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Health Policy Analyses

Comparisons of Food and Drug Administration and European Medicines Agency Risk Management Implementation for Recent Pharmaceutical Approvals: Report of the International Society for Pharmacoeconomics and Outcomes Research Risk Benefit Management Working Group

Yvonne Lis, PhD[1], Melissa H. Roberts, MS[2], Shital Kamble, PhD[3], Jeff J. Guo, PhD[4], Dennis W. Raisch, PhD[5,]*

[1]*PAREXEL International, Uxbridge, UK;* [2]*Lovelace Clinic Foundation Research, Albuquerque, New Mexico, USA;* [3]*Quintiles-Outcome, Rockville, MD, USA;* [4]*College of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH, USA;* [5]*College of Pharmacy, University of New Mexico, Albuquerque, NM, USA*

ABSTRACT

Objective: 1) To compare the Food and Drug Administration's (FDA's) Risk Evaluation and Mitigation Strategies (REMS) and European Medicines Agency's (EMA's) Risk Management Plan (RMP) guidances and 2) to compare REMS and RMPs for specific chemical entities and biological products. **Methods:** FDA, EMA, and pharmaceutical company Web sites were consulted for details pertaining to REMS and RMPs. REMS requirements include medication guides, communication plans, elements to ensure safe use, implementation systems, and specified assessment intervals. RMP requirements are increased pharmacovigilance and risk minimization activities. We compared these requirements for drugs requiring both REMS and RMPs. **Results:** We identified 95 drugs on FDA's REMS list as of March 2010. Of these, there were 29 drugs (11 biologics and 18 new chemical entities) with EMA RMPs. REMS and RMPs are similar in objectives, with comparable toolkits. Both allow flexibility in product-specific actions, recognizing adverse effects of potential concern. Of the 29 drugs reviewed, REMS requirements not included in RMPs were patient medication guides (100% of the drugs), provider communication plans (38%), and routine monitoring of REMS (66%). RMP requirements not included in REMS were specific adverse event reporting (45% of the drugs), prospective registry studies (34%), prospective epidemiology studies (24%), additional trial data (28%), and Summary of Product Characteristics contraindications (76%). **Conclusions:** Both REMS and RMPs provide positive guidance for identification, monitoring, and minimization of risk to patient safety. Currently, neither agency provides specific guidance on how risk should be related to benefit either qualitatively or quantitatively.

Keywords: European Medicines Agency, Food and Drug Administration, Pharmaceuticals, Risk benefit management.

Introduction

Partly in response to the withdrawal of high-profile branded drugs such as Vioxx [1], Seldane [2], Rezulin [3], Propulsid, Baycol [4], and Lotronex [5] over the last few years, regulatory authorities have changed emphasis from the reactive collection of safety data to a more proactive risk management approach. Public scrutiny of regulatory bodies has also increased the focus on drug safety surveillance with the downstream impact of increased regulatory requirements for postmarketing pharmacovigilance.

From discussions on potential approaches for establishing acceptable methodologies for quantitative benefit-risk assessment, both European and US constituents determined that transparency and consistency were required, as well as flexibility in judgment [6,7]. The European Medicines Agency (EMA) has issued a reflection paper [6] and initiated a benefit-risk methodology project aimed at making the assessment of risks and benefits of medicines more consistent and transparent. The U.S. Food and Drug Administration (FDA) is also working on providing a framework to facilitate a more structured approach to risk-benefit assessment [8].

The FDA identifies risk management as an iterative process designed to optimize the benefit-risk balance for regulated products throughout the product life cycle [9]. In March 2005, the FDA issued three guidance documents that defined the formal basis of risk management. These were Premarketing Risk Assessment [10], Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [11], and the Development and Use of Risk Minimization Action Plans (RiskMAPs) [12]. These three documents subsequently provided the building blocks for the more recent Risk Evaluation and Mitigation Strategies (REMS) [13]. The final content of a product's REMS, however, reflects the unique mix of product attributes as well as the intended prescriber and patient populations.

For several years, the focus by the EMA has been directed toward a proactive approach in ensuring patient safety, while

* *Address correspondence to:* College of Pharmacy, University of New Mexico, 1 University of New Mexico, MSC 09 5360 Albuquerque, NM 87131.

E-mail: draisch@salud.unm.edu.

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continuing efforts to further improve the spontaneous reporting scheme. This resulted in a number of legislative changes in 2005 and the introduction of new tools including the concept of Risk Management Plans (RMPs) [14]. In September 2008, the EMA issued guidelines on risk management systems, a template for an RMP, and new regulations governing pharmacovigilance [15]. The EMA emphasizes the importance of having pharmacovigilance systems in place and mandates the creation of the position of a Qualified Person for Pharmacovigilance to be responsible for a company's pharmacovigilance efforts for marketed products. Much of the emphasis is placed on databases and reporting systems, especially for postmarketing; however, different EMA member states have taken varying approaches to the collection and reporting of safety data [15]. In summary, through REMS and RMPs, both the FDA and the EMA require proactive approaches for drug safety surveillance. As a result, they have reframed the traditional business model of the pharmaceutical industry.

FDA REMS Overview

Many of the principles articulated in previous FDA RiskMAP guidance have been incorporated into the provisions of REMS [16]. The Food and Drug Administration Amendments Act of 2007, enacted in March 2008 [13], provided the FDA with authority to request a REMS at any point during a product life cycle. The requirement applies to all new drug applications, abbreviated new drug applications, and biologics license applications. Chemical entities and biologics approved prior to March 2008 with a RiskMAP were also required to have REMS.

The REMS program seeks to manage known or potential serious risks, and the content must have a timetable for submission of assessments. Additional components for a particular REMS program vary according to the severity of identified risks, the population likely to be exposed, and other factors. These can include a medication guide, a patient package insert, a communication plan, and elements to ensure safe use. Examples of elements to ensure safe use include 1) dispensing only by pharmacies, practitioners, or health care settings that are specially certified and (2) the product being dispensed only when there is evidence of safe-use conditions and monitoring of patients either individually or by enrolment in a registry.

Currently, there are no set rules or direct guidance for when the FDA might impose REMS during the product life cycle. There are, however, some considerations that drive its decision-making process, which include the estimated size of the patient population, the seriousness of a disease or condition, the expected benefit of the medication, the anticipated duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new chemical or biological entity. The FDA's Drug Safety and Risk Management Advisory Committee, composed of various stakeholders including patients, physicians, pharmacists, and other health care professionals, provides input on implementation requirements and performs evaluation of each program. After the product has received marketing authorization, the timings for routine assessment of the incorporated REMS program by the manufacturer are 18 months, 3 years, and 7 years. The FDA can remove the need for assessments after 3 years if serious risks have been adequately identified, assessed, and managed or, if necessary, stipulate shorter or longer intervals between assessments [12].

The FDA has also published several guidance documents relating to specific safety issues that include drug-induced liver injury [17], a recommended approach for communicating important drug safety information to the public [18,19], pharmacovigilance planning at the time of license application [20], and quality risk management [18]. The intent of the set of guidance documents is to provide regulators and industry with principles and tools for risk management as a basis for consistent risk-based decisions throughout a product's life cycle [18].

EMA RMP Overview

The European Union (EU) legislation necessitates that, when required, a description of the risk management system should be submitted in the form of an EU-RMP. This comprises a Safety Specification with a Pharmacovigilance Plan (Part I) and a Risk Minimization Plan (Part II). Similar to the FDA, there are no set rules or specific guidance; however, experience suggests that an RMP will be required when routine pharmacovigilance practice is considered to be insufficient. This can be interpreted as being applicable to a product containing a new active substance, a significant change in indication, or new to a class for which a serious or potentially serious safety risk has been previously identified. Also included are similar biological medicinal products and generic/hybrid medicinal products where a safety concern requiring additional risk minimization activities has been identified for the referenced medicinal product [21].

The EMA recommends that Part I of the RMP should comprise a summary of important identified risks of a medicinal product, significant potential risks, and important missing information. It should contain information on populations potentially at risk together with any outstanding safety questions that warrant further investigation. The intent is to determine whether routine postauthorization pharmacovigilance will be sufficient or whether there is a need for additional pharmacovigilance activities.

Part II should contain details of any additional pharmacovigilance or risk minimization activities. No precise guidance is given on which activities are to be used in any given situation as each safety concern needs to be considered on a case-by-case basis. The guidance does, however, recommend early and full consultation with appropriate EMA experts.

An essential part of pharmacovigilance includes accurate and timely communication of emerging data on risk. An important component in risk management and minimization activities is risk communication. Presenting product information, the Summary of Product Characteristics (SPC), and patient information leaflets is a prime vehicle for communicating any potential risks to prescribers and patients. Additional risk minimization activities of RMPs include provision of educational materials or educational programs for health care professionals and patients. Once the RMP is agreed upon, updated documents including any reported signals and safety evaluations should be submitted along with the Periodic Safety Update Report.

Objective

Both the FDA and the EMA have implemented proactive approaches for safety surveillance and risk assessment, and our earlier article compared FDA and EMA regulatory guidelines for pharmaceutical risk management [22]. The purpose of this study is twofold: 1) to compare the details of REMS and RMP guidances and 2) to compare REMS and RMPs requirements for specific pharmaceuticals approved in both the United States and the EU. This study provides information on whether both the FDA and the EMA implement consistent, transparent, and flexible approaches for evaluating the risk and benefit of chemical entities and biologics.

Methods

A descriptive study was conducted to review and compare the FDA and EMA risk management implementations after the introduction of REMS in January 2007. Our comparison method was to review how risk management for identical drugs was implemented by the FDA and the EMA. As of March 2010, a total