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Risk Management
A European Regulatory Perspective

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Abstract

Risk management for European regulators means the detection and assessment of risks, the development and selection of measures to reduce risk, and monitoring of the effectiveness of risk control; all aspects of pharmacovigilance intended to minimise risk to European Union citizens associated with use of medicinal substances. This incorporates earlier and better planning of pharmacovigilance through formal product risk-management plans, better use of information tools to protect public health and routine audit of effectiveness of regulatory action.

1. Introduction

Regulatory authorities approve medicinal products based on acceptable benefit-risk profiles under clinical trial conditions. However, we know that drug hazards may become apparent post-approval because of greater patient exposure in normal clinical practice and the limitations of clinical trial populations. We need pharmacovigilance principles and processes in place to systematically and efficiently capture emerging information on previously unrecognised or changing patterns of undesirable drug effects. Assessing this information and taking regulatory action, if necessary, are core European regulatory pharmacovigilance functions to optimise the safe and effective use of medicines. Subsequent sections of this article examine how these functions are carried out on a European basis, why European regulators are seeking to strengthen pharmacovigilance capability[1] and what risk management means in the European pharmacovigilance context as set out in the Heads of Agencies Working Group Report 'Establishing a European Risk Management Strategy'. This paper also alludes to new provisions for risk management under the 2001 review legislation.

1.1 Current European Pharmacovigilance System

The European Union (EU) Member States have set up common institutions so that decisions on matters of joint interest can be made at European level. Comprising 25 Member States from 1st May 2004,[1] the estimated EU population is 450 million.[2] The European harmonisation of pharmaceutical legislation was completed in 1992. Until 1994, the National Licensing Authority was the sole source of licences to market medicinal products in each Member State. However, since 1995 procedures were introduced under European legislation providing for the issue, for certain medicinal products, of a single marketing authorisation valid throughout the European Union (known as the Centralised Procedure). A

1 Member States are: Belgium, France, Germany, Italy, Luxembourg, The Netherlands, Denmark, Ireland, United Kingdom, Greece, Spain, Portugal, Austria, Finland, Sweden, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia.

Table I. Roles of regulatory parties involved in European pharmacovigilance

Regulatory parties	Route of authorisation		
	nationally authorised products	mutual recognition procedure	centralised procedure
MS	The authorities of the MS are the CAs for medicinal products authorised nationally through national procedures, including the MRP. The responsibilities for PhV rest with the CAs of all the MS in which the authorisations are held. In accordance with the legislation, each MS has established a PhV system for the collection and evaluation of information relevant to the benefit to risk balance of medicinal products. The CA continually monitors the safety profile of the products available on its territory and takes appropriate action where necessary and monitors the compliance of MAH with their obligations with respect to PhV	The responsibilities of PhV rest with the CAs of all of the MS in which the authorisations are held. For practical reasons, the MS agree that the reference MS will normally take the lead for medicinal products authorised through the MRP and responsibility for evaluating and producing assessment reports on PhV issues related to that mutually recognised product, in accordance with an agreed timetable. The reference MS takes responsibility for the co-ordination of communication with the MAH on such matters and for the monitoring of the compliance of the MAH with its obligations with respect to PhV. These arrangements do not replace the legal responsibilities of the MAH with respect to individual CAs.	The CAs of the MS are responsible for monitoring centrally authorised medicinal products in their respective territories. However, the pre-authorisation Rapporteur takes the lead in PhV, unless otherwise decided by the CPMP. The Rapporteur is responsible for evaluating and producing assessment reports on PhV issues related to a centrally authorised product, in accordance with an agreed timetable and for the monitoring of the compliance of the MAH with its obligations with respect to PhV.
The Agency	The role of the agency secretariat is one of co-ordination in the case of referrals of nationally authorised products made to the CPMP. The CPMP, aided by its PhVWP, is responsible for evaluating evidence and formulating Opinions on matters referred to it	The role of the agency secretariat is one of co-ordination in the case of referrals of mutually recognised medicinal products made to the CPMP. The CPMP, aided by its PhVWP, is responsible for evaluating evidence and formulating Opinions on matters referred to it.	The role of the Agency secretariat is one of co-ordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community in the centralised procedure and the provision of advice on the measures necessary to ensure their safe and effective use, in particular by evaluating and making available through a database information on adverse reactions to the medicinal products in question. The Agency's scientific committee, the CPMP, aided by its PhVWP is responsible for evaluating evidence and formulating Opinions on emerging drug safety issues with centrally authorised products, based on the Rapporteur's assessment report. The Agency secretariat is responsible for communicating with the MAHs of centrally authorised products on such issues and for the co-ordination of issues relating to the monitoring of the compliance of the MAH with its PhV obligations.
EC	The EC is responsible for the adoption of Decisions on the basis of CPMP Opinions relating to specific referrals	The EC is responsible for the adoption of Decisions on the basis of CPMP Opinions relating to specific referrals	In the case of centrally authorised medicinal products the EC is the CA. The EC is responsible for the adoption of Decisions on the basis of CPMP Opinions relating to centrally authorised products and specific referrals

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Table I. Contd

Regulatory parties	Route of authorisation nationally authorised products	mutual recognition procedure	centralised procedure
MRFG		Established by the Member States in March 1995 to co-ordinate and facilitate the operation of the decentralised MRP. A forum where procedural issues can be discussed and resolved. Scientific discussions are not discussed within the group, but through 'breakout sessions' which are organised and chaired by the specific reference MS	
PhVWP	The PhVWP of the CPMP under an original mandate agreed in 1995 was a forum for dialogue and understanding between MS and the EMEA on PhV on organisational matters such as developing common principles and procedures for signal detection, evaluation, routine assessment and evaluation of safety issues, developing common principles for sharing information and communicating on urgent issues, signals, and other issues, preparation and revision of guidelines on PhV. Product related issues were also discussed at the request of CPMP for centralised products and referrals or at the request of other MS for nationally authorised products.		

CA = competent authority; **CPMP** = Committee for Proprietary Medicinal Products; **EC** = The European Commission; **EMEA** = European Agency for the Evaluation of Medicinal Products; **MAH** = market authorisation holder; **MRFG** = Mutual Recognition Facilitation Group; **MRP** = mutual recognition procedure; **MS** = Member States; **PhV** = pharmacovigilance; **PhVWP** = Pharmacovigilance Working Party.

second facility was established whereby Member States could recognise product licences granted in one reference Member State (known as the Mutual Recognition Procedure). However, the principles of pharmacovigilance apply to all products. The roles and responsibilities of each of the parties; (Member States, the European Commission, the European Agency for the Evaluation of Medicinal Products [EMEA] and Marketing Authorisation Holders), involved in the conduct of pharmacovigilance according to the route of authorisation are laid out in legislation as codified in Directive 2001/83 EEC and in Regulation 2309/93 as amended with further guidance in Volume IX of the rules governing Medicinal Products for Human and Veterinary Use in the EU.[3,4] The 2001 pharmaceutical review legislation will bring further modifications.[5,6] Table I outlines the broad roles of the regulatory parties involved in European pharmacovigilance.[7]

The Community pharmaceutical legislation has also created a binding Community arbitration mechanism, known as 'Referrals' which may be invoked on the basis of a number of Articles; for example, Article 29 where a Member State considers that there are grounds for supposing that the marketing authorisation of the medicinal product concerned may present a risk to public health, or Article 31 where the Member States or the Commission or the applicant or holder of the marketing authorisation may, in specific cases where the interests of the Community are involved, refer the matter to the Committee. Time scales for these formal procedures, including appeal, final Opinion, and Commission Decision are also given in legislation.

1.2 Achievements of European Pharmacovigilance

The current system affords a peer review process; signal detection or benefit-risk assessment carried out in parallel or reviewed serially, can increase the sensitivity and quality of such processes. Recognised achievements include high quality benefit-risk assessment, harmonised regulatory action through the system of Referrals, the interagency communication systems and the potential for the Eudravigi-

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lance database to manage adverse drug reaction (ADR) data on an EU-wide basis. Member States have contributed to major developments in data management and automated signal detection. Member States collect data locally, respond locally to national pharmacovigilance concerns, provide feedback to local audiences and implement specific risk minimisation activities with a degree of flexibility. Such flexibility is required because national variability in healthcare delivery systems and legislation relevant to measures such as patient confidentiality or use of registries, which are not harmonised, may preclude identical risk minimising measures in each Member State.

1.3 Rationale for Establishing a European Risk-Management Strategy

From the regulatory view, the complex interplay between the responsibilities and functions of the various European partners in the conduct of pharmacovigilance, requires a well defined and co-ordinated framework. We need efficient use of scarce expertise distributed among Member States in the face of challenges such as increasing workload, technological developments, EU enlargement and calls for consistent regulatory approaches. We must ensure early detection of safety hazards with medicines, rapid assessment and action to minimise risk. We also need monitoring and enforcement of marketing authorisation holders' compliance with regulatory requirements.

2. Components of European Union Risk-Management Strategy

The Medicines and Healthcare products Regulatory Agency (MHRA) Excellence in Pharmacovigilance Model,[8] presented a long-term vision of how pharmacovigilance should be conducted in the future. In this model, the main concepts of 'best evidence', 'robust decision making' and 'tools to protect public health' form the backbone of the process supported by a culture of scientific development and the routine use of outcome measures and audit of regulatory actions to demonstrate effectiveness in protecting public health. European pharmacovigilance systems can also be considered along these concepts.

2.1 Best Evidence, Sources and Uses of Data

The Excellence Model calls for a better balance between detection of harm and demonstration of safety. In the model, this means that pharmacovigilance should be guided not only by the need to find unexpected hazards but also by gathering positive evidence of safety. There is also a call for a shift upwards in the evidence hierarchy, away from evidence in the lower end of the hierarchy towards larger simple trials. The methods by which we can improve data collection and management, risk detection, risk quantification and risk assessment in European pharmacovigilance are outlined below.

2.1.1 Spontaneous Reports of Suspected Adverse Drug Reactions

Spontaneous reports have been the principal early warning system for previously unrecognised ADRs post-authorisation in Europe. The strengths and weaknesses of spontaneous reporting systems are well known. The strengths include cost effective detection of rare and unexpected ADRs, uniquely capturing the suspicions of reporters. Weaknesses include under-reporting, varying reporting by time since marketing, stimulated reporting, poor coverage of latent reactions or those ADRs with an insidious onset, difficulties in wider generalisation or causality attribution, poor quality reports with insufficient data, and difficulties in comparing between drug substances. Despite these recognised limitations, such reporting systems will need to remain in place until alternative methods have been demonstrated to work. Methods to encourage and facilitate reporting, particularly for serious and unexpected ADRs, and from the hospital sectors are needed. Widening the reporting base to additional healthcare professionals and to patients, education of prescribers, and electronic reporting are possible ways to increase reporting. Improvements in data quality and full compliance with reporting requirements will also bolster this system. Eudravigilance, the ADR database based at the EMEA, will provide the facility for exchange of individual case safety

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reports and signal detection across the EU. However, in view of the limitations of spontaneous reporting systems, additional data sources must be developed and utilised.

2.1.2 Drug Utilisation Data

The extent and nature of the exposed population, the distribution of doses, indications, and average duration of exposure to a given medicine, provides important information when safety signals arise and need to be evaluated. These data can inform the scale and urgency of the public health hazard, assist with interpretation, suggest hypotheses or provide a method for monitoring the effects of regulatory actions. At present, we often struggle to acquire or combine data in the most appropriate form from all market sectors for the safety issue in question. There is a need to address these data limitations throughout Europe.

2.1.3 Periodic Safety Update Reports

European periodic safety update reports (PSURs) follow the format and content for safety updates as in International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines E2C and E2CA.[9] In Europe, regulatory authorities consider PSURs as important summaries and analyses of drug safety data. With a focus on all serious reactions, and non-serious unlisted reactions, they can prove a valuable source of drug safety signals and updates on emerging and/or urgent safety issues. The accumulation of all clinical and non-clinical safety data from all relevant sources provides an opportunity to carry out an overall safety evaluation of the product. However, PSURs have some deficiencies; they only present the view of the marketing authorisation holder, the quality is variable and regulatory assessment can be duplicated across Europe. Further efficient regulatory assessment of these reports has been recommended. Extending electronic data management to PSURs and safety studies is one such measure to improve efficiency of assessment.

2.1.4 Active Surveillance

Registries, comprising systematic follow-up of groups of subjects exposed a specific product or groups with a specified diagnoses, can help provide data on an enumerated population and thus constitute more active follow-up than relying on passive follow-up through spontaneous reports. Predominantly useful for hypotheses generation, registries may also, in some cases, assist with signal evaluation when appropriate control groups can be selected. Situations where registries may be useful include novel biological and xenogenic cellular products, intrauterine exposure, orphan medicinal products or other situations when spontaneous reporting needs to be supplemented. The setting up and running of such registries is likely to be through formalised agreement between regulatory authorities with academia and is to be encouraged. European disease registries include asthma, cancer, communicable diseases, congenital anomalies, coronary heart disease, diabetes mellitus, epilepsy, hypertension, mental health disorders, musculoskeletal disorders and stroke.[10]

2.1.5 Post-Authorisation Safety Studies

Guidance on these studies was developed in the UK, revised further in 1993 and incorporated into Volume IX of the rules governing Medicinal Products for Human and Veterinary Use.[7] This gives a framework whereby a variety of data collection methods can be used to evaluate the safety of authorised medicines. This guidance applies to studies sponsored or partly sponsored by the pharmaceutical industry which evaluate the safety of products with a marketing authorisation. Situations where studies may be appropriate include: (i) a medicine with a novel chemical structure or novel mode of action; (ii) where there is uncertainty as to the clinical relevance of a toxic effect in animals; (iii) where there is uncertainty as to the safety profile; (iv) where there is a need to better quantify adverse effects identified in clinical trials and elucidate risk factors; or (v) where there is a highly specific use requiring specialist monitoring. A variety of designs may be appropriate including observational cohort studies, or case-control studies. Thus, post-

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authorisation safety studies can test specific hypotheses, provide estimates of risk and or constitute active surveillance in normal conditions of use of medicines. While quality has been variable in the past, such studies need to be strengthened; well designed, feasible, good quality studies need agreed study protocols detailing aims and objectives prior to commencement. They must be carried out to the highest ethical and professional standards. Regulatory endorsement of these study protocols and time scales is required pre-authorisation.

Because of the urgency with which pharmacovigilance must answer questions, validated automated healthcare databases linking existing prescribing and clinical records offer the possibility of relatively quick studies compared with real-time or field-based studies when estimating risks associated with medicines. Several such studies in different sites may be needed for sufficient power depending on the safety question. These database studies are still resource intensive and require significant skills, experience and access to the data. Such databases need to be fostered and access secured by regulatory agencies throughout Europe allowing the possibility of non-market authorisation holder sponsored studies.

2.1.6 Pharmacovigilance Expertise

It is recognised that nurturing the scientific expertise necessary to carry out all aspects of pharmacovigilance is essential for all competent authorities. Personnel engaged in pharmacovigilance have a variety of skills in scientific and other disciplines including pharmacoepidemiology and statistics, pharmacology, medicine, toxicology and communication. Collaboration between academia and Competent Authorities to enhance skills and allow practical arrangements for the conduct of studies will further this culture of scientific development. Inter- and intra-regulatory agency communication on relevant post-authorisation safety issues will bring pharmacovigilance expertise into licensing assessment. The Council for International Organizations of Medical Sciences (CIOMS) IV structured format for benefit-risk assessments should be employed more consistently.[11]

2.1.7 Summary

Further strengthening of spontaneous reporting by increasing the scope of electronic transmission and handling of such data, using methods to enhance the quantity and quality of reports, particularly for medicines used in the hospital sector, applying flexible tools to aid signal detection, and efficient assessment of PSURs are first steps in risk management. Promotion and development of registries in collaboration with learned societies with strengthening of post-authorisation safety studies will deliver more active surveillance and evidence of a higher hierarchy level and quality. Support, development and use of automated databases will enhance regulatory capability to conduct hypothesis testing pharmacoepidemiology studies within the timescales required for pharmacovigilance.

2.2 Robust Decision Making and Implementation of Regulatory Decisions

Formulating transparent, objective, equitable and timely regulatory decisions on the basis of new information, to minimise risk and promote the safe and effective use of human medicines is an essential function of pharmacovigilance. Current aspects of this decision-making process and how these can be improved are considered below.

2.2.1 Decision-Making Processes

The scientific Committee for Proprietary Medicinal Products (CPMP – to be replaced by the Committee for Medicinal Products for Human Use or CHMP), has formulated opinions on pharmacovigilance concerns for centralised products and referrals with binding Decisions issued by the Commission. The Pharmacovigilance Working Party (PhVWP) of the CPMP considered pharmacovigilance issues at the request of CPMP but also provided a forum for dialogue between Member States on national and mutual recognition drug safety issues, providing non-binding recommendations. In many cases within Member States, expert advisory committees provide advice to competent authorities on most significant drug safety issues. Additionally, the Mutual Recognition Facilitation Group (MRFG) has assisted the Mutual Recognition proce-

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dure, with the formation on occasion of expert subgroups to agree a core summary of product characteristics. These bodies are considered further.

Referrals to CPMP, as alluded to earlier can occur when agreement cannot be reached by Member States or where the interests of the community are involved. Recently, there has been a trend towards increasing numbers of referrals to CPMP with set formal time scales, and binding Decisions on all Member States. It has been questioned whether 'Community Interest' requires a more precise definition.

The PhVWP, under an original mandate, agreed in 1995, was a forum for dialogue and understanding between competent authorities on pharmacovigilance. Since then, PhVWP has worked continuously to improve its practices while dealing with an increasing pharmacovigilance workload. Evaluating issues with national and mutual recognition products, it has reached consensus regulatory recommendations. For products without CPMP referral, PhVWP recommendations need to be implemented nationally within Member States or through the mutual recognition process. The implementation of these non-binding PhVWP recommendations is subject to variability at a national level. Increased transparency, follow-up on implementation of PhVWP recommendations and time scales with revision of the PhVWP mandate have been identified as measures for reform.

The Member States established the Mutual Recognition Facilitation Group (MRFG) in March 1995. The MFRG meets monthly at the same time as the CPMP and comprises senior representatives from each Member State. The MFRG has had no formal position in European Community legislation, but provided a forum where procedural issues can be discussed and problems resolved. Scientific discussions related to individual applications are not discussed within the MFRG, but rather are handled through 'breakout sessions'. If the MFRG identifies that work is required on further scientific issues, then the possibility exists for CPMP referral. *Ad hoc* expert groups can bring together expertise without necessarily the need for formal referral to the CPMP. This can facilitate rapid appraisal although consensus recommendations still need to be implemented nationally.

2.2.2 Summary

Reform of PhVWP and formalisation of the MRFG should facilitate collaboration between Member States utilising necessary expertise to resolve issues quickly and reserving formal referral for major public health hazards thus, avoiding overload on one system and ensuring high quality, timely decision making.

2.3 Tools to Protect Public Health, Regulatory Action and Implementation and Product Risk-Management Plans

Risk management means the detection and assessment of risks, the development and selection of measures to reduce risk and follow up with monitoring of the effectiveness of risk control. Pharmacovigilance has already been applying most of these principles to reduce risks associated with medicinal products to individuals and populations. Measures to control risk have been selected from options such as: product information on ADRs, contraindications, warnings, monitoring, the restriction of prescribing or dispensing or the need for registration, consent or product suspension. However, the monitoring of effectiveness of most regulatory or other measures to control risks associated with medicinal products has not been routinely applied. The MHRA Excellence in Pharmacovigilance Model has suggested developments to this risk-management approach, which include early, formalised and better pharmacovigilance planning, better use of information tools to protect public health and routine audit of effectiveness.

The rationale is that earlier and better planning of pharmacovigilance and risk management is likely to be more effective in protecting public health. This could be achieved by starting to plan risk management early in the life cycle of a drug, ideally before a product gains a marketing authorisation and by formal product risk-management plans submitted at the time of the authorisation application. A product risk-management plan aims to identify the risks asso-

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ciated with a medicinal product, further clarify the safety profile of a product, and employ measures to minimise risk to individual patients in clinical use. A product risk-management plan is made of three elements: the pharmacovigilance specification, the pharmacovigilance plan, and the risk minimisation 'tool kit'.

2.3.1 The Pharmacovigilance Specification

The pharmacovigilance specification is a structured method for documenting the established risks of a drug and the potential for unidentified risks at the time of marketing authorisation. As noted above, the judgement of the benefit-risk balance at the time of authorisation of a medical product is based on limited data. The specification will set out very clearly the limitations of this knowledge with respect to populations studied and not studied, the extent of the safety database with clear reference to duration, doses and characteristics of subjects who were exposed at the time of licensing. The pharmacovigilance specification will also document the established risks of a drug (from preclinical and clinical studies) and the potential for significant unidentified risks. The specification will help regulators to identify any need for additional information that should be collected in the post-approval period. It will therefore facilitate the construction of the pharmacovigilance plan and the risk-minimisation plan. Elements of the specification might include: identified preclinical safety concerns, any missing preclinical data, ADRs in clinical trials (including seriousness and predictability), potential ADRs requiring further evaluation, populations not studied in the pre-approval phase, documented interactions, the potential for unidentified interactions that may occur post-approval, the epidemiology of the target and at risk population and recognised class effects.

2.3.2 Pharmacovigilance Plan

The pharmacovigilance plan proposes the collection of data relevant to the safety profile of a medicinal product once it is marketed, aiming to demonstrate safety as well as to identify harm. The plan will be driven by the questions raised by the specification, and should lay out how to better define the safety profile of the drug in normal clinical practice. The plan will be scrutinised by regulators at the time of the marketing authorisation application and be agreed between the company and regulators following discussion and modification, prior to granting a marketing authorisation. The plan will then be implemented by the company.

2.3.3 Risk-Minimisation 'Tool Kit'

The risk-minimisation 'tool kit' proposes strategies to reduce risk to individual patients and populations. These strategies for controlling risk would focus on practical measures to prevent, where possible, avoidable adverse drug reactions or to detect and intervene where early signs of reversible reactions in patients are apparent. The risk-minimisation tool kit includes the Summary of Product Characteristics (SPC) and labelling, which denotes the correct product use for populations, indications, warnings, contraindications and monitoring. While the use of medicinal products remains governed by the SPC as a regulatory document, its limitations in terms of routine risk communications are recognised. Educational materials for healthcare professionals and the public both pre- and post-launch, is an essential component of risk minimisation to communicate information over and above the SPC. Good patient information leaflets which convey key points that patients need to be able to understand in order to take their medicine safely are basic features that must be implemented more consistently. Access to more detailed levels of information for those who require this, should also be available. Other elements of the tool kit may include treatment protocols or guidelines, and control of distribution, prescribing or dispensing and registries and consent. Choice of risk-minimisation measures will depend on factors such as the level and nature of risk, the place of drug in disease treatment, the nature of target disease and target population. Plans also need to be in place to assess the effectiveness of these programmes possibly through prescribing surveillance and outcomes research.

During the course of implementing the components of the product risk-management plan, any important emerging information on risk will be discussed and the plan revised. A further key aspect of

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the plan will be the setting of milestones in terms of patient exposure. When these milestones are reached, the specification for a particular drug would be modified and the pharmacovigilance plan amended and updated.

3. The 2001 Review Legislation

The 2001 review legislation will make it a regulatory requirement for the applicant to submit at marketing authorisation application, "a detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce".[5] A submission in standard format based on the ICH E2E guideline[9] would cover the detailed description of pharmacovigilance through pharmacovigilance specifications and pharmacovigilance plans but not risk-minimisation plans, which would also need to be addressed. It is envisaged that product risk management plans would be particularly relevant to new chemical entities and biotech-derived products, orphan medicinal products, significant changes in established products (e.g. new form/route of administration), established products introduced to new populations or significant new indications, or when reclassified from prescription-only to non-prescription availability. European regulators will develop more detailed guidance as necessary, on what might be expected in terms of content, format, procedures and circumstances when product risk-management plans would be desirable. Until the new legislation comes into force, product risk-management plans are being piloted on an informal basis with European regulatory authorities. Other changes to the existing regulatory system relevant to pharmacovigilance are proposed. Details of the finalised legislative text should be consulted for precise details of provisions.[5,6] These include the following: the CPMP will be replaced by the CHPM, with one voting representative per Member State and up to five additional co-opted members with voting rights. The scope of the centralised procedure will be widened, with reduction in some administrative time scales. PSURs are to be submitted more frequently after the first 4 years post-authorisation: 3-yearly as opposed to 5-yearly previously. The MRFG will become the co-ordination group with EMEA secretariat. The EMEA will be renamed the European Medicines Agency (retaining the acronym EMEA), which will include in its roles, a mandate to develop a database of all medicines approved in the EU. There will be a requirement that product information leaflets must reflect results of consultations with target groups to ensure legibility, clarity and ease of use. The Commission will review the current system of information provision to patients and make proposals, if necessary, for a strategy to provide good quality, objective, reliable and non-promotional information. ADR information is to be shared between Member States and the EMEA on a database. A new provision allows for the competent authority to suspend, revoke, withdraw or vary a marketing authorisation where the risk benefit is not positive under normal conditions of use. Furthermore, the committee will be required to prepare an opinion if a Member State suspends or revokes a marketing authorisation, or if a Member State requests it during a variation procedure. There are also measures to improve transparency of the regulatory process. For pharmacovigilance overall, these provisions will impact on the evidence base, on decision making and on tools to protect public health, implementing some but not all aspects of the European Risk Management Strategy.

4. Conclusions

We can strengthen pharmacovigilance through a better evidence base, improved decision making and a better tool kit of measures to protect public health including the provision of expert and timely information. This can be achieved by building on our current pharmacovigilance infrastructure and operations. Risk management for European regulators means the detection and assessment of risks, the development and selection of measures to reduce risk, with monitoring of effectiveness of risk control; all aspects of pharmacovigilance intended to minimise risk to EU citizens associated with use of medicinal substances. This incorporates earlier and better planning of pharmacovigilance through for-

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mal product risk-management plans, better use of information tools to protect public health and routine audit of effectiveness of regulatory action.

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