Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (Text with EEA relevance)

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012

of 19 June 2012

on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[(1)], and in particular Article 87a thereof,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[(2)], and in particular Article 108 thereof,

Whereas:

(1) Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products[(3)] strengthened and rationalised the monitoring of the safety of medicines that have been placed on the market in the Union. Similar provisions were introduced by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use[(4)] into Directive 2001/83/EC.

(2) Pharmacovigilance activities cover the whole life-cycle management of medicinal products for human use in relation to safety.

(3) Regulation (EU) No 1235/2010 and Directive 2010/84/EU introduced the concept of the pharmacovigilance system master file. In order to accurately reflect the pharmacovigilance system used by the marketing authorisation holder, the pharmacovigilance system master file should contain key information and documents

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covering all aspects of pharmacovigilance activities, including information on tasks that have been subcontracted. It should contribute to the appropriate planning and conduct of audits by the marketing authorisation holder and the supervision of pharmacovigilance activities by the qualified person responsible for pharmacovigilance. At the same time it should enable national competent authorities to verify compliance concerning all aspects of the system.

(4) The information contained in the pharmacovigilance system master file should be maintained so as to reflect any modifications that have been made and ensure easy accessibility and availability by national competent authorities for the purpose of inspections.

(5) Quality systems should form an integral part of the pharmacovigilance system. The minimum requirements for the quality system for the performance of pharmacovigilance activities should ensure that marketing authorisation holders, national competent authorities and the European Medicines Agency (hereinafter 'the Agency') establish an adequate and effective quality system, which provides for an effective monitoring of compliance and the accurate and proper documentation of all measures taken. They should also ensure that marketing authorisation holders, national competent authorities and the Agency have at their disposal sufficient competent, appropriately qualified and trained staff.

(6) Adherence to a well-defined quality system should ensure that all pharmacovigilance activities are conducted in such a way that they are likely to produce the desired results or quality objectives for the fulfilment of pharmacovigilance tasks.

(7) As part of their quality system, national competent authorities and the Agency should establish contact points to facilitate interaction between national competent authorities, the Agency, the Commission, marketing authorisation holders and persons reporting information on the risks of medicinal products, as referred to in the second subparagraph of Article 101(1) of Directive 2001/83/EC.

(8) If marketing authorisation holders, national competent authorities and the Agency use performance indicators to monitor the good performance of pharmacovigilance activities, those indicators should be documented.

(9) Pharmacovigilance activities rely increasingly on the periodic monitoring of large databases, such as the Eudravigilance database. Whereas the Eudravigilance database is expected to be a major source of pharmacovigilance information, account should also be taken of pharmacovigilance information coming from other sources.

(10) Marketing authorisation holders, national competent authorities and the Agency should continuously monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the risk-benefit balance of the medicinal product. They should validate and confirm signals, as appropriate, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, literature information or other data sources. It is therefore necessary to establish common requirements for signal detection, to clarify the respective monitoring roles of marketing

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authorisation holders, national competent authorities and the Agency, to clarify how signals are validated and confirmed where appropriate and to specify the signal management process.

(11) As a general principle, signal detection should follow a recognised methodology. However, the methodology may vary depending on the type of medicinal product it is intended to cover.

(12) The use of internationally agreed terminology, format and standards should facilitate the interoperability of systems used for the performance of pharmacovigilance activities and avoids the duplication of encoding activities concerning the same information. It should also allow for an easier information exchange between regulatory authorities on an international level.

(13) In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holder and the Member States should report those reactions only to the Eudravigilance database. The Eudravigilance database should be equipped to immediately forward reports on suspected adverse reactions received from marketing authorisation holders to the Member States on whose territory the reaction occurred. It is therefore necessary to establish a common electronic format for the transmission of suspected adverse reaction reports by marketing authorisation holders and Member States to the Eudravigilance database.

(14) Periodic safety update reports are an important instrument to monitor the development of the safety profile of a medicinal product after it has been placed on the Union market, including an integrated (re-)evaluation of the risk-benefit balance. In order to facilitate their processing and evaluation, common format and content requirements should be established.

(15) Risk management plans are required for all new marketing authorisation applications. They contain a detailed description of the risk management system used by the marketing authorisation holder. In order to facilitate the production of risk management plans and their evaluation by the competent authorities, common format and content requirements should be established.

(16) Where competent authorities have concerns as to the safety of a medicinal product, they should be able to impose on marketing authorisation holders the obligation to conduct post-authorisation safety studies. The marketing authorisation holder should submit a draft protocol before those studies are conducted. Moreover, the marketing authorisation holder should provide, at the appropriate stage, a study abstract and a final study report. It is appropriate to provide that the protocol, the abstract and the final study report follow a common format in order to facilitate the approval and oversight of those studies by the Pharmacovigilance Risk Assessment Committee or the competent authorities in case of studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC.

(17) This Regulation should apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such

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data[5] and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data[6]. The fundamental right to protection of personal data should be fully and effectively guaranteed in all pharmacovigilance activities. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process. National competent authorities and marketing authorisation holders may apply pseudonymisation where appropriate, thereby replacing identifiable personal data with pseudonyms.

(18) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS REGULATION:

CHAPTER I

Pharmacovigilance system master file

Article 1

Structure of the pharmacovigilance system master file

1 The information in the pharmacovigilance system master file shall be accurate and reflect the pharmacovigilance system in place.

2 The marketing authorisation holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products. Each such system shall be described in a separate pharmacovigilance system master file.

All medicinal products for which the marketing authorisation holder obtained a marketing authorisation in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 shall be covered by a pharmacovigilance system master file.

Article 2

Content of the pharmacovigilance system master file

The pharmacovigilance system master file shall contain at least all of the following elements:

(1) the following information relating to the qualified person responsible for pharmacovigilance:

(a) a description of the responsibilities demonstrating that the qualified person responsible for pharmacovigilance has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities;

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(b) a summary curriculum vitae of the qualified person responsible for pharmacovigilance, including proof of registration with the Eudravigilance database;

(c) contact details of the qualified person responsible for pharmacovigilance;

(d) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;

(e) responsibilities of the contact person for pharmacovigilance issues where such a person has been nominated at national level in accordance with Article 104(4) of Directive 2001/83/EC, including contact details;

(2) a description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the following pharmacovigilance activities are undertaken: individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to the terms of a marketing authorisation;

(3) a description of the location of, functionality of and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose;

(4) a description of data handling and recording and of the process used for each of the following pharmacovigilance activities:

(a) the continuous monitoring of the risk-benefit balance of the medicinal product(s), the result of that monitoring and the decision-making process for taking appropriate measures;

(b) operation of the risk management system(s) and of the monitoring of the outcome of risk minimisation measures;

(c) collection, assessment and reporting of individual case safety reports;

(d) drafting and submission of periodic safety update reports;

(e) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public;

(5) a description of the quality system for the performance of pharmacovigilance activities, including all of the following elements:

(a) a description of the management of human resources referred to in Article 10 containing the following elements: a description of the organisational structure for the performance of pharmacovigilance activities with a reference to the location of qualification records of the personnel; a summary description of the training concept, including a reference to the location of training files; instructions on critical processes;

(b) a description of the record management system referred to in Article 12, including the location of the documents used for pharmacovigilance activities;