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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

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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.

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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

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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

of 95 drugs were listed by the FDA as having REMS [23]. As no equivalent list is published by the EMA, publicly available information on the EMA and pharmaceutical company Web sites was searched to identify which of the FDA-listed products had also been approved by the EMA. This resulted in 29 products for review including 11 biologics and 18 chemical entities (Table 2). While there are minimal differences in the approval and postapproval review processes of chemical entities and biologics, and supplemental applications, historically there have been differences between the two types of drugs; therefore, we separated them in the summaries.

Multiple aspects of the safety components, including medication guides, patient package inserts, communication plans, elements to ensure safe use, Periodic Safety Update Report reporting requirements, and educational programs, were compared and consensus reached among all coauthors who reviewed the details of the safety components. To further illustrate the differences between REMS and RMP safety regulatory requirements, we summarized and compared the REMS and RMP details for an antiplatelet product and a tumor necrosis factor inhibitor.

Results

Comparison of Positions between FDA and EMA Guidance

A comparison of FDA and EMA guidance indicates a similarity in overall objectives with respect to the identification, monitoring, and minimization of risk and a good degree of synergy in respective toolkits. Both agencies allow flexibility in the determination of product-specific actions required, recognizing the dependency on differing adverse effects of potential concern. However, they do differ on elements such as monitoring the implementation of risk minimization actions and reporting time requirements. Importantly, neither agency provides specific guidance regarding tolerances or limits on how risk should be related to benefit, either qualitatively or quantitatively. The FDA

REMS and EMA RMP components that were compared and the rationale for their comparison are summarized in Table 1. Major components unique to FDA REMS are the need to assess the success of risk communication using provider and patient surveys, as well as restrictions on the distribution of products only to providers who have completed training programs. In EMA's RMP, unique components comprised additional data analysis, supplementary trial and other study data, as well as the development of diagnostic tests for early detection of adverse reactions.

Selection of Products

The summary of products from both agencies that were found to be approved is displayed in Table 2. Table 3 displays the selected products reviewed as well as the therapeutic area and specific risks included in REMS and RMPs. Although a total of 30 new chemical entities and biologics were initially identified, interferon alfacon-1 was excluded as the manufacturer had voluntarily withdrawn it from marketing in Europe in 2006.

Comparisons of REMS and RMPs for 29 Products

The broad categories that were assessed are shown in Table 4; they are displayed for the drugs overall and separately for new clinical entities (NCEs) and biologics. Specific REMS and RMP components for each category and drug are available from the corresponding author on request. The specific head-to-head comparisons between REMS and RMPs are shown in Appendix 1 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2012.06.019>. Of note are some differences between biologics and NCEs. For REMS, more of the biologics required provider communication plans (45% vs. 28%) while more of the NCEs specified distribution of the medication guides (61% vs. 9%). For RMPs, more of the biologics included SPC contraindications (100% vs. 61%) and SPC undesirable effects (100% vs. 44%). Prospective registry (55% vs. 22%) and epidemiologic studies (36% vs. 17%) were also more

Table 1 – Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) and European Medicines Agency (EMA) Risk Management Plans (RMPs) Components.

FDA REMS components	EMA RMPs components	Rationale for comparison
Medication guide, patient information sheet	Patient alert cards, patient information leaflet	Information given to patients with dispensed medication summarizing key aspects of efficacy and safety
Provider communication plan	Educational programs	Similar scope and purpose
Provider information sheet	Summary of Product Characteristics (SPC) contraindications, special warnings and precautions for use, undesirable effects	Similar scope and purpose
Highlighted information for prescribers	SPC contraindications, special warnings and precautions for use, undesirable effects	Similar scope and purpose
Monitoring of patients receiving medication	Prospective registry studies Specific adverse event and Periodic Safety Update Report (PSUR) requirements Prospective epidemiology studies	Similar scope and purpose
Training of health care professionals	Educational programs	Provider-based training
Audit of communication plan, patient and/or physician survey to evaluate comprehension of risk	None	Not evaluated as part of RMPs
REMS print advertisement	None	Not evaluated as part of RMPs
Specification of distribution and/or dispensing, monitoring of distribution	None	Not a component of RMPs
None	Additional data analysis, supplementary trial or other study data	Addressed by FDA as part of approval process
None	Development of diagnostic test	Not included in REMS

Table 2 – Products approved by both Food and Drug Administration (FDA) and European Medicines Agency (EMA) with risk management components during the study period.

Strategy components	Total FDA REMS [†]	Also approved by EMA with RMP
Medication guide only	69	19*
Medication guide and communication plan	18	9
Medication guide, elements to ensure safe use (ETESU), implementation system	3	1
Medication guide, communication plan, ETESU, implementation system	3	1
Communication plan, ETESU, implementation system	2	0
Grand total	95	30
*Marketing authorization removed		1
Drug types for reviewed products		
Biologics		11
Chemical entities		18

REMS, Risk Evaluation and Mitigation Strategies; RMP, Risk Management Plan.

* Marketing authorization for interferon alfacon-1 withdrawn by the manufacturer in 2006; therefore, it was not included in comparison.

† Approved REMS as of March 8, 2010.

frequently included in RMPs for biologic drugs. Conversely, 44% of the RMPs for NCEs included requirements for additional trial and study data, while none of the biologics had the requirement.

We also summarized the differences between REMS and RMPs for two specific drugs (Table 5), a new chemical entity (prasugrel) and a biological product (certolizumab pegol). For both products, REMS provides more specific information regarding the communication of risks directly to health care providers as well as patients. In contrast, the RMPs for these products focus more on surveillance and providing additional information to the EMA, while giving less specific information regarding the communication of risk to providers through educational programs. For example, for both products, a prospective registry was established in the respective RMP to further characterize known and potential risks as well as to supplement missing information.

Discussion

A comparison of risk management regulations between the FDA and the EMA suggests that the current sets of FDA and EMA guidance documents are driven by similar objectives with regard to the identification, monitoring, and minimization of risk and as a consequence lead to similar data needs [22]. This is important for the international pharmaceutical industry as any significant divergence would inevitably lead to increased pre- and postmarketing approval costs. Further, in today's global market environment the need for similar data also facilitates the exchange of information between the major regulators.

A total of 95 drugs were identified in the United States from FDA's REMS list and of these, 29 could be easily matched with a corresponding EMA-approved drug. We did not find records of

EMA approval for the remaining products. The REMS and RMPs for each of the products identified were mostly issued at different dates because of differences in FDA approval and EMA marketing authorization dates. Similarly, revisions to the REMS and RMPs were implemented at different times depending on the planned timetable for review. In both situations, therefore, different safety data were available for review and consideration by the agencies, and a direct head-to-head comparison of specific actions required was not entirely possible. However, in general terms, warnings and use restrictions were broadly in line.

The review did identify some differences in emphasis between the agencies relating to the communication of risk to both physicians and patients. For the EMA, the SPC is the key communication tool for physicians on treatment effect, serious adverse effects, contraindications, and special warnings. Communication to the patient is principally through contact with and advice from the physician at the time of prescribing as well as the patient information leaflet provided as a package insert. In contrast, the REMS specifies the provision of a communication plan for ensuring that risks are fully conveyed to health care professionals and patients. A further difference arises in FDA's requirement for the measurement of the effectiveness of the communication plan by survey and other means to determine whether the information was communicated and understood by the patient. We note that the REMS guideline for communication plans only specifies that "The program may require periodic re-certification and re-enrollment." Therefore, the timing of evaluation of the communication plan is specific to each REMS proposed by the manufacturer. If the FDA recommends changes, the manufacturer must respond to those changes.

Implementation of REMS and RMPs has advanced the evolution of the risk management model for pharmacovigilance. In the current model, risks must be assessed more carefully before product marketing and any serious risks identified must be proactively monitored and actions taken to reduce the likelihood of occurrence. The modified standards for approval, new label models, patient inserts, special advertising, and mandatory monitoring have been quickly established as essential risk minimization tools. Central to the concept of risk assessment is the determination whether the level of risk is acceptable; however, none of the current guidelines directly addresses this acceptability in the context of the potential benefit delivered by the product.

This study provides a detailed comparison by specific components, highlighting the differences between REMS and RMPs among the 29 study products reviewed. Significant differences in the approaches to risk management of the FDA and the EMA had not been expected, but what does appear to differ currently is the way that the FDA may require monitoring and measurement of any elements to ensure safe use (ETESUs) specified in the REMS whereas the EMA appears to rely principally on routine adverse event reporting, regular Periodic Safety Update Report submissions, postauthorization surveillance studies, and patient registries to detect the risk being experienced in clinical practice. Implementing similar approaches to monitoring and measurement within different health care systems and medical practices as well as the diversity of cultures among the 27 EU member states and 3 European Economic Area countries is practically and politically challenging. However, new draft EMA pharmacovigilance legislation intended to increase harmonization between member states. The draft Guidelines on Good Pharmacovigilance Practices represent the biggest change to the legal framework for medicines since 1995 and assuming their adoption, will harmonize and further strengthen the pharmacovigilance process in Europe [24,25].

We note that the regulatory process for pharmaceutical risk management is dynamic. In 2011, the FDA issued a guidance on REMS that includes updated information on how to remove a

Table 3 – List of products with a Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) and European Medicines Agency (EMA) Risk Management Plans (RMPs) as of March 8, 2010.

FDA Brand and (chemical) names	Date REMS approved	Date EMA revision	Drug type	Therapeutic area	REMS Risks	RMP Risks*
Actos (pioglitazone hydrochloride) tablets	9/9/2009	5/10/2009	Chemical entity	Diabetes	Heart failure, edema, weight gain, hepatic dysfunction	Heart failure, hepatic dysfunction, weight gain/peripheral edema, neoplasia
Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets	12/2/2008	1/9/2009	Chemical entity	Diabetes	Myocardial ischemia, congestive heart failure, hepatic dysfunction	Cardiovascular events, pancreatitis, interaction with warfarin
Byetta (exanatide) injection	10/30/2009	6/25/2009	Chemical entity	Diabetes	Undiagnosed and complicated pancreatitis and renal failure	Allergic/immunologic events, cardiovascular malignant adverse events, metabolic disorders, acute renal impairment, pancreatitis, dehydration, hypovolemia, increased international normalized ratio (INR) with concomitant warfarin
Cimzia (certolizumab pegol) lyophilized powder for solution for subcutaneous injection	Modified 12/31/2008, 5/13/2009, 11/3/2009	1/21/2010	Biologic	Crohn's disease/ rheumatoid arthritis	Invasive opportunistic fungal infections including histoplasmosis, coccidioidomycosis, blastomycosis	Infections, malignancies, cardiovascular events, demyelinating disorders, blood disorders, lupus and lupuslike illness, immunogenicity, hepatitis B reactivation, risk in different age groups and populations, risk in concomitant use, risk due to medication errors and off-label use
Effient (prasugrel) tablets	7/10/2009	12/2/2009	Chemical entity	Platelet inhibitor	Serious bleeding	Serious bleeding
Enbrel (etanercept) for subcutaneous injection	6/23/2008	3/4/2010	Biologic	Histoplasmosis	Serious infections such as tuberculosis	Serious infections, tuberculosis, lupuslike reactions, injection site reactions, allergic reactions, central demyelinating disorders, aplastic anemia and pancytopenia events, malignancy, change in morphology and/or severity of psoriasis, growth and development
Extavia (interferon beta-1b)	8/14/2009	12/7/2009	Biologic	Multiple sclerosis	Major depression and allergic reaction	Depression and suicidal behavior, hypersensitivity, hepatotoxicity, infection site necrosis, blood disorders, capillary leak syndrome, pancreatitis, seizures, thyroid disorders, cardiac disease, pregnancy outcomes
Forteo (teriparatide [rDNA origin]) injection	7/22/2009	9/21/2009	Chemical entity	Osteoporosis	Blood pressure; increased calcium levels in your blood	Osteosarcoma
Intron A (interferon alfa-2b)	5/2/2008; modified 8/7/2009	1/21/2010	Biologic	Chemotherapy	Depression, suicidal thoughts, stroke, cerebrovascular complications, vision problems, low blood cell counts (white blood cells and platelets); certain populations should not use	Central nervous system effects, suicidal thoughts, peripheral ischemia seizure, ophthalmic, hypertriglyceridemia, aplastic anemia
Kaletra (iopinavir and ritonavir) oral solution	4/6/2009; modified 1/29/2010	1/29/2010	Chemical entity	Human immunodeficiency virus (HIV) infection	Potential cardiac arrhythmias	Dosage errors due to coexistence of capsule and tablet formulations
Keppra, Keppra XR (levetiracetam) tablets, extended-release tablets, oral solution, and injection	4/23/2009	9/18/2009	Chemical entity	Antiepileptic	Mood and behavior changes, problems with muscle coordination	Abnormal behavior, blood dyscrasias, seizures, worsening, long-term effects on physical and mental function, safety in patients younger than 12 mo and younger than 4 y
Lyrica (pregabalin)	2/23/2009; modified 1/4/2010	1/27/2010	Chemical entity	Neuropathic pain	Suicidal thoughts and behavior, muscle problems, eyesight and weight gain	Weight gain, peripheral edema, dizziness, somnolence and potential for accidental injury, ophthalmological safety, withdrawal effects. hemangiosarcoma

(Continued on next page)

Multaq (dronedarone) tablets	7/1/2009	12/16/2009	Chemical entity	Atrial fibrillation	Increased mortality in patients with severe unstable heart failure, bradycardia (slowed heartbeat)	Drug-drug interactions with potent Cytochrome P450 3A4 (CYP3A4) inhibitors, use in unstable hemodynamic conditions, drug-drug interactions with digitalis, calcium antagonists with heart rate-lowering properties, beta-blockers, statins, tacrolimus and sirolimus, potent CYP3A4 inducers, amiodaronelike effects: interstitial lung disease, severe skin disorders including photosensitivity, neuropathy including optic, hepatic injury
Nplate (romiplostim) for subcutaneous injection	8/22/2008; modified 8/14/2009	3/8/2010	Biologic	Chronic immune thrombocytopenia	Changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a preexisting hematological malignancy or myelodysplastic syndrome, medication errors associated with serious outcomes	Reoccurrence of thrombocytopenia after cessation of treatment, increased bone marrow reticulin, thrombocytosis, thrombotic thromboembolic complications, neutralizing antibodies that cross-react with endogenous thrombopoietin, progression of existing hematological malignancies or myelodysplastic syndrome, bone marrow fibrosis, leukocytosis in preclinical setting, off-label use, medication errors, risk during pregnancy/lactation
Pegasys (peginterferon alfa-2a)	Modified 8/7/2009	11/16/2009	Biologic	Chronic hepatitis C	Anemia, neutropenia, thrombocytopenia, monitoring thyroid and blood sugar, and eye problems	Pneumonia, sarcoidosis, anaphylaxis, diabetes, suicidal ideation, wheezing, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss, supraventricular tachycardia, congestive heart failure, angina, myocardial infarction, hepatic failure, bilirubin increase, anemia in females, decrease in hematological values; certain populations should not use
PegIntron (peginterferon alfa-2b)	12/11/2008; modified 8/7/2009	1/22/2010	Biologic	Chronic hepatitis C	Depression or anxiety, sleep problems, hypertension; certain populations should not use	Psychiatric events

Table 3 (continued)

FDA Brand and (chemical) names	Date REMS approved	Date EMA revision	Drug type	Therapeutic area	REMS Risks	RMP Risks*
Rebetol (ribivarin) capsules	11/6/2009	1/22/2010	Chemical entity	Chronic hepatitis B	Pancreatitis, pneumonia, eye problems, severe depression; certain populations should not use	Anemia, neutropenia, depression, myalgia, viral infection; certain populations should not use
Remicade (infliximab) vial	11/18/2009	11/24/2009	Biologic	Tumor necrosis factor (TNF) blocker for autoimmune disorders	Unrecognized histoplasmosis and other invasive fungal infections associated with concomitant TNF-blocker use	Serious infections, infusion-related reactions, worsening of heart failure, hematological reactions, neurological disorders, antibody development, malignancy
Samsca (tolvaptan) tablets	5/19/2009	8/18/2009	Chemical entity	Hyponatremia	Osmotic demyelination syndrome, overly rapid correction of serum sodium, need for initiating tolvaptan in a hospital to ensure proper titration and monitoring	Renal toxicity, volume depletion, acute urinary retention, electrolyte shifts (patients with urinary outflow obstruction), dehydration, cardiac arrhythmias, rapid rise of serum sodium and neurologic sequelae, gastrointestinal bleeding in patients with liver cirrhosis, hyperglycemia, diabetes mellitus, hyperuricemia and gout, hypercoagulability and stroke, posttreatment myocardial ischemia, dyspnea, teratogenicity, hepatic-impaired, interaction with CYP3A4 inhibitors/inducers, drug-drug interactions, off-label use
Simponi (golimumab) injection	4/24/2009; modified 11/3/2009	10/20/2009	Biologic	TNF blocker for autoimmune disorders	Unrecognized histoplasmosis and other invasive fungal infections associated with concomitant TNF-blocker use	Serious infections including sepsis, pneumonia, and tuberculosis, demyelinating disorders, malignancy, hepatotoxicity, hepatitis B reactivation, congestive heart failure; certain populations should not use
Stelara (ustekinumab) injection	9/25/2009; modified 12/30/2009	1/25/2010	Biologic	Moderate to severe plaque psoriasis	Serious infections and malignancy, reversible posterior leukoencephalopathy syndrome	Serious infection, malignancy, cardiovascular events, systemic hypersensitivity events, serious depression; certain populations should not use
Tracleer (bosentan) tablets	8/7/2009	2/11/2010	Chemical entity	Pulmonary arterial hypertension	Hepatotoxicity; certain populations should not use	Hepatotoxicity; certain populations should not use
Trizivir (abacavir sulfate, lamivudine, and zidovudine)	3/9/2009	12/9/2009	Chemical entity	HIV-1 infection	Hepatotoxicity	Hypersensitivity, lipodystrophy
Vimpat (lacosamide) injection	10/28/2008	8/18/2009	Chemical entity	Antiepileptic	Suicidality, anxiety, insomnia	Cardiovascular events, hepatotoxicity, worsening of seizures, dizziness, abuse, suicidality; certain populations should not use
Viramune (nevirapine) tablets and oral suspension	6/24/2008; modified 1/13/2010	6/11/2009	Chemical entity	HIV infection	Hepatotoxicity	Hepatotoxicity, skin rash including severe or life-threatening skin reactions, granulocytopenia
Xolair (omalizumab)	7/24/2009	2/17/2010	Biologic	Asthma	Anaphylaxis and other severe allergic reactions	Hypersensitivity reactions, blood antitherapeutic antibody identification, anaphylaxis and malignant neoplasms
Ziagen (abacavir sulfate) tablets and oral solution	7/18/2008	2/12/2010	Chemical entity	HIV infection	Hypersensitivity	Hypersensitivity
Zonegran (zonisamide) capsules	4/23/2009	8/13/2009	Chemical entity	Antiepileptic	Serious skin rash, suicidality	Pruritis, peripheral edema, hypersensitivity, osteopenia, renal events, metabolic acidosis, suicidality, risk in elderly, "toxic epidermal necrolysis"
Zyprexa, Zyprexa Zydis (olanzapine) tablets	3/19/2009; modified 12/4/2009	8/20/2009	Chemical entity	Schizophrenia	Hyperglycemia, hyperlipidemia, weight gain	Hyperglycemia, weight gain, acute overdoses

* Includes identified risks, potential risks, and important unidentified information assessed by routine or additional pharmacovigilance activities.

Table 4 – Summary of Food and Drug Administration (FDA) and European Medicines Agency (EMA) risk management components for 29 products.

Components	n (%)		
	New chemical entities	Biologics	Total
FDA Risk Evaluation and Mitigation Strategies (REMS)			
REMS Components			
Patient medication guide	18 (100)	11 (100)	29 (100)
Provider communication plan	5 (28)	5 (45)	10 (34)
Elements to ensure safe use	1 (6)	1 (9)	2 (7)
Implementation system	1 (6)	1 (9)	2 (7)
Additional REMS attributes			
Routine monitoring of risk mitigation plan	11 (61)	8 (73)	19 (66)
Patient survey	1 (6)	1 (9)	2 (7)
Review of promotional materials	2 (11)	0 (0)	2 (7)
Increased frequency of assessment	1 (6)	0 (0)	1 (3)
Distribution of medication guide	11 (61)	1 (9)	12 (41)
Patient survey	2 (11)	1 (9)	3 (10)
Registry	1 (6)	2 (18)	3 (10)
Monitoring of patients receiving medication	0 (0)	1 (9)	1 (3)
EMA Risk Management Plans (RMPs)			
Risk minimization activities			
SPC Special warnings and precautions for use	13 (72)	11 (100)	24 (83)
SPC Contraindications	11 (61)	11 (100)	22 (76)
SPC Undesirable effects	8 (44)	11 (100)	19 (66)
Educational programs	2 (11)	2 (18)	4 (14)
Patient alert cards	2 (11)	2 (18)	4 (14)
Development of diagnostic test	1 (6)	0 (0)	1 (3)
Additional pharmacovigilance			
Specific AE and PSUR reporting requirements	9 (50)	4 (36)	13 (45)
Prospective registry studies	4 (22)	6 (55)	10 (34)
Prospective epidemiology studies	3 (17)	4 (36)	7 (24)
Additional data analysis	1 (6)	0 (0)	1 (3)
Additional trial and study data	8 (44)	0 (0)	8 (28)
Prescription surveys	1 (6)	0 (0)	1 (3)
Noninterventional studies to capture off-label use	1 (6)	0 (0)	1 (3)

AE, adverse event; PSUR, Periodic Safety Update Report; SPC, Summary of Product Characteristics.

product from REMS [26]. Specifically, if the REMS is limited to a medication guide, a communication plan, and a timetable for assessment, the manufacturer can submit a request for removal from REMS. The request is accompanied by a REMS assessment within the last 18 months and/or update of the results of data collected from a postapproval study or clinical trial. The assessment must substantiate the proposition that the REMS is no longer needed to ensure that benefits outweigh the risks. If approved by the FDA, the medication guide continues to be part of the product labeling and must still be provided to patients prior to receiving the drug. However, the release from REMS removes the manufacturer from responsibility for providing further assessments to the FDA. We note that of the 29 products included in this review, the FDA released 21 of them from REMS requirements between April and December 2011. Subsequently, a manufacturer may submit a supplement to the FDA requesting removal of the medication guide from the approved labeling.

Regarding the differences between NCEs and biologics within REMS and RMPs, it appeared that REMS requirements were similar. In contrast, we found that RMPs for all biologics included SPC contraindications and undesirable effects as well as more frequently requiring patient registries and additional pharmacovigilance studies. Although we hesitate to draw firm conclusions from this convenience sample, these findings may indicate heightened concern for adverse effects from biologics. This is a potential area for further study, using a more comprehensive sample.

While the evolution of risk management approaches is important, the results will still leave the decision makers handicapped because of the current absence of acceptable methods for evaluating risks versus benefits. The regulator is always likely to side with caution and if products are withheld from the market as a consequence, many patients may be denied the opportunity to make an informed risk-benefit judgment in consultation with their physician while taking into account individual circumstances.

Discussions on potential approaches to establishing acceptable methodologies for quantitative benefit-risk assessment in both European and US constituents determined that transparency and consistency were required, as well as flexibility in judgment [6,7]. The EMA issued a reflection paper [6] and has initiated a benefit-risk methodology project aimed at making the assessment of risks and benefits of medicines more consistent and transparent. The FDA is developing a framework to facilitate a more structured approach to risk-benefit assessment [8].

More recently, the EMA published its public consultation document titled “The EMA Road Map to 2015: The Agency’s Contribution to Science, Medicines and Health” [27]. The major challenges and priorities identified in the document are the appropriateness of the current legal/regulatory framework with regard to benefit-risk evaluation and the development of tools for the anticipation of potential safety issues. The EMA indicates that although the RMPs are increasing the knowledge of a medicine in the postauthorization phase, there would be merit in systematically including

Table 5 – Comparison of the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) and European Medicines Agency (EMA) Risk Management Plans (RMPs) for an antiplatelet agent and a recombinant tumor necrosis factor (TNF) inhibitor.

FDA REMS	EMA RMP
<i>Prasugrel (Effient), an antiplatelet agent</i>	
Risk of interest	Risk of interest
<ul style="list-style-type: none"> ● Bleeding 	<ul style="list-style-type: none"> ● Identified risk—hemorrhage, anemia ● Potential risks—off-label use, phototoxicity, hepatic injury, allergic reactions, thrombocytopenia, neutropenia, thrombotic thrombocytopenic purpura ● Missing information—concomitant use with fibrinolytics, clopidogrel, and nonsteroidal anti-inflammatory agents; pediatric population, pregnant/lactating women; subjects without clinical manifestations of acute coronary syndrome; subjects with severely compromised cardiac status; subjects with severe hepatic impairment
Communication	Communication
<ul style="list-style-type: none"> ● Dear health care provider letter and prescriber brochure for specialists and primary care physicians to convey information on serious risk of bleeding, appropriate patient selection ● Information in health care provider brochure to discuss with patients ● Limited to 2-y postlaunch ● Medication guide distributed to every outpatient/inpatient ● Instructions on dispensing for pharmacists 	<ul style="list-style-type: none"> ● Contraindications and special warnings in Summary of Product Characteristics (SPC) ● Educational materials for treating physicians
Timetable	Timetable
<ul style="list-style-type: none"> ● First REMS assessment in 18 mo ● Second REMS assessment in 3 y ● Third REMS assessment in 7 y 	<ul style="list-style-type: none"> ● Routine and targeted surveillance; prospective in-hospital registry for risk of hemorrhage and off-label use ● Missing information—routine surveillance and additional analysis of adverse events from clinical trials and safety database
<i>Certolizumab pegol (Cimzia), a recombinant TNF Inhibitor</i>	
Risk of interest	Risk of interest
<ul style="list-style-type: none"> ● Histoplasmosis and other invasive fungal infections 	<ul style="list-style-type: none"> ● Identified risks—infections, including serious opportunistic ● Potential risks—malignancies including lymphoma; congestive heart failure and ischemic cardiac events; demyelinatinglike disorders; aplastic anemia; pancytopenia, neutropenia, leukopenia thrombocytopenia; serious bleeding events; lupus and lupuslike illness; immunogenicity; hepatitis B reactivation ● Missing information—pregnancy and lactation; children, adolescents, elderly; patients with renal or hepatic impairment; immune function; potential for overdose or medication errors; off-label use; concomitant use with disease-modifying antirheumatic drugs other than methotrexate; previous use of TNF inhibitor therapy
Communication	Communication
<ul style="list-style-type: none"> ● Dear health care provider letter, Web-based materials, and a medical scientific liaison slide deck ● To convey information on the risk of invasive fungal infections, information on signs and symptoms as well as treatment of fungal infection; benefit-risk assessment prior to restarting therapy after recovery from fungal infection ● Information in health care provider brochure to discuss with patients ● Medication guide distributed to every outpatient/inpatient ● Limited time frame 	<ul style="list-style-type: none"> ● Contraindications and special warnings in SPC ● Educational program (target audience not specified in European Public Assessment Report)
Timetable	Timetable
<ul style="list-style-type: none"> ● First REMS assessment in 18 mo ● Second REMS assessment in 3 y ● Third REMS assessment in 7 y 	<ul style="list-style-type: none"> ● Identified and potential risks—routine and active surveillance using a registry; evaluation of risk from information gathered in Periodic Safety Update Reports (PSURs) ● Missing information—routine and active surveillance using a registry; evaluation of risk from information gathered in PSURs

information on the benefits of a medicinal product throughout its life cycle. It is anticipated that a revised concept of postauthorization commitments in a benefit-risk management plan could provide efficiencies in the system. In support of this, the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance, initiated in 2006, is charged with conducting independent multicenter postauthorization studies focused on safety and/or lack of efficacy [28]. The EMA has an ongoing Benefit-Risk Methodology Project that is developing and testing tools and processes for balancing multiple benefits and risks [29].

A limitation of this review is that the assessment of REMS and RMPs was completed in September 2010. Any updates to these documents or new approvals since that time point are not reflected in our findings. Another potential limitation is that by using only publicly available documents for this review certain details may have been unavailable. Further, only products approved in both jurisdictions, that is, the EMA and the FDA, were evaluated. It is likely that the findings could show some bias toward harmonization. However, to perform a head-to-head comparison between both jurisdictions, it was important to

review products with both REMS and RMPs and such an approach clearly delineated key differences in the practical implementation of respective regulatory agencies' risk benefit management processes.

Conclusions

Both REMS and RMPs provide positive guidance for identification, monitoring, and minimization of risk to patient safety. They do differ on elements such as the monitoring of the implementation of risk minimization actions and the reporting time requirements. Currently, neither agency provides specific guidance on how risk should be related to benefit either qualitatively or quantitatively. The authors recommend that this review exercise should be repeated in 2013 to detect any new trends or threats to the current degree of harmony between the approaches of the FDA and the EMA and to examine what progress, if any, is being made in the development and implementation of quantitative risk and benefit approaches.

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