Applying for an EU marketing authorisation: a pharmacovigilance perspective

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Abstract
For small and medium-sized enterprises, the prospect of applying for an EU marketing authorisation for a medicinal product for the first time can be daunting. EU pharmacovigilance requirements are arguably the most comprehensive, complex and strict of any country or region in the world. In this article, we outline the pharmacovigilance activities that a prospective marketing authorisation holder (MAH) will need to accomplish in advance of and throughout the marketing authorisation application (MAA) process, with particular focus on building an EU-compliant "pharmacovigilance system" and drafting the product-specific risk management plan (RMP). We also highlight some common misunderstandings, as well as pitfalls to be avoided.

Introduction

The EU legislation and core guidance documents applicable to peri- and post-approval pharmacovigilance (PV) throughout the EU and wider European Economic Area (EEA) amount to more than 500 pages, excluding countless other ancillary documents. Furthermore, the content of the EU good pharmacovigilance practices (GVP) guidance documents[1] (GVP modules) is considered binding and, along with the legislation, enforced by a tough regimen of inspections and legal sanctions, including high financial penalties. In contrast, equivalent US peri- and post-approval PV requirements, although also enforced by inspections, are covered in fewer than 50 pages of legislation and final (yet nonbinding) guidance documents.

To those companies that therefore only have experience of complying with clinical trial PV obligations, or that only hold marketing authorisations (MAs) outside of the EEA, the prospect of "upgrading" their PV systems to comply with EU peri- and post-approval requirements can be daunting.

In this article, we examine the preparation that a company needs to do to comply with EU PV requirements during the marketing authorisation application (MAA) process, up until the point of MA approval. We focus on two PV documents that need to be included within Module 1 of the MAA: Section 1.8.1 'Pharmacovigilance System' (not product specific), namely the summary of PV system (SPS); and the product specific risk management plan (RMP) in Section 1.8.2 'Risk Management System'.

Within the EU medicinal product regulations, "pharmacovigilance system" is a collective term used to encompass everything that a prospective marketing authorisation holder (MAH) needs to put in place in order to comply with the PV aspects of the legislation. The definition is not therefore limited to electronic systems, such as safety databases, but extends also to organisational structures, responsibilities, procedures, processes and resources; not only within the PV function, but more broadly within the organisation.

The majority of MAHs operating within the EEA implement a single PV system that covers all of their products. Therefore, while for first-time EEA medicinal product MAAs the effort required to build an EU-compliant PV system may seem tremendous, once it is implemented the same system should serve future MAAs.

Provided that appropriate oversight is maintained, an MAH can outsource fulfilment of some or all of its PV obligations to a suitably qualified PV provider. Given the depth of understanding needed, coupled with the volume of procedures and systems required to comply with EU legislation, full PV system outsourcing has become an increasingly attractive choice for companies that fall within the small to medium-size enterprise category. As well as having established procedures and templates, and providing access to pre-validated systems, established PV providers are able to offer access to a large number of experienced professionals who can be called upon for specialist advice.

Qualified person for pharmacovigilance

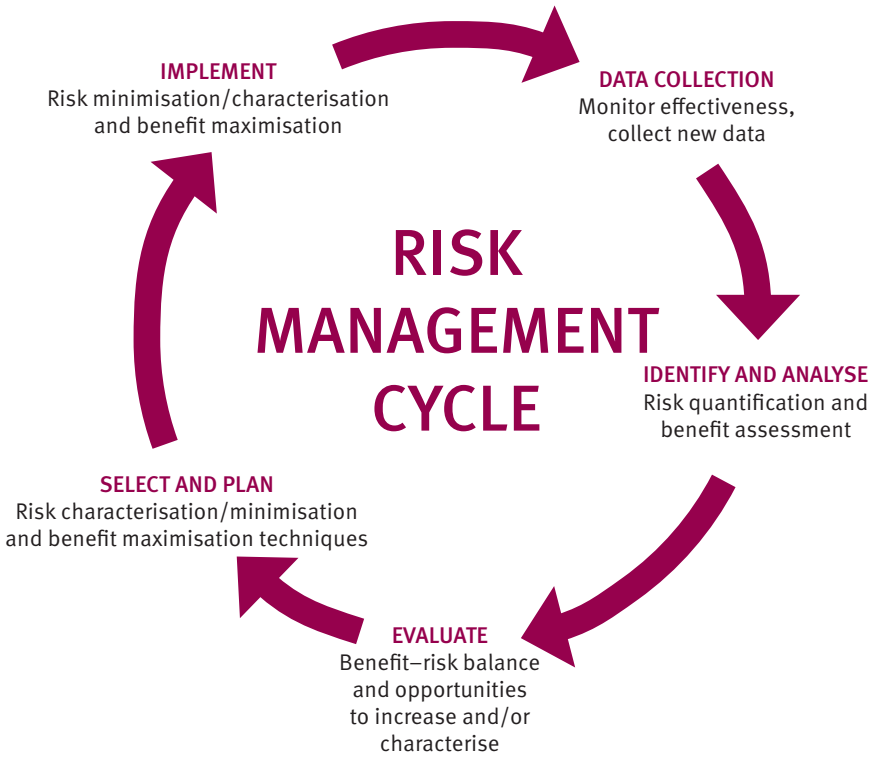
There is a requirement for medicinal product MAHs operating within the EEA to have a suitably qualified and experienced QPPV both operating and residing within the EEA, which is detailed in GVP Module 1.[1] The QPPV has personal liability in overseeing the compliant running of the PV system to which he/she is assigned. Responsibilities of the QPPV, and the MAH in respect of the QPPV, are described in GVP Module 1.[1]

It is vital that there is a strong relationship between the MAH and its QPPV and this will be critically examined in the event of a PV inspection. Inspectors look for evidence that the MAH has appropriately cooperated with and given sufficient authority to the QPPV so that he/she can positively influence the PV system. For their part, QPPVs need to be proactive and sufficiently authoritative, which, in an outsourcing situation, can at first feel like an inverted relationship between client and PV provider, but which, in our experience, ultimately yields positive results.

Pharmacovigilance system master file

The pharmacovigilance system master file (PSMF) is a complex reference document describing in detail all aspects of the PV system

Figure 1: Risk management cycle.



that the MAH is using to comply with the EU PV legislation. Designed to be maintained "on file" internally by the MAH, it should be kept up to date because it can be requested by EEA regulators at any time, in which case it must be submitted within seven calendar days of the request. Contrary to common misconceptions, the PSMF contains no scientific or medical information regarding the products it relates to, and does not need to be submitted at the time of MAA. Detailed requirements for PSMF content and format are contained within GVP Module II.[1]

The most significant challenge to authoring the first version of a PSMF is that it requires an MAH to already have planned in substantial detail how its end-to-end PV system will work; not only those PV activities that will be required between MAA and MA grant, but also those PV activities that will be required post-approval. While it is permissible within the PSMF to refer to aspects of the PV system that are under development, these must be clearly distinguished from aspects that are al ready in place. Care should be taken, since while some processes (eg, periodic safety update report preparation and safety variation submission) will not be exercised until the post-authorisation phase, others (eg, individual case safety report [ICSR] submission and signal detection) may need to be utilised throughout the MAA phase.

MAHs also should bear in mind that the legislation dictates specific topics that must be addressed in formal procedural documents (ie, standard operating procedures).

One significant advantage of partnering with an established PV provider is that it already will have been through the PV system development process with multiple other MAHs. A provider will establish what the client has in place in house, what it intends to have in place in house in the future and what it has outsourced. By drawing upon a library of optimised template text built up through development of multiple PSMFs, they then should be able to efficiently build up the MAH's PSMF, incorporating contemporary experience and best practices, and referring to the appropriate mix of client, provider and other third-party processes and procedures.

What the PV provider will require from the MAH in return is efficient decision-making, provision of requested information and final PSMF review. However, it should be remembered that as a living document, the PSMF can easily be updated as the PV system evolves.

If significant process or procedural gaps are identified for areas that the MAH intends to develop future infrastructure in house, one interim solution is to expand the scope of outsourcing so the PV providers' processes/procedures can be described in the PSMF until the final internal infrastructure is ready. With that said, PV provider processes/procedures only should be described in a PSMF when the corresponding services are explicitly referred to within an outsourcing agreement.

A further common misconception is that PV providers have their own registered PSMFs. PSMFs must be written from the perspective of the MAH, and so while an established PV provider will have procedures, templates and text libraries to support PSMF development and maintenance, it ultimately will deliver a bespoke PSMF for each MAH.

EudraVigilance profile

EudraVigilance (EV) is the European Medicines Agency's (EMA) central database for PV activities; not only for housing ICSRs but also as a repository of administrative information regarding the QPPV, PSMF location and MAs pertaining to each MAH.

MAHs are required to register for an EV profile, or when in possession of an existing clinical trial sponsor profile, apply for this

Figure 2: Structure of the risk management plan.

Part I	Product(s) overview	
Part II	Safety specification	
	Model SI	Epidemiology of the indication(s) and target population(s)
	Model SII	Nonclinical part of the safety specification
	Model SIII	Clinical trial exposure
	Model SIV	Populations not studied in clinical trials
	Model SV	Post-authorisation experience
	Model SVI	Additional EU requirements for the safety specification
	Model SVII	Identified and potential risks
	Model SVIII	Summary of the safety concerns
Part III	Pharmacovigilance plan	
Part IV	Plans for post-authorisation efficacy studies	
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)	
Part VI	Summary of the risk management plan	
Part VII	Annexes	

to be reconfigured to MAH status. The QPPV, or a nominated "trusted deputy", will be required to attend one or more face-to-face EV training courses, which occur several times a year and incur an attendance fee. Evidence of QPPV registration within EV is required to be included within the appendices of the PSMF.

In the event, however, that an MAH is outsourcing QPPV and EV profile management, established PV providers will likely already have employees with the required EV certifications, meaning that unnecessary delay and costs can be avoided.

Pharmacovigilance obligations

Certain EU PV obligations, including but not limited to ICSR reporting and signal detection, begin at the point of MAA. However, the degree to which activities are required in practice will depend in part on the global status of the product in question.

For example, a product that has neither been launched nor is under named patient supply anywhere in the world will generate no ICSRs for reporting under the EU post-approval PV legislation, and signal detection activities can remain focused on data from ongoing clinical trials (where applicable) and product class surveillance. However, a product launched outside of the EEA prior to or part way through the EEA MAA phase could result in non-EEA ICSRs that require 15-day reporting to EV, and require an adjusted approach to signal detection.

MAHs are reminded that it is a requirement of the legislation that all global post-approval PV data regarding the product must be accessible from a single designated point in the EEA. In practical terms, this means that it should be held in one global safety database, surfaced in the EEA.

Summary of pharmacovigilance system

The summary of pharmacovigilance system (SPS) is a simple (typically one page) document that attests the MAH has secured the services of a QPPV, has a PSMF in place and has the means to fulfil its PV obligations. The SPS is submitted as part of the MAA in Module 1, Section 1.8.1, and requirements for what it should include can be found in GVP Module 1.[1]

The MAH should not submit an SPS without having first contractually secured the services of a QPPV, or without having first finalised a PSMF. To do so could constitute a false declaration to the regulatory authorities, and has previously been highlighted by EEA PV inspectors as a source of significant PV inspection findings (ie, MAHs who submitted an SPS at a point in time when no finalised PSMF was in existence; drafts are not considered acceptable).

Dependencies

Ultimately, the MAA only requires submission of the SPS. From a regulatory filing perspective, compared with other aspects of dossier preparation, this can therefore look like a straightforward task to complete. However, it should be remembered that the SPS cannot legitimately be filed until after the initial version of the PSMF is finalised (something that is likely to be verified during a future EEA PV inspection).

Even the PSMF itself, the initial version of which usually can be developed within a few days or weeks, is dependent on the MAH having in place certain key processes/procedures, being able to make detailed decisions on its future PV system, and having secured the necessary EV registration (itself dependent on attendance at external EV training courses that do not run each month) and service provider contracts.

Risk management

Overview

Proactive risk management is a cornerstone of the EU regulatory framework governing medicinal products. The concept encompasses: 1) characterisation of "safety concerns", ie, the material risks of the product, and then for each safety concern; 2) the "pharmacovigilance plan," ie, a detailed description of planned activities intended to gain further knowledge; and 3) "risk minimisation plan," ie, a detailed description of activities that are intended to reduce the possibility of harm to the patient.

All three aspects are brought together in the RMP, a complete draft of which must be included within the MAA dossier. The content of the RMP is then negotiated between the prospective MAH and the applicable regulatory authority during the MAA review phase and agreed by the regulatory authority at the point of MA approval.

Following MA approval, the RMP is considered a living document and therefore continues to be updated over time, with each update

requiring review/approval by the applicable regulatory authority via an appropriate regulatory procedure.

Figure 1 describes the typical risk management life cycle (reproduced from GVP Module 5[1]).

The risk management plan

The RMP must be prepared in accordance with the EU guideline on GVP Module 5 – Risk management systems[1] and the corresponding template[2], and included in Section 1.8.2 'Risk Management System' of the initial MAA.[3,4] Content requirements for generic and established use applications are somewhat abbreviated.

The RMP establishes and characterises the "safety concerns" regarding the medicinal product in question, together with any MAH commitments, with the objective of learning more about and mitigating each concern. Safety concerns fall under three categories:

- **Important identified risks** Risks that are both clinically important and have been confirmed by a robust clinical study or spontaneous data;
- **Important potential risks** Risks that are both clinically important and have been postulated on the basis of nonclinical data or marginal clinical study or spontaneous data;
- **Missing information** Foreseeable clinically significant use in populations not studied during the clinical trials.

The RMP is broadly structured into three sections:

- **Safety specification** Provides general product background information, as well as detailed characterisation of each important identified and potential risk, and includes a list of missing information topics. For the initial RMP version, the safety specification is largely derived from, and aligns with, content presented elsewhere within the MAA dossier;
- **Pharmacovigilance plan** For each safety concern, outlines routine (eg, follow-up questionnaires) and additional (eg, post-authorisation safety study [PASS]) commitments with the objective of gathering more data. All PASS commitments that are a condition of the MA should be included here;
- **Risk minimisation measures** For each safety concern, outlines routine (eg, summary of product characteristics [SmPC]/package leaflet [PL] text) and, exceptionally, additional (eg, educational material) activities with the objective of minimising harm to patients.

The detailed structure of the RMP is provided in Figure 2 (reproduced from GVP Module 5[1]).

Link between the RMP and product information

The RMP and product information are inextricably linked, with routine risk minimisation measures primarily being implemented via the SmPC Section 4 'Clinical Particulars' that then translate to the PL.

Risk management is therefore a critical consideration in developing the SmPC, particularly in relation to sections 4.3 (contraindications), 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects), as well as the PL. Of note, it is also important when deriving SmPC and PL wording to take account of the mandated text in the EMA's quality review of documents template.[5]

RMP development considerations

Prospective MAHs are encouraged to seek the advice of applicable regulatory authorities in the development of their RMP and product information. While such advice may be sought through a scientific advice procedure, for applications via the centralised procedure, discussion on proposed RMP safety concerns, PV activities and risk minimisation activities should take place at the pre-submission meeting.[3] A summary of the proposed safety concerns, and corresponding PV/risk management activities in the form of an initial draft RMP outline, is expected to be provided as part of the pre-submission meeting briefing materials.

It is vital that there is a strong relationship between the marketing authorisation holder and its qualified person for pharmacovigilance and this will be critically examined in the event of a pharmacovigilance inspection

In addition, when developing RMPs for generic and established use applications, prospective MAHs should refer to the published RMP summary for the reference product or, when this is not available, to public assessment reports and/or the SmPC of the reference product to determine the safety concerns to be included in the RMP.

While the contents of an RMP are largely subjective, an experienced provider will be able to help the prospective MAH develop an initial strategy for its draft list of safety concerns, PV activities and risk minimisation activities, factoring in experience with prior applications, other products and experience with the applicable templates and regulatory authorities. This should help reach a faster consensus with the regulatory authorities on the final content of the RMP, and reduce the likelihood of requests for extensive revisions in the period between MA submission and authorisation.

It should be noted that some practices considered acceptable in non-EEA regions (eg, routine use of "Dear health care provider" letters and the use of websites as a means of communicating information on additional risk minimisation measures) are not usually considered acceptable within the EEA and should not typically be proposed in the RMP as a means of communicating information on risk minimisation measures. Risk minimisation measures must not be promotional in nature and should not be a repetition of information already stated in the product information. The mention of a specific medicinal product on a website is regarded as promotional in some member states and may not be permissible.

A review of the RMP is an integral part of the assessment of the benefit–risk of a medicinal product and review comments will be received during the MAA review phase on the draft RMP, including proposed PV and risk minimisation measures, as well as product information wording. It is important during this review and assessment phase to ensure continued alignment between the RMP, SmPC and PL because these documents undergo revision in line with responses to assessors' comments.

Post-approval

Upon MA approval, the RMP forms part of the MA and, for centrally authorised products, part VI of the RMP will be made publicly available via the EMA website. This publication is intended to provide wider public insight into the decision-making of the EMA during the assessment and review of the safety of medicinal products.

In the post-approval phase, the RMP will be revised on an ad-hoc basis in conjunction with the regulatory authorities, as knowledge of the safety profile of the medicinal product evolves and as commitments are met.

Conclusion

From a PV system perspective, the SPS that is included within the dossier should be viewed as a final accumulation rather than a simple standalone document. The underlying PSMF only can be fully completed if the MAH has planned out its end-to-end PV system, put in place the required procedures and/or service provider contracts, and completed the necessary registrations (eg, EV). In our experience, these latter aspects are often the rate-limiting steps, rather than the SPS or PSMF development itself.

From a risk management system perspective, early engagement with regulatory authorities on the list of safety concerns is essential to success, since these are the backbone of the RMP and have an impact on the product information. Development of the RMP itself can be a time-consuming process and is potentially challenging given that a substantial amount of content is dependent on aspects of the dossier that may not be fully available until just prior to submission (eg, extracts from the integrated safety summary and proposed product information).

When developing submission plans, early and robust cross-functional coordination is vital to ensure the PV sections of the dossier do not unintentionally become critical path items that impact the ability to meet submission deadlines. It is particularly important to note the interdependencies between the draft RMP and the draft product information; therefore, the PV and regulatory affairs/labelling functions need to work collaboratively to ensure continued alignment across dossier sections.

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