SCOPE Work Package 7
Quality Management Systems

Exchange of Information between PV Assessors and PV Inspectors: Best Practice Guidance

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SCOPE

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Contents

Acknowledgments

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide practical guidance on how National Competent Authorities (NCAs) who have separate departments or teams for the conduct of pharmacovigilance assessment and inspections can effectively exchange information within their NCA to maintain a high level of public health protection. This paper has been developed and approved by all Work Package (WP) 7 active partners (BG, ES, HU, IT, PT and UK).

1.2 Definitions and abbreviations

Terminology	Description
AR	Assessment Report
ADR	Adverse Drug Reaction
AIFA	Italian Medicines Agency
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
DCP	Decentralised Procedure
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EPITT	European Pharmacovigilance Issues Tracking Tool
EVDAS	EudraVigilance Data Analysis System
GVP	Guideline on Good Pharmacovigilance Practices
HALMED	Agency for Medicinal products and Medical Devices (HR)
HCP	Healthcare Professionals
ICSR	Individual Case Safety Report
IAG	Inspection Action Group
IT	Information Technology
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency (UK)

Terminology	Description
MRP	Mutual Recognition Procedures
MS	Member State
NCA	National Competent Authority
RSI	Reference Safety Information
PIL	Patient Information Leaflet
PV	Pharmacovigilance
PSUR	Periodic Safety Update Report
PASS	Post-authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person Responsible for Pharmacovigilance
QMS	Quality Management System
RMP	Risk Management Plan
RMS	Reference Member State
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
WP	Work Package
VRMM	Vigilance and Risk Management of Medicines

1.3 Preamble

Sharing information between inspectors and pharmacovigilance (PV) assessors within the same National Competent Authority (NCA) is essential for ensuring the successful prioritisation of inspections and a more comprehensive fulfilment of the responsibilities for facilitating compliance. Recognising that NCAs have limited resources, the aim of this topic is to elucidate what information should be shared between PV assessors and inspectors and the methods by which this information is shared to maintain a high level of public health protection. Using this information, areas of good practice will be presented together with a series of recommendations to facilitate information sharing between inspectors and PV assessors.

The overall quality objectives for PV include promoting the safe and effective use of medicinal products and contributing to the protection of public health through strengthened vigilance. The objectives of PV inspections as defined in the Guideline for Good Pharmacovigilance Practices (GVP) Module III include to *'determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations'* and to *'identify, record and address non-compliance which may pose a risk to public health.'* Furthermore, the GVP Module III states the *'sharing of information and communication between inspectors and assessors is important to ensure successful prioritisation and targeting of these inspections'* and that this is critical for the proper follow-up of inspections and provision of recommendations on actions to be taken in relation to issues of EU interest.

1.4 Background

The European Union's (EU's) PV legislation[1] that came into force in 2012 aimed to further strengthen the protection of public health through more clearly defined roles and responsibilities of Marketing Authorisation Holders (MAHs) and NCAs with respect to PV systems, more focus on proactive and risk proportionate safety monitoring and robust and timely decision making. Consequently, implementation of the legislation has required many changes to procedures and processes at both a European and national level. The quality of the PV inspection process is covered by the NCA's PV systems and their quality systems.

As highlighted in the Strengthening Collaboration of Pharmacovigilance in Europe (SCOPE) Joint Action survey report for Work Package (WP) 7 on interactions between PV assessors and inspectors, the majority of the NCA respondents have separate inspection departments from PV operations departments. Information sharing can be both routine or in reaction to a specific trigger. The results of the survey showed that, in general, NCAs have at least informal processes in place to cover instances where significant non-compliance is identified, either via assessment or inspection activities. However, less formal, or no process at all, existed for routine ongoing exchange of information. This information may not represent an urgent need for an inspection or corrective action, but can be useful for the planning and conduct of inspections and can be valuable to inform the understanding of information submitted by the MAH.

[1] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 onthe 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

1.4.1 SCOPE project

The SCOPE Joint Action was created to help NCAs comply with the new PV legislation in all aspects. WP7 of the SCOPE project tackled Quality Management Systems (QMSs) in European Member States (MSs), using surveys to collect data on how NCAs manage the quality of their PV operations (Annex 1). This topic within WP7 aims specifically at the exchange of information between PV assessors and inspectors.

The SCOPE survey report on this topic highlighted the importance of the sharing of information between PV departments and inspectors. As part of the SCOPE survey, MSs were asked to identify good practice and any particular challenges they faced. In response to this, MSs stated that the logistics of sharing of information may be difficult especially when it is unclear what information would be useful or necessary for either department. As a result, either too much information is exchanged which can overburden both sides, or not enough. Capacity and workload were highlighted by a number of NCAs and that the Information Technology (IT) systems to facilitate the exchange of information could be optimised. Collaborative approaches were considered as good practice such as joint training initiatives and joint inspections. Some MSs noted the benefits of combined roles, either an assessor also being a PV inspector, or some shared role also enabled collaboration. In addition, many NCAs highlighted the importance of involving assessors in circumstances where product specific expertise is required, where inspection outcomes require referral to the Pharmacovigilance Risk Assessment Committee (PRAC), or other critical findings leading to the potential for enforcement action.

1.4.2 SCOPE guidance document

As part of the WP7 deliverables, a toolkit has been developed to include this guidance document, which presents examples of good practice across Europe, and aims to help NCAs optimise their processes and where possible to overcome their major challenges. This document aims to provide recommendations on the information that could be shared between PV departments and inspectors, to ensure that inspection resources are used in an efficient way in the scheduling and conduct of inspections. In addition, examples of good practice are highlighted on how to make accessible information on MAH non-compliance to both PV assessors and inspectors, reducing the burden of repeated requests for information.

While job descriptions and responsibilities associated with a PV assessor and PV inspector may differ, the legislative framework that governs these applies to both sets of activities. This document is intended to provide examples of good practice in how an NCA can implement joint training opportunities for PV assessors and inspectors. These training initiatives will allow for the consistent understanding of the key concepts of good PV practice, as well as making efficient use of time and resource in the coordinated delivery of training. Joint training initiatives can also provide mutual benefit from sharing knowledge and experience. It is acknowledged that job specific training will still be required for both PV assessors and inspectors and the good practices described in this document refer to areas where training topics could be shared.

Guiding principles will be presented in this document, together with NCA case studies and the results from the SCOPE survey. It should be noted that the implementation of these recommendations is not mandatory, and that the aim is to provide NCAs with practical advice on how they can enhance information sharing within their organisations. This guide aims to present feasible guidance and recommendations for applicability across all NCAs in Europe. However, WP7 recognises that NCAs may only reference guidance that is appropriate within their current systems. The WP7 outputs provide ideas and suggestions for NCAs to optimise quality management, and comply with PV legislation, within their own means.

2. Recommendations for the exchange of information between PV departments and PV inspectors

Key points

- Information that can be considered when preparing the inspection programme includes marketing authorisation status, MAH compliance with regulatory submissions, product-specific concerns raised by PV departments, intelligence, information from other regulators and inspection outcomes from other GXPs.
- If inspection findings have the potential to impact the benefit-risk profile of a product, recommendations for interactions should be in accordance with the 'Union procedure on the management of PV inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products'.
- Access for PV assessors to the repository in which all inspection reports produced by the NCA are stored is recommended.
- Dedicated inspection review groups within NCAs could communicate feedback on significant inspection outcomes to other relevant departments of the NCA.

Interactions and exchanges of information between PV departments and inspectors can take place both pre- and post-inspection. This can be on an ongoing basis, as and when the information becomes available, or in response to a specific request. Identifying efficient mechanisms for the sharing of information may help to reduce the resource burden of information sharing, and the different mechanisms are explored within this section. Nevertheless, it is acknowledged that there are differences in the maturity of PV systems across the network and that this should be taken into account by NCAs to identify the most appropriate mechanisms for information sharing within their organisations.

2.1 Recommendation 1: Pre-inspection interactions (assessors to PV inspectors)

PV departments have access to a lot of information regarding a MAH. This information can be helpful to inspectors in relation to the following activities:

- The scheduling of PV inspections, for example, information regarding MAH compliance with regulatory submissions (Individual Case Safety Reports (ICSRs), Periodic Safety Update Reports (PSURs), safety variations) may feed into the risk assessment performed to prioritise inspections.
- Determining the scope of PV inspections, for example, awareness of non-compliance detected by PV departments can help focus the topic areas that are reviewed during a specific inspection.
- Determining whether additional product specific expertise would be required as part of the inspection. For example, participation of an assessor in an inspection.

Assessors could actively communicate the following issues when detected during their day-to-day assessment activities: issues with MAH's delays/failure to notify NCAs with regulatory measures taken for safety reasons in other countries, failure to provide PV data to competent authorities or the Agency which may impact ongoing safety assessments, failure to notify NCA for temporary suspension/shortage of provision, information for communication of PV concerns to the public without prior notification to NCA or complaints/quality problems not adequately addressed.

The following information can be considered for sharing when preparing inspection schedules.

2.1.1 Marketing Authorisation (MA) status

Information on MAHs with no previous Marketing Authorisations (MAs); the number of MAs according to authorisation procedure and legal status; newly authorised products and/or recent variations (for verification of compliance with Article 57(2) of Regulation (EC) No 726/2004); MAs subject to additional monitoring; products withdrawn for safety reasons; products with safety restrictions, products associated with additional risk-minimisation activities or products formally referred to PRAC for safety reasons.

Significant changes in the organisation, such as mergers and acquisitions, and MAHs that have acquired MAs by change of ownership procedures are important for inspectors, namely in the assessment of the integration of the new MAs in the current Pharmacovigilance System Master File (PSMF) and the maintenance and access to the old PSMF and related medicine safety data.

It should be noted that information regarding MA status may not always be under the ownership of PV departments, and may need to be sourced from other parts of the NCA or via the EU Network (for example via the Article 57 database).

2.1.2 Regulatory submission compliance: Individual Case Safety Reports (ICSRs)

It is important to communicate information concerning repeated submissions after the required deadlines and compliance with the 15 and 90 day reporting for Individual Case Safety Reports (ICSRs).

The quality of data in the regulatory submissions relating to drug safety is a leading principle across the EU, any information and comments from PV assessors regarding repeated poor quality submissions towards standards, formats, terminology, content or translations, should also be communicated to the inspectors. Quality requirements for PV processes are specified in the relevant GVP modules e.g. the data quality of ICSRs transmitted electronically in the GVP Module VI.

In addition, the volumes of ICRSs submitted by the MAH (especially when underreporting is suspected) and where available information regarding instances of lack of follow-up (especially reports of drug exposure during pregnancy and lack of therapeutic efficacy) is recommended to be made available to the inspectors, particularly if their access to the EudraVigilance database or local NCA databases is limited.

2.1.3 Regulatory submission compliance: Periodic Safety Update Reports (PSURs), Risk Management plans (RMPs)

For periodic submissions (PSURs, Risk Management Plans (RMPs)), it is important to communicate non-compliance identified in the assessment process, such as failures to fully address Assessment Report (AR) comments, erroneous evaluation of ICSRs and literature articles, or inadequate discussion of issues of concern, or inappropriate criteria for judging the success of the proposed risk minimisation measures. Submission of incomplete documents and/or falsified information, or failure to submit requested documents could be of use for the PV inspectors.

2.1.4 Ongoing safety monitoring: Information on signals and referrals

As stated in the legislation MAHs should continuously monitor the safety of their medicinal products and inform the authorities of any changes that might have an impact on the risk-benefit balance of the product. Information regarding any validated signals or emerging safety issues, both identified by NCAs or by the MAH and reported to NCAs, should be considered for communication to inspectors. Additionally evidence for MAH failures to communicate new safety issues in a prompt manner or omission to include information from all relevant sources should also be shared.

2.1.5 Reference Safety Information (RSI): Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL)

With regards to the MAH requirement to keep product information up-to-date; data in relation to repeated failures and/or delays in submitting variations to update the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) or failures in addressing NCA's or the PRAC's recommendations if considered appropriate for examination through an inspection should be shared with the inspectors department.

2.2 Recommendation 2: Post-Inspection interactions (PV inspectors to assessors)

Following the conduct of an inspection, if findings have been identified that have the potential to impact the benefit-risk profile of a product, recommendations for interaction with PV assessors and PRAC representatives to discuss implications are described in the "Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products". Impact on robustness of the product(s) benefit-risk profile(s) in this case is considered to refer not only to cases where the benefit-risk profile itself might be altered, but also to cases where deficiencies in the PV system may have occurred with potential to impact the safety profile of the MAHs authorised product. For example, a failure to update risk-minimisation measures and/or failure to communicate safety information to healthcare professionals (HCPs) and patients.

In practice the proportion of inspections that report significant failings that require to be referred to PRAC is small. To date, the total number of inspections that have been referred to PRAC is seven. It should be noted that in accordance with *'Union procedure on the management of pharmacovigilance inspections findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products'*, that *'inspection findings have been identified with potential to impact on the benefit-risk profile of the concerned product, the lead inspector should contact the PRAC representative of their own MS to discuss the safety implications and next steps. In order for inspectors and assessors to determine whether PRAC escalation may be appropriate, the inspection findings should be placed in context of their potential public health impact'*.

It is recommended that information on all inspection outcomes is made available to PV assessors. For example, information on the following findings may be useful to assessors when performing benefit-risk assessments of a product; violation of the provisions regarding the recording and reporting of ICSRs, such as lack of submission, incorrect seriousness assessments, incorrect coding; inadequate literature searches, and inclusion of literature cases in the safety database and submission; signal analysis performed by the MAH was not in accordance with the provisions, failure to implement necessary actions identified in the signal management process.

PV assessors should be made aware of any reasons that lead to an inspection being terminated. The termination of an inspection is rare and should be communicated to assessors either:

- Promptly, if the inspection was terminated due to product specific issues
- At routine meetings, if the inspection had been terminated due to failure to provide documents and logistical issues etc.

Additionally as part of a renewal application, MAHs are required to provide information on regulatory inspections that had been performed and their outcome. By making inspection outcomes available to assessors responsible for these assessments, they will be able to corroborate this information and confirm the correct reporting by the MAH.

The simplest way to ensure that assessors are able to routinely access inspection outcomes is to allow access to inspection reports. This can be achieved via the following mechanisms:

- Enable assessors within the PV department access to the repository in which all inspection reports produced by the NCA are stored, so that they are able to access this information when needed. Such repositories could include a folder on a shared drive, or a folder within a formal electronic document management system (see Section 3).
- If access to shared systems is not possible PV departments can be alerted to the issue of new inspection reports via email or during regular meetings.

Case Study 1

The Medicines and Healthcare products Regulatory Agency (MHRA), UK

- At the MHRA, post-inspection actions following a PV inspection can involve internal communication to other groups and divisions which may include other GXP inspectors, Defective Medicines Report Centre, Enforcement Group, Intelligence Unit, Vigilance and Risk Management of Medicines (VRMM) division, Clinical Trials Unit, MHRA Licensing and MHRA Communications divisions depending on the nature and seriousness of the finding(s). GXP refers to all of the Inspectorate Technical Groups.
- Critical inspection findings will be referred to the MHRA Inspection Action Group (IAG) 2, which is an independent, non-statutory, multi-disciplinary group, and membership includes pharmacovigilance inspectors, regulatory specialists and pharmacovigilance scientific and medical assessors. The group is chaired by an independent secretariat.
- Upon receipt of a referral, IAG 2 provides advice to divisional directors on any recommendations for referral or enforcement action that arise from non-compliance detected during inspections, specifically where the non-compliance represents a serious breach of legislation or could affect public health or the rights, safety or well-being of patients.
- Post-inspection actions available to MHRA include hosting a meeting with the MAH to discuss appropriate corrective and preventative actions (CAPA), requesting periodic updates on the implementation of CAPA, early re-inspection (within 12-18 months), issuing an Infringement Notice, which is a statutory notice that specifies the steps that the MAH must take and in what timeframe, actions taken in relation to marketing authorisations and, in extreme cases, referral for criminal prosecution.
- The IAG 2 meets on a monthly basis and provides an opportunity to rapidly communicate information on significant inspection outcomes to other relevant parts of the agency and to agree any post-inspection actions that need to be completed.

3. Best practice in accessibility and sharing information between PV departments and PV inspectors

Key points

- A checklist for information sharing can be used to aid both inspection and assessment activities and to identify process improvements
- Routine access for PV inspectors to IT systems is recommended, for example access to NCA adverse drug reaction (ADR) database, Article 57 database
- Create an information system to track MAH non-compliance e.g. a spreadsheet on a shared drive or store information on MAH non-compliance in a risk-based inspection database to prioritise inspection scheduling
- Exchange of information can take place through routine/ad hoc meetings between inspectors and PV departments
- PV departments should consider risk based factors described in GVP Module III when deciding whether it may be appropriate to request a PV inspection. Templates can be used for the request of PV inspections by PV departments.

3.1 Recommendation 3: Determine what information is available how to retrieve it

As described in the introduction the amount of information held by a NCA may differ depending on the nature and maturity of the PV system that they operate. Therefore, before a NCA begins to implement new procedures to exchange information, it is recommended to determine what information is available within the NCA and how that information can be accessed. The NCA will then be able to identify where there may be gaps, and implement actions to extend access (for example, if information regarding MA status is recorded within the NCA, access to the system could be opened up to inspectors).

Annex 1 (checklist for information sharing) summarises the types of information that could be available within the NCA and an example of an assessment. The aim is to aid both inspection and assessment activities, focusing on how to improve processes within NCAs. The type of information ranges from MA status, compliance information and quality of regulatory submissions, ongoing safety issues, risk-minimisation measures, urgent safety restrictions and inspection outcomes.

3.2 Recommendation 4: Routine access to IT systems

At the NCA and EU level there are IT systems that hold information which is important and useful to PV inspectors and assessors. While inspectors may not populate these systems as part of their day-to-day job, allowing routine 'read only' access to these systems can enable inspectors to source the information they need, rather than make specific requests to PV departments each time information is required. Examples of such systems include:

- Access to NCA ADR databases (where applicable) to retrieve 15 and 90 day reporting compliance, and to identify individual cases
- Access to NCA tracking systems to collect information on MA status, including information on any submitted safety variations
- Access to the EudraVigilance database via the EudraVigilance Data Analysis System (EVDAS) to retrieve 15 and 90 day reporting compliance and to identify individual cases
- Access to the European Pharmacovigilance Issues Tracking Tool (EPITT) to retrieve information on any product specific signals and safety alerts
- Access to the Article 57 database to retrieve information on the MAH including location of the PSMF and associated Qualified Person for Pharmacovigilance (QPPV)
- PSUR Repository.

3.3 Recommendation 5: Tools to track MAH non-compliance

To ensure the maximum sharing of information and communication between PV assessors and inspectors it is useful to have in place a common repository stored in a shared folder or common area. The common repository could be used to store any information regarding MAH non-compliance that could be used by PV assessors and inspectors in their routine job. In its simplest form the common repository can take the form of an excel spreadsheet, or other form of tracking table. This table can be populated by PV personnel who identify instances of MAH non-compliance in the course of their day-to-day job.

Case Study 2

The Agency for Medicinal products and Medical Devices (HALMED) of Croatia

- HALMED has implemented a shared tracking document used jointly by PV assessors and inspectors to track cases of MAH non-compliance.
- Procedures for tracking MAH compliance and completion of the spreadsheet are documented in a Standard Operating Procedure (SOP).
- The spreadsheet is stored in a shared folder with access by both departments (PV and inspections).
- The data fields that are collected are presented in Annex 2, including details of the identified MAH non-compliance, an estimated priority and information on corrective actions and regulatory actions. The data in the spreadsheet is entered by both assessors and inspectors.
- The spreadsheet is taken into account by inspectors both for creating and revising the annual plan of PV, and for assessing the need for triggered inspections, in collaboration with PV inspectors. The departments hold regular monthly joint meetings where the observed MAH non-compliance is discussed.

Case Study 3

The Medicines and Healthcare products Regulatory Agency (MHRA), UK

- The MHRA has in place a risk-based inspection database where information on MAH inspection history, risk factors and incidences of non-compliance are stored. Some of this risk information is loaded automatically into the database (e.g. past inspection history) other information is entered and graded manually.
- When an instance of non-compliance is identified by the PV department, this is emailed to a dedicated email address that is monitored by the inspection personnel. The non-compliance is then entered into the database and graded according to perceived risk.
- On a monthly basis a bespoke statistical engine builds a state-space model based on all data available within the database. This model is used to calculate a risk score per PV system. The risk score can be expressed as a percentage where 100% is the average risk across all PV systems in the inspection universe and individual PV systems typically vary between approximately 20% low risk and 250 % very high risk.
- PV systems with the highest overall risk scores are selected for inspection and there is automated distribution of email alerts for PV system whose risk is seen to be increasing significantly relative to the previous risk calculations
- In addition to contributing to MAH risk scores, records in the database can be searched and accessed by inspectors to aid with inspection preparation.

3.4 Recommendation 6: Routine/ad hoc meetings

Exchange of information can take place through routine meetings between PV inspectors and PV departments. Examples given as part of the SCOPE survey included director and section manager meetings, and ad hoc meetings, triggered to discuss significant or critical findings identified during an inspection. The frequency of routine meetings differed between NCAs, with some taking place every two weeks, others on a monthly or quarterly basis. Additionally in instances where staff within PV departments have contributed significantly to an inspection, a meeting between the two departments can be used to feedback the overall results of the inspection and discuss any post-inspection actions. The following topics could be considered for discussion in routine periodic meetings:

- The inspection schedule: oversight for the PV department of why MAHs have been selected for inspection and an opportunity to decide whether assessor input would be required.
- Inspections performed: discussion of inspections that have been performed and any significant inspection findings, including practicability of the proposed corrective and preventative actions towards terms for completion or adequacy. Any intentions for follow-up such as short term re-inspection or reports for progress of the implementation of proposed CAPA.
- Communications received from MAHs: exchange of information of MAH self-reported issues, reported to either the PV department or inspectors.
- Technical topics: opportunity to share training experiences or discussion of hot topics, emerging new guidance (see good practice for the training of PV assessors and inspectors).

Case Study 4

The Medicines and Healthcare products Regulatory Agency (MHRA), UK

- The MHRA hold quarterly meetings between the Vigilance and Risk Management of Medicines division (VRMM) (responsible for the conduct of PV operations within the Agency) and the Inspection, Enforcement and Standards Division (I, E and S) (responsible for the conduct of PV inspections).
- There is a standard agenda for each meeting which includes the following items: team updates, updates on issues arising from inspections and requests for inspections.
- Ad-hoc agenda items also provide the opportunity to discuss specific technical topics and other emerging operational matters.
- A report is compiled in preparation for this meeting with information regarding MAH compliance with ICSRs reporting. The report highlights overall reporting figures, with relevant news and updates that have been communicated to the VRMM division. A template of the report is presented in Annex 3.
- The minutes of the meetings are accessible to both assessors and inspectors.

Case Study 5

The Italian Medicines Agency (AIFA)

- AIFA has in place an agreement between PV assessors and PV inspectors.
- The agreed documents cover the practical management of:
- Sharing of information including how to request a PV inspection and how to request information, for example in relation to the management of PSURs, ICSRs, and risk-benefit balance.
- Transmitting inspection reports and communication of critical and/or major findings.
- Define areas where assessors and inspectors can participate in common training.

3.5 Recommendation 7: Procedure to request a PV inspection

There may be scenarios where the PV department identifies concerns or critical issues during their assessment work for example in relation to PSURs, evaluation of safety issues or in the management of ADR reports. As a result the department may consider it appropriate to request a PV inspection.

In addition, in the context of a new MA procedure, if during the evaluation of an application the quality/clinical assessors raise critical issues pertaining to PV aspects, it can be considered appropriate to request a PV inspection. The guidance below describes some practical steps for NCA PV departments to consider when requesting a specific inspection.

The procedure used by the assessors to request an inspection can depend on the regulatory procedure. For national applications and Mutual Recognition Procedures (MRP)/Decentralised Procedure (DCP) with the agency acting as Reference Member State (RMS), the request is handled within the agency.

For MRP/DCP with the Agency acting as Concerned Member State (CMS) the request can be raised during the EU procedure and the need for and timing of an inspection is agreed with the RMS.

For centralised procedures when the Rapporteur's team deems as appropriate to request a PV inspection, "for cause" inspections will be adopted by the Committee for Medicinal Products for Human Use (CHMP) in accordance with the "Union procedure on the coordination of EU PV inspections".

The need for a PV inspection can be raised by any department within the NCA. The request can be done in accordance with a template (Annex 4) or a PV inspection request.

Case Study 6

The Italian Medicines Agency (AIFA)

- AIFA has in place a procedure to request a PV inspection, with a structured process documented in SOPs. An example of a template is included in Annex 4– 'Example of template to request a PV inspection'.
- In line with the SOP, the request from the PV department should clarify the reason for inspection. Section III.B.1.2 of the GVP Module III on PV inspections outlines the triggers that may result in raising a request for a "for cause" inspection.
- Following the request for an inspection, the PV inspection department communicates the possible acceptance/denial with an official note, timelines and whether to involve an assessor in the inspection.
- Once the inspection is performed, its outcomes (inspection reports and communication of critical/major findings) are communicated to the concerned Department/Office that originally raised the need to conduct the inspection and also the PV department as appropriate.
- In addition the concerned departments within AIFA are kept informed in case the grading of any deviation or finding identified during the inspection changes as consequence of the CAPA plan provided by the MAH.

4. Technical training in relation to PV topics

Key points

- Joint initiatives in relation to training in technical topics can support consistent understanding of the key concepts of GVP. For example implementing training covering PV legislation requirements as set out in GVP modules or a rolling programme of training presentations covering the core PV areas.
- Joint inspections are recommended, for example when there is a product-specific element or objective to an inspection
- Shadowing of a PV assessor or inspector can offer development opportunities.

A basic understanding of the requirements described in PV legislation and guidance is required for both assessor and inspector roles. Therefore there is opportunity for developing joint initiatives in relation to training in technical topics.

4.1 Recommendation 8: Identification of common areas of training

To prevent the duplication in the production of training materials and/or delivery of training, PV departments working together with their corresponding inspectorates can perform an assessment to determine which technical areas require the same or similar basic training for both assessors and inspectors. Topics can include:

- Legislative structure governing PV activities
- ICSR requirements (including collection, coding and reporting of ICSRs)
- PSUR requirements (including the structure and content of the PSUR and submission requirements)
- Signal management (including the signal management steps, understanding of detection methodologies, urgent safety restrictions and the interface with risk management plans and minimisation measures)
- Quality Management System (QMS) – key concepts, and how they contribute to the better accomplishment of everyday work of both PV assessors and inspectors

Once identified, common training materials (such as slide presentations, job aides, information sheets) can be produced and made accessible by both assessment and inspectorate teams and where logistically possible the delivery of training can be coordinated. Responsibility for the maintenance of the training materials should be assigned so that the materials remain up-to-date and current.

When revised or new EU legislation and guidance (for example new and updated GVP Modules) are published, workshops for assessors and inspectors can be organised to discuss the changes. Input and comments are encouraged from both assessors and inspectors, who can share their interpretation of the guidance and aid the agency in understanding the impact of the revised guidance on existing procedures and where required changes can be harmonised across the teams.

Case Study 7
The Medicines and Healthcare products Regulatory Agency (MHRA), UK

- The MHRA have implemented a rolling programme of training presentations covering the core PV topic areas. Each topic is discussed on at least an annual basis.
- These presentations also include a question and answer session.
- Attendance is open to both PV department personnel and PV inspectors.
- They are attended by new staff in addition to existing staff that require refresher training or are interested in expanding their knowledge outside of the topic area in which they work.
- A list of topic areas is presented in Annex 5.

Case Study 8

The Agency for Medicinal products and Medical Devices (HALMED) of Croatia

- HALMED holds joint GVP meetings periodically. The topics of these meetings are PV legislation requirements as set out in GVP modules.
- The aim of the meetings is to reach a common interpretation of GVP modules and to discuss the practical implications for operating the national PV system and for performing PV inspections.
- The meetings can be triggered either if there is a difference in the interpretation of the requirements between PV assessors and inspectors or if an updated GVP module has been issued.
- The benefits of the training for PV assessors are that they receive feedback from PV inspectors on specific PV processes e.g. PSURs from inspections they have performed, but also from the discussions held at the Pharmacovigilance Inspectors Working Group. PV assessors can also consider whether this feedback can be used to improve internal processes.
- The benefits of training for PV inspectors are that they receive in-depth insight from assessors on specific processes within HALMED. PV inspectors can consider this feedback when preparing and performing inspections e.g. by using internal sources of data more efficiently when searching for compliance data prior to an inspection.
- As an example, training on GVP Module I was held on ‘PV systems and their quality systems’. Discussion on possible improvements of the PV quality system included taking forward relevant suggestions in the next revision of the PV quality manual e.g. development of a template for the agenda of weekly meetings of the PV department.
- The main challenge of the training is that the meetings have been time consuming because of the complexity of the topics discussed and competing priorities of workload.

4.2 Joint Inspections

Joint inspections involving both assessors and inspectors can provide on-the-job training opportunities for both PV assessors and inspectors. Whilst inspectors expertise includes an in-depth understanding of the legislation and guidance, product specific knowledge which can be important for determining the public health impact of an inspection finding lies with the assessor. The presence of an assessor during an inspection allows real-time access to this information and also provides an opportunity for assessors to see how the broader PV system contributes to the submissions such as PSURs, RMPs and ICSRs that they frequently assess. The collaboration between an assessor and inspector on product specific issues can contribute to the decision making process with regards to inspection outcomes and post-inspection actions.

4.2.1 Recommendation 9: Identification of opportunities for joint inspections

Due to resource limitations and considerations of workload it is often not possible for an assessor to participate in every PV inspection. Therefore NCAs can define which inspection scenarios would benefit the most from the presence of an assessor and which would provide the better training opportunities. Criteria could include:

- Has the inspection been triggered as a result of a product specific concern?
- Does the MAH portfolio include:
  - Products for which additional PV activities are required (e.g. additional monitoring, risk minimisation measures)?
  - Novel or niche products?
- Does the PV department have any ongoing concerns regarding the quality of MAH submissions (such as PSURs, ICSRs, Post-Authorisation Safety Study (PASS) protocols etc.)?

The decision may require input from both PV departments and inspectors and therefore inspection schedules created by inspectorates should be shared with PV departments. This will allow timely decision making and allocation of resource and workload.

4.3 Recommendation 10: Job shadowing

For new staff the shadowing of a PV assessor or inspector may provide an opportunity to further develop an understanding of the application of PV legislation and guidance.

A trainee PV inspector could spend time shadowing the work of an assessor. This will allow the inspector to understand how the documents they review for completeness during an inspection are used and evaluated by an agency. This could then allow an inspector to account for areas of greater priority when planning and preparing for an inspection.

An assessor can shadow a PV inspector as they complete each of the steps in the inspection process. This will allow the assessor to understand the origin of the information that they receive from MAHs for evaluation and enhance their own assessment capabilities. It may also allow the assessor to understand the broader PV system and the impact it has on the submissions that they routinely assess and give them insight to additional information that a MAH may hold that could be requested to supplement the information.

5. Conclusion

The introduction of the 2012 PV legislation sought to achieve greater clarification of the roles and responsibilities of MAHs and NCAs, more focus on proactive and risk proportionate safety monitoring, and robust and timely decision making. The effective interaction between PV departments and inspectors and consequent sharing of information is essential for NCAs to comply with PV legal obligations to maintain a high level of public health protection. It is important to feedback information on inspection outcomes to PV departments in order to aid with post-inspection decision making regarding any regulatory action and in the case of missing information (from ICSRs, PSURs, safety reviews etc.) to reconsider benefit-risk assessments following inclusion of the missing information.

Both inspectors and assessors play an important part in the overall surveillance programme, by verifying the compliance status of MAHs. One NCA illustrated the importance of this interaction in the SCOPE survey, noting that inspections should be an integrated part of the surveillance process, including assessments and inspections as quality tools. Furthermore, the complementary but different skill of inspectors and assessors was also noted as good practice in planning and conducting PV inspections.

This document has highlighted good practice in how a NCA can make information accessible to PV inspectors and assessors to aid their day-to-day work. It is acknowledged that there are differences in resource, internal organisational structures and the maturity of PV systems across the network and that NCAs should identify the most appropriate mechanisms for information sharing within their organisations. By implementing effective mechanisms to share knowledge, training and experience gained by inspectors and assessors in their day-to-day activities, NCAs can improve their own efficiencies, whilst fulfilling their role as a regulator.

6. References and related documents

- Regulation 726/2004 European Commission (EC) as amended
- Directive 2001/83 EC as amended
- Commission Implementing regulation 520/2012
- Good Pharmacovigilance Practice (GVP) Modules (specifically GVP Module III – Pharmacovigilance Inspections)
- Pharmacovigilance Inspection Union Procedures
- SCOPE WP7 Survey Report: Interaction with Pharmacovigilance Assessors.

Annexes

Annex 1. Checklist for information sharing

The table below summarises the information held within NCAs that can be shared between inspectors and assessors to aid both inspection and assessment activities, with examples of how the form can be filled in. This table can be used by NCAs to identify where there may be gaps in the information shared, evaluate how both groups access the information and identify areas where the process could be improved and shared.

Data source	Information readily accessible by Inspectors (Y/N)	How is the information currently sourced by inspectors	Information readily accessible by assessors (Y/N)	How is the information currently sourced by assessors	Can the process be streamlined / consolidated
Marketing authorisation status					
Number of MAs					
Newly authorised products					
Products subject to additional monitoring					
Change of ownership					

Data source	Information readily accessible by Inspectors (Y/N)	How is the information currently sourced by inspectors	Information readily accessible by assessors (Y/N)	How is the information currently sourced by assessors	Can the process be streamlined / consolidated
Compliance information					
ICSRs (15 and 90 days)	Y	For NCA submissions: • Validated business objects query that can be run when required by inspectors. • On a quarterly basis MAHs with poor compliance are identified by pharmacovigilance operations and communicated to inspectors For the European Medicines Agency (EMA) submissions: • Validated query of EVDAS	Y	For NCA submissions: • Validated business objects query that can be run when required by pharmacovigilance operations. • Same query is run on a quarterly basis to identify trends in non-compliance. When late submissions are present as a result of an inspection finding: • Access to inspection reports. • Significant number of late submissions will be communicated via monthly IAG meeting • Specific examples discussed at quarterly meetings.	At present mechanisms are in place to access this information on both a routine and ad-hoc basis.
PSURs (70 and 90 days)					
Safety reviews					

Data source	Information readily accessible by Inspectors (Y/N)	How is the information currently sourced by inspectors	Information readily accessible by assessors (Y/N)	How is the information currently sourced by assessors	Can the process be streamlined / consolidated
Safety variation submission					
Quality of regulatory submissions					
ICSRs					
PSURs					
RMPs					
Ongoing safety issues					
Validated (PRAC) signals	Y	• List of PRAC signals on the EMA website • PRAC meeting minutes	Y	• List of PRAC signals on the EMA website • PRAC meeting minutes • MHRA PRAC representative • EPITT	At present inspectors do not have access to EPITT.

Data source	Information readily accessible by Inspectors (Y/N)	How is the information currently sourced by inspectors	Information readily accessible by assessors (Y/N)	How is the information currently sourced by assessors	Can the process be streamlined / consolidated
Validated (NCA) signals	N	Specific requests per product can be made by inspectors to assessors	Y	• Internal tracking system • Internal signal detection meeting minutes	Could inspectors have read only access to the internal tracking system or the tools used to extract information from this system (.e.g. validated extraction queries). Access to this could reduce the amount of individual requests sent to assessors (improve efficiency)
Risk-minimisation measures					
Urgent safety restrictions					
Inspection outcomes					
Serious non-compliances (e.g. critical inspection findings)	N/A		Y	• Inspections reporting critical deficiencies are referred to a monthly cross-agency meeting which include representatives from the pharmacovigilance operations unit.	

Data source	Information readily accessible by Inspectors (Y/N)	How is the information currently sourced by inspectors	Information readily accessible by assessors (Y/N)	How is the information currently sourced by assessors	Can the process be streamlined / consolidated
Standard inspection outcomes (all inspections reporting major and minor findings)	N/A		Y	• All inspection reports are uploaded into the Agency document management system that can be accessed by pharmacovigilance assessors • Inspections of specific interest (but have not reported critical findings) are presented at a quarterly meeting held between pharmacovigilance inspectors and operations.	

Annex 2. The Agency for Medicinal Products and Devices (HALMED) of Croatia non-compliance tracking sheet

The following table provides an example of the types of information that can be collected in a non-compliance tracking sheet. This sheet can be completed by both inspectors and assessors, and used by both parties to inform their assessment or inspection activities.

MAH *	Process being assessed * (e.g. ICSR, PSUR, RMP)	Details of identified PV non-compliance*	Date identified *	Identified by*	Estimated priority / risk**	Corrective actions requested?** (if yes, provide date requested and agreed)	Regulatory actions taken ** (Y/N, if Y, provide details)	Additional comments*	Inspectors comment**

**Fields completed by pharmacovigilance assessors*

***Fields completed by pharmacovigilance inspectors*

Annex 3. The MHRA report for overview of MAH compliance with ICSR reporting

This report serves as an overview of compliance from companies reporting ICSRs via E2B data.

This report contains overall reporting figures, including total numbers of late submissions.

Companies who have been poor with compliance will be raised in this report, with information being made available for companies who need closer monitoring.

Finally the report will re-cap any risk information that has emerged during the month.

Overall E2B figures

Between Month X 2013 to Month Y 2013, there was a total of XXX cases submitted by XXX number of companies. Of these XXX cases submitted, XX were submitted late, which is XX% of total cases.

Total Cases	
# of companies	
# Late cases	
# of Late as a %	

Company watch

Performance in terms of late submissions were ABC PHARMA, DEF PHARMA and GHI PHARMA. The stats are in appendix one of this report.

Late reporters were:

- MHRA Outbound compliance
  Outbound compliance including details of investigations and discussion with companies regarding their database receiving ASPR's/sending acknowledgements back to the agency.
- Signals
  New signals/signal information will be discussed in this section.
- News/updates

Appendix 1

PHARMA ABC

PHARMA		
Compliant	No. Reports	%
Y		
N		
Total		

Days between	No. Reports
>15	
16	x
17	x
…	x

PHARMA DEF

PHARMA		
Compliant	No. Reports	%
Y		
N		
Total		

Days between	No. Reports
>15	
16	x
17	x
…	x

PHARMA GHI

PHARMA		
Compliant	No. Reports	%
Y		
N		
Total		

Days between	No. Reports
>15	
16	x
17	x
…	x

Appendix 2

--- Includes specific details of companies ---

Annex 4. The Italian Medicines Agency (AIFA) template to request a pharmacovigilance inspection

1) Date of the request:

2) Department/Office:

3) Name of the person requesting inspection:

4) Type of Inspection:

☐ Pharmacovigilance system inspection

☐ Product-related pharmacovigilance inspection

5) Name and address of the company for which you are requesting inspection:

Brand Name of the product (if applicable):

MA Procedure:

☐ CAP

☐ MRP

☐ DCP

☐ National

6) Triggered for the request of inspection:

☐ change in the risk-benefit balance of the product

☐ failure to fulfil reporting obligations (expedited and periodic)

☐ inadequate or failure provision of data to fulfil requests for information from the competent authorities

☐ failure to fulfil of commitments

☐ others

(summarise the concerns and issues raised):

7) Any documents supporting this request:

8) Signature of the Head of the Requesting Department/Office:

Annex 5. The MHRA rolling programme of training presentations of Vigilance and Risk Management of Medicines (VRMM)

- The life cycle of a Yellow Card – introduction to the daily routine for Pharmacovigilance
- Signal Detection Overview
- Overview of the Post Authorisation Signal Unit
- Introduction to the work of the European Business Team
- Introduction to the work of the Post Authorisation Regulatory Team
- Freedom of Information requirements
- Introduction to the work of the Pharmacovigilance Inspectors
- Overview of the Benefit Risk Management Group
- Overview of the Epidemiology unit
- Overview of the Advertising Standards Unit
- Introduction to label and leaflets requirements
- Overview on self-medication unit
- Drug Safety Update and Communicating safety messages
- Yellow Card Strategy
- Overview on Special Populations (Paediatrics)