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Subject: **Overview of Member States biennial reports on audits of their pharmacovigilance systems (2013 reporting year)**

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This document is a Health and Food Safety Directorate General document for information purposes. It does not represent an official position of the Commission on this issue, nor does it anticipate such a position.

Contents

1. Introduction and background

All medicinal products for human use have to be authorised either at Member State or Union level before they can be placed on the EU market. They are subject to a strict testing and assessment of their quality, efficacy and safety before being authorised. Once placed on the market they continue to be monitored so as to assure that aspects which could impact the safety profile of a medicine are detected and assessed and that necessary measures are taken.

The legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004[1] with respect to centrally authorised medicinal products and in Directive 2001/83/EC[2] with respect to nationally authorised medicinal products (including those authorised through the mutual recognition and decentralised procedures).

The EU pharmacovigilance legislation was subject to a major review that led to the adoption of new legislation in 2010[3] which was further refined in 2012[4]. New requirements introduced by the pharmacovigilance legislation of 2010 that came into effect in July 2012 constituted the biggest change since the establishment of the centralised procedure in 1995.

The new pharmacovigilance legislation places an obligation on Member States to operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities (Article 101(1) of the Directive 2001/83/EC). The legislation also states that 'Member States shall perform a regular audit of their Pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter' (Article 101(2) of the Directive 2001/83/EC). Also, Article 101(3) of the same Directive specifies that each Member State shall designate a competent authority for the performance of pharmacovigilance tasks. Section 3 of Chapter II of the Commission Implementing Regulation (EU) No 520/2012[5] specifies the minimum requirements for the quality systems of the performance of pharmacovigilance activities by national competent authorities.

On 13 December 2012 the European Medicines Agency (EMA) first published Module IV: Pharmacovigilance audits as part of its Guideline on good pharmacovigilance practices.

This report provides an overview of the audit activities reported by the Member States in relation to their pharmacovigilance system as provided for in the legislation. It provides the first overview of the Member State audits based on a compilation and review of the audits reports submitted by Member States in accordance with Article 101(2) of the Directive 2001/83/EC. It does not provide a detailed description of audit findings.

The national competent authorities who submitted information on their audits activities is given in the Annex. It should be noted that the information provided by the national competent authorities was not directly comparable.

[1] 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 (OJ L 136, 30.4.2004, p. 1)

[2] 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 (OJ L 311, 28.11.2001, p. 67)

[3] Regulation (EU) No 1235/2010 (OJ L 348, 31.12.2010. p 1), Directive 2010/84/EU (OJ L 348, 31.12.2010. p 74)

[4] Regulation (EU) No 1027/2012 (OJ L 316, 14.11.2012. p 38), Directive 2012/26/EU (OJ L 299, 27.10.2012. p 1)

[5] 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

2. Pharmacovigilance Audit Facilitation Group

The Pharmacovigilance Audit Facilitation Group (PAFG) has been set up by the Heads of Medicines Agencies (HMA) to foster a common approach to pharmacovigilance audits related to human medicines performed by national competent authorities and the EMA.

The group is composed of experienced auditors and other experts (e.g. pharmacovigilance) from the national competent authorities, the Pharmacovigilance Risk Assessment Committee (PRAC) and the EMA. It acts as a forum for agreement on common principles and processes to improve harmonisation of the audit approach by undertaking the following:

- providing support and advice to Member States for the implementation of the requirements of the legislation for the performance of audits of their pharmacovigilance systems;
- facilitating pharmacovigilance audit training, continuing professional development and the sharing of best practices;
- establishing, reviewing and refining the common audit methodology and common reporting format.

The PAFG consults and reports to the HMA on all cases where consistent practices are considered to be in the interest of the European Medicines Regulatory Network.

The PAFG prepared a template to facilitate the national competent authorities reporting of their audit activities under Article 101(2) of the Directive 2001/83/EC. The template gave the main elements to be reported but it was not intended to fully harmonise the reporting of the audit activities by the individual national competent authorities.

3. Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action

Beyond the tasks undertaken by the PAFG, several EU-wide and national strategic initiatives covering various areas (e.g. training) are being developed to assess performance and improve the operation of the EU pharmacovigilance systems.

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action[6] is a 3-year initiative funded by the European Commission and Member States that runs from 2013 until 2016. It has been set up to support operation of pharmacovigilance in Europe. The SCOPE Joint Action is developing and will deliver guidance, training in key aspects of pharmacovigilance, and tools and templates to support best practice.

Through this approach the SCOPE Joint Action aims to support consistent approaches in pharmacovigilance operations in the European Medicines Regulatory Network, in particular within its Work Package 7, which will develop common quality standards in pharmacovigilance systems, based on an understanding of EU national systems.

[6] For more information see: http://www.scopejointaction.eu/

4. Pharmacovigilance systems of the Member States

4.1. Overview of the pharmacovigilance systems of the Member States

The operation of the pharmacovigilance systems of the Member States within the European Medicines Regulatory Network relies at national level on competent authorities which coordinate and cooperate with regional pharmacovigilance centres or units, hospitals and healthcare professionals, marketing authorisation holders and patients.

In some national competent authorities, the pharmacovigilance systems are integrated with the quality management system which can be subject to various certifications and accreditations obtained prior to the implementation of the pharmacovigilance legislation.

The integration of the pharmacovigilance system into certified and/or accredited quality management system has facilitated its establishment, development, performance monitoring and early identification and correction of non-conformities. It also contributes to the strengthening of a risk-based system approach considering all interfaces both at national and European levels.

4.2. Audit programmes

According to the Member States' reports, national audit programmes are elaborated on the basis of audit strategies adopted by the Head of Agency and senior managers in each competent authority.

Further to their adoption at senior management level, audit programmes are, in some Member States, circulated to all staff.

Audit strategy and risk assessment
The development of each national competent authority's audit strategy takes account of past audits and on-going implementation of corrective actions, as well as the outcome of a risk assessment exercise. The outcome of the risk assessment is, in a few Member States, sent to the relevant ministry (e.g. Ministry of Health). The strategy supports the prioritisation and the frequency of audits to be performed within the national competent authority.

Risk assessment and audit prioritisation
On the basis of a regular assessment of the risk level accepted by the Head of Agency and senior managers, the national competent authorities adapt the frequency of audits to the level of risk (e.g. perform an audit at least every three years on high risk pharmacovigilance activities, at least every five years on medium risk pharmacovigilance activities and when audit capacity allows for low risk pharmacovigilance activities).

Audits of pharmacovigilance systems and independence of auditors
Member States have reported that the pharmacovigilance systems of their national competent authorities have been audited by internal and/or external auditors that are independent from the pharmacovigilance activities, in accordance with set audit methodology and process.

Reports on audit activities submitted to the European Commission
Across all audit reports submitted by the Member States, the findings have been documented with different levels of detail, for example with respect to the audit scope, findings description and grading of findings as minor, major or critical.

In general, following the completion of all pharmacovigilance audits, the audit reports are

distributed to the management teams for decisions on actions and timeframes prior to being adopted by senior managers.

A wide range of pharmacovigilance activities has been audited. Although, all details about the findings and their grading were not consistently provided across all the Member States audit reports, reference was made to on-going implementation of corrective actions.

4.3. Organisation structure, responsibilities and resources

Organograms
Organisation structures are commonly displayed through nominative organograms which show the hierarchical relationships within an organisation. In general organograms were presented in the Member States reports. Where organograms were not provided the description of hierarchical relationships within the national competent authority and with the relevant ministries (e.g. Ministry of Health) were generally less easy to understand. For transparency at national level, some Member States have reported that they publish their organograms on the website of the competent authority.

Organisational structure and decision-making
Organisational structures across the European Medicines Regulatory Network have been described in many ways, varying from matrix to more vertical organisations. A short description of the decision-making from pharmacovigilance assessors to national technical scientific committees was sometimes provided.

Description of responsibilities
The responsibilities of the competent authorities are commonly captured in mission statements and mandates while responsibilities of individuals are outlined in job descriptions, internal guidelines and procedures. For transparency at national level, the organograms, mission statements, mandates and job descriptions are sometimes published on the website of the competent authority.

Management of human resources
The implementation and operation of pharmacovigilance systems that comply with EU and national legislative requirements have an impact on resource needs. Where possible, the effective implementation and operation have led to recruitment of additional personnel in various roles (e.g. pharmacovigilance assessors, administrative support, experts for technical committees). Some Member States have referred to a recruitment process which is fully documented to support the hiring of personnel with adequate qualification and training.

Further to an assessment of workload and need for competence, the adequate level of resources is fulfilled through request of new staff or re-allocation of existing staff. Some agencies have promoted mechanisms for collaboration and cooperation to allow staff with specific expertise (e.g. medication errors) to support pharmacovigilance activities. In other agencies, all pharmacovigilance personnel receive the same training and qualifications in order to ensure the continuity of pharmacovigilance activities in case of absence.

Funding
The overall funding model is similar across the national competent authorities, based on fees from the pharmaceutical industry and contribution from national governments. The proportion between the different components varies between Member States.

4.4. Training

Training and personal development commonly constitute a way to gain new skills and improve the expertise, competence and knowledge of staff and experts involved in pharmacovigilance tasks.

Overall, the organisation of activities related to training and personal development in the Member States follows a structured set of common principles. However, in some instances an informal approach to training and personal development has been reported. The lack of overarching training strategy can sometimes lead staff members to attend trainings on an *ad-hoc* basis rather than on the basis of identified training needs. Although it has not been mentioned by all Member States, any training undertaken by pharmacovigilance staff and experts should be recorded.

In some competent authorities, some staff involved in pharmacovigilance tasks is unable to attend training due to limited training budget. In order to avoid this, some national competent authorities have suggested that there should be an optimisation of the training and exploration of cost-efficient training mechanisms across the European Medicines Regulatory Network. The need for specific training on data management, including data quality, integrity and record management, has been raised by some Member States.

Training needs and training plans
Some agencies have reported that the training needs are defined at senior management level, in line with the strategy, objectives and budget of the organisation. Those training needs are then translated into departmental and individual training plans which include measurable training objectives. Individual training plans are established during the annual appraisal of staff.

Mandatory introductory training and continuous training
In all Member States, every new staff member receives a mandatory introductory training while exiting staff undertake continuous training. Across the Member States there is a wide range of training scope (e.g. science, regulatory affairs) and means (e.g. webinars, lectures). Some Member States have mentioned specific training frameworks which involve mentors or tutors linked to specific job profiles. In various Member States trainings are documented, recorded and their effectiveness is assessed annually.

In a couple of Member States, it has been suggested by the auditors to review the duration of the mandatory introductory training in order to foster rapid and flexible availability of human resources.

4.5. Facilities and equipment

Member States have overall reported adequate facilities, including building, storage rooms and office space as well as appropriate information technology (IT) equipment (e.g. computers, servers, applications) to support the effective performance of pharmacovigilance activities.

Across all the agencies, the access to the buildings is overall secured and includes different level of secured access for specific premises (e.g. archives, laboratories). Access to the IT systems is also controlled and secured.

4.6. Compliance management

Compliance management is achieved through various activities which encompass regular management and quality reviews. It relies on compliance with EU and national legislative

requirements, good pharmacovigilance practice (GVP) and relevant guidelines and policies, as well as any relevant quality documentation.

Member States have overall reported the existence of appropriate resources and tools to support compliance management of their pharmacovigilance systems, some explained implementation of their code of conduct. Some Member States mentioned their whistle-blowing procedures. Some audits highlighted opportunities for improvements (e.g. improved data quality and integrity, increased workflow automation, further transparency) to enhance compliance management.

Several Member States have described their compliance management system relying on quality objectives pre-set at senior management level, monitoring of compliance through quality controls and review of performance measures, documentation and analysis of deviations and implementation of corrective actions.

4.7. Record management

Objectives and characteristics of record management system

Record management systems are maintained across all competent authorities to handle data, information and documents used for pharmacovigilance activities with the aim to achieve traceability, version control, consistency and retrievability.

In line with requirements linked to personal data protection and other relevant legislation, the description of the record management system often specifies for every record the retention time, storage location, secured and timely access, system to safeguard integrity in case of physical disaster, regular (e.g. daily, weekly) back-up, disposal and provision of record upon external request.

The functioning of the record management system is described in general procedures. This has been reported to sometimes lead to unclear responsibilities for record management, as well as inconsistent practices between pharmacovigilance assessors.

In some agencies, every incoming document is assigned a unique identifier. The record management procedures are often supported by the use of templates and automated document workflow with control of timelines.

Some Member States have a certified record management system in place.

4.8. Documentation of the quality system

The national competent authorities reported that the quality system for pharmacovigilance activities is described in various documents. However, the hierarchy between documents describing the quality system and their lifecycle management are not always clearly described across all Member States reports. This sometimes impedes the consistency and alignment across quality documents.

Overall, when specified, the hierarchy of quality system documents refers to EU and national legislations, good pharmacovigilance practice (GVP) and relevant guidelines, overarching quality manual (sometimes referred to as quality handbook), standard operating procedures (SOPs) (sometimes grouped by categories), working instructions, process charts, decision chains, lists and decision logs.

Some agencies also make reference to additional quality documents such as communication

policy, IT and business management regulation.

Quality manual
In general, the competent authorities reported that their quality manual outlines all pharmacovigilance processes, interfaces and responsibilities.

Overall management and maintenance of quality documents
Most agencies reported that the documents related to the quality system are signed off by the Head of Agency directly or by delegation of signature before they can be accessed electronically by all staff. Regular information sessions and trainings on quality documents are also arranged for all staff on a regular basis.

The update of all documents related to the quality system takes account of non-conformance, improvement plans and outcome of risk assessment.

4.9. Business continuity arrangements

Although all competent authorities have arrangements in place for business continuity and crisis managements, some have underlined the need to further develop and implement planning and tools.

Business continuity and crisis management plans
The business continuity and crisis management plans are mainly based on the definition of critical processes and include reference to safety communications, distant working location, escalation process and decision matrix in case of system failure, regular data back-up and disaster recovery plan.

The continuous update of business continuity and crisis management plans takes account of lessons learnt and outcome of simulation exercises and drills used to test the plans. These plans also cover the contact points (e.g. 'out of hours') and the governance (e.g. crisis management group) to adhere to in case of business continuity and crisis situation. The plans often outline the activities of the national competent authorities in relation to their involvement in the Incident Review Network (IRN) and the management of rapid alerts and non-urgent information.

Some agencies have signed a memorandum of understanding with other agencies to guarantee to secured mutual exchange of information in case of crisis or business continuity situations.

4.10. Monitoring of performance and effectiveness

National competent authorities have overall reported having adequate tools and mechanisms to monitor the performance and effectiveness of their pharmacovigilance systems. This monitoring relies on targets and objectives pre-set by senior management and cascaded down to all staff through annual appraisal. This top-down approach ensures that individual performance objectives are linked to the objectives of their department and the overall organisation.

The principles and processes for monitoring performance and effectiveness are often referred to in the quality manual and dedicated SOPs.

Quantitative and qualitative performance measures such as performance indicators and key performance indicators are reassessed annually on the basis of inputs, outputs, metrics and outcomes of the pharmacovigilance system.

Although most performance and effectiveness reports are submitted quarterly to senior management, some agencies have developed a scorecard framework allowing the provision of monthly dashboards.

The process for monitoring the performance and effectiveness is subject to continuous review and improvement through management reviews, audits, external assessment, enquiries management, complaints management and customer satisfaction survey.

In some cases, it has been highlighted that there is a need to further define additional performance measures as well as to increase the frequency of the planning/reporting cycle to enhance the early identification of deviations and accelerate the implementation of corrective actions.

For greater transparency, the agencies publish the relevant information on the performance and effectiveness in their annual reports.

5. Overview of audits

All Member States submitted reports or information with respect to their audit activities since the application of the new pharmacovigilance legislation in July 2012. Most competent authorities reported on their activities up to September 2013, the month in which the reports were due for submission to the Commission. Seven national competent authorities also included information on their audit activities prior to July 2012 in their report. Two smaller Member States reported that no audits had been completed during the reporting period, one of which mentioned that audits were planned to take place in the months following the submission of the report.

Where audit reports had been completed, the national competent authorities reported between 1 and 18 audits having been undertaken. The level of detail given about the scope of the audits varied between the individual reports. In some Member States there were audits of their pharmacovigilance system overall whilst others had audited specific activities within the system.

Some of the national competent authorities gave information on the audit outcomes in terms of the number of areas where there was need for improvement and the grading of the identified audit outcome. The majority of the audit outcomes were graded as "major" with a few considered "critical". Except for one audit which was completed at the end of the reporting period in September 2013, where communicated, follow up action had been implemented or was in progress.

6. Summary

The Member States were obliged to submit reports on the results of the audits of their pharmacovigilance system for the first time in 2013. This document provides an overview of the reports submitted.

In July 2012 the new pharmacovigilance legislation became applicable and the new systems and procedures were being implemented by the Member States. The reporting period covered a period of transition during which the EMA good pharmacovigilance practices on certain pharmacovigilance related activities, including audits, became available. The Member States plan the audit of their pharmacovigilance system according to a risk assessment of the various activities.

All Member States indicated whether audits had been completed between July 2012 and September 2013 and submitted information on the audits that had been completed during that

period or other identified period. Areas for improvement were identified in some of the audits. There were a few critical findings and several major findings. Where information was provided, in nearly all cases follow up actions had been implemented or were in progress.

The Member States submitted the reports in a timely fashion. The preparation of a template by the Pharmacovigilance Audit Facilitation Group of the Heads of Medicines Agency to provide the basic structure of the reports meant that, in general, the main issues were covered by the individual reports. For future reports it could be explored if, in cases where an individual audit covers more than one pharmacovigilance activity, more information on the specific areas that were audited should be identified.

The submitted reports provided an initial view of the audits of the pharmacovigilance systems of the Member States. The next reports should summarise the follow up to audit outcomes identified in the previous reporting period. The Member States are due to submit the next reports by September 2015.

ANNEX

The following designated competent authorities submitted information on their audit activities to the European Commission.

Member State	Competent Authorities
Belgium (BE)	Federal Agency for Medicines and Health Products
Bulgaria (BG)	Bulgarian Drug Agency
Czech Republic (CZ)	State Institute for Drug Control
Denmark (DK)	Danish Health and Medicines Authority
Germany (DE)	- Federal Institute for Drugs and Medical Devices - Paul-Ehrlich-Institute, Federal Institute for Vaccines and Biomedicines
Estonia (EE)	State Agency of Medicines
Ireland (IE)	Irish Medicines Board
Greece (EL)	National Organization for Medicines
Spain (ES)	Spanish Agency for Medicines and Medical Devices
France (FR)	National Agency for the Safety of Medicines and Health Products
Croatia (HR)	Agency for Medicinal Products and Medical Devices of Croatia
Italy (IT)	Italian Medicines Agency
Cyprus (CY)	Pharmaceutical Services, Ministry of Health
Latvia (LV)	State Agency of Medicines
Lithuania (LT)	State Medicines Control Agency
Luxembourg (LU)	Ministry of Health
Hungary (HU)	National Institute for Quality and Organisational Development in Healthcare and Medicines, Directorate: National Institute of Pharmacy
Malta (MT)	Medicines Authority
Netherlands (NL)	- Medicines Evaluation Board - Netherlands Pharmacovigilance Centre Lareb
Austria (AT)	Austrian Medicines and Medical Devices Agency
Poland (PL)	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal (PT)	National Authority of Medicines and Health Products
Romania (RO)	National Agency for Medicines and Medical Devices
Slovenia (SI)	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Slovakia (SK)	State Institute for Drug Control
Finland (FI)	Finnish Medicines Agency
Sweden (SE)	Medical Products Agency
United Kingdom (UK)	Medicines and Healthcare Products Regulatory Agency

In addition the Norwegian Medicines Agency (NO) submitted a report on its pharmacovigilance audits.