Another aspect that would need clarification if evidence is to be shared is the difference in validity of the data that are required by the different assessors. Whereas regulators prefer the internal validity provided by the RCT, payers are more interested in the external validity obtained from real-life clinical practice or observational studies. Though ideally all assessors prefer data obtained over the longest possible period of time, regulators are more accepting of shorter time horizons as evidenced in the duration of clinical trials. The payers are more interested in longer time horizons, for example, through the long-term follow-up of MS patients in the patient access scheme in the United Kingdom. It is unclear whether a requirement for RE assessment is likely to streamline this process.

Even if all these questions can be answered, many remain on matters of implementation and methodology, such as how RE will be implemented in practice and who would be responsible. Current thoughts are that the EMA may be given responsibility, however, this aspect still remains unclear. Even if such a requirement were implemented, it is possible that evidence on RE will not be required for all licensing decisions but could be reserved for cases where there is a clear comparator or a substantial innovation. As part of any procedure, in case RE assessment takes place, an appeals/complaints procedure will need to be established. This is a substantial undertaking. Further thoughts should be given as to how and to what extent data will be made publicly available. The RE assessment may include substantial commercial-in-confidence data which will not be suitable for publication, and so mechanisms will need to be put into place to ensure the confidentiality of these data, while still sharing results with the wide public.

In conclusion, though the reasoning behind the need for RE assessments is clear, and even though this type of assessment could result in important time savings and manufacturers should, regardless of the requirements, aim to provide more evidence on the comparative value of their new products, it is evident that the actual implementation requires more detailed discussions around process, methodology, timelines and tasks.

References
The focus is on the generation, acquisition, analysis and presentation of premarketing safety data and the document contains a comprehensive set of recommendations for conducting clinical studies.

The Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidance defines pharmacovigilance as, “all observational post-approval scientific and data gathering activities relating to the detection, assessment and understanding of adverse events with the goals of identifying and preventing these events to the extent possible.” It contains recommendations for reporting and analytical practices to monitor safety concerns and risk associated with medical products. The guidance also recognizes the heterogeneous nature of benefit and risk assessment stating that, “because different products pose different benefit risk considerations including seriousness of the disease, the nature and frequency of the safety signal, it is impossible to delineate a universal set of criteria to identify the point at which a pharmacoepidemiologic safety study should be initiated.”

The RiskMAP was defined as a strategic safety program designed to minimize known risks of a product while preserving its benefits. It described how industry could address specific risk-related goals and objectives, suggesting various tools to minimize the risks of drug and biological products. The FDA recommended that a plan should target at the achievement of particular health outcomes related to known safety risks and be stated in absolute terms. For example ‘patients prescribed drug X should not also be prescribed drug Y’. The FDA also recognized that a variety of tools could be used to minimize risk, including: targeted education and outreach, reminder systems and performance based systems.

Enacted in March 2008, the Food and Drug Administration Amendments Act of 2007 (FDAAA) [11] provides the FDA with authority to request a REMS at any point during a product’s life cycle. The REMS requirement which effectively replaces the RiskMAP applies to all new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs). Certain products approved prior to March 2008, and those with elements to assure safe use, were deemed to have an approved REMS but were also required to submit a proposed REMS within 180 days of the FDAAA.

Currently there are no set rules or direct guidance for when the FDA might impose a REMS, however, considerations that drive their decision include: the estimated size of the patient population; the seriousness of a disease or condition; the expected benefit of the intervention; the anticipated duration of treatment; the seriousness of known or potential adverse events; and whether the drug is a new chemical entity. Other considerations after approval may include new evidence that REMS requirements are needed to ensure that the benefits of the drug outweigh its risks.

Where required, the REMS is intended to manage known or potentially serious risks and the REMS’ elements vary according to the severity of identified risks, the population likely to be exposed, and other factors. The REMS guidance provides a general framework for mandated post marketing safety activities and incorporates many of the principles in the original RiskMAP guidance [12]. The requirements may include the provision of a medication guide, a patient package insert, a communication plan or other Elements to Assure Safe Use (ETASU). ETASUs may include such provisions as dispensing only by pharmacies or practitioners in health care settings that are specially certified, the product only being dispensed where there is evidence of safe-use conditions, or monitoring of patients either individually or by enrolment in a registry. Provision must also be made for monitoring the implementation of ETASU requirements.

Evaluation of each REMS is conducted by the FDA’s Drug Safety and Risk Management Advisory Committee comprised of various stakeholders including patients, physicians, pharmacists and other health care professionals who provide input on implementation requirements and management strategy. After approval, timings for routine assessment of the program are 18 months, 3 years and 7 years. If considered appropriate the FDA may stipulate shorter or longer intervals between assessments and can remove the need for assessments after year 3 if serious risks have been adequately identified, assessed and managed.

With the introduction of REMS requirements, the FDA also issued a number of guidance documents relating to specific safety issues which include: drug-induced liver injury [13], a recommended approach for communicating important drug safety information to the public [14], pharmacovigilance planning at the time of license application [15] and quality risk management to provide regulators and industry with principles and tools for risk management as a basis for consistent risk-based decisions throughout a product’s lifecycle [16]. More recent guidance [17] is focused on detailing the circumstances and type of post-marketing studies and clinical trials that may be required for safety evaluation and other agreed upon post marketing commitments.

The EMA Approach

Within the European Union (EU), the focus has also been on a proactive approach in ensuring patient safety, with continuing efforts to improve the spontaneous reporting scheme. In 2005, legislation formalised the introduction of risk management plans [18] and subsequently the European Medicines Agency (EMA) issued guidelines on risk management systems, a template for a Risk Management Plan (RMP), and new regulations governing pharmacovigilance [19].

An RMP is required when routine pharmacovigilance practice for medications is considered to be insufficient. Products containing a new active substance, or for which there is a significant change in indication or for which serious or potentially serious safety risks have been previously identified, generally fall into this category. An RMP is also required for biological medicinal products and generic/hybrid medicinal products, for which a safety concern requiring additional risk minimisation activities has been identified [20].

The process comprises a Safety Specification with a Pharmacovigilance Plan (Part I) and a Risk Minimisation Plan (Part II). Part I is intended to enable determination of whether routine post authorisation pharmacovigilance will be sufficient or whether there is a need for additional pharmacovigilance activities. It requires a summary of important identified and significant potential risks of a medicinal product, information on populations potentially at risk together with any outstanding safety questions which warrant further investigation.

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

Accurate and timely communication of emerging data on risk is considered an essential part of pharmacovigilance with risk education, risk management and any risk minimization activities being essential components. The Summary of Product Characteristics and Patient Information Leaflets are the prime vehicles for communicating any potential risks to prescribers and patients. Once the overall RMP has been approved, updated documents including any reported adverse event signals and safety evaluations should be submitted along with the periodic safety update report (PSUR).

In the recent EMA draft, ‘The European Medicines Agency Road Map to 2015’ [21], a key strategic area identified for optimization is the safe use of medicines. Plans include revisions to the overall risk management concept and enhancements to current pharmacovigilance activities including the on-going strengthening of post authorisation monitoring. In support of this EMA strategy, the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP), set up in 2006, was charged with conducting independent multi-centre post-authorisation studies focused on investigating safety and a lack of efficacy [22]. The Road Map to 2015 >
also set out several priority challenges, including the development of tools for the anticipation of potential safety issues and the appropriateness of the current legal/regulatory framework with regard to benefit/risk evaluation. The EMA indicates that although the risk management plans are increasing the knowledge of a medicine in the post-authorization phase, there is also merit in systematically gaining information on the benefits of a medicinal product throughout its lifecycle. Evidence of evolution in the EMA approach can be seen in the recently revised Regulations [23] and Directives [24] effective from July 2012 which is aimed at improving routine pharmacovigilance activities, strengthening the EudraVigilance system and harmonizing access across member states.

A Comparison of Approaches
The current sets of FDA and EMA guidance are driven by similar objectives for the identification, monitoring and minimization of risk to patient safety. As a result, they frequently lead to the generation of similar data needs. In today’s global market environment such similar data requirements facilitate the exchange of information between the regulators. Although the central concept for both agencies is assessing risk and determining if it is acceptable, none of the current guidelines directly define risk acceptability.

Implementation of REMS and RMP requirements initiated new risk management approaches for pharmacovigilance. When serious safety concerns are identified, they must be rigorously monitored and action taken to reduce risk to patients. Modified standards of approval, new label models, patient inserts, special advertising and mandatory registry monitoring have become established risk minimization tools.

The authors had not expected to find significant differences in the approaches to risk management between the FDA and the EMA and a detailed comparison of respective guidance documents suggests similarity in overall objectives with respect to the identification, monitoring and minimization of risk. Similarly, both Agencies allow flexibility in the determination of product specific actions required, recognizing the dependency on differing potential concerns. From an enforcement perspective, both agencies have the power to assure that manufacturers adequately implement approved REMS/RMPs.

Differences in the timing of the approval or revisions to REMS/RMPs for the same product are also known to occur; however, these are usually driven by the timing of entry into the different markets and the new information that becomes available as a result.

There are cases, however, where the two Agencies have made different decisions in response to the safety issues identified in currently marketed products. For example, in December 2010 EMA suspended Avandia®, Avandamet® and Avaglim® on the basis of data suggesting elevated risk of heart attacks in patients treated with rosiglitzone. The FDA, however, decided only to restrict access and the REMS was modified accordingly in May 2011.

There are differences in emphasis for the communication of risk to patients and physicians. In the EU, the Summary of Product Characteristics is the key communication to physicians, including data on treatment effects, serious adverse effects, contraindications and special warnings. Communication to the patient is principally through the Patient Information Leaflet provided as a package insert with every prescription, supplemented with advice from the physician at the time of prescribing. In the United States, the Medication Guide represents the basic vehicle for communicating information on medicinal risks to patients. A communication plan for ensuring that risks are fully communicated to health care professionals is not always required.

There are also differences in monitoring implementation of risk minimization actions and the reporting time requirements which are generally related to geographic and logistic factors. Where there are known safety concerns, in its single market, the FDA requires monitoring and measurement to be implemented through the ETASU plan. Given the range of health care systems, varying medical practice and diversity of cultures among the 27 EU Member States and 3 EE/EA countries that EMA oversees, implementing a standard approach to monitoring and measurement is currently both practically and politically challenging. Therefore, the EMA relies principally on routine adverse event reporting and regular PSUR submission to detect risk experienced in clinical practice. Like the FDA it also places emphasis on additional data collection in the form of prospective studies, such as Registries, to further characterize known or potential risks and to fill specific safety information gaps.

One other dimension to consider is that while the EMA has an overarching role within Europe, national agencies may still take independent action. One example is the case of pioglitazone, where recently available five year results indicated a possible increased risk of bladder cancer in some patients. Both the FDA and EMA are currently reviewing the risks and benefits pending any decision on the marketing status of the product; however, the French Medicines Agency (Afssaps) has already suspended its use pending the review of available evidence.

A summary of conceptually similar FDA REMs and EMA RMP elements are detailed in Table 1, while components not shared by the two agencies are shown in Table 2.

Table 1. Conceptually similar components between FDA’s REMs and EMA’s RMPs

<table>
<thead>
<tr>
<th>FDA – REMS</th>
<th>EMA – RMPs</th>
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<tbody>
<tr>
<td>Medication guides</td>
<td>Patient alert cards</td>
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<tr>
<td>Patient information sheet</td>
<td>Patient information leaflet</td>
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<tr>
<td>Container labels</td>
<td>Summary of Product Characteristic (SPC) contraindications SPC special warnings and precautions for use</td>
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<tr>
<td>Provider communication plan</td>
<td>Summary of Product Characteristic (SPC) contraindications Educational programmes</td>
</tr>
<tr>
<td>Monitoring of patients receiving medication</td>
<td>Specific adverse event and pharmacovigilance surveillance reporting requirements Prospective observational studies</td>
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<tr>
<td>Prescriber and patient database</td>
<td>Additional trial and study data</td>
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<tr>
<td>Post marketing studies Registry</td>
<td>Specific adverse event and pharmacovigilance surveillance reporting requirements Registry</td>
</tr>
</tbody>
</table>

Table 2. Requirements not shared between FDA’s REMs and EMA’s RMPs

<table>
<thead>
<tr>
<th>FDA – REMS</th>
<th>EMA – RMPs</th>
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<tbody>
<tr>
<td>Monitoring of patients receiving medication</td>
<td>SPC undesirable effects Development of diagnostic tests for adverse event</td>
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<tr>
<td>Specification of distribution or dispensing locations</td>
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<tr>
<td>Monitoring of distribution</td>
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<tr>
<td>Patient or physician survey to evaluate understanding of risk</td>
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<tr>
<td>REMS print advertisement</td>
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<tr>
<td>Audit of communication plan</td>
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<td>Audit of pharmacies</td>
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Although neither agency currently provides specific guidance for risk versus benefit assessment [25], the need for a more consistent, structured yet flexible approach by the Regulator to the evaluation of risks versus benefits is being discussed by both European and United States constituents with ongoing initiatives to identify acceptable methodologies [26,27]. The EMA reflection paper issued in 2008 [28] was followed by a benefit risk methodology project aimed at providing a more consistent and transparent approach for evaluating the risks and benefits of medicines. The FDA is also working towards developing a framework for a more structured approach to risk benefit assessment [29].

In summary, both FDA REMS and EMA RMPs currently provide broadly comparable comprehensive post approval guidance for the identification, monitoring and minimization of risk to patient safety with some differences in respective implementation toolkits. There is also an increasing tendency towards collaborative efforts between the two regulatory agencies in approaches to monitoring and minimizing risk for patients.

References