Pharmacovigilance Legislation: The Impact of What Is Happening in Europe

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Abstract

Pharmaceutical companies, regulatory agencies, and contract service organizations are managing substantial and ongoing changes to pharmacovigilance legislation in the European Economic Area, and penalties for noncompliance are potentially large. Given that the majority of pharmaceutical companies and contract service organizations have global reach, the impact of this change is being felt far beyond the boundaries of the European Economic Area.

Keywords

Pharmacovigilance, Europe, legislation, Good Pharmacovigilance Practice

Overview of the New EEA Pharmacovigilance Legislation

Regulation (EU) No. 1235/20101 and Directive 2010/84/EU2 were approved in December 2010 by the European Parliament and Council. All pharmaceutical companies, regulatory agencies, and other stakeholders had 18 months to implement these requirements, with an implementation deadline of July 2012. The Regulation and Directive were supported by Commission Implementing Regulation (EU) No 520/2012,3 published in June 2012. This provides additional information and includes transitional time frames for several elements of the new legislation through 2016.

The final layer of documentation for the new legislation is the Good Pharmacovigilance Practices (GVP).4 GVP is a new concept in the European Economic Area (EEA) and describes the expected operational application of the Regulation, Directive, and Implementing Regulation. GVP is presented in 16 modules that are being released throughout 2012 and 2013 **(Table 1)**.

GVP Module I: Pharmacovigilance Systems and Their Quality Systems

This module focuses on the application of International Organization for Standardization (ISO) 9000 Standards on Good Quality Management Systems to pharmacovigilance systems. The concept of a quality cycle is introduced, with the following steps described:

- Quality planning: for example, development of standard operating procedures (SOPs) to plan consistent quality of processes, training of personnel, provision of appropriate facilities and equipment
- Quality adherence: for example, conduct of processes in accordance with SOPs to include quality control steps to ensure compliance with required standards, documentation of activities
- Quality control and assurance: for example, departmental monitoring of compliance metrics, conduct of a robust internal audit program, implementation of an internal compliance monitoring program
- Quality improvements: for example, a corrective and preventive action (CAPA) program

The responsibilities of management and upper management personnel in relation to the pharmacovigilance system are described, including the provision of sufficient personnel, facilities, and equipment; motivation of personnel; and monitoring the compliance status of the pharmacovigilance system. As described in previous legislation, the accountability for the pharmacovigilance system is shared between the marketing authorization holder (MAH) and the EEA Qualified Person for Pharmacovigilance (EEA QPPV); every MAH is required to appoint an EEA QPPV. The description of the role of the EEA QPPV has been expanded in this GVP module.

The pharmaceutical industry and contract service organizations (CSOs) are increasingly centralizing and

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Table 1. Overview of good pharmacovigilance practices

Module no.	Module title	Status at time of publication
I	Pharmacovigilance systems and their quality systems	Published (June 2012)
II	Pharmacovigilance system mast file	Published (June 2012)
III	Pharmacovigilance inspections	Published (December 2012)
IV	Pharmacovigilance audits	Published (December 2012)
V	Risk management systems	Published (June 2012)
VI	Management and reporting of adverse reactions to medicinal products	Published (June 2012)
VII	Periodic safety update report	Published (June 2012)
VIII	Post-authorisation safety studies	Published (June 2012)
IX	Signal management	Published (June 2012)
X	Additional monitoring	Consultation closed
XI	Public participation in pharmacovigilance	Consultation pending (Q2 2013)
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication	Consultation pending (Q2 2012)
XIII	Unassigned	Not applicable
XIV	International cooperationv	Consultation pending (Q2 2013)
XV	Safety communication	Consultation closed
XVI	Risk minimisation measures: Selection of tools and effectiveness indicators	Consultation pending (Q2 2013)

off-shoring global pharmacovigilance activities. As a consequence, pharmacovigilance activities subject to these requirements may not be conducted in the EEA but may located in a global pharmacovigilance unit based in North America or off-shored to countries where expenses are lower, such as India or China. However, any pharmacovigilance activity conducted in relation to a product with a pending or approved marketing authorization in the EEA is still required to adhere to the quality standards and processes described in GVP. Consequently, robust oversight of centralized and/or off-shored activities is required to ensure that they meet the requirements of the EEA in addition to any requirements of their local jurisdiction.

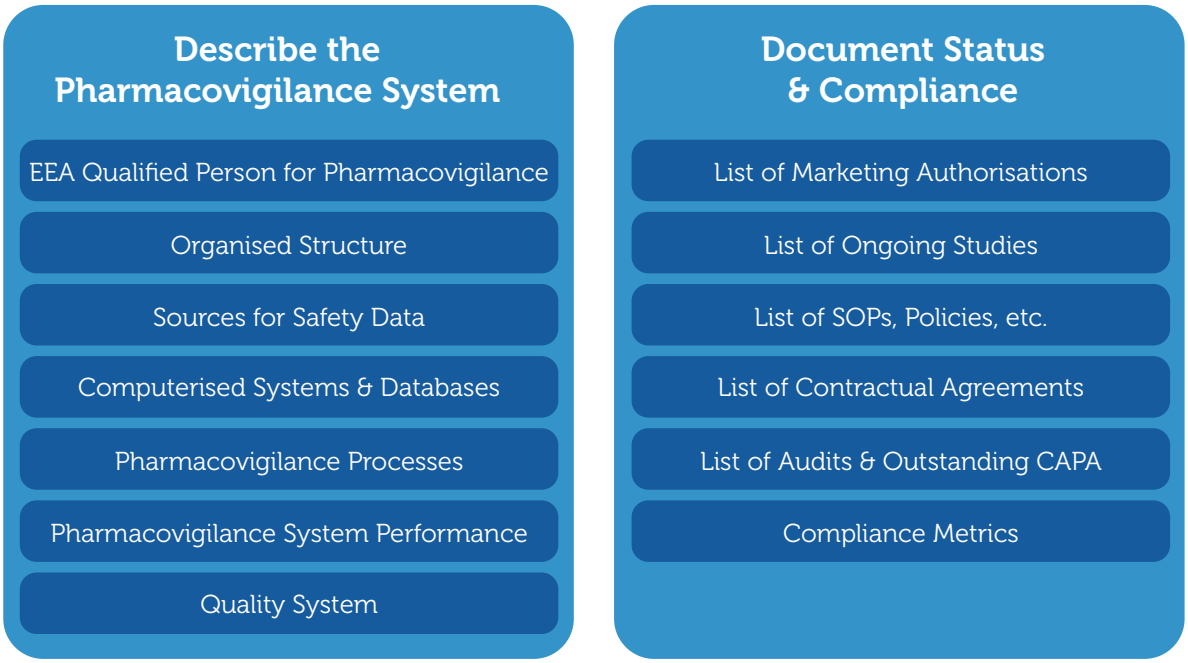
GVP Module II: Pharmacovigilance System Master File

The Pharmacovigilance System Master File (PSMF) is a new legal requirement for the EEA. The PSMF describes the organization and administration of the pharmacovigilance system and must be continually updated to document the current status of the pharmacovigilance system and its compliance with legislative requirements **(Figure 1)**.

All MAHs are required to implement their PSMF either by the date on which a marketing authorization is renewed or by July 2015, whichever is earlier. Consequently, until July 2015 it is likely that some marketing authorizations will be linked to the PSMF and some will be linked to the previous Detailed Description of Pharmacovigilance Systems. MAHs may choose to eliminate this period of dual documentation of the pharmacovigilance system by submitting work-sharing variations in each country to change all their marketing authorizations to the PSMF simultaneously.

The PSMF contains not only information specific to the EEA but also global information derived from activities that take place outside of the EEA but that affect a MAH's EEA obligations. For example, the PSMF may describe the activities of a central Individual Case Safety Report (ICSR) processing center that is located outside of the EEA,

Figure 1. Pharmacovigilance system master file. CAPA, corrective and preventive action; EEA, European Economic Area; SOPs, standard operating procedures.



explain how adverse events from a non-EEA country are available for submission in the EEA, or declare studies occurring in a non-EEA country that involve a product authorized in the EEA. All MAHs will need to assess their global processes and data to determine which data need to be maintained in the PSMF.

GVP Module III: Pharmacovigilance Inspections

European regulatory agencies have an active inspection program focused on pharmacovigilance systems. There is a routine inspection program supplemented by ad hoc inspections conducted on a ''for cause'' basis. Routine inspections are usually scheduled using a risk-based approach. ''For cause'' inspections may arise from one of a number of triggers, including lack of communication with agencies when a change in the benefit-risk balance of a product has occurred, compliance issues with expedited and periodic reporting obligations, information from other regulatory agencies, or issues with fulfillment of obligations relating to safety. Inspections are generally announced, although GVP Module III allows for the possibility of unannounced inspections, which are known to have occurred.

The inspection will review global activities and processes that involve products with a pending or approved marketing authorization in the EEA. This may include inspection of the global ICSR processing center regardless of its location, review of relationships with contract partners in non-European countries, and other actions.

Sanctions are available to regulatory agencies if there are significant concerns about the status of the pharmacovigilance system. These sanctions can range from repeat inspection, suspension or withdrawal of a marketing authorization, suspension of a clinical trial, financial penalties, and criminal prosecution. Although many of these are used by regulatory agencies infrequently, the potential impact on a pharmaceutical company's financial performance could be significant. Additionally, the EEA QPPV and senior management personnel (regardless of whether they are located in the EEA) may be personally affected by criminal proceedings and should consider their liability insurance arrangements, whether provided by their employer or procured personally.

GVP Module IV: Pharmacovigilance Audits

This module focuses on a risk-based approach to planning and conducting audits of the pharmacovigilance system, with the expectation that all MAHs have an active internal audit program. All activities in the pharmacovigilance system should be subject to an assessment of risk that examines the impact of not performing that activity and the likelihood that the activity will not be performed appropriately. Typically, a numerical scoring system is used to calculate an overall risk score for each area of the pharmacovigilance system. These risk scores are then used to design the long-term audit strategy schedule (typically for the next 2-5 years) and the current audit tactical plan (typically for the current year) and to plan individual audits.

The audit plans are expected to include all global processes used to comply with EEA legislative requirements: for example, the global IT department located outside of Europe that is maintaining the safety database and the global legal department that is approving agreements with contract partners.

GVP Module V: Risk Management Systems

The role of the Risk Management Plan (RMP) in managing the benefit-risk balance of a product has been significantly reinforced in GVP. RMPs are now mandatory for all new marketing authorization applications, regardless of whether the active substances are new or well established. In addition, RMPs are now mandatory for all significant changes to existing marketing authorizations, such as a new dose form, new route of administration, new manufacturing process for biotechnology products, a pediatric indication, or any other significant change in indication. The industry should be prepared for a significant increase in the number of RMPs that are required.

A significantly revised format for the European RMP was released in November 2012 and introduces a modular concept. The modular format is intended to allow uniform presentation of data across multiple regulatory documents, with interchangeable modules across the RMP, the Periodic Benefit Risk Evaluation Report (PBRER), and the Development Safety Update Report (DSUR) **(Table 2)**. The new format also introduces the concept of postauthorization efficacy studies, which may be required for products with an outstanding question of efficacy from the clinical development program or if the understanding of the target disease changes such that the premise of how the product works is invalidated. This requires a discussion of the known efficacy of the product to indicate where there may be knowledge gaps that need addressing. The new RMP format is required for all new RMPs and all updates to RMPs from 2013 onward.

GVP Module VI: Management and Reporting of Adverse Reactions to Medicinal Products

GVP Module VI is the most detailed of the GVP modules, describing a wide range of requirements to be considered when processing ICSRs. These will largely be familiar from the evolution of volume 9 and volume 9A of the Rules Governing Medicinal Products in the European Union.5,6 These requirements should be applied to any ICSRs received for a product with a pending or approved EEA marketing authorization, regardless of where the ICSR originated (ie, including non-European countries).

There are some key changes that need to be considered by any group responsible for expedited submission of ICSRs to EEA regulatory agencies. As of July 2012, all serious related adverse events need to be submitted to regulatory agencies within 15 days, regardless of the country of occurrence and including events that are both expected and unexpected. Of more impact, however, is the new requirement to submit non-serious ICSRs to regulatory agencies on an expedited basis. This does not affect nonserious adverse events occurring outside of the EEA, but nonserious adverse events occurring within the EEA will require expedited submission within 90 days. This requirement is currently in a transition phase. Six countries in the EEA required this from July 2012 onward; Iceland subsequently removed this requirement and Croatia requested it upon its accession to the European Union on July 1, 2013. This will be required for all countries in the EEA by 2016. Finally, ICSRs received from consumers and other non-health care professionals are now eligible for expedited submission, where previously EEA regulatory agencies required health care professional confirmation **(Figure 2)**.

Table 2. Periodic Benefit Risk Evaluation Report (PBRER), Development Safety Update Report (DSUR), and Risk Management Plan (RMP) interchangable modules.

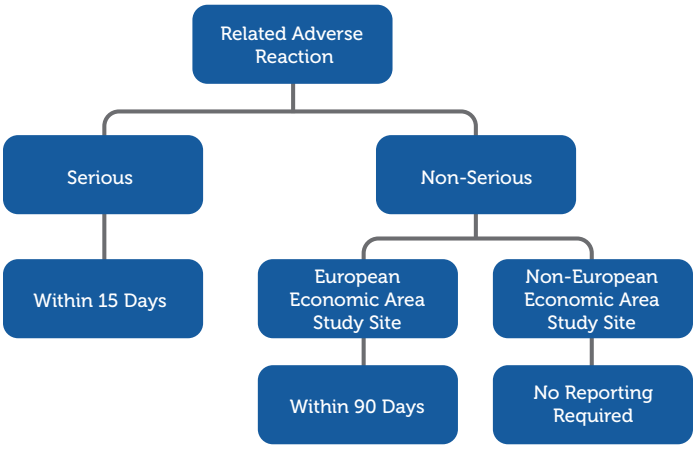
PBRER	DSUR	RMP
Section 2 Worldwide Marketing Authorization Status	Section 2 Worldwide Marketing Approval Status	
Section 3 Actions Taken in the Reporting Interval for Safety Reasons	Section 3 Actions Taken in the Reporting Interval for Safety Reasons	Part II Module SV Regulatory and Marketing Authorization Holder Action for Safety Reason
Section 5.1 Cumulative Subject Exposure in Clinical Trials	Section 6.1 Cumulative Subject Exposure in the Development Program	
Section 5.2 Cumulative & Interval Patient Exposure From Marketing Experience	Section 6.2 Patient Exposure From Marketing Experience	Part II Module SV Nonstudy Post-Authorization Exposure
Section 6.2 Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials	Section 7.3 Cumulative Summary Tabulations of Serious Adverse Events	
Section 7 Summaries of Significant Findings From Clinical Trials During the Reporting Interval	Section 8 Significant Findings From Clinical Trials During the Reporting Period	
Section 8 Findings From Noninterventional Studies	Section 9 Safety Findings From Noninterventional Studies	
Section 9 Information From Other Clinical Trials and Sources	Section 10 Other Clinical Trial/Study Safety Information	
Section 10 Nonclinical Data	Section 12 Nonclinical Data	
Section 11 Literature	Section 13 Literature	
Section 13 Lack of Efficacy in Controlled Clinical Trials	Section 15 Lack of Efficacy	
Section 16.1 Summary of Safety Concerns		Part II Module SVIII Identified and Potential Risks
Section 16.3 Evaluation of Risks and New Information	Section 18.1 Evaluation of the Risks	
Section 16.4 Characterization of Risks		Part II Module SVII Identified and Potential Risks
Section 16.5 Effectiveness of Risk Minimization		Part V Evaluation of the Effectiveness of Risk Minimization Activities

GVP Module VII: Periodic Safety Update Reports

The format and philosophy of Periodic Safety Update Reports (PSURs) are evolving on a global basis after the release of ICH E2C (R2) in December 2012.7 ICH E2C (R2) introduced the concept of the PBRER, with increased focus on analysis of available data from all sources to characterize the benefit-risk profile of a product. Line-listings of ICSRs are no longer required, with the assumption that the majority of ICSRs will already be available to European regulatory agencies through the revised expedited reporting requirements described in GVP Module VI.

GVP introduced the PBRER concept 6 months before ICH but did not mandate the new format until January 2013. The US FDA issued a draft Guidance for Industry8 in April

Figure 2. ICSR expedited submissions requirements.



2013, indicating that its existing waiver program for Periodic Adverse Drug Experience Reports (PADERs) will now extend to the PBRER format. Existing waivers that have been granted allowing submission of the previous ICH E2C (R1)9 format in place of a PADER are automatically extended to include the PBRER format. New waivers may be requested to submit a PBRER in place of a PADER. Waivers may also be requested to adjust data lock points for reports, allowing opportunity to prepare a PBRER for submission in multiple jurisdictions. Health Canada10 issued a notice in April 2013 indicating that the PBRER format meets its requirements for Annual Summary Reports. Agencies across the world are now starting to indicate their acceptance of the PBRER format, which is welcomed by the industry and should reduce the resource burden on pharmaceutical companies. However, a minority of countries still require periodic reporting in the previous ICH E2C (R1)9 format, and therefore companies should be prepared to submit periodic reports in both the old and new formats to meet international requirements. Due to legal technicality, periodic reports are still referred to as Periodic Safety Update Reports (PSURs) in the European Regulations, Directives, and GVP Modules. However, this PSUR terminology refers to ICH E2C (R2)7 and not ICH E2C (R1).9 The scheduling of PSURs in Europe has seen a radical change, with the introduction of the list of EU Reference Dates and Frequency of PSUR Submissions. Previously, the submission of PSURs was based on the birth date of an individual marketing authorization. Now PSUR submissions are based on the EU Reference Date for the active substance, as defined by the European Medicines Agency (EMA) and usually based on the birth date of the innovator product. Consequently, all MAHs that have a product containing the same active substance will be required to submit their PSURs at the same time. This allows the regulatory agencies to assess the cumulative data set for the active substance across all MAHs to detect any trends. This will result in the issuance of a single opinion that will apply to all MAHs, and recommended updates to approved product information are to be added to all products with that active substance.

GVP Module VIII: Post-Authorization Safety Studies

The content of Module VIII of GVP is largely aligned with the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Society of Pharmacoepidemiology (ISPE). It is not mandatory for an organization to be registered with ENCePP to comply with GVP, although use of ENCePP-registered organizations will provide a level of reassurance to regulatory agencies.

A Post-Authorization Safety Study (PASS) is defined in Directive 2010/84/EU as follows:

> *Any study relating to an authorised medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.*[2]

This differs from previous definitions with the addition of the measurement of the effectiveness of risk management measures. Throughout the revised pharmacovigilance legislation, an expectation that risk minimization activities will be monitored for their effectiveness is reinforced, and it is anticipated that PASS will be a common tool used in this activity.

PASS may be interventional or noninterventional (observational). Interventional studies must follow the requirements outlined in the Clinical Trial Directive (2001/20/EC).11 The requirements described in GVP largely apply to noninterventional studies only.

Information regarding both interventional and noninterventional studies is recommended to be included in the EU electronic register of PASS: the EU PAS Register. This will be an evolution of the current ENCePP register and

is currently under development by the EMA. GVP Module VIII provides guidance on the conduct of PASS, including research contracts with investigators, the development of the protocol, management of substantial amendments to the protocol, requirements for progress reports, and preparation of the final study report. Recommended formats and contents for these documents are described, and the use of ENCePP checklists and guidance documents is recommended.

A key impact of the revised pharmacovigilance legislation is the management of adverse events in PASS. Although adverse events occurring in interventional clinical studies continue to follow traditional processes, the adverse event management within observational studies has become increasingly complex. GVP Module VIII requires that adverse events from observational studies be managed in accordance with the requirements of GVP Module VI (see previous discussion). Adverse events observed in studies based on retrospective record review do not require submission to regulatory agencies outside of the final study report. However, the requirements for collection of adverse events in studies based on primary data collection has been subject to extensive debate.

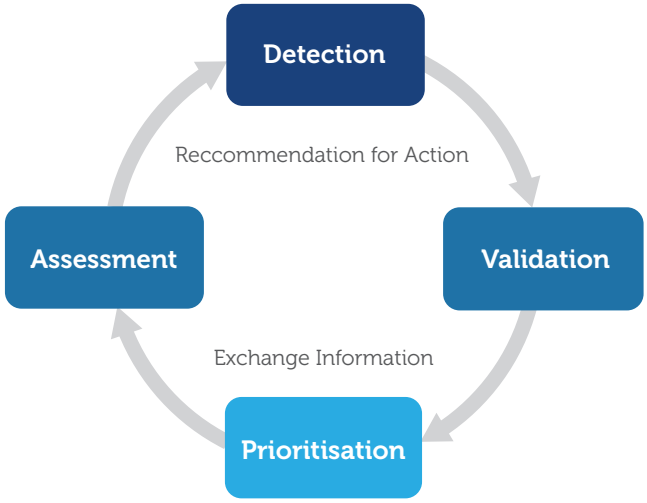
GVP Module VI stated that all reports of adverse reactions occurring in PASS should be recorded, leading to confusion as to whether active collection of all serious and nonserious adverse reactions was mandated, whether this collection of data could be limited to causally related events only due to the use of the word reaction, or whether collection of a smaller subset of adverse reactions applicable to the objective of the PASS only was acceptable. In response to questions received from the industry, the EMA released a revision to GVP Module VI for consultation in June 2013. The wording for the consultation clarified that the protocol should specify which adverse events should be actively sought. It also mandates that death and fatal adverse events must be actively collected, unless specifically exempted in the protocol, with robust justification required for any exemptions. The revision to GVP Module VI is due to come into effect in the fourth quarter of 2013.

All serious related adverse events (ie, reactions) must be submitted to regulatory agencies within 15 days, including events that are both expected and unexpected. Of more impact, however, is the new requirement to submit nonserious adverse events to regulatory agencies on an expedited basis. This does not affect nonserious adverse events occurring in a site outside of the EU, but nonserious adverse events occurring in a site within the EU require expedited submission within 90 days. This requires the industry to review its procedures for management of nonserious adverse events in PASS to ensure that information about appropriate nonserious adverse events is available to pharmacovigilance functions who are responsible for expedited submissions of adverse events from these studies. This may require investigators to send nonserious adverse event data directly to the pharmacovigilance function within fixed time frames; alternatively, the pharmacovigilance function may require direct access to the study database to obtain this data.

GVP Module IX: Signal Management

GVP Module IX introduces a structured lifecycle for the signal management process, providing detailed guidance for each step **(see Figure 3)**. Data sources for signal detection should include ICSRs from spontaneous and study sources, scientific literature, clinical studies, PASS, and any other resources available to the MAH. The nature of the data reviewed should include product quality, nonclinical information, clinical information, pharmacovigilance data, and pharmacoepidemiological data. Methodology for signal detection may be based on a review process, statistical analysis, or (usually) a combination of both.

Figure 3. Signal management life cycle.



In the validation step, the available data are reviewed to determine if there is sufficient evidence to demonstrate the existence of a new potentially causal association or a new aspect of a known association, considering the clinical relevance, previous awareness of an issue, and availability of addition supportive data. An analysis is then formed to determine the public health impact or the impact on the benefit-risk profile of the product in order to determine which signals require urgent attention and should be prioritized for further action. A full assessment is then performed to identify the need for additional data collection or for regulatory action. Finally, a recommendation for action or no further action is required.

Pharmaceutical companies are required to inform European regulatory agencies of ''emerging safety issues.'' These are defined as signals that may have implications for public health and/or the benefit-risk profile of the product. Notification is required immediately. The EMA has provided a dedicated email address for this purpose. Other validated signals that do not meet these criteria are provided to regulatory agencies during routine pharmacovigilance activities: for example, preparation and submission of PSURs (GVP Module VII) and RMPs (GVP Module V), including a description of the outcome of the evaluation of these (see sections for GVP Module V and GVP Module VII).

Robust tracking systems should be implemented to document that each step has been completed appropriately, to record decisions that have been made by groups responsible for signal management, and to monitor the completion of associated action items (eg, submission of a variation to update the approved product information).

The implementation of this regimented approach to signal detection and management has required the pharmaceutical industry to reevaluate its signal management processes to ensure that these processes reflect the requested lifecycle of a signal and to ensure that documentation practices are sufficiently robust.

Finally, GVP Module IX introduced a new requirement for MAHs to conduct signal detection in EudraVigilance (the repository of ICSRs held by the EMA), to the extent of their accessibility. The EMA has a project to increase accessibility to the EudraVigilance data over the next few years via the EudraVigilance Data Warehouse and Analysis System (EVDAS). All regulatory agencies currently have access to EVDAS, and MAHs will be granted access to EVDAS at a future date that is yet to be confirmed. Further information regarding this project will be released by the EMA in due course. It is perceived that there will be a significant resource burden for the industry to develop novel processes for monitoring EudraVigilance data and to understand how the data fit into existing signal detection processes.

GVP Module X: Additional Monitoring

GVP Module X introduces the concept of additional monitoring to collect information as early as possible during the postauthorization clinical use of a project and to increase awareness about the safe and effective use of certain medicinal products.

Products containing new active substances not included in any authorized product prior to January 1, 2011 (including biological products), and biological products authorized after January 1, 2011, will be included by the EMA in a list of products subject to additional monitoring, as will certain products authorized with obligations to conduct various pharmacovigilance and/or risk minimization activities. Products on the additional monitoring list will have an inverted black triangle on the approved product information, a statement confirming that the product is subject to additional monitoring, and an explanatory paragraph encouraging health care professionals and patients to report suspected adverse reactions. In general, new active substances will remain on the list for 5 years, although this period may be extended at the request of the Pharmacovigilance Risk Assessment Committee. This committee will also determine the length of time a product with pharmacovigilance and/or risk minimization activities is on the list.

The Quality Review of Documents (QRD) templates for Summary of Product Characteristics and Package Inserts are in the process of being updated to include the language for products subject to additional monitoring. A consultation of phasing-in of these requirements was completed in January 2013. MAH responsibilities will be limited to submission of appropriate variations to include or remove the black symbol, statement, and explanatory paragraph; however, a process for monitoring changes to the additional monitoring list may be required to ensure that MAHs have included or removed the black triangle where required. Of note, the paragraph encouraging reporting of adverse reactions is required for all

products, regardless of whether they are on the additional monitoring list.

In March 2013, the EMA issued an implementation plan for the revised QRD templates. For existing products that are placed on the additional monitoring list, a variation has to be submitted and approved by the end of 2013. For existing products that are not on the additional monitoring list, MAHs are encouraged to use the first upcoming regulatory procedure to include the standard paragraph regarding reporting of adverse reactions.

Modules XI (Public Participation in Pharmacovigilance) and XII (Continuous Pharmacovigilance, Ongoing Benefit Risk Evaluation, Regulatory Action and Planning of Public Communication) had not been released for consultation at the time this article was prepared. Module XIII was originally intended to be a module on Incident Management, but this information has now been incorporated into other modules and Module XIII currently is retracted. Module XIV (International Cooperation) also had not been released for consultation at the time this article was prepared.

GVP Module XV: Safety Communication

Module XV provides guidance on the communication of safety information to patients and health care professionals, describing the content that should be included in announcements related to safety and the methods of communication that may be used. Particular focus is given to the Direct Healthcare Professional Communication (DHCP), and a template is provided. The module recommends measurement of the effectiveness of safety communication using research methods to ensure that DHCPs have been disseminated to the appropriate audience and that the message is understood in the way it was intended. The processes for agreeing on content of safety announcements with regulatory agencies and for coordinating safety announcements across the European regulatory network are described. Of note, MAHs are required to inform European regulatory agencies of announcements intended for release outside of the EEA if they involve a product with a pending or approved authorization in the EEA.

The method of communication and the public perception of the organization performing the communication will significantly influence public perception. The role of media is critical. GVP Module XV makes it clear that communication needs to come from regulatory agencies in addition to MAHs to ensure that information is understood in the manner it was intended.

The pharmaceutical industry should review its communication processes to ensure they are aligned with the requirements of GVP. In particular, the effectiveness of safety communication is not frequently monitored, and the industry may be required to explore new methods for this purpose.

GVP Module XVI: Risk Minimization Measures: Selection of Tools and Effectiveness Indicators

GVP Module XVI was released for consultation in June 2013 and is not due to be implemented until the fourth quarter of 2013. It provides considerations for the selection of risk minimization activities and how to measure their effectiveness. These will largely be part of RMPs prepared in accordance with GVP Module V.

Although measuring the effectiveness of risk minimization was a requirement of previous legislation, there was minimal guidance available and a general lack of understanding of how to interpret the requirements. This new module provides the industry with an insight as to agency expectations; however, detailed operational guidance is not provided. The recommendations may change as a result of the consultation process.

GVP Module XVI focuses on the most common risk minimization activities, noting that the design and objectives can differ widely. The module provides some thoughts about educational tools, particularly when considering the different needs of a health care professional and a patient or carer. It also considers the variety of controlled access programs available, including actions taken at the patient, dispenser, and prescriber levels. The module comments on pregnancy prevention programs and the need to combine these programs with the use of educational tools. Finally, it references GVP Module XV for the use of Direct Health Care Professional Communications as a risk minimization strategy.

Module XVI introduces two indicator concepts for the measurement of the effectiveness of risk minimization. Process indicators show whether risk minimization was implemented successfully—whether the target audience

was reached, the audience gained the appropriate clinical knowledge, and the audience took the appropriate clinical actions. Outcome indicators are focused on the safety outcomes. The module strongly indicates that PASS should be used in this context and that spontaneous reporting rates are not an acceptable indicator.

The pharmaceutical industry is encouraged to provide feedback on the consultation of this module, as it is likely to have a significant impact on processes and resourcing of risk minimization activities.

Discussion

The scope of the changes affecting European pharmacovigilance legislation reaches far beyond the borders of the EEA, affecting global pharmacovigilance processes for the pharmaceutical industry, CSOs and regulatory agencies.

There are numerous challenges in aligning requirements across international territories; these include significantly different expedited reporting requirements for ICSRs received spontaneously or in the context of a PASS study, inclusion of global processes and data in an EEA PSMF, formal reporting of signals to EEA regulatory agencies, and others.

Furthermore, new requirements will be introduced on a rolling basis from now until 2016 that will affect global pharmacovigilance processes. Three GVP modules are not due to be released for consultation until the third quarter of 2013. Expedited reporting requirements will continue to change, with the introduction of expedited submission of nonserious adverse reactions for all EEA countries and centralization of reporting to the EMA. ICH E2B (R2) is due to be implemented in the EEA in 2016, affecting the electronic submission of ICSRs between all stakeholders.

All organizations conducting pharmacovigilance activities should consider this impact when planning resources and process development for their global pharmacovigilance department over the next few years. The skill set required by a pharmacovigilance department will need to be significantly expanded to manage the diversity of requirements reflected in the GVP modules. Departments need sophisticated logistics management to juggle the increasing complexity and interdependencies of these regulatory requirements across multiple functional areas. Increased focus on measuring real-world effectiveness of pharmaceutical products will require a strong understanding of the marketplace and use of epidemiological methods, both to design the right pharmacovigilance study and to evaluate the pharmacovigilance data received from these and other postmarketing sources. Biostatistics is becoming increasingly important to understand the complex data sets generated by these postmarketing activities and to manage the considerable confounding factors that exist for any pharmaceutical product. The many departments in a pharmaceutical company that are involved in the pharmacovigilance system (pharmacovigilance, medical affairs, regulatory affairs, clinical development and operations, epidemiology, data management, library services, legal, vendor management) are all affected by this legislation, and most, if not all, will require additional resourcing over the next few years as the full impact of the implementation of GVP becomes apparent.

The new European legislation was implemented after a period during which many high-profile safety issues were raised: for example, connections between rosiglitazone and cardiovascular events, rofecoxib and cardiovascular events, and natalizumab and progressive multifocal leukoencephalopathy. The intention of this legislation is to identify potential safety issues as early as possible in the lifecycle of a pharmaceutical product and to take early action to protect public health. Will it achieve its aim? Certainly there will be increased focus on generating higher quality pharmacovigilance data and a new focus on the balance between benefit and risk. However, there are finite resources available within any pharmaceutical company, large or small, and there is significant concern that the complexities of process involved in the new legislation mean that resources will be focused more on procedural compliance and less on the overall safety of patients.

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