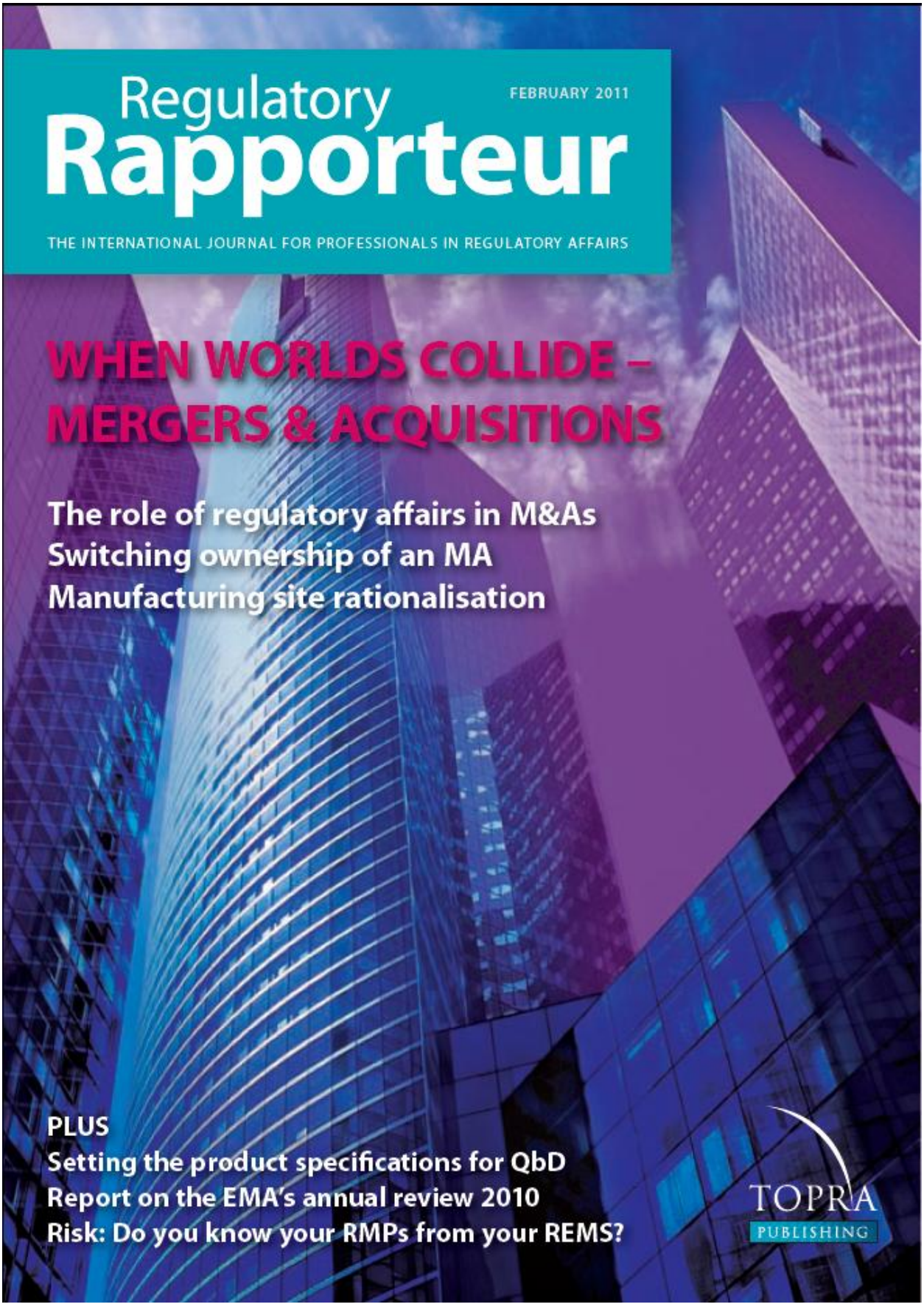
Regulatory
Rapporteur
FEBRUARY 2011
THE INTERNATIONAL JOURNAL FOR PROFESSIONALS IN REGULATORY AFFAIRS
WHEN WORLDS COLLIDE – MERGERS & ACQUISITIONS
The role of regulatory affairs in M&As
Switching ownership of an MA
Manufacturing site rationalisation
PLUS
Setting the product specifications for QbD
Report on the EMA's annual review 2010
Risk: Do you know your RMPs from your REMS?
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Regulatory Rapporteur

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Cover illustration: Image of La Défense, a business district in Paris, France, described by the UK's Prince of Wales, as "a place for those statements of corporate aspiration to be made".

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Designed by The Upper Room
Croydon, Surrey
Printed by Newman Thomson
Burgess Hill, West Sussex

ISSN 1742-8955

Regulatory Rapporteur is free to TOPRA members. Annual membership to TOPRA is €210. Alternatively, the journal can be purchased by non-members at the following rates:

Annual subscription:	€280
Library subscription:	€600
Current issue:	€30
Back issues:	€50

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Regulatory Rapporteur *is indexed on two Elsevier academic databases, Embase and Scopus. To access these go to* ***http://www.info.embase.com/embase-pharmaceutical-research*** *and* ***http://info.scopus.com***

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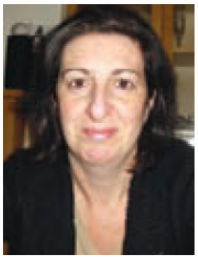
Consolidating pharma's financial future



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Rarely does a day go by without news in the pharmaceutical arena that a company has bought another company or that two companies have merged to become a larger pharmaceutical entity. This sounds like a simple process of gathering assets together and registering a new name for the newly formed company. More or less like buying a new house or car – you just add your name to your new asset. If only it was that simple!

Mergers and acquisitions (M&A) usually open Pandora's box. Inside this box is a whole world of implications and complications – a merger or acquisition is a complex and laborious process that can take years to complete. It affects assets, people, authorities, ways of working and cultural differences, to name but a few issues. It touches all company departments at a higher or lower level. That is why this important topic is the special focus of this month's issue of *Regulatory Rapporteur*, giving us all the opportunity to broaden our knowledge on the many aspects of the M&A process.

In our first focus article, Bill Griffiths introduces us to M&A by explaining the regulatory affairs role and our impact on the success of a merger or acquisition. Our author examines the process and strategy needed to successfully complete the various steps of the M&A. Regulatory Affairs (RA) will be highly involved in its two most important processes: commercial and manufacturing site rationalisation. RA will need to establish an M&A group to manage all the cross-functional activities and projects. The importance of the RA leadership role within a team at this time of uncertainty and change is also highlighted.

Exploring the process of manufacturing rationalisation in depth is an article co-authored by Ahmed Motara and Ivan Fisher. This discusses the importance of a regulatory strategy, and reviews the challenges and requirements needed to complete the process in a timely manner. The authors give some examples of situations in which regulatory colleagues can find themselves and how to handle them. Regulatory compliance is a key issue.

> Mergers and acquisitions affect assets, people, authorities, ways of working and cultural differences, to name but a few issues

Adding to this interesting topic, Christopher Carr and Gagandeep Sudera underline the key area of commercial rationalisation (changes of legal entities). They address the complexity of the process and the diverse approaches taken by different markets. The authors offer advice on how to handle the process and give some specific examples.

Elsewhere in this issue, the first part of a two-part paper examines the various aspects of Quality by Design (QbD), with this month's article focusing on how product specifications are set. Davina Stevenson describes QbD's systematic development approach which, rather than the more traditional batch-based approach, involves comprehensive process understanding and quality risk management. Success relies on cross-functional cooperation within the company, accompanied by the ability to adapt to changes and adopt new technologies.

On an equally important topic, Hoss Dowlat examines the impact and diverse requirements of risk management systems in Europe and the US, aimed at ensuring the safety of medicines throughout their lifecycles. The communication of risk to prescribers and patients is central to both the EU risk management plan (RMP) and the US risk evaluation and mitigation strategy (REMS). Our author updates us on the regulatory ways and means adopted to minimise harm and maximise benefits of sponsors' medicinal products.

Finally, our reporters Helene Thybo and Tove Illing have provided us with in-depth coverage of December's annual joint EMA/TOPRA meeting, the "European Medicines Agency Review of the Year and Outlook for 2011 and beyond". This important regulatory event focuses on the agency's future plans, including the Road Map to 2015 and the Heads of Medicines Agencies Strategy Paper II, as well as other initiatives that will impact on all industry stakeholders. Other session topics included information on the centralised procedure, EMA and HTA scientific advice, the agency's new working party structure and, of keen interest to delegates, an open forum where responses were given to previously set questions on the future role of regulatory agencies.

The importance and impact of the EU RMP and US REMS to risk–benefit assessments

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Keywords

Risk management plan (RMP); Risk evaluation and mitigation strategy (REMS); Risk minimisation action plan (RiskMAP); Pharmacovigilance; Summary of product characteristics (SmPC); Patient information leaflet (PIL); Package leaflet (PL).

Abstract

The EU RMP is an engagement of wider scope than the US REMS, and is binding on a larger set of medicines. The US REMS is compulsory only for some medicines, and can be limited to two years post product launch. The REMS concerns itself with communication of risk; with the prescriber information, the package insert (PI), being central to risk minimisation. Components of a typical FDA REMS are a communication plan; patient selection; web-based materials and a medical scientific liaison; elements to assure safe use; an implementation system; a patient or physician survey; and patient understanding of risk.

The EU RMP is a more comprehensive, more extensive safety package that the sponsor is obligated to follow throughout the lifecycle of all new drugs or biologics. The main components of an EU RMP are risk assessment, pharmacovigilance activities, and finally risk minimisation activities (which are mainly associated with the SmPC and PL).

The EU and the US have very different histories and philosophies when approaching drug safety. In Europe, the EU has been faced with the diverse experiences of 30 long-established institutions, that is, 27 member states plus three national agencies. It also has the harmonising influence of the fledgling but efficient European agency, the EMA, established in 1995. Some of the most stringent requirements for drug safety have probably been introduced through the largest EU agencies, Germany's BfArM and the French agency, AFSSAPS.

Conversely, the US FDA is a single large agency with different but complementary experiences in human medicines drawn from three of its centres: the Center of Biologics Evaluation and Research (CBER); the Center for Devices and Radiological Health (CDRH); and the Center for Drug Evaluation and Research (CDER). The safety reporting system, the periodic safety update report (PSUR), which has been operating in Europe for more than a decade, was relatively recently introduced in the US through the instrument of ICH and elements of the Council for International Organisations of Medical Sciences (CIOMS); a CIOMS Working Group IX was established in April 2010, dedicated to the minimisation aspects of risk management.[1]

The obvious medium of risk management is the product label, since it is a communication tool between the manufacturer and the user, the healthcare professional and the patient and, importantly, an agreed position with regulatory agencies on the product characteristics.

Since 2000, in Europe, the EU Commission and the EMA have placed emphasis on the patient having product information awareness through the patient information leaflet (PIL, or PL) to make an informed decision.

In the US, the FDA has focused on the prescriber since 2006, due to concerns that the doctor/prescriber finds the package insert (PI) too long and too detailed, and also does not address changes in prescribing such as "Dear Doctor" warning letters. The size, organisation and content of the US PI and the European Summary of Product Characteristics (SmPC, from which the PIL is drawn up) were different until 2006; they are better aligned since the 2006 FDA Labeling Rule, although the SmPC remains a more executive product summary than the US PI regarding clinical development, warning and precautions, adverse reactions, etc. The classification of adverse events (AEs) in the US PI is still very different from the SmPC, with 2% or 5% cut-offs, normally compared head on with placebo; causality has seldom been medically evaluated in recent practice. In addition, changing the AEs of PIs to conform with the Medical Dictionary for Regulatory Activities (MedDRA) classifications is a very gradual process. Warnings and precautions on the US PI also tend to be more exhaustive than the SmPC. The perception of risk can consequently be seen to be different between the US PI and the EU SmPC.

More than 90% of the content of a PI or SmPC relates to product safety, but the message is not the same in both. The US REMS consists of:

- A. Medication Guide
- B. Communication Plan
- C. Elements to Assure Safe Use
- D Implementation System
- E. Timetable for Submission of Assessments.[2]

The REMS actually concerns itself with communication of risk, with the PI being central to this, as part of risk minimisation (exemplified by Table 1); the EU RMP[3] is a more complex, more far-reaching safety package that the sponsor is obligated to implement (outlined in Table 2). The PI uses scientific language, as with the SmPC, and there is no US equivalent of the EU PIL (or PL), which is a progressive document comprehensively covering every aspect of the SmPC but written in plain English and subject to strict readability requirements. Therefore, it is evident that in the concise SmPC and the extensive PL the fundamentals of a good risk minimisation plan are already met.

The FDA invariably requests a Medication Guide as part of the REMS (see Table 1); this is the equivalent of an EU PIL but is not in the same plain language and fixed template. The RMP and REMS are risk strategy systems that are, in fact, distinctly different. The EU RMP follows the structure of a 2006 published template and guidance,[3] and requires careful attention and extensive work. No new drug or biologic is excluded, and in fact it is obligatory to include an RMP in the regional information in Module 1, namely section 1.8.2, where the RMP is located

Table 1: Examples of FDA-approved 2010 risk evaluation and mitigation strategies (REMS).

Name	Application	Date REMS approved	REMS components (All REMS include timetable for assessment)
Actemra (tocilizumab) Injection (PDF - 456KB)	BLA 125276/0	1/8/2010	Medication guide, communication plan
Aranesp (darbepoetin alfa) Injection (PDF - 11288KB)	BLA 103951/5197	2/16/2010	Medication guide, communication, elements to assure safe use, implementation system
Botox/Botox cosmetic (onabotulinumtoxinA) Injection (PDF - 148KB) *[Updated]*	BLA 103000/5215	7/31/2009; modified 3/9/2010, 10/15/2010	Medication guide, communication plan
Epzicom (abacavir sulfate and lamivudine) Tablets (PDF - 38KB)	NDA 21-652/S-011	3/9/2009; modified 8/4/2010	Medication guide
Isotretinoin Capsules (PDF - 315KB) *[New!]*	List of application numbers and sponsors (PDF - 21KB)	10/22/2010	Medication guide, elements to assure safe use, implementation system
Lamictal XR (lamotrigine) Extended-Release Tablets (PDF - 259KB)	NDA 22-115/S-009, S-010	5/29/2009; modified 1/29/2010, 4/14/2010, 10/24/2010	Medication guide
Revlimid (lenalidomide) Capsules (PDF - 3819KB)	NDA 21-880/S-013	8/3/2010	Medication guide, elements to assure safe use, implementation system
Suboxone (buprenorphine and naloxone) Sublingual Film (PDF - 960KB)	NDA 22-410	8/30/2010	Medication guide, elements to assure safe use, implementation system

for formal assessment by the national competent authority during a decentralised submission, or the CHMP/EMA during a centralised submission. The RMP will be subject to as rigorous an authority assessment as the CTD dossier pivotal clinical overview, Module 2.5.

Biosimilar medicines are not exempt from RMPs in the EU, while most small molecule generics are. If the reference medicinal product has an RMP, then the generic will also require one. Generic hybrid medicines, which are salts or other line extensions of the reference product, also require RMPs as with all new EU approved products.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 provided new regulatory authority to require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS) to ensure the benefits of a drug or biological product outweigh its risks. The REMS requirements in the FDAAA have been built on prior experience with risk management programmes and the "Guidance for Industry – Development and Use of Risk Minimisation Action Plans (RiskMAPS)" (March 2005).[2]

One hundred and fifty REMS have been approved as of 13 October 2010; some 2010 examples are outlined in the Table 1. These approvals were for products that were the focus of both new drug applications (NDAs) as well as biologics license applications (BLAs). Approximately two-thirds of the approved REMS contain only a Medication Guide. The remainder required additional components such as elements to assure safe use (ETASU), a communication plan and an implementation system. Less than 25% of the REMS have a communication plan as the primary element, and less than 10% have the ETASU as the primary element. The FDAAA legislation triggered approximately 300 post-marketing commitments. In addition, approximately 40 label changes have been recommended. These have typically been for classes of products. REMS may also be modified, and between 10% and 15% have undergone revision.

Determinations about a REMS requirement are made jointly by the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). Currently, a limited percentage of drugs and biologics are candidates for REMS; these include narrow therapeutic range drugs, epilepsy and anticancer agents, monoclonal antibodies and fusion proteins, antiviral fixed combinations, certain modified release dosage forms, and identified severe risk classes such as glitazones or teratogenic drugs, etc.

In 2004, the unexpected stroke and heart attack adverse reaction findings of the EU centrally-approved selective COX-2 inhibitor and NSAID, Vioxx – which impacted on the whole NSAIDs class – triggered the EMA requirement that all NSAIDs, irrespective of national, mutual recognition procedure (MRP) or centralised procedure approval, would be subject to an RMP.

Another concern for the EMA was that after years of marketing and huge patient exposure, the diabetes drug Avandia (rosiglitazone) was associated with unlisted heart ADRs in 2007.

The RMP EU model, with its built-in precautionary measures, proactive features and comprehensiveness, should reduce such unexpected developments as Vioxx and Avandia, and many others, in the future.

Avandia also illustrates the different decision-making in the EU and US, as the EMA requested the withdrawal of Avandia, whereas the FDA

Table 2: Outline of an EU RMP (CTD Module 1.8.2).	
ACTION	
1. Safety specification	
Nonclinical	
1.1.1. <Outline of safety concerns that have not been adequately addressed by clinical data or which are of unknown significance>	1.1.2. <Specify need for additional non-clinical data if the product is to be used in special populations>
Clinical	
1.2 Limitations of the human safety database 1.2.1. Exposure	1.3 Populations not studied in the pre-authorisation phase
1.4 Post authorisation experience 1.4.1. <Projected post-authorisation usage data> 1.4.2. <Actual post-authorisation usage data> 1.4.3. <Regulatory action taken>	1.5 Adverse events/Adverse reactions 1.5.1. Newly identified safety concerns 1.5.2. Details of important identified and potential risks Seriousness/outcomes recovered/with/without treatment/sequelae, % not recovered, % hospitalised Severity and nature of risk Frequency with 95 % CI 1) randomised, blinded trial population only 2) all clinical trial 3) epidemiological studies stratified by indication Preventability Clinical trials, safety studies, pharmacoepidemiological studies, PSUR, other safety reports etc. Regulatory action taken
1.6 Identified and potential interactions with other medicinal	1.7 Epidemiology of the indication(s) and important adverse events
ACTION	
	1.7.1. For each indication, discuss the incidence, prevalence, mortality and demographic profile of the target population 1.7.2. For each indication, discuss the important co-morbidity in the target population 1.7.3. For each identified or potential risk e.g. hepatic failure, provide the epidemiology
1.8 Pharmacological class effects (Identify risks)	1.9 Additional EU Requirements Potential 1.9.1. for overdose/ 1.9.2 transmission of infectious agents/1.9.3. misuse for illegal purposes/1.9.4. off-label use/1.9.5. off-label-paediatric use
1.10 Summary – ongoing safety concerns	
2. Pharmacovigilance plan	3. EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES Medication errors/Routine risk minimisation activities (i.e. product information, labelling and Packaging; educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes: review period

placed it under a REMS and tightened the labelling. The FDA stipulates that "Avandia will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take Actos (pioglitazone), the only other drug in this class. Current users of Avandia who are benefiting from the drug will be able to continue using the medication if they choose to do so. Doctors will have to attest to and document their patients' eligibility; patients will have to review statements describing the cardiovascular safety concerns associated with this drug and acknowledge they understand the risks. The agency anticipates that the REMS will limit use of Avandia significantly."

Drugs such as isotretinoin (Roaccutane) and thalidomide (Revlimid) are teratogenic and both under a REMS in the US and an RMP in Europe. However, despite the strong proactive measures of an RMP, a medical alert card, and a signed consent form, unfortunately there have been more than 20,000 pregnancies among adolescent girls taking isotretinoin.

Sponsors are challenged by the increasing burden of proactive drug safety monitoring needed to ensure no safety signal is missed. All signals, even weak ones, should be evaluated systematically, especially serious adverse events. Unfortunately, downplaying or misinterpreting signals by sponsors is a cause of unexpected outcomes and withdrawals.

The EU RMP affords a systematic and comprehensive strategy to avoiding problems and ensuring the best outcomes. The RMP was established as a definitive EU requirement in connection with the 2004/27 EC directive implemented into law in 2005, and the publication of the template and guidance in 2006, which was well-conceived and so has remained unchanged. What is new is the recognition that paediatrics (ages 0-28 days, 1-23 months, 2-12 years, 13-18 years) may require a separate RMP. In addition, since 2009, aspects of the RMP have become part of the SmPC warnings and precautions, under Section 4, Clinical Particulars: 4.3 Contraindications; 4.4 Special warning and precautions for use. Such proactive labelling instructions are consistent with the EU Commission's definition that the risk management system is "a set of pharmacovigilance activities and interventions designed to proactively identify, characterise, prevent or minimise risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimisation intervention".[3]

Components of an EMA EU RMP

Risk assessment (RMP). Safety specifications consist of a summary of important identified risks, including safety pharmacology and toxicology (with current emphasis on juvenile animals), important potential risks and missing information obtained from clinical studies, spontaneous reporting, and scientific literature. For example:

- **Identified risks** – Haemorrhage, anaemia – infections including serious opportunistic
- **Potential risks** – Off-label use; phototoxicity; hepatic injury; allergic reactions; thrombocytopenia; neutropenia; thrombotic thrombocytopenic purpura; malignancies including lymphoma
- **Missing information** – Concomitant use with fibrinolytics, clopidogrel and NSAIDs; paediatric population, pregnant/lactating women; subjects with severely compromised cardiac status; subjects with severe hepatic impairment; children, adolescents, elderly; patients with renal or hepatic impairment; immune function; potential for overdose or medication errors; off-label use.

Pharmacovigilance activities (RMP). For example:

- **Identified and potential risks** – Routine and targeted surveillance; Prospective in-hospital registry for risk of haemorrhage and off-label use
- **Missing information** – Routine surveillance and additional analysis of AEs from clinical trials and safety database. The pharmacovigilance plan includes practices and action plan to investigate specific safety concerns based on safety specification. Prospective epidemiology can furnish new signals.

Risk minimisation activities (RMP). Contraindications and special warnings and precautions in the SmPC; educational materials for treating physicians. This must cover the need for additional pharmacovigilance (PV) activities; effectiveness of risk minimisation measures which concern ensuring attention to labelling SmPC and PL through training/educational meetings, patient alert cards, etc. The user testing of PILs, (recommended by the EMA since 2000, in law since 2005), provides confidence in the readability of PILs and is a risk minimisation measure.

Components of typical FDA REMS

Such components include a medication guide distributed to every outpatient/inpatient; a communication plan including instructions on dispensing for pharmacists/Dear Healthcare Provider letter and prescriber brochure for specialists and primary care physicians to convey information on serious risks such as bleeding, pregnancy, the risk of invasive fungal infection, etc, together with the need to discuss this with patients; appropriate patient selection; web-based materials and a medical scientific liaison; elements to assure safe use (ETASU); implementation system; patient or physician survey; evaluate patient understanding of risk; limit to two years post launch.

Aspects that appear to be covered by FDA REMs and not in EMA RMPs are: specification of distribution or dispensing; monitoring of distribution; REMS print advertisement; audit of communication plan; audit of pharmacies; review of promotional materials.

Conclusion

The importance of risk management cannot be over-emphasised and the regulatory burden is increasing, and appropriately so. It is in the interests of patients, industry and agencies that the least harm and maximum benefit results when taking a medicine; risk strategies such as the US REMS and the EU RMP contribute to this. They also channel drug developers to give greater consideration to how patients can avoid some adverse reactions to drugs and achieve better tolerance, by paying attention to criteria such as contraindications, warnings and precautions. The EU RMP is an engagement of wider scope, and is binding on a wider set of medicines than the US REMS.

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