were the most frequently reported endpoints. Out of the 180 products here selected, 99 (55%), 67 (37%), and 30 (17%), respectively, used LROs, CROs and PROs as primary endpoints (PEs). PROs as any endpoints were used in 82 (46%) products. Out of these, PROs were documented as PE in 30 (37%), with 27 (33%) products having used PROs both as primary and non-PEs. PRO usage was most frequently identified with nervous system and antineoplastic agents. During the study period, the use of all the three types of endpoints appeared to be static. Both the regulatory bodies and the industry should ensure complete and clear reporting of all endpoints used, including PROs, to improve transparency.

1. Introduction

The European Public Assessment Report (EPAR) made available by the European Medicines Agency (EMA) contains the index pharmaceutical product regulatory information [1,2]. It is published with the aim of granting the marketing authorization

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http://dx.doi.org/10.1016/j.jegh.2015.04.006
2210-6006/

(MA) for any new pharmaceutical, and it is publicly accessible to allow satisfactory levels of transparency in the decision-making process [2]. The related scientific evidence is described in the scientific discussion part (SDP) and the molecule pharmacodynamics in the EPAR Summary of Product Characteristics (SPC) section. The SPC contains the information about both the clinical study endpoints and the health outcomes used during the evaluation phase of the product [3].

The regulatory drug approval is based on a range of clinical trial endpoints which are used to determine the biological activity, the clinical benefits, and the molecule safety profile [4]. The traditionally used endpoints include: the clinician-reported outcomes (CROs; e.g., those observed by the physician or which require an interpretation by the physician, i.e., radiography results) [4,5]; and the laboratory reported outcomes (LROs; e.g., objective measures performed by instruments) [4,5]. Finally, the patient-reported outcome(s) (PRO) is a generic term applicable to any health-related data reported directly by the patient without requiring an interpretation by the physician. These data typically include: symptoms, functional status, satisfaction with therapy, or treatment adherence [5,6]. PRO measures extend the range of patient outcomes that can be assessed beyond the traditional measures of survival rates, clinical efficacy and side effects. Thus, PROs allow researchers to capture the patient's perspectives on a range of parameters, including: symptoms, overall health status, and the impact of disease and treatment on quality of life [7]. Health-related quality of life (HRQoL) is a specific subset of PROs defined as the patient's subjective perception of the impact of disease and treatment(s) on daily life, physical, psychological, social functioning and well-being [7].

Although CROs and LROs are valuable, they may miss significant components of the patient's experience. These endpoints are inadequate in conditions such as pain, depression and fatigue, typically requiring patients' evaluation of their symptoms and health status [8]. PROs are used particularly for products used for treating chronic, disabling and incurable conditions, the treatment of which is administered with the purpose of improving both symptomatology and HRQoL levels [9,10].

Arguably, PROs may be considered as primary endpoints (PEs) in drug development for diseases such as cancer, pain, migraine, and irritable bowel syndrome. As non-PEs, PROs are also used in diseases such as depression, insomnia, and asthma. In rheumatoid arthritis and cancer, PROs are used to assess the treatment benefits and tolerability to better assess the medication impact on HRQoL. PROs can also be used in clinical trials to assess treatment satisfaction, compliance, and the caregiver burden [7]. Finally, PROs are also included in safety reporting, as discussed by the patient-reported outcomes safety event reporting (PROSPER) consortium [11]. Previous PRO usage analyses have been relatively focused on drug approvals [12]; labelling claims [5,13,14]; or single assessment tools [15]. PRO measures have also been examined in disease-specific contexts, including cancer [16—18] and rheumatoid arthritis [19]. Concerns relating to HRQoL increased usage, requirements of internal and external validation, and terminology standardization led to the release in 2006 of a reflection paper by the EMA [20]. This paper has provided broad recommendations on HRQoL usage in the context of already existing clinical guidance documents.

Improvement of recovering and survival rates remains the key target for drug development. However, identifying a range of parameters that can better describe the improvement levels in terms of patients' feelings, overall HRQoL, and/or their overall functioning is an increasingly demanding goal. One could argue that drugs with a similar efficacy may present with different PRO levels, hence, PROs may be seen as an important gauge in the development of new treatment options [21,22]. The present study aimed at systematically reviewing the role and extent of PRO use within the package of scientific evidence considered for marketing authorization, as documented by the EPAR, over a period of 5 years (2008—2012). This study also aimed at exploring both the disease areas and the types of PROs being used.

2. Materials and methods

2.1. Search strategy

A systematic comprehensive electronic and manual search was performed herein for all the product-level regulatory documents (EPAR) published by EMA [23] from January 2008 to December 2012, with a special emphasis given to PROs being used in the regulatory process. The present analysis reviewed the distribution of CRO/LRO/PRO as clinical trial endpoints during the medicinal product approval prior to marketing authorization.

2.2. Selection criteria

EPARs of all medicinal products registered with the EMA were individually reviewed. The inclusion