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Short communication

Legal framework for pharmacovigilance inspection

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Introduction

The safety of drugs is of paramount importance for patients and healthcare professionals. The pharmaceutical industry has an ethical and legal responsibility to ensure quality, efficacy and safety of authorized products.

Well established pharmacovigilance system is pivotal for monitoring the safety, efficacy and effectiveness of drug use throughout its life cycle and identification of any potential risk in post marketing period. Every marketing authorization holder (MAH) is obligated to maintain pharmacovigilance system for all marketed drugs. This system ensures fulfillment of legal tasks and responsibilities of MAH for pharmacovigilance and surveillance of authorized medicinal products safety and detection of any alteration to their risk-benefit balance. As part of the pharmacovigilance system, the MAH shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV). The PSMF, shall describe the pharmacovigilance system for one or more medicinal products of the MAH.

In order to determine that MAH, comply with pharmacovigilance obligations established within the EU, and to facilitate compliance, competent authorities of the Member States concerned shall conduct, in cooperation with the Agency, pharmacovigilance inspections of marketing authorization holders or any firms employed to fulfil marketing authorizations holder's pharmacovigilance obligations. Such inspections shall be carried out by inspectors appointed by the national competent authorities and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorizations holder or any firms employed by the marketing authorizations holder to perform the activities described in Title IX of Directive 2001/83/EC in accordance with Articles 111(1) and 111(1) (d) (Directive is referenced as DIR). In particular, marketing authorizations holders are required to provide, on request, the pharmacovigilance system master file, which will be used to inform inspection conduct [DIR Art 23(4)].

Materials and methods

Relevant European, UK, US and Macedonian legislations have been reviewed, in particular, Directive 2010/84/EU, Regulative (EU) 1235/2010, rulebooks, as well as PubMed, Medline and other relevant web sites for articles with empirical analysis, are evaluating the impact of European and non-European regulatory activities.

Results and discussion

The focus of most European pharmacovigilance inspections is on the systems and processes in place to monitor drug safety, for products in pre- and post-marketing stages. However, product-specific inspections may take place if there are concerns about safety, or the effectiveness of monitoring safety by the license holder. All inspections are resource intensive and require significant planning and preparation by the inspectors to ensure a positive outcome.

Marketing authorization holders (MAHs), may be subject to inspection at any time. Most inspectorates apply a risk assessment model to target limited resources at the highest risk areas. In EU, EMA planned to conduct inspections of all MAHs every 3 years, but because of the large number of drugs licensed in, EU they have had to adopt a risk assessment strategy. Companies are selected on the basis of several criteria, such as not providing details of the qualified person for pharmacovigilance (QPPV) to the EMA, companies with new products on the market, products with a known safety risk, poor compliance history, or non-compliance with 15-day reporting.

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Statutory inspections may be notified to the MAH in advance (usually 1-3 months in Europe), or they may be given virtually no notice if there is a valid reason for a 'triggered' or 'for cause' inspection. The notification letter will include a request for documentation describing the pharmacovigilance quality system, both nationally and globally (if a global company). EMA requires sponsor companies to complete a specific document called the 'Summary of Pharmacovigilance Systems' or SPS (Summary of PV Systems Document. This document requires the contact details of key pharmacovigilance personnel, both in the United Kingdom and at the company headquarters (if not EU), including the QPPV; the number of licenses in place in the EU; the company structure and operating model for pharmacovigilance; the pharmacovigilance system (responsibilities of the UK department and interface with other functions); computer systems used; quality systems in place and archiving arrangements. Several appendices should be attached to provide further detailed information such as all organization charts; full product portfolio; details of clinical studies; list of SOPs; compliance statistics; third party agreements in place; and product-related safety issues. The time taken to compile this information can be quite extensive.

Once the inspection team have reviewed all of the documents sent to them, they prepare an 'Inspection Plan', which is essentially an agenda indicating which functions will be interviewed and when. The company has an opportunity to comment on the Inspection Plan to ensure that they can get the right people in the right place at the right time. The Inspection Plan will include interviews with non-pharmacovigilance personnel such as Medical Affairs, Regulatory Affairs, Sales and Marketing and Clinical Operations. Companies must ensure that all affected personnel are aware of the inspection and make themselves available.

The number of inspectors and the duration of the inspection are dependent on the size of the company's product portfolio. Inspectors may want to conduct interviews in parallel to maximize the time available, so companies must be prepared to find appropriate facilities to accommodate the inspection interviews.

Unless it is a focused inspection, inspectors will test all aspects of the pharmacovigilance system. In Europe, the QPPV has a pivotal role and is legally responsible for all pharmacovigilance activities within Europe for marketed drugs. The QPPV must be continuously and permanently available, and the inspectors will test the out-of-hours systems before the inspection to ensure that they are meeting their legal responsibilities. The level of oversight by the QPPV will be scrutinized including their input into risk management plans and post-authorization safety study protocols. The Deputy QPPV will also be interviewed to establish how well-informed they are about the pharmacovigilance system and current drug safety issues.

The FDA has established an independent Drug Safety Oversight Board in 2005 to oversee the management of drug safety issues. In addition, it has issued guidance for industry on good pharmacovigilance practices and pharmacoepidemiologic assessment (FDA Guidance for Industry: GPV and pharmacoepidemiologic Assessment. March 2005) The guidance includes the requirement for routine risk management and risk minimization activities to be conducted by the industry.

Conclusion

The GPvP inspection program has been evolving through the years and now includes four inspection arms, each with a focused inspection scope. The GPvP Inspectorate will apply a revised risk-based methodology in the future, selecting pharmacovigilance systems, products and non-interventional studies considered to be the highest risk to inspect under the relevant inspection arms. Unprecedented change and challenges, pharmacovigilance inspections will respond accordingly to enable continued supervision of pharmacovigilance systems and ensure ongoing regulatory compliance. Regulation and rulebooks for good pharmacovigilance practice related to pharmacovigilance inspections approved and implemented in by EMA are solid base for introduction of PV inspections on national level and should be adopted and harmonized in The Republic of North Macedonia with

References

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Guideline on good pharmacovigilance practices (GVP) Module III – Pharmacovigilance inspevtions (Rev 1), 16/09/2014.

Guidelines for Conducting Pharmacovigilance Inspections

Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections (01/06/2014)

Union procedure on the coordination of EU pharmacovigilance inspection (01/06/2014)

Union guidance on record keeping and archiving of documents obtained or resulting from pharmacovigilance inspections (01/01/2017)

Union procedure on the follow-up of pharmacovigilance inspections (01/05/2020)

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Summary of PV Systems Document. Available from: http://www.mhra.gov.uk.