Pharmacovigilance medical writing: An evolving profession

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Abstract

The preparation of pharmacovigilance documents is a global and cross-functional activity. The pharmacovigilance medical writer has a key position in this complex activity, leading the whole document creation process. This process includes drafting the document, coordinating the input of the involved functions, providing valuable expertise on the required format and contents and detailed guideline knowledge, and coordinating the review and consolidation of comments. Furthermore, different submission scenarios and document requirements exist, depending upon, for example, the medicinal product, therapeutic indication, and authorisation procedure. The result should always be a high-quality state-of-the-art document meeting all requirements for an electronic submission to health authorities worldwide.

Keywords: EU pharma package, Pharmacovigilance medical writer, Lifecycle, RMP

Introduction

Medical writing is an established professional field in the pharmaceutical industry that takes account of changing legislation and requirements for professional medical communication. Based on the new pharmacovigilance legislation issued in the context of the so-called 'EU Pharma Package', the EMA introduced the Good Pharmacovigilance Practices[1] (GVP) in 2012. This framework (in the following referred to as EU Pharma Package for the purpose of this article) provided the opportunity for a new medical writing role to develop: the pharmacovigilance medical writer. The ideal profile description of a pharmacovigilance medical writer includes pharmacovigilance expertise; extensive knowledge of formal requirements and guidelines; document, format, and content expertise; and writing, communication, and project management skills. Moreover, the pharmacovigilance medical writer often needs to look beyond the preparation of a single document and to take into account further regulatory aspects regarding document planning and assessment (as described in the examples below).

The lifecycle of a medicine

In pharmacovigilance, document-related activities do not end with the submission of a document to health authorities, but continue throughout the lifecycle of a medicine, along with pharmacovigilance and risk minimisation activities (see Table 1 for some examples) and benefit-risk analyses. The EU Pharma Package emphasises the concept of lifecycle with regard to the risk management system for a medicine (Figure 1) and reflects this concept in the new contents and requirements for Risk Management Plans (RMPs)[2] and Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports (PSURs/PBRERs).[3] At the time of marketing authorisation, only limited clinical experience and knowledge about the risks of a medicine are available. Marketing authorisation is granted based on clinical trial data indicating that the benefits exceed the risks (i.e. the benefit-risk profile is positive). Pharmacovigilance activities are planned to further characterise the risks (e.g. to assess risk frequency or severity) or to investigate whether subsets of patients within the target population (e.g. patients with hepatic impairment) are at higher risk. Measures aimed at minimising risks associated with the use of a medicine are planned at the time of marketing authorisation. The EU Pharma Package introduced the requirement to assess the effectiveness of these measures in the post-authorisation phase. Depending upon this assessment, different risk minimisation measures (RMMs) may need to be planned (Table 1). Risk management according to the EU Pharma Package is not just managing risks, but also understanding risks in the context of benefits and

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Table 1: Pharmacovigilance activities and RMMs

Pharmacovigilance activities		RMMs	
Routine	Additional	Routine	Additional
• Periodic reports (DSURs, PSURs/PBRERs) • Signal detection and evaluation • Monitoring • Specific adverse reaction follow-up questionnaires[a]	• Non-clinical studies[a] • Clinical studies[a] • Non-interventional studies[a] • PASS[a] • PAES[a] • Pharmacoepidemiology studies[a] • PK studies[a] • Further pre-clinical work[a] • DUS[a] • Registries[a]	• SmPC[a,b] • Package leaflet[a,b] • Labelling[a,b] • Pack size and design[a,b] • Legal (prescription) status[a,b]	• Education programme[a,b] • (different educational tools depending upon the target audience, e.g. patient alert cards)[b] • Controlled access programme, pregnancy prevention programme, direct health care communication[b] • Surveys (including questionnaires for data collection)[b] • Studies, PASS, etc. • Prescriber guides

Abbreviations: DSUR, Development Safety Update Report; DUS, Drug Utilisation Study; PAES, Post-Authorisation Efficacy Study; PASS, Post-Authorisation Safety Study; PBRER, Periodic Benefit Risk Evaluation Report; PK, Pharmacokinetic; PSUR, Periodic Safety Update Report; SmPC, Summary of Product Characteristics.
[a]GVP Module V Rev 1.[2]
[b]GVP Module XVI Rev 1.[5]

maximising the benefit-risk balance of a medicine. In fact, the effectiveness of the medicine in real-life settings might differ from the efficacy shown in clinical trial settings. A subset of patients within the target population might turn out to be at higher risk or to benefit to a lesser or greater extent from the use of a medicine. This would impact the benefit-risk balance of the medicine. Last but not least, post-authorisation safety and efficacy studies may be needed to further characterise risks, assess the effectiveness of RMMs, or maximise benefits.

In a nutshell, the link between risk management and pharmacovigilance medical writing is the RMP, which gives a detailed description of the risk management system, contains information on a medicine's safety profile, and explains the measures taken to prevent or minimise the medicine's risks in patients. As a medicine progresses throughout its lifecycle, emerging evidence on safety and efficacy/effectiveness needs to be evaluated in the context of baseline knowledge, and pharmacovigilance activities and RMMs are planned dynamically and proportionally to risks. In this sense, the RMP is also dynamic and proportionate to risks. Unlike other regulatory documents (e.g. clinical study reports, clinical summaries, periodic safety reports), an RMP is a living document that is updated continuously throughout the lifecycle of a medicine during the pre- and post-authorisation phases. Updates may be needed at any time point of the lifecycle of the medicine.

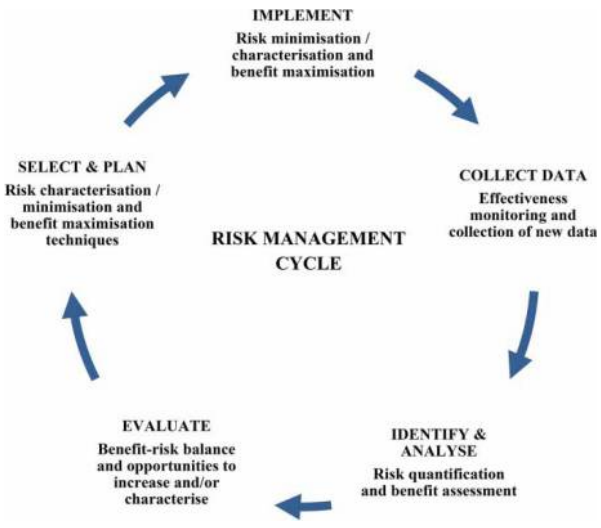

Figure 1: The risk management cycle. Source: GVP Module V Rev 1.[2]

After marketing authorisation, the PSUR/PBRER periodically evaluates risks and benefits of a medicine and the effectiveness of the RMMs in place. Evidence on risks and benefits that emerges during the reporting interval is presented in the context of baseline knowledge and culminates in an integrated benefit-risk analysis. The PSUR/PBRER and the RMP are closely related: if new safety concerns arise in the context of PSUR/PBRER preparation, an RMP update is needed in parallel and new pharmacovigilance activities and RMMs are planned.

A task for pharmacovigilance medical writers

Prior to the EU Pharma Package, RMPs and PSURs/PBRERs were normally prepared by drug safety professionals. With the new pharmacovigilance legislation, both RMPs and PSURs/PBRERs became complex, multidisciplinary documents with a new modular format, requiring a large amount of

data and analyses that encompass the pre- and post-authorisation phases. In other words, a task for highly specialised pharmacovigilance medical writers.

A multidisciplinary document requires a skilled writer who ensures clear data presentation, effective medical communication, and content- and style-wise consistency across modules. Furthermore, the pharmacovigilance medical writer plays a critical role in managing a high number of document files and versions, and ensuring that all contributions are provided and reviewed in a timely manner. Moreover, the pharmacovigilance medical writer must have sound knowledge of guidelines and should ensure that all contributions comply with the GVP requirements. They must also ensure that information contained in other submission documents (e.g. clinical summaries) is in line with the data presented in an RMP. Last but not least, in view of their expertise and knowledge of guidance and requirements, the pharmacovigilance medical writer adds value to planning of the most appropriate document format (of, for example, an RMP) and the level of detail of data presentation; discussions on risks and their categorisation as safety concerns (Table 2); and the strategic planning of submission of different yet related documents.

Table 2: Definition of safety concerns

Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed
Important identified risk and important potential risk	An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant
Safety concern	An important identified risk, an important potential risk, or missing information
Risk-benefit balance	An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety, or efficacy of the medicinal product as regards patients' health or public health

Source: GVP Annex I Rev 3.[6]

There are many different situations a pharmacovigilance medical writer could face. The next section presents a few of them in reference to RMPs.

Pharmacovigilance medical writing task: Preparing RMPs for different authorisation procedures

In Europe four different authorisation procedures exist: centralised, decentralised, mutual recognition, and national. Depending upon the type of medicinal product, the intended therapeutic indication, and several other legal regulations, a new marketing application is submitted via one of the four procedures. Detailed guidance regarding the application type is given on the EMA homepage.[4]

An RMP is part of the submission dossier and is required for all new marketing applications which are planned for submission in the EU/European Economic Area (EEA), regardless of the authorisation procedure. Unlike other regulatory documents, the RMP is not a classical single-file document but is set up in a modular fashion, meaning that an RMP consists of several parts, some of which are further subdivided into several modules or appendices. Each part/module can be updated and re-submitted independently from the others. Also, not all parts/modules of an RMP might be required for an initial application.[2]

In general, the RMP undergoes a preparation phase, followed by a writing and review phase, a finalisation phase, an agency review phase, and finally the post-approval phase (Figure 2).

In the following examples, different submission scenarios and their impact on RMP writing are presented.

Example 1

A new active substance for a new marketing application is planned for submission via the centralised procedure in the EU/EEA.

In the preparation phase, the pharmacovigilance medical writer conducts kick-off meetings with the team. These kick-off meetings serve to raise the team's awareness of the upcoming task and to clarify timelines, responsibilities, and deliverables. They also permit discussion of the content, required analyses, planned pharmacovigilance activities, and RMMs, to name a few topics. As a next step, the pharmacovigilance medical writer prepares a so-called 'shell RMP', which contains all required information that can be provided independently of the statistical data outputs. For example, epidemiological, non-clinical, and pharmacokinetic information is usually available well in advance and

Figure 2: RMP lifecycle phases.

can be finalised at an early stage. The aim of this front-loading approach is to agree in advance on the key outline of the RMP and the required analyses, pharmacovigilance, and RMMs, and to free up the team's capacity for the interpretation of data during subsequent writing and review (see below). The preparation of a shell RMP includes one or two review cycles in the team and discussion of comments meetings. To the extent possible, the pharmacovigilance medical writer then finalises the shell RMP before the statistical analyses arrive.

The next step is the writing and review phase. Taking into consideration the statistical data analyses and the accompanying implications for the medicinal product (e.g. Are the safety concerns observed so far in line with expectations? Are additional measures required?), the pharmacovigilance medical writer creates first and final draft versions of the RMP. These draft versions are reviewed and thoroughly discussed in the team before they are sent to management for review and company approval. Alignment with other documents of the submission dossier also takes place in this phase, as it is important that the entire dossier is consistent and tells the same overall story. Also, a thorough quality check against the source data is performed at this stage.

In the finalisation phase, the pharmacovigilance medical writer takes the last management decisions into consideration and then finalises the RMP content-wise. The RMP is now ready to undergo the last technical steps in the electronic document management system, which are required to deliver a high-quality state-of-the-art document for electronic submission. These technical steps include checking of format, setting of hyperlinks, and electronic approval in the system. After successful completion of all these steps, the RMP is now available for electronic submission to the agency.

The RMP now enters the agency review phase. In the case of the centralised procedure, the agency review follows a defined review schedule. The advantage of this procedure is that the timelines of the agency questions are known well in advance. This facilitates internal capacity and timeline planning enormously. Depending upon the type of questions received, the RMP will be updated several times during an agency review procedure. In addition to the RMP update, the pharmacovigilance medical writer also helps the team with the responses to questions on the RMP. Questions can, for example, refer to re-classification or addition or demotion of the proposed safety concerns, additional data analyses, requests for post-approval measures, and changes to the proposed labelling (i.e. Summary of Product Characteristics and Package Leaflet). Towards the end of the approval procedure the frequency of the agency interaction increases and RMP updates can be requested several times at extremely short notice. Good team interaction and internal processes allowing for these demands are crucial here. Finally, if positive opinions are obtained from the Pharmacovigilance Risk Assessment Committee and Committee for Medicinal Products for Human Use, the new medicinal product is given approval by the European Commission. During this last phase, agency review of RMP Part VI (the public summary of the RMP written in lay language) also takes place.

The first task in the post-approval phase is the preparation and submission of RMP Annex 1 within the required timelines. RMP Annex 1 provides the key information regarding the RMP in a structured electronic format and can also be prepared by

a pharmacovigilance medical writer, in collaboration with selected team members. After this task has been completed, the RMP is now subject to various updates as long as the product is on the market.

An RMP update is required upon request of the EMA or a national competent authority within the EU/EEA, or whenever the risk management system changes (i.e. when new information leads to a significant change in the benefit-risk profile or when the result of an important pharmacovigilance activity is obtained or a risk minimisation milestone is reached).[2]

Example 2

A new active substance for a new marketing application is planned for submission via the decentralised procedure in the EU/EEA. The RMP follows the same preparation, writing and review, and finalisation phases as described above for the centralised procedure. Differences exist with regard to the agency review phase: the applicant does not receive consolidated comments by one agency but several comments from different national agencies, according to various local requirements and also different review timeframes. A major challenge for the applicant is to consolidate all these comments content- and timeline-wise. For example, will the changes requested by one national agency be implemented globally in the RMP, and therefore apply to other countries as well? Or are these requested changes applicable to this one particular country only, and is it therefore advisable to create 'local' versions of the RMP? Other differences include the requirements for RMP Annex 1 and the handling of RMP Part VI, as these procedures follow local requirements as well. In the post-approval phase, RMP updates can be requested at any time by any of the national agencies involved and not only by a single central body like the EMA. This can lead to the same questions as in the agency review phase, such as whether requested updates apply to all countries or are country-specific.

Example 3

A generic medicine, on the market for decades, is planned for submission via the national procedure in a new EU/EEA country. The initial RMP for generic medicines can follow an abridged format:[2] epidemiological, non-clinical, clinical, and post-authorisation data can be omitted, as well as the RMP module on important risks and, in most cases, the parts on pharmacovigilance activities and efficacy studies. What happens if the reference medicine is no longer on the market? Should epidemiological data for the indication/target population and non-clinical data, possibly based on the scientific literature, be provided to discuss the risks of the medicine? Would it make sense to present proprietary data, for example on post-marketing experience with the generic medicine? Should the company's own risk analyses be provided? The pharmacovigilance medical writer plays a keys role in facilitating solutions to these often complex issues. National competent authorities may appreciate a proactive, tailored approach that follows the general principles of the GVP guidance.

Conclusions

With the recent implementation of the EU Pharma Package, complex pharmacovigilance documents and new processes were introduced. The pharmacovigilance medical writer has a key position in this novel context, leading the document creation process and providing oversight and guidance to the multidisciplinary authoring team.

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Publications: Is help from medical writers acceptable and useful?

In the October 2014 issue of *Current Medical Research & Opinion*, Jackie Marchington and Gary Burd present a survey in which they asked academics and clinicians about the value of professional medical writers.[1] In 2012, they sent out a 9-question SurveyMonkey survey to 260 academics/clinicians. The survey covered various aspects of medical writing assistance and included one open question: '*Is there anything you would like to tell us about your experience of working with professional medical writers*?'

Regrettably, only 76 people (29.2%) responded, but their responses are revealing. The highest number of respondents (61/76) felt medical writers were useful for '*Editing for grammar, spelling, journal style (including referencing), etc.*' By contrast, only 9 respondents (12%) valued a medical writer's scientific expertise. These findings mirror my experience as an in-house science editor, working with professors and physicians: the 'Science' in my job title sometimes felt superfluous.

The survey also aimed to 'evaluate academic/clinician authors' perceptions regarding the acceptability […] of using [medical writers] in the development of publications'. 83% of respondents felt that it was OK. However, extreme selection bias – the people surveyed were all current or former clients of the communications agency Marchington and Burd work for – limits the value of the data relating to this question.

Only 13 people answered the open question, and some of their answers are not useful, so it's difficult to draw conclusions. One person commented that the medical writer should be the first author, but this would normally contravene ICMJE (International Committee of Medical Journal Editors) guidelines.[2] Another felt that medical writers *could* be authors, depending on their contribution, while acknowledging that this isn't really their role.

Happily, most respondents valued the assistance of medical writers (63/75) and reported positive experiences of working with them (61/70), although there are issues with validity: four people rated their experience of working with medical writers but reported having no such experience. The study's flaws are clear, but it does provide welcome insights into the views and experiences of researchers who have sought professional help with their publications.

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