SCOPE Work Package 7
Quality Management Systems

Survey Report: Interaction with Pharmacovigilance Inspectors

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SCOPE

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Contents

Acknowledgments

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The authors acknowledge all Member States who took part in this survey.

1. Introduction

1.1 Purpose of the document

The purpose of this report is to summarise the outcomes of the Work Package (WP) 7, Topic 3 survey addressing pharmacovigilance (PV) inspections and the communication that takes place between PV departments and inspectors. Upon analysis of the survey results, this report presents suggestions for achieving good practice in European Union (EU) Member States (MSs). Information gathered from the questionnaire will only be referred to in general and will be anonymised in this report.

1.2 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
BEMA	Benchmarking of European Medicines Agencies
CAPA	Corrective And Preventive Action
CHMP	Committee for Medicinal Products for Human Use
DHPC	Direct Healthcare Professional Communication
EC	European Commission
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
EVDAS	EudraVigilance Data Analysis System
GVP	Guideline on Good Pharmacovigilance Practices
HMA	Heads of Medicines Agencies
ICSR	Individual Case Safety Report
IT	Information Technology
KPI	Key Performance Indicator
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMD	Managing Meeting Document
MS	Member State
NCA	National Competent Authority

Terminology	Description
PASS	Post Authorisation Safety Studies
PDF	Portable Document Format
PSUR	Periodic Safety Update Report
PSMF	Pharmacovigilance System Master File
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
QMS	Quality Management Systems
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOP	Standard Operating Procedure
WP	Work Package

1.3 Executive summary

This report outlines the collection of information from European National Competent Authorities (NCAs) regarding Quality Management Systems (QMS), focusing on the interactions between NCA PV assessors and inspectors. This is part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action, which aims to support each EU MSs in operating their PV systems. SCOPE consists of eight separate Work Packages (WPs) designed to tackle a different area of PV. This report focusses on WP7, exploring QMS in PV.

To gain an understanding of how each NCA operates, questionnaires were created and sent out for completion. The main aim was to gather information on PV quality systems operated by NCAs in order to identify areas that are challenging and are managed successfully as examples of good practice. The questionnaires for WP7 covered the three main topics below:

- Understanding national quality systems
- Resource management
- Interactions with PV inspectors

This report summarises results from a survey, that was answered by 27 MSs, which explores the communication and interaction between PV inspectors and assessors to identify areas of good practice. The first three sections of this survey were aimed at PV departments and assessors, with the remainder of the survey aimed at PV inspectors only.

1.4 The survey results

1.4.1 Assessors survey questions

The first section of the survey addressed the organisational structure and communication between PV inspectors and assessors. Most NCAs appear to have separate departments for assessors and inspectors; however there seems to be good communication between the two when an inspection is requested. Most of this communication is through ad-hoc meetings or via email, and not with regularly scheduled meetings. The output from these meetings generally centres on inspection schedules and meeting minutes. Interestingly, two NCAs stated that they have a shared document between assessors and inspectors which tracks cases of non-compliance, suggesting a more continuous and structured line of communication.

Section two of the survey covered in more detail the sharing of information between assessors and inspectors, and whether their training was integrated or separate. The information shared between inspectors and assessors generally covers all non-compliance and quality issues, together with product-specific issues and inspection findings. Enquiries about PV and accounts from whistle-blowers are less commonly discussed between assessors and inspectors. One NCA stated that all of this information was openly available to inspectors, and therefore was not routinely requested by inspectors. For NCAs that have a more structured information sharing process, most present this information on a monthly or quarterly basis. Interestingly, a third of NCAs felt that the frequency of information sharing was not adequate in their MSs.

Regarding training of assessors and inspectors, almost half of NCAs have integrated training for both roles. Three NCAs highlighted the involvement of the Inspectors Working Group in training. In some cases inspectors provide training to assessors on inspections, and assessors provide training to inspectors about assessor's processes.

When asked the circumstances by which an assessor, or PV department employee, may become involved in the inspection process, most NCAs highlighted impact on benefit-risk profile of a product, outcomes requiring referral to the Pharmacovigilance Risk Assessment Committee (PRAC), critical findings and potential for enforcement action as key factors.

Section three of the survey requested free-text comments from NCAs regarding best practice and asked them to highlight their most challenging areas. Regarding difficulties suffered by MSs, the lack of staff was highlighted in addition to inefficiencies in information sharing, whether this is insufficient or too burdensome if the amount of information required is not specified. Good practice approaches centred on collaboration between assessors and inspectors including joint training initiatives, joint-inspections and establishment of more opportunities for teamwork between the two roles including formal and informal meetings.

1.4.2 Inspectors' survey questions

The fourth section requested information from NCAs regarding PV inspections, where the number of inspections requested of NCAs per year ranged from 0 to 15, with many NCAs stating that they did not receive any specific requests for inspections. However, for some the number of inspections actioned was less than officially requested, and in other cases more inspections were actioned in comparison to the number requested. Only half of NCAs shared the inspection schedules with the PV department.

When asked what factors are taken into account when scheduling an inspection, NCAs stated that quality issues and product-specific information were key decision makers, however, some highlighted that a more complex risk-based approach was used and others that capacity was an important factor.

When inspectors were asked what information is shared with assessors, inspection feedback and inspection schedules were highlighted sources. However, if an inspection was a result of non-compliance, had a product-specific impact, or if the assessor had been present at the inspection, information would all be shared with the PV department.

The fifth section of the survey requested information from NCAs regarding the use of information by inspectors. Nearly all NCAs stated that a risk-based approach is used to plan inspections. When asked for occasions where an assessor's input would be provided during preparation and conduct of the inspections, the request for information regarding PV assessment status and the need for product specific expertise were agreed by most NCAs. Only half of MSs stated that all inspection outcomes were shared with assessors, with under half stating that inspection outcomes that have an impact on the benefit-risk profile of products would be shared.

In asking NCAs to comment on how this information is shared, there were a variety of responses. Some having no formal process in place, some having formal meetings and others making available inspection reports in shared locations that can be accessed by both inspectors and assessors.

The sixth and final section of the questionnaire asked NCAs to provide comments on where they feel they are most challenged and make any suggestions for good practice regarding inspections. Interestingly, joint training and an increase in communication were again highlighted as examples of good practice, however some NCAs stated that it would be a challenge to find the time to increase communication and training.

One NCA noted that PV inspections should be more integrated into the surveillance process. Increasing communication and training between assessors and inspectors would address this challenge. Capacity and workload were highlighted by a number of NCAs and they commented that a lot of time is required to review all inspection documents, and even that the Information Technology (IT) systems available to inspectors do not always support this and IT systems to facilitate the exchange of inspection information between inspection departments and MAHs could be optimised.

The use of a checklist was suggested by one NCA to help integrate and track both the assessor and inspector roles. Involving assessors in the decision making process for inspections was also suggested to increase communications. Some NCAs stated that they have a combined assessor/inspector role in their MS and that this was considered a great advantage by them, again feeding into the joint training aspects.

1.5 Good practice

Proposing good practice methods for NCAs is a challenging prospect, given the significant variation in existing organisational structures, resources and processes. For this reason it is difficult to measure what 'good practice' is, and how effective the proposals might be across Europe. Nevertheless the most common practices highlighted by the collective NCAs that took part in the survey are a good reference. The deliverables for good practice approaches may take place through face-to-face training, e-learning or as part of a practical quality toolkit that NCAs can use as a reference.

- The current proposals for good practice to optimise assessor and inspector interactions within NCAs are summarised below:
- Develop mechanisms for the efficient sharing of information regarding Marketing Authorisation Holder (MAH) compliance within NCAs
- Ensure PV departments can access inspection reports and feedback
- Establish joint training programs for assessors and inspectors
  - Common training on Guideline on Good Pharmacovigilance Practices (GVP) modules
  - Rolling training provided by both assessors and inspectors
  - Increase opportunity for exposure i.e. meetings or assessor attendance at inspections.

1.6 Future work

In light of these proposed approaches to 'good practice', the following next steps will be implemented to gather the information required to provide adequate training on these good practices:

- Identify the best way to formally share information between assessors and inspectors regarding MAH non-compliance
- Establish the requirements for exchange of information between assessors and inspectors within NCAs
- Identify case studies of joint training initiatives.

1.7 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action aims to support European Union (EU) Member States (MSs) in operating their pharmacovigilance (PV) systems as part of the EU network making the best use of experience and practices to achieve the most effective use of available national resources. SCOPE is gathering information and expert knowledge on how MSs run their national PV systems. Using this information, SCOPE will develop and deliver tools, guidance and training to support MSs in their PV activities. Through this approach SCOPE aims to support consistency across MSs to provide greater knowledge and help to identify and promote their strengths, thereby strengthening the protection of public health[1].

The legal requirements for quality systems were introduced by Directive 2010/84/EU and Regulation (EU) No 1235/2010 to strengthen PV in the EU. The minimum requirements of these quality systems are set out in the European Commission (EC) Implementing Regulation (EU) No 520/2012.

SCOPE is divided into eight Work Packages (WPS). This report focusses on WP7, which addresses the development and function of national PV systems from a quality management perspective. There are three topics within WP7. This report covers Topic 3, investigating the interactions between PV departments and PV inspectors within National Competent Authorities (NCAs).

Routine PV activities in European MSs can be performed by separate staff from those who inspect PV systems and capabilities of Marketing Authorisation Holders (MAHs). However, there needs to be a level of interaction in order for information to be shared between these parties to optimise the work completed by them and to prevent duplication. Information on MAH compliance, quality of PV submissions and other intelligence gathered by MS PV departments during their routine work could produce important risk information that can be used in the planning or triggering of PV inspections. Conversely, PV inspectors may identify information pertinent to PV departments during the course of an inspection, such as non-compliances that may have an impact on the assessment of the benefit/risk profile of an authorised product (e.g. non-reported Individual Case Safety Reports (ICSRs), non-inclusion of ICSRs in Periodic Safety Update Report (PSUR) submissions and failure to fully investigate potential safety signals).

[1] http://www.scopejointaction.eu/ Accessed: [12/06/2015]

The aim of this survey was to thoroughly examine the interactions between NCA PV departments and inspectors, where these operate as either separate or combined departments, including the sharing of information held by each party and the methods by which this information is shared. Recognising that NCAs have limited resources, particularly for inspections, the aim of this topic is to elucidate what inspectors want from PV operations/assessors and to recommend how to obtain and sustain effective and efficient collaboration between them. Using this information, areas of good practice will be identified and gathered together to provide a series of recommendations for such operations in individual MSs.

The overall deliverables from WP7 are to develop introductory training materials together with a quality toolkit presenting case studies of good practice from MSs, practical guidance documents and specific tools to share expertise and set priorities for EU NCAs, thus allowing further development depending on their resources and maturity of quality systems.

A number of EU NCAs were visited as part of a data gathering exercise of WP7 to consider how a PV quality system was run in practice at NCAs. Information shared during site visits served as a basis for a comprehensive questionnaire on the quality management practices of EU MSs focusing on the general structure and functioning of the Quality Management System (QMS) and that of PV, resource management and interface of PV assessors with PV inspectors.

This WP7 sub-package will contribute to this through delivery against the following:

- Development of a questionnaire on interactions between PV departments and PV inspectors
  - One on PV department perspectives
  - One on PV inspection perspectives
- Analysis of responses and production of a summary report
- Identification of areas of good practice.

1.8 Context and scope of report

This report provides a basis for the further work in relation to interactions with PV inspectors. Responses are not attributed directly to MSs who responded to the survey in order to preserve confidentiality.

1.8.1 Main goal

This report aims to summarise results of the SCOPE survey answered by MSs about interactions with PV inspectors within NCAs and to identify recommendations and final deliverables.

1.8.2 Objectives

Results from the survey help to identify the range of practices across EU MSs, and will be used to produce guidance and tools to support MSs to meet the requirements set out in the EU PV legislation.

1.8.3 Challenges

The harmonisation of results and comparison of responses between MSs could be impacted by differences in interpretation. For recommendations themselves, there may be challenges in national applicability with the significant range of contexts, stakeholders and factors relevant in different MSs.

There appeared to be some misunderstanding regarding the split of the survey into two sections: the first section to be completed by the PV department and the second by the PV inspectors. In some cases, all questions were responded to by the PV department, leading to some duplication in the responses given. Where this was observed this has been considered in the interpretation of the responses.

2. Methodology

2.1 Tool and survey method

WP7 used questionnaires to gather information from NCAs of MSs in the EU on the topics investigated. A questionnaire, as a tool for collecting information, has advantages over other methods like interviews:

- Responses to questions are gathered in a standardised way
- They allow information to be collected quickly (via an online survey tool)
- Information can be collected from a large portion of the target group (NCAs of MSs in the EU).

The following three questionnaires were developed in the frame of QMS in SCOPE WP7:

- General (49 questions)
- Resource management (28 questions)
- Pharmacovigilance inspections (27 questions).

2.2 Data collection methodology

In the first step of the development phase, objectives and types of information to be collected for each questionnaire were defined and identified. Next, all possible questions were collected using brainstorming sessions with SCOPE WP7 team members via face-to-face meetings, teleconferences and emails. These collections were considered as source data for the three planned questionnaires.

2.3 Preparing draft questionnaires

In the second step of the development phase, the proposed questions were restructured using the following principles:

- Keep questions as simple as possible
- Avoid ambiguous, leading questions or those asking two questions in one
- Avoid questions on overly sensitive topics in order to get accurate responses
- Limit the number of questions to those absolutely necessary, so that questionnaires were not too long, but still able to fulfil their purpose

All three questionnaires contained closed[2] and open-ended[3] (free text) questions.

Closed and open-ended questions are appropriate in different contexts and provide different information. Closed questions should be used where alternative replies are known, limited in number and clear-cut. Open-ended questions are used where the issue is complex, where relevant dimensions are not known and where the process/issue is being explored.

The main advantage of closed questions is that they are less time consuming for a respondent to complete, and avoid misinterpretation. The main disadvantage of closed questions is that they may mislead if poorly designed.

The main advantage of open questions are their flexibility, however, the respondent may require more thought and time to answer.

As such, the three WP7 questionnaires primarily contained closed questions (Yes/No, Yes/No/Partially, single and multiple choice, and rating scales). Nevertheless, to get as much information as possible from MSs and so not to limit response options unnecessarily, an 'Other' option in closed questions was generally included to allow for additional information and for NCAs to provide context to their answers, in case the selectable options were not appropriate. Furthermore, closed questions with a 'Yes' option were frequently accompanied by a gentle request to provide more details in free-text to reduce misinterpretation and maintain short, to-the-point, flexible questions. Nevertheless, it has not been evaluated whether adding these options carried any excess gain in the level of granularity of responses.

2.4 Piloting draft questionnaires

In the third step of the development all three questionnaires were tested using a pilot trial, in order to avoid the problems mentioned above and improve global quality.

Qualification of a questionnaire involves establishing that the questionnaire as a "measuring instrument" delivers data that are reliable and true. Testing a questionnaire prior to use is strongly advised[4], following five general criteria:

- **Purpose**: One has to be absolutely clear about the purpose
- **Directness**: The questionnaire should ask questions that address as directly as possible the issue wished to be evaluated
- **Utility**: This criterion relates to the practicalities of implementing and using the questionnaire

[2] **Closed or closed-ended question with ranked answers:** Questions in which all possible answers are identified and the respondent is asked to choose one or more of the answers.

[3] **Open or open-ended question:** Questions that allow the respondent to answer in any way they wish.

[4] M. Bloom and J. Fischer (1982) Evaluating practice: Guidelines for accountable professional. Prentice Hall, pp. 45-69

- **Reliability**: A questionnaire is reliable if similar results would be obtained by others using the same questions and using the same sampling criteria (repeatability)
- **Validity**: A questionnaire is valid if it actually measures what it sets out to measure. Validity much depends on the quality of the questions themselves. Validity is not an absolute quality. A questionnaire can be valid to a certain degree in certain circumstances, and developers must decide (a priori) what degree of validity is considered sufficient[5].

Testing reliability was not applicable by the pilot trial as all members of the target group (NCAs of EU MSs) were involved in the WP7 surveys.

Regarding the validity of questionnaires, the main purpose of the pilot trial was to improve the content and linguistic validity of the three WP7 questionnaires. These two kinds of validity have an impact on internal validity of the questionnaire (a subject will respond to similar questions in a similar way). They also affect the likelihood of producing false positive or negative answers.

Nine NCAs (BG, CZ, ES, HR, HU, IT, LT, PT, UK) were invited in the testing phase of the development including NCAs participating in WP7 and agencies involved in other WPs (pilot trial). They were asked to complete all three questionnaires via the online survey tool and asked to give feedback via email. All comments and proposed modifications received by email were analysed by the WP7 team and modifications/changes to the questionnaires were made.

2.5 Development of final questionnaires

As a result of this pilot trial, final versions of the three questionnaires were produced by 22 January 2015 through online survey tools.

In the final step of the development phase, an introduction text was added to each questionnaire in order to support respondents. These texts described the purpose of the questionnaire, together with simple instructions on how to complete them, the deadline of responding/completing and a note of thanks to respondents for completing.

2.5.1 Survey participants

Data capture

A single contact person was identified with his/her email address for each NCA. Only one response was accepted from each NCA via SurveyMonkey (an affordable, user-friendly web-based application for survey creation, distribution and analysis).

[5] K. Howard (2008) Validating questionnaires, *Kestrel Consultants, Inc.* http://kestrelconsultants.com/reference_files/Validating_Questionnaires.pdf [Accessed 04/11/2015]

Twenty-nine invitation emails were sent from SurveyMonkey to contact persons on 23-24 January 2015. Twenty-seven of these invites were sent to active SCOPE partners, with two invites sent to non-active SCOPE partners.

The questionnaires were also sent to each contact person in Portable Document Format (PDF) format by email in order to discuss/delegate certain groups of questions with/to suitable person(s) within or outside a given NCA.

A one month period was left for respondents to complete the questionnaires. The deadline was set to 25 February 2015.

Two reminder emails were sent to all contact persons (on 16 and 23 February 2015).

Requests were received from some NCAs via email to modify the deadline for completing the questionnaires (reasons included change of contact person). Therefore the deadline was extended twice in order to collect as much information as possible. The second and third (final) deadlines were set at 15 March 2015 and 15 April 2015, respectively.

Information about responses

After the 1st and 2nd deadlines the response counts and rates were as follows (**Table 1** and **Table 2** below).

Table 1. Response counts and rates by the 1st and 2nd deadlines. Twenty-seven MSs were included in the survey.

Topic – Title of questionnaire	1st deadline		2nd deadline	
	Number of responses	Response rate (%)	Number of responses	Response rate (%)
1 – General QMS	19	70.4	25	92.6
2 – Resource management	18	66.7	21	77.8
3 – PV inspections	16	59.3	23	85.2

All twenty-seven active SCOPE MSs were expected to answer (100%); the response rates (%) by the final deadline were as follows (**Table 2**).

Table 2. Response counts and rates by the final, 3rd, deadline for the twenty-seven active SCOPE partners and 2 non-active partners

Topic – Title of questionnaire	Response count from 27 active SCOPE partners	Response count from 2 non-active SCOPE partners	Response count from all partners	Response rate (%)*
1 – General QMS	25	1**	26	92.6
2 – Resource management	26	0	26	96.3
3 – PV inspections	26	1**	27	96.3

*Response rates were calculated for active SCOPE partners (n=27)

**Although Topic 1 had a total of 26, and Topic 3 of 27 responses, there were only 25 and 26 responses from active SCOPE partners, respectively, with 1 additional response from a non-SCOPE partner in both cases. This additional response from a non-SCOPE partner is included in the survey discussions, but not in the response rate calculation as this was not an anticipated respondent.

The trend in responses justified the extension of deadlines given the high response rates and allowed a large amount of information to be gathered by the final deadline. **Figure 1** summaries these findings graphically and **Table 3** lists the MSs taking part in the survey.

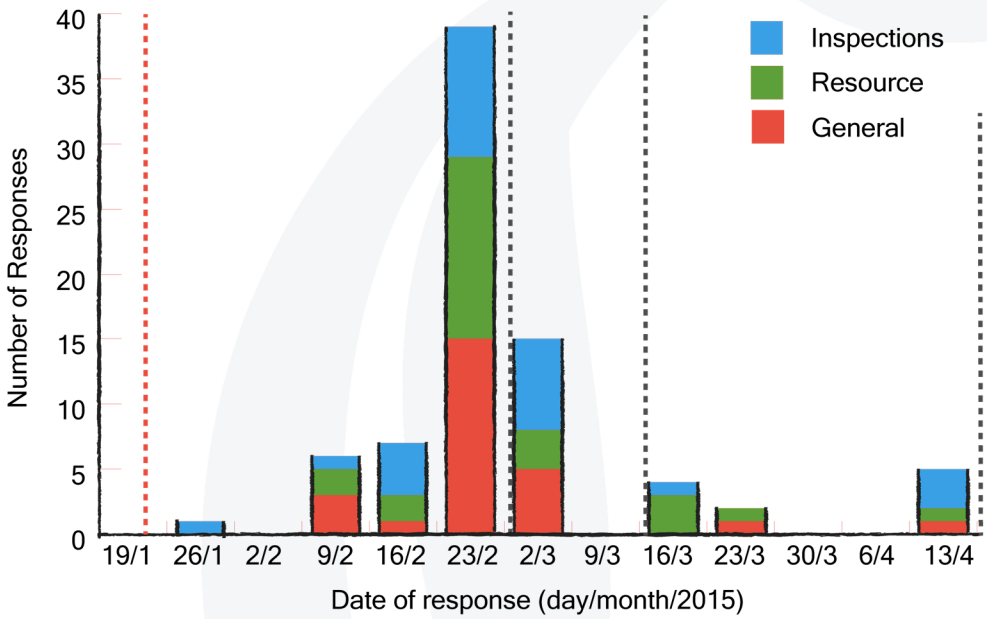

Figure 1. Trend of responses with starting dates and deadlines of responding

Far left, red dotted line = start date, with the following three grey lines = 1st, 2nd and 3rd deadlines, respectively.

Table 3. List of MSs who took part in the survey

Austria	Finland	Lichtenstein	Romania
Belgium	France	Lithuania	Slovakia
Bulgaria	Greece	Malta	Slovenia
Croatia	Hungary	Netherlands	Sweden
Czech Republic	Ireland	Norway	UK
Denmark	Italy	Poland	
Estonia	Latvia	Portugal	

*Non-active SCOPE partner

Response rates of closed and open-ended questions

Closed questions were mandatory to complete, but open-ended questions were not. Thus, the response rates were 100% regarding the closed questions but considerably less for open-ended. For example, the last two open questions (**Q48** and **Q49**) in the questionnaire were completed by only 16 and 14 respondents, respectively. Nevertheless success of the questionnaire was not judged on the rate of response to each question, as there were several questions linked and thus required a positive response for a lead question in the series to be able to proceed with the others. NCAs who provided a negative answer to the first question in a set of linked questions were therefore expected to skip the remaining associated ones. Furthermore, response rates of mixed (open and closed) questions were difficult to assess. Finally, responding to a question did not imply that the response given was relevant to the question. Several examples were found where MSs indicated 'Not applicable' or 'No' instead of leaving the response blank.

Factors that contributed to the success of the survey

One important factor that contributed to the success of WP7 surveys was the high response rate across the three questionnaires. Another is the careful preparatory work together with a pilot phase allowing the exclusion of ambiguous questions. A third factor may be that the mixture of closed and open questions allowed MSs to add items to lists most relevant to their situation, and thus give more detailed explanations.

Factors that limited the success of the survey

Overall the survey reached its intended objectives. Nevertheless, there could have been improvements if some of the limitations had been eliminated or addressed.

Using too many free-text questions can be risky, as the willingness of respondents to give detailed responses cannot be predicted, i.e. the level of granularity of responses cannot be communicated to respondents. More active contributions from respondents and more detailed explanations on potential good practices and examples were expected. Furthermore, free-text questions were skipped by a considerable amount of respondents (probably as they were defined as 'Not mandatory').

Additionally, it was hard to control the content of free-text answers, and keep respondents linked to the issue in question. Interpretation of responses may also be difficult, in particular when responses are brief. In order to overcome challenges we developed a consistent approach in data analysis that is presented in the next section. Furthermore, when responses were ambiguous but essential to record, respondent NCAs could be contacted to clarify answers.

2.5.2 Data analysis

Methodology and display of results

SurveyMonkey was used for the WP7 questionnaires, and has inbuilt plotting capabilities. However, for all of the analyses in this report, questionnaire responses were exported into excel and downstream data processing performed.

Files were extracted from SurveyMonkey with the responses of each NCA, as identification of NCAs and linking them to their answers was necessary for assessors to have a deeper understanding and to present and discuss data in the most comprehensive way. Nevertheless, as already stated, data are presented and discussed in an anonymised way.

Data obtained from the questionnaire has been analysed by two assessors and a PV inspector independently to ensure an unbiased assessment and presentation of data, paying special attention to free-text questions and questions where answers required adjustments (detailed later on). When assessors were not in agreement, issues were discussed. Assessors had a background in PV with some knowledge of quality management and PV inspections, for a better understanding and interpretation of responses. Assessors were cautious not to add any further meaning to any of the responses.

Single and multiple-choice, closed questions

For the display of results, pie charts were used for single choice questions and bar graphs for multiple choice. Free-text answers are presented as part of the surrounding text discussion.

Open-ended questions

There are many methods for evaluating open-ended (free-text) questions, e.g. to extract important keywords and visualise relationships among sentences[6] or to summarise results using hierarchical classification[7].

Our approach to the assessment of free-text responses used the following principles:

- Responses that were considered equivalent to leaving the question blank (i.e. responses of '-', 'No', 'Not applicable', 'No comments', etc.) were excluded.
- Content of responses were analysed by searching for keywords relevant to the question.
- Responses that, based on content analysis, did not add any relevant information to the question were excluded.
- Relevant information from responses were summarised and presented arbitrarily by assessors to the best of their knowledge. The cross-checking of assessor interpretations was performed in all cases.

Challenges in data interpretation

Assessors encountered a number of challenges while analysing the data; including the following examples:

- Concise, list-like responses or keywords were hard to interpret by assessors not familiar with the internal procedures of a given MS
- Analysis of a response where the question had been misinterpreted by the respondent
- Response was uninterpretable for the assessor.

Usually, such responses were rejected or included only to a limited extent in the analysis. Furthermore, some questions might be interpreted only in context with other types of information that might or might not be available for the assessors. This was partially overcome by using data collected during a WP1 (Project Coordination) survey in which MSs were asked general NCA operational questions. For example Q9 in this survey asked NCAs to comment on whether their PV assessors and inspectors were based in the same departments or whether based in separate institutions (data not shown).

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[6] Y. Uchida *et al.* (2009) Extraction of important keywords in free text of questionnaire data and visualization of relationship among sentences, *FUZZ-IEEE*, pp. 1604-8.

[7] M. Garcia-Constantino, F. Coenen, PJ. Noble and A. Radford. (2012) Questionnaire free text summarisation using hierarchical classification. Research and Development in Intelligent Systems XXIX, Springer London. pp35-48

Definition of criteria for inclusion of topics for further investigation

In line with Section 1.8.2 (objectives), data obtained from the survey has been screened and analysed to identify any areas and pieces of information that could potentially be included in any of the three categories listed as objectives: good examples and practices, challenges, and lack of unified understanding of quality concepts requiring further clarification and guidance.

No specific inclusion criteria were defined, to avoid loss of information by setting up unnecessary limitations. A higher weighting was allocated to the interpretation of questions where multiple MSs provided the same response. These were flagged for inclusion in the proposals for further investigation.

3. Findings/Results

3.1 Structure/responsibilities for pharmacovigilance inspections and communications between departments (Q1-6)

Summary points

- The majority of respondents have a separate inspection department from that of PV operations
- The majority of respondents had defined criteria used by PV departments to trigger an inspection, most of which are formally defined in Standard Operating Procedures (SOPS)
- Most respondents said that assessors receive feedback from inspections either in response to the initial inspection request, or following an inspection that has taken place
- The outcome of assessor and inspector interactions is largely in relation to the inspection schedules

Q1 asked whom within the NCA is responsible for PV inspections; 15 (55%) respondents had specific inspections departments who were responsible and 8 (30%) respondents stated that the responsibility for the conduct of PV inspections was within the PV department itself. The remainder of MSs had other arrangements in place whereby inspections were performed by a separate organisation entirely.

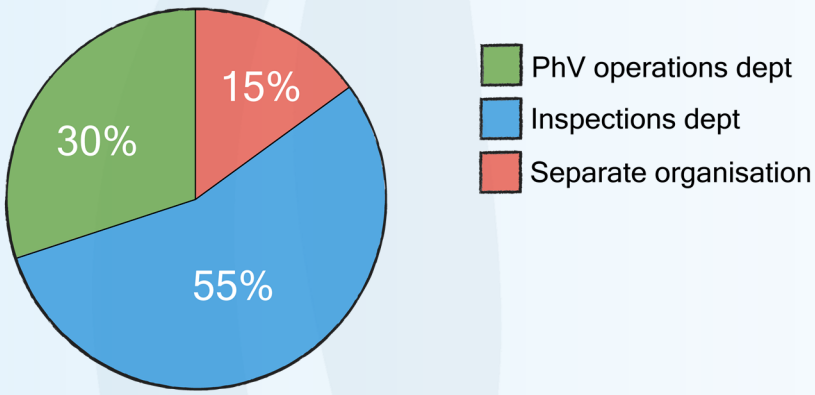

Figure 2. Responses to **Q1**: Within your National Competent Authority (NCA), who is responsible for performing pharmacovigilance inspections?

In **Q2**, 19 (70%) respondents indicated they had mechanisms such as SOPs, work instructions or templates for PV assessors to request or trigger an inspection.

Overall the responses indicated that the majority of MS had defined criteria by which their PV department could use to trigger an inspection. Of the 19 respondents that provided further free-text comments, 10 stated that these triggers were defined in a formal SOP.

Additionally, in the free-text comments, respondents provided examples of triggers that would be communicated to PV inspectors. These were largely consistent with the potential triggers listed in the GVP Module III[8], which was also directly referred to in the responses. Examples of these triggers included:

- Non-compliance with regulatory submissions (ICSRs, PSURs, safety variations)
- Quality issues identified in the assessment of ICSRs, PSURs and other PV-related submissions.
- Failure of companies to meet regulatory obligations/measures
- Companies showing poor knowledge of PV obligations and regulations.
- Companies with significant changes to the PV system or services e.g. major contractual arrangements
- Volumes of Adverse Drug Reaction (ADR) reports received, particularly when there is considered to be underreporting.

[8] Guideline on good pharmacovigilance practices: Module III – Pharmacovigilance inspections. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172400.pdf Accessed 03/06/2015

In **Q3**, the survey asked whether feedback from PV inspectors was provided when requests were made for inspections.

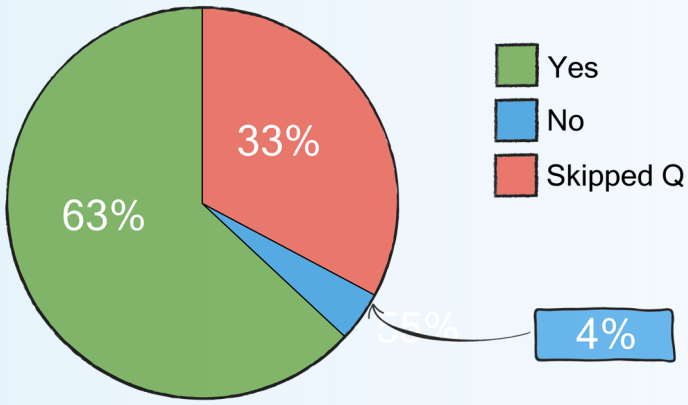

Figure 3. Responses to Q3: Was feedback from pharmacovigilance inspectors provided when requests are made for inspections?

Most respondents, 17 (63%), said that feedback was received. 9 (33%) did not respond to this question although no reason was given for this.

The responses indicated that there are two points at which feedback is received by PV departments: either in response to the initial inspection request, or following an inspection that has taken place. Where feedback is received before, typically requests for inspections appear to be discussed at meetings between PV departments and inspectors. This collaborative approach was mentioned by several respondents and the discussion had in these meetings contributed to the development of the inspection schedule. For those occurring following inspections, typically feedback is provided through inspection reports, sometimes accompanied by face to face feedback at scheduled meetings to discuss more urgent or serious inspection outcomes.

In **Q4** respondents provided information about interactions between inspectors and PV departments.

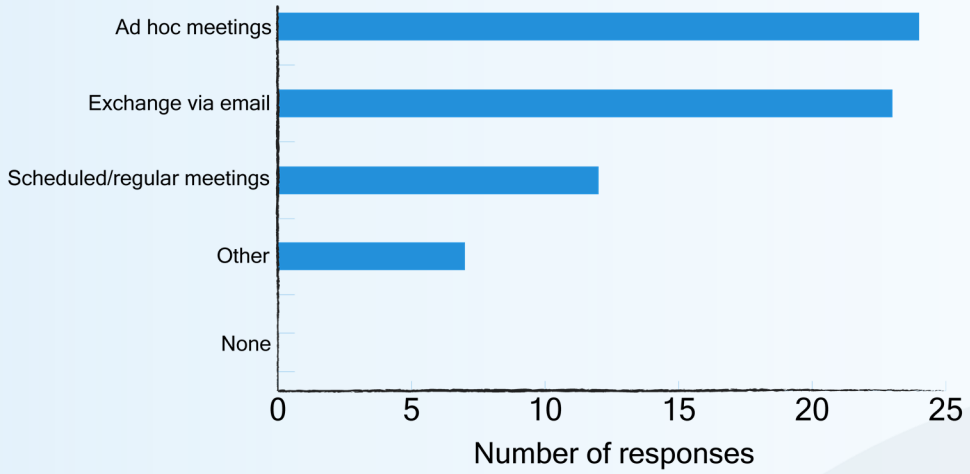

Figure 4. Responses to Q4: What interactions are in place between pharmacovigilance operations and pharmacovigilance inspectors?

The majority of respondents interact through ad hoc meetings (24, 89%) or email (23, 85%). Just under half of respondents, 12 (44%), have regular scheduled meetings which take place with inspectors.

Those who reported other methods of interaction indicated that staff from PV departments occasionally participated in inspections, or that the role of the PV assessor and PV inspector was combined. Two respondents indicated that a shared 'tracking' document was used collaboratively between PV departments and inspectors to track instances of non-compliance.

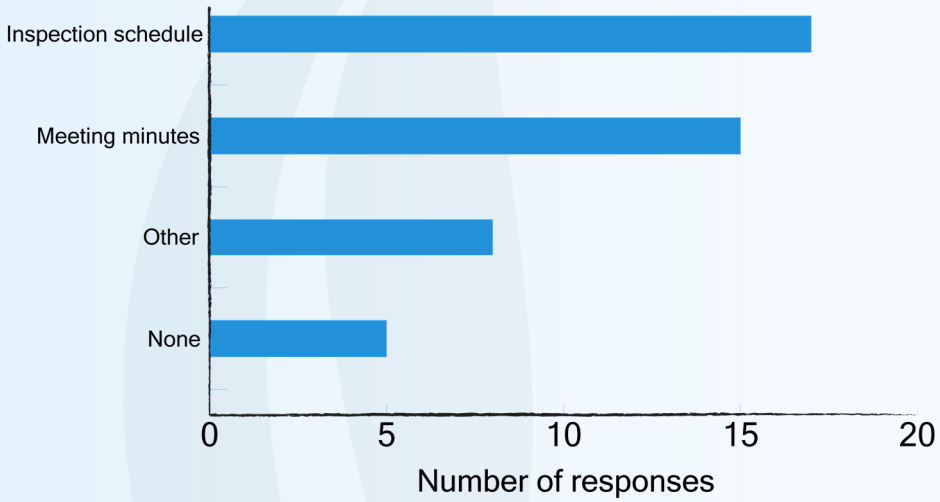

Figure 5. Responses to Q5: What are the outputs from these interactions?

Results from **Q5** show that the outcome of assessor and inspector interactions is largely in relation to the influence on inspection schedules. Additional outputs from these interactions included procedural outputs such as meeting minutes. In the free-text comments respondents also identified lists of action, either in form of a table or document in a shared location.

Following the schedule of a specific PV inspection, **Q6** asked for more qualitative feedback on how PV departments interact with inspectors during the preparation, conduct and reporting of an inspection. All twenty-seven respondents indicated that they did have some form or interaction during these activities.

Free-text comments provided detail about the types of information shared:

- Summary of pharmacovigilance system of the MAH to be inspected
- Individual Case Safety Report (ICSR) compliance listings
- Lists of PSURs submitted and the last PSUR submitted by the MAH
- Conditions on the marketing authorisation
- Any other non-compliance recognised
- Review of Corrective And Preventive Action (CAPA)
- Outstanding safety issues.

Several MSs noted that combined roles, either an assessor also being a PV inspector, or some other shared role, enabled helpful collaboration for the preparation and reporting on inspections.

Many respondents also explained that a PV assessor/expert would often attend alongside inspectors, or that they would join an inspection when specific expertise was required.

3.2 Information sharing and training (Q7-13)

Summary points

- The majority of respondents indicated they share compliance data on ICSRs, PSURs and safety variations, with some having this readily accessible to inspectors without the need for specific requests
- Data shared was mainly regarding instances of non-compliance with nearly half of all respondents sharing only this data with inspectors, but several responses indicated no data was shared at all
- Nearly half of respondents shared data with inspectors on at least a monthly basis. A further 9 (33%) shared data quarterly
- The majority (18; 66%) considered the frequency of sharing to be adequate. The remaining suggesting that there should be an increase in frequency of sharing
- Nearly half of respondents indicated joint training but for others training was provided on an ad hoc basis, or never

The next set of questions focused on what information is routinely shared between PV departments and inspectors.

Firstly, **Q7** asked what metrics and intelligence is shared.

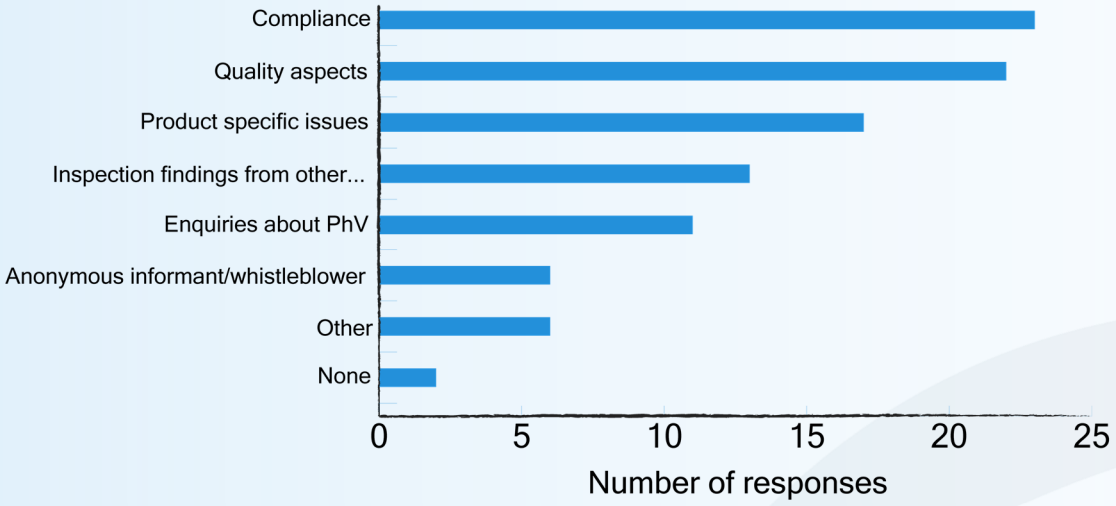

Figure 6. Responses to Q7: What metrics and intelligence is shared between inspectors and pharmacovigilance assessors?

(Where Compliance includes timely submission of ICSRs, PSURs, safety variations etc., and Quality aspects include poor quality PSURs, safety variations, ICSRs, line listing).

The most commonly selected response, with 23 (85%) of respondents, indicated they share compliance data regarding the submission of ICSRs, PSURs and safety variations. Quality aspects closely followed where 22 (82%) respondents share this information.

Information about product-specific issues was shared by 18 respondents (66%), followed by inspection findings from other authorities by 13 (48%).

A small number of free-text comments were provided where respondents explained the national arrangements – some noting that sharing of intelligence was on an ad hoc basis, or when an assessor notes non-compliance and shares with inspectors on a case by case basis. A further response stated that relevant information in the topic areas described above are readily accessible to inspectors and are therefore not routinely requested by inspectors or provided by individual assessors.

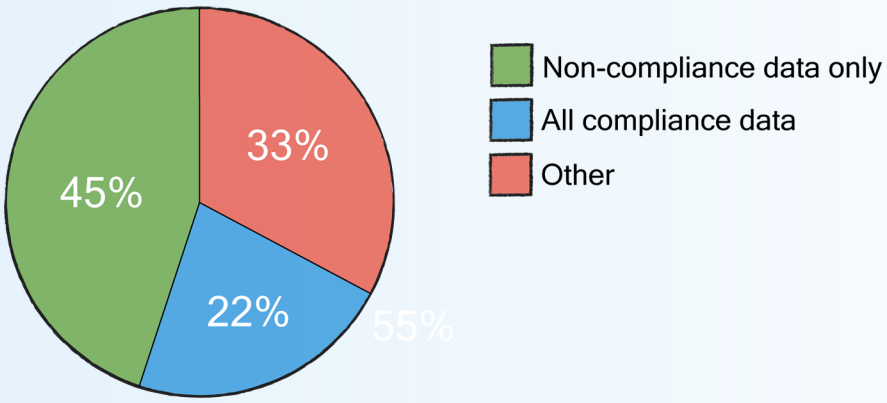

Figure 7. Responses to Q8: What data is routinely shared?

MSs mainly shared data on non-compliance with nearly half of all respondents sharing this data with inspectors alone, in **Q8** 6 (22%) respondents indicated they shared 'All compliance data'. For the remaining 9 respondents, several indicated that no data was shared with inspectors.

In line with responses from earlier questions, one respondent indicated that the role of PV assessor and inspector was combined, so that data sharing was daily and continuous. Free-text comments were also used to describe the type of documents shared which include inspection reports, yearly inspection programmes and relevant meeting minutes.

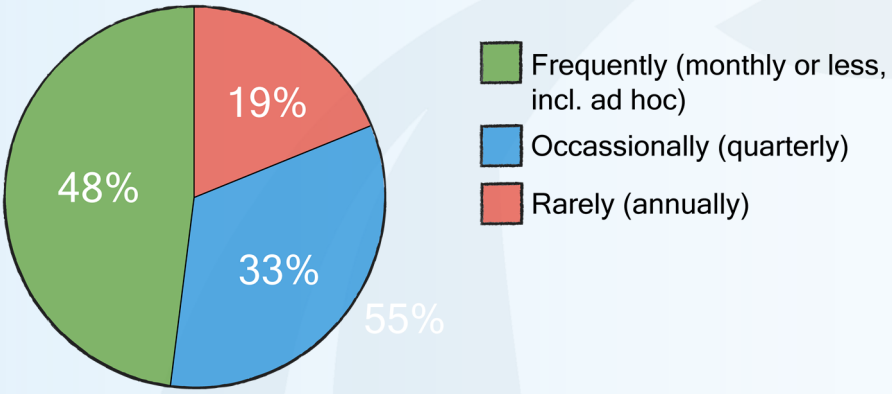

Figure 8. Responses to Q9: How frequently is information shared with pharmacovigilance inspectors?

Nearly half of MSs (13; 48%) shared data with inspectors on at least a monthly basis, with a further 9 (33%) on a quarterly basis.

Q10 asked MSs for their opinion on whether they considered the frequency of exchange of information with PV inspectors to be adequate. The majority (18; 66%) considered the frequency of sharing to be adequate. The remaining 9 (33%) suggested there should be an increase in frequency of sharing, with no MS proposing that information was shared too frequently.

MSs provided information about whether any PV assessors and inspectors have any common training in **Q11**. 12 (44%) of respondents indicated that there was joint training and provided more information about this in free-text comments.

Some joint training appeared to be on an ad hoc basis, with two MSs indicating that there was no systematic training performed.

One respondent noted that continuous common training on the GVP modules and inspection methodology is organised for both assessors and inspectors. Another respondent indicated that a 'rolling' programme of training was in place with inspectors delivering training to assessors and vice versa.

Several MSs referred to the training arranged by the EU PV Inspectors Working Group, which were also attended by PV assessors.

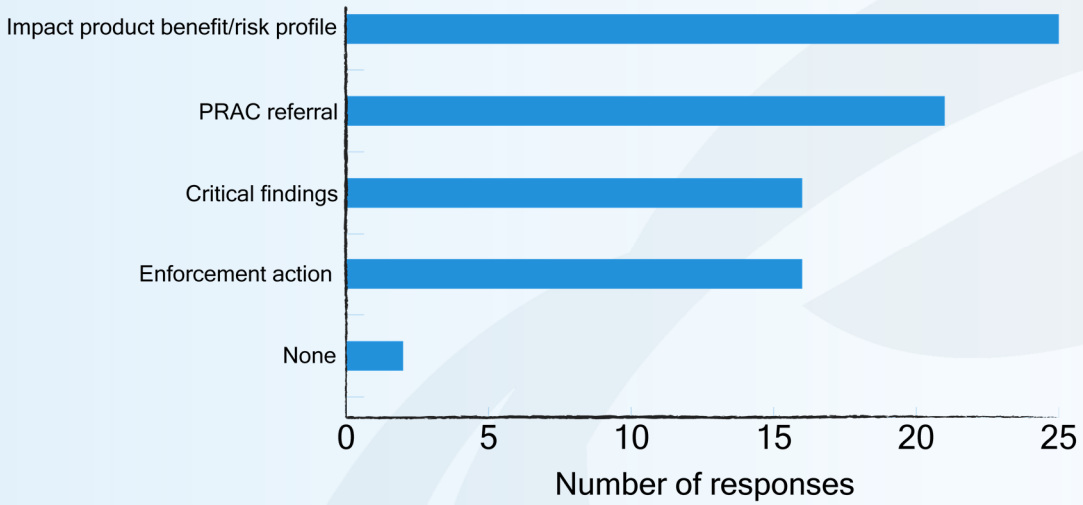

Figure 9. Responses to Q12: In what instances would pharmacovigilance departments get involved in post-inspection actions?

The survey results for **Q12** showed that the majority of PV departments are involved in actions following PV inspections. 25 (93%) respondents indicated that they would be involved where inspections reported outcomes that had a potential impact on the benefit/risk profile of a product. Outcomes requiring a referral to the Pharmacovigilance Risk Assessment Committee (PRAC) was closely followed with 21 (78%) respondents indicating involvement. 18 (67%) respondents indicated they would be involved following inspections resulting in critical findings, or where there was the potential for enforcement action. Only 2 (7%) respondents indicated there was no interaction following inspections.

MSs were asked to complete an optional free-text comment on any additional information they would like to receive from inspectors (**Q13**). 15 responses were received from the 27 respondents with 8 answering 'No'. Some noted that the roles were combined with PV assessments and others that there were regular joint meetings where inspection outcomes were presented. Four respondents highlighted that they would want to receive updates on the outcomes from inspections.

One respondent indicated the importance for re-inspection and enforcement of repeated non-compliance in companies.

3.3 Free-text comments on challenges and best practice (Q14-15)

Summary points

- A common trend in responses from MSs was the limited resources, in terms of staff and time
- The exchange of information was sometimes considered insufficient, or burdensome
- Solutions offered included managing limited resources through strict prioritisation
- Increasing opportunities for meetings, training and joint inspections with attendance from pharmacovigilance assessors was suggested
- Examples of good practice included the collaboration and cooperation between inspectors and assessors or PRAC delegates, including assessors attending inspections

In **Q14** and **Q15**, MSs were given the opportunity to write free-text answers about challenges or problems they have experienced in the area of PV inspections, and the interactions between departments. MSs were encouraged to provide information on how these had been overcome as well as aspects of national systems that they consider particularly useful, or 'good practice'.

A common trend in responses from MSs was **limited resources** – in terms of staff and time available to either provide inspectors the information needed to prepare/complete inspections, or to participate in inspections themselves.

Exchange of information was considered **insufficient**, or **burdensome** if not made clear how much information should be shared. Some respondents indicated specific problems with the setup of their agency where a separate entity is responsible for inspections making it more difficult to share information effectively.

Another respondent indicated that there was an issue from companies who may lobby PV operations in order to alter the impact of inspection findings. The solution offered was to coordinate responses to enquires from MAHs to provide a consistent position. Another respondent had a similar suggestion, with the establishment of a service desk which enables operations and inspections shared access to query responses.

For resource limitations, solutions offered included prioritisation of the companies subject to inspection. To limit the burden of sharing information with inspectors one respondent indicated that when assessors request information they are provided a short assessment report, followed by a discussion/meeting with the inspector.

Some MSs find a combined role of inspector and PV assessor to be particularly helpful. Where this is not possible, increasing opportunities for meetings, training and joint inspections with attendance from PV assessors is suggested. Sharing of information at these meetings, including press releases in relation to safety issues, safety communications, PRAC, safety signals, Direct Healthcare Professional Communication (DHPC) and lines to take on safety issues by assessors would be useful.

In **Q15**, where MSs were asked to identify helpful practices, collaboration between NCA assessors and inspectors was a theme which arose most often. Collaboration and cooperation with assessors or PRAC delegates, including assessors attending inspections was noted by a number of respondents. In instances where the responsibility for inspections and assessment is within the same department the fact that PV inspectors have an overview of PV due to their direct involvement in operations was highlighted. Conversely active involvement of PV staff in an 'Inspection Action group' (a group responsible for the discussion of serious inspection outcomes) was considered helpful and allowed them to have input into the decision-making following the identification of serious non-compliance.

Collaboration through ensuring information is available to inspectors was also noted – with one respondent outlining the fact that inspectors search the European Pharmacovigilance Issues Tracking Tool (EPITT) before inspection for safety issues and signals.

Collaboration could also be offered on an ongoing basis, in those cases where there are no regular meetings between inspectors and assessors. During the assessment process the assessors may identify issues that by themselves are not strong enough to trigger an inspection, but when the issues are repeated it may become an important item to be inspected. It is very important to propose how to share this ongoing information avoiding being burdensome for both parties.

Use of questionnaires to gather information from MAHs and the results are used to aid risk-based inspection planning was also highlighted.

3.4 Inspections (Q16-19)

Summary points

- The average number of both requests for inspections and of actioned inspections in a year ranged from 0 to 15; however, the most common response received was zero
- The inspection plan/schedule is shared with the PV departments according to 19 (70%) of the respondents
- Quality aspects and product specific issues were the most common information used to schedule PV inspections
- Feedback on inspection outcomes was most commonly shared in 64% of responses

The next section of the survey focused on information about inspections performed.

Q16 asked MSs to report a yearly average on how many requests were made for inspections, and how many of these actually led to an inspection.

Responses about the average number of requests for inspections and the average number of actioned inspections in a given year ranged from 0 to 15, but the most common response received was zero for both. Many respondents indicated approximate numbers. The following graph shows the difference between the average number of inspections requested and the number of those inspection requests that were actioned (δ).

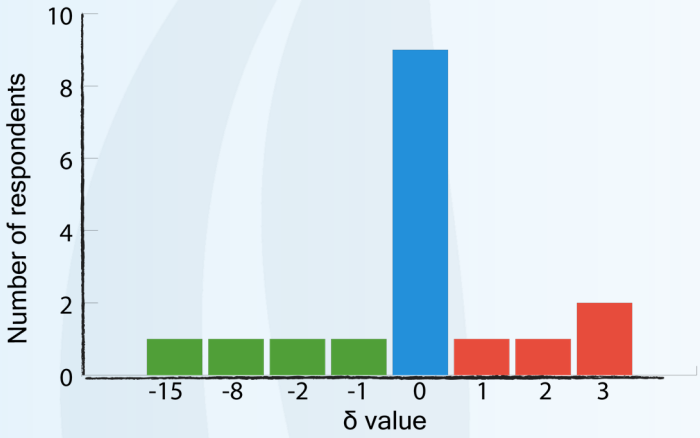

Figure 10. (A) Responses to Q16: Since implementation of the new legislation, how many requests were made for an inspection and how many of the requests led to an inspection (average number per year)?

Where δ = (number of inspection requests) – (number of actioned inspections), in an average year. Bars in green correspond to respondents who had more requests than actioned inspections, red for respondents who had more inspections actioned than were requested, and blue for the respondents who actioned all requested inspections.

Figure 10 (B): Q16 – number of inspections requested (red) and number of inspections actioned (green) by each MS.

Excluding respondents who had not requested any inspections, most respondents stated that they had actioned all inspection requests. Four respondents indicated that some of the requests for inspections did not result in an inspection being completed (red bar) and another four respondents (green bar) responded that more inspections had taken place than requested; although this situation is likely in many MSs with inspection departments following agreed inspections plans with other triggers for inspections, including from the European Medicines Agency (EMA) requests, re-inspections based on previous inspection outcomes and MAHs identified via a risk-based planning exercise. However, the aim of this question was to understand the number of requests made by PV departments that resulted in inspections.

Interpretation of this question should also take into account the way that PV inspections are scheduled and planned throughout the EU Network, in considering the reasons as to why inspections may appear not to have been fulfilled by the requested inspectorate. These reasons may include the following:

a) PV inspections in the EU operate under a Supervisory Authority model; each MAH with one or more centrally approved authorisations are “assigned” a Supervisory Authority based on the location of the Pharmacovigilance System Master File (PSMF). The Supervisory Authority is then responsible for the conduct of PV inspections on behalf of the EU Network. On receipt of a request for an inspection, the inspectorate could have passed the information and request onto the inspectorate acting as the Supervisory Authority for consideration in their inspection programme.

b) All PV inspectors in the EU have access to the inspections performed by other MSs through a common repository using the EMA Managing Meeting Documents (MMDs) System and following a request it could be that another MS had recently performed an inspection of that MAH and therefore mitigated the need for the requested inspectorate to conduct an additional inspection.

c) Many MSs schedule their inspection based on the EU PV inspection plan produced by the EMA (of which they have a legal obligation to fulfil) and if resource allows supplement the programme with additional inspections identified through a risk based approach. Whilst a request for an inspection may not have been fulfilled, the specific information supplied as part of this request is likely to have been considered in the context of all the other intelligence available on that MAH and a risk based decision reached on whether an inspection needed to be performed at that time, or whether the concerns raised could be resolved through another mechanism.

MSs were asked to explain whether the inspection schedule was shared with PV departments in **Q17**.

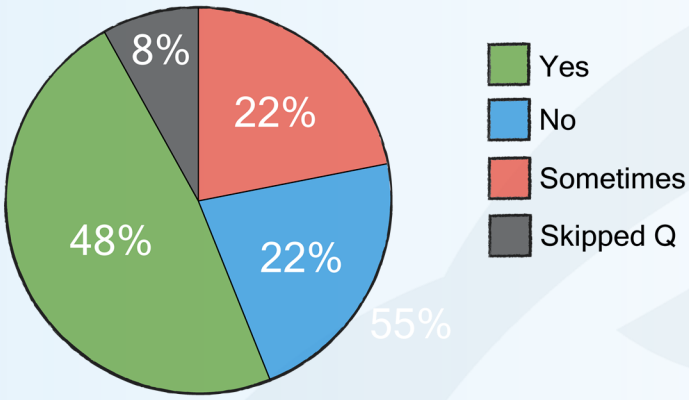

Figure 11. Responses to Q17: Is the inspection plan/schedule shared with the pharmacovigilance department?

Thirteen (48%) and 6 (22%) said 'Yes' or 'Sometimes', respectively, meaning that the schedule is shared in 19 (70%) of the respondents. Two respondents skipped the question, which may be due to the similarity with **Q5**, although that question focused on sharing of information between departments which resulted from specific interactions. In **Q5** 63% of respondents reported that interactions resulted in sharing of the inspections plan/schedule.

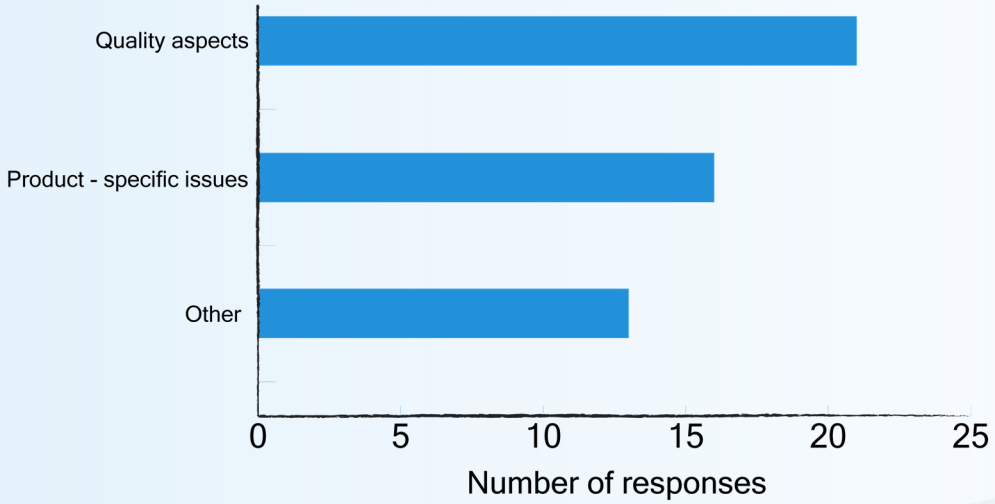

Figure 12. Responses to Q18: what information is used to schedule pharmacovigilance inspections?

Where product-specific issues included the Committee for Medicinal Products for Human Use (CHMP) referrals, Risk Management Plan (RMP) commitments and product recalls. Quality aspects included poor quality PSURs, ICSRs and safety variation submissions.

When responding to the question about what information is used to schedule PV inspections (**Q18**) quality aspects were the most common response at 84%, with product specific issues slightly lower at 64%.

In the free-text responses provided by 8 respondents the use of **risk-based approaches** was mentioned or that risk-based approaches were being developed. Another 2 respondents noted the **resources available** were a factor in the scheduling of PV inspections.

Q19 asked what inspections information was routinely shared with PV assessors.

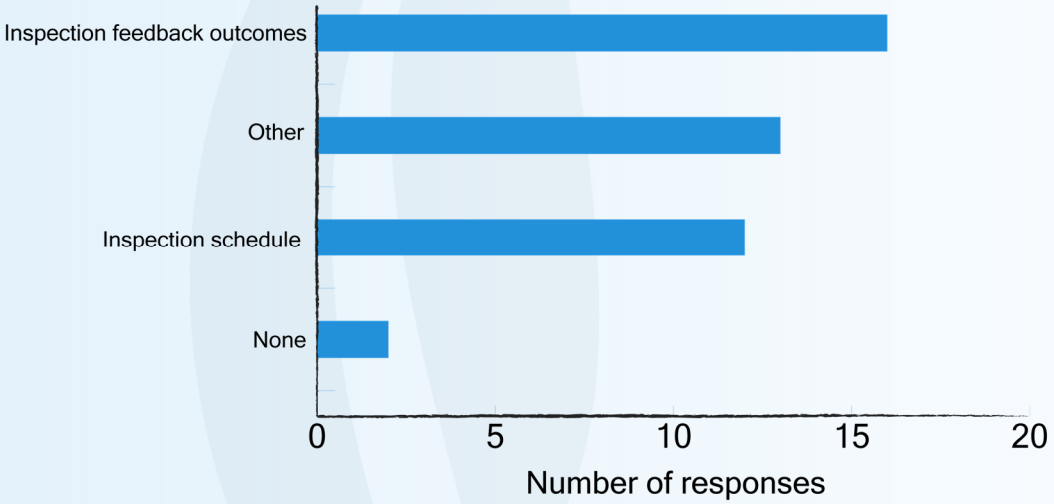

Figure 13. Responses to Q19: What information is routinely shared with pharmacovigilance assessors?

Feedback on inspections outcomes was routinely shared in 64% of responses, with the schedule routinely being shared according to 48% respondents.

In free-text comments respondents indicated that feedback was shared when an inspection had been triggered as a result of non-compliance or product related problems previously **raised by PV assessors**. Also feedback was provided when **PV assessors had participated in the inspection** or when the inspection identified **product related issues**.

It was apparent that there may have been some confusion that the question duplicated part of **Q5** earlier in the survey. **Q5** focused on the sharing of information between departments which resulted from specific interactions.

3.5 Use of information from pharmacovigilance departments by inspectors (Q20-25)

Summary points

- Information is mainly qualitatively assessed by inspectors, on a case-by-case basis
- A limited number of respondents reported input of information into a formal risk-based inspection tool, although nearly all reported using a risk-based inspection approach
- Requests for information made by inspectors were mainly in relation to PV assessment statuses or product-specific topics
- Over half of respondents reported that inspection outcomes were always shared
- Many respondents used informal processes to share feedback from inspections, with fewer using scheduled meetings or systems to provide common access to inspection reports or shared tracking tables
- Inspectors would like more information from assessors e.g. non-compliance, quality of documentation

Q20 asked how information received by inspectors from PV departments is used for the scheduling of inspections.

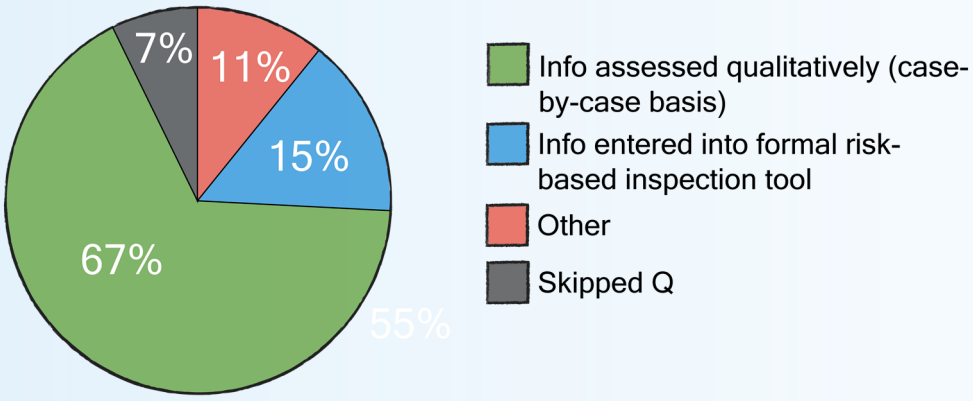

Figure 14. Responses to Q20: How is the information/intelligence received from pharmacovigilance departments used by pharmacovigilance inspectors?

The responses indicated that information appeared to be mainly assessed qualitatively on a case-by-case basis, in 18 (67%) NCAs. 4 respondents (15%) indicated the information was entered in a formalised risk-based inspection scheduling tool.

In response to **Q21**, 25 respondents indicated that they use a risk-based approach for planning inspections. 21 respondents provided more detail on the factors considered in the risk-based assessment in free-text comments. Common risk information considered in inspection planning included:

- The EMA requests for inspection
- Previous inspection history, including previous outcomes and the amount of time passed since the last inspection
- Changes to the PV system of the MAH since the last inspection
- Significant mergers and acquisitions/change of ownership
- Information on the MAH product portfolio (including number and type of products, including products subject to additional monitoring)
- Pharmacovigilance activities performed (e.g. Post-Authorisation Safety Studies (PASS), risk minimisation measures etc.)
- Number of ICSRSs, non-compliance of ICSR reporting and underreporting
- Location of the EU- Qualified Person Responsible for Pharmacovigilance (QPPV) and Pharmacovigilance System Master File (PSMF).

Several respondents also provided information on how this information was sourced and reviewed; two respondents stated that information was actively solicited from MAHs via questionnaires with one respondent combining this with internal information, whilst others stated that the information was extracted from internal data sources such as product databases and systems maintained by internal PV departments.

As indicated in the response to **Q20**, the majority of the data was reviewed qualitatively; however, 2 respondents for **Q21** stated that a numerical figure was applied to the data to allow prioritisation of MAHs for inspection.

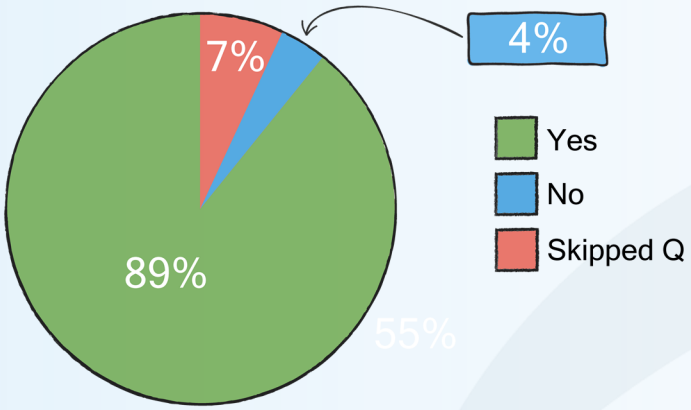

Figure 15. Responses to Q21: Is there a risk-based approach for planning pharmacovigilance inspections?

Q22 asked MSs to explain when inspectors would ask for input from PV departments in the preparation, conduct or reporting of an inspection.

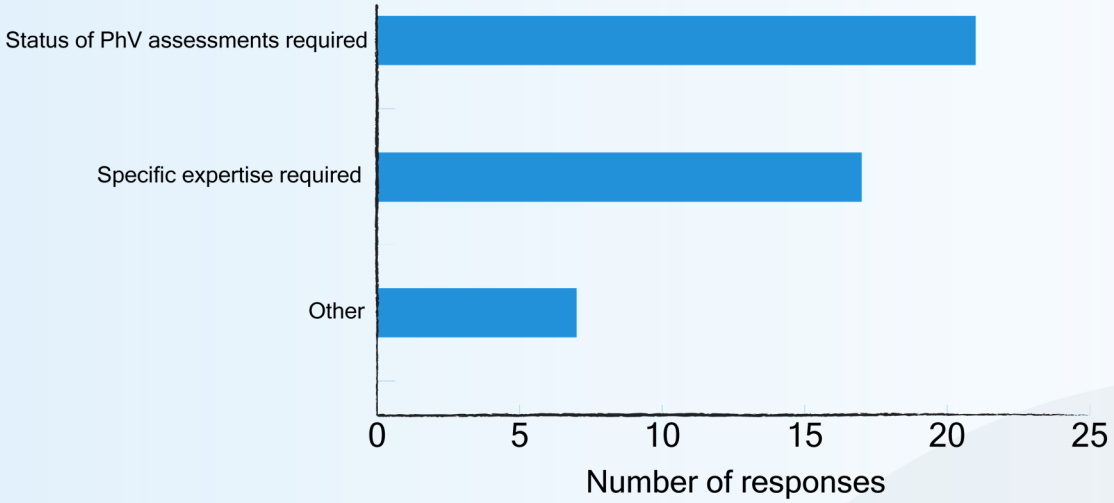

Figure 16. Responses to Q22: In what instances would input from pharmacovigilance departments be requested during the preparation, conduct and reporting of an inspection?

Twenty-two (84%) respondents indicated that PV department input would most often be sought where information was required regarding the status of PV assessments (such as PSURs, referrals and RMPs), 19 (73%) reported input was sought for product specific topics where expertise was required.

In free-text comments respondents explained that PV departments were asked for data on non-compliance e.g. in reporting ICSRs, or implementation of risk minimisation measures.

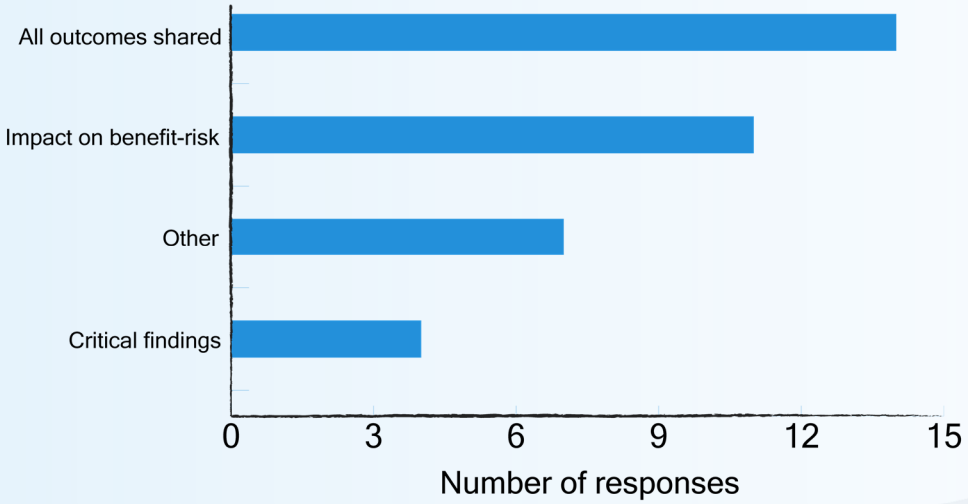

Figure 17. Responses to Q23: In what instances would pharmacovigilance inspection outcomes be shared with pharmacovigilance assessors?

Fourteen (52%) respondents reported that all inspection outcomes were shared (**Q23**). And a further (11 respondents, 42%) noted that outcomes having an impact on the benefit risk profile were shared. 4 (16%) provided feedback only when critical findings were reported. One respondent in free-text feedback stated that inspection outcomes are discussed at monthly meetings and other respondents indicating that changes were being made to ensure feedback on all inspections were provided in future.

The method by which this information was reported is discussed in **Q24**.

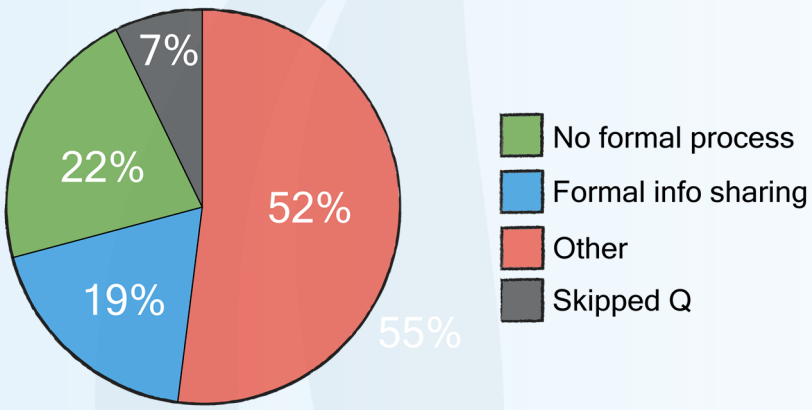

Figure 18. Responses to Q24: If they are shared, how are inspection outcomes shared with pharmacovigilance assessors?

Many respondents mentioned the use of informal processes such as emails. Others had more structured processes such as scheduled meetings, Information Technology (IT) systems to provide common access to inspection reports or tracking tables stored in a shared location. 5 (19%) respondents indicated that they have a formal information sharing process.

In **Q25** respondents were given the opportunity to explain what additional information inspectors would like to receive from PV assessors. Common themes previously raised were highlighted again, with inspectors wanting more information about identified non-compliance, the quality of regulatory submissions including ICSRs, PSURs and DHPCs, press releases on safety issues, PRAC and safety communications. A few noted common training could facilitate enhanced information sharing.

One respondent in particular noted that they wanted to have more input '*on inspection triggers*' and problems encountered with MAHs, and to have feedback about what aspects of the risk management plan should be checked with the MAH at inspection.

3.6 Free-text comments on challenges and best practice (Q26-27)

Summary points

- Significant challenges were noted as relating to workload and collaboration
- Joint training of assessors and inspectors, as well as collaborations on inspections were suggested to help assessors understand the value of inspections
- Cooperation between inspectors and PV assessors is particularly helpful in planning and conducting inspections with complementary but different skills
- Agencies where PV inspectors and assessor roles are combined, or situations where inspectors are in PV departments, is considered an advantage

Q26 provided inspection departments in MSs the opportunity to describe any challenges or problems encountered, and offer solutions used to overcome these.

There was a continuation of suggestions to collaborate and share training between inspectors and assessors, although one respondent noted that it was "*a challenge to find time for sufficient communication and shared training between inspectors and assessors*". Increased attendance of assessors at inspections was suggested to help ensure consistency of communications with MAHs from different areas of NCAs.

Another respondent noted that the value of inspections was sometimes not clear for PV assessors. It was suggested that the "*Inspection process should be an integrated part of the complete surveillance process (including assessments and inspections as quality tools) and should be perceived internally as such*".

An example was provided by one respondent to ensure PV assessors were aware of non-compliance data being recorded by inspectors; a weekly discussion of non-compliance data was introduced as the point in the agenda of PV department meetings.

Workload was a theme brought up by a number of respondents. One noted that the volume of data and documents which require review prior to and during an inspection was the greatest challenge. The solution recommended was simply to provide additional time for review. Another comment found the lack of other inspectors to discuss issues a challenge due to there being only one inspector in that agency.

Another comment was received that an IT system to establish the "*connection between pharmacovigilance data (including compliance) and MAHs would be desirable*".

Q27 asked MSs to describe anything about PV inspections in their agencies considered particularly helpful or best practice.

Again cooperation between inspectors and PV staff was highlighted as being particularly helpful in planning and conducting inspections. The complementary but different skills of inspectors and assessors were noted. Use of a checklist was suggested for activities completed during preparation of inspections, and definitions of clear responsibilities between PV assessors and inspectors.

Information sharing between departments was highlighted as something which works well and specific areas highlighted "*involvement of pharmacovigilance staff in decisions*", "*receipt of compliance information on a routine basis by the Inspectorate from pharmacovigilance staff*" and "*direct interactions with assessors for product-specific issues*".

Training of inspectors in the PV processes utilised within the NCAs was suggested to help improve common understanding of the responsibilities of each of the roles. A common theme highlighted from previous questions again was noted with agencies where PV inspectors and assessor roles are combined or situations where inspectors are in PV departments, was considered an advantage.

A number of respondents referred back to information provided in Questions 13-15 which indicated the survey had been answered fully by one department rather than obtaining input from PV operations and inspections departments, as was the aim of the survey.

4. Discussion

Twenty-six of twenty-seven active SCOPE MSs responded to the survey, with an additional one non-active SCOPE partner contributing as well.

With respect to the organisational arrangements within NCAs, the majority have separate departments for PV assessors and inspectors, with generally good communication when an inspection is requested. The survey results indicated that most respondents had defined criteria for triggering inspections, most of which are formally defined in SOPs. Several NCAs noted that combined roles, either an assessor also being a PV inspector, or some shared role, also enabled helpful collaboration.

Overall the response to the survey demonstrates that interaction between PV departments and inspectors is essential in the monitoring and assessing of MAH compliance with PV obligations. One respondent illustrated the importance of this interaction, noting that inspections should be an integrated part of the surveillance process, including assessments and inspections as quality tools. This is in support of the concepts described in GVP Module III[9], that inspections form an important part of the overall surveillance programme, by verifying the compliance status of MAHs. Improvement in the collaboration between inspectors and assessors will contribute towards NCAs achieving this integrated approach. In addition many NCAs highlighted the importance of involving assessors in the inspection process in circumstances where product specific expertise are required, when inspections identify outcomes that require referral to PRAC, or other critical findings leading to the potential for enforcement action.

It is interesting to note that inspector access to existing data repositories such as the EPITT was considered a useful pre-inspection data source regarding ongoing signals. Nearly half of respondents share PV data with inspectors on at least a monthly basis and a third of PV departments considered that there should be an increase in frequency information sharing in their MSs.

[9] Guideline on good pharmacovigilance practices: Module III – Pharmacovigilance inspections.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172400.pdf
Accessed 03/06/2015

The number of PV inspections requested of NCAs per year ranged from 0 to 15, with many NCAs stating that they did not receive any requests for inspections, although this question was subject to differences in interpretation. This includes taking into account the way that PV inspections are scheduled and planned throughout the EU network. The reasons as to why inspections may appear to not have been fulfilled could be: 1) because some of the inspections programmed as Supervisory Authority could have been performed recently by another MS; 2) when studying information gathered in preparation for inspections a risk decision is made on whether an inspection is needed at that time or issues raised could be resolved via another mechanism. Nearly all NCAs use a risk based approach to plan inspections, with a limited number of respondents inputting information into a formal risk-based inspection planning tool.

Information shared with assessors included the inspection schedule and feedback on the outcome of the inspection, particularly if the inspection had a product specific impact, or if the assessor had been present at the inspection. Nearly all respondents would share inspections outcomes where there is an impact on benefit-risk profile of a product. When inspectors were asked what additional information they would like to receive from assessors, NCAs stated non-compliance, quality of documentation including ICSRs and DHPCs, press releases on safety issues, PRAC and safety communications.

In summary, the majority of respondents indicated that some form of interaction between PV departments and inspectors takes place within MSs. However the implementation of such interactions into formal procedures differed between respondents. The recommendations arising from this survey could be used by MSs to formalise interactions between their PV departments and inspectors to ensure consistency in the sharing of information to support PV assessment and inspection activities.

4.1 Good practice in how to make information accessible regarding MAH non-compliance within NCAs

Clearly, for NCAs intelligence regarding MAH non-compliance is fundamental in facilitating MAH compliance with pharmacovigilance obligations and fulfilling their regulatory responsibilities. Good practice identified from the survey included the use of a shared 'tracking document' by two NCAs that was used collaboratively between PV inspectors and assessors to track cases of non-compliance. Whilst it may not be necessary for all MSs to have a specific tracking document, the concept of collecting information regarding MAH non-compliance in a central location that can be updated and accessed by both inspectors and assessors could be considered good practice. Such a system would allow assessors to record information regarding non-compliance that they become aware of during their routine assessment activities (for example late regulatory submissions), poor quality of regulatory submissions (such as ICSRs, PSURs, RMPs and safety variations). If such information is made readily available to inspectors for use when required, e.g. preparing for an inspection, this could reduce the number of ad-hoc requests for information made by inspectors during the inspection planning phase, which in turn could improve efficiency.

4.2 Information Sharing within NCAs

In response to the survey, the majority of respondents indicated that information is routinely shared between PV departments and their inspectors. 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 that they should determine what information is available within the NCA and how that information can be accessed. 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.

It is considered good practice to ensure that PV departments are able to access information on the outcomes of inspections. However, as indicated in the responses to **Q12**, in some instances input from the PV department is required in determining actions to be taken as a result of an inspection. Therefore it is important to consider when inspection outcomes should be referred to PV departments in an expedited manner, in contrast to when the outcome of the inspection can be made accessible for information only.

4.3 Training

Nearly half of respondents indicated that elements of PV training were shared between PV departments and inspectors. NCAs highlighted several examples of good practice in training including continuous common training on GVP modules and inspection methodology organised for both assessors and inspectors, together with a 'rolling' programme of training in place with inspectors delivering training to assessors and vice versa. Whilst the application of technical information described in legislation and guidance may differ for an assessor and inspector, joint training of PV assessors and inspectors will support 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.

The survey also indicated that some MSs performed inspections where inspectors were accompanied by assessors. Whilst this would not be considered appropriate for all inspections, where there is a product-specific element or objective to an inspection then joint attendance should be considered good practice. 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. Additionally, where resources allow assessor attendance at

PV inspections can provide a useful training opportunity for both assessors and inspectors.

In addition, it is also important to note the role of the EU Network Training Centre[10] which is an initiative aimed at creating a European central platform for exchange of information and supply of regulatory and scientific training across the EU regulatory network. The EU Network Training Centre is committed to the improvement of quality, consistency and efficiency of the work of the European Regulatory Network by promoting the harmonised operation of the regulatory framework and guidelines and fostering science based, pragmatic and consistent assessment, inspection, pharmacovigilance and decision making. It will also provide continuous professional development for regulatory agencies and possibly other stakeholders involved in the development of medicines regulation.

[10] http://www.hma.eu/otsg.html Accessed: [24/06/2015]

4.4 BEMA

Finally, it is important to recognise that NCAs may have already provided information on management of interfaces as part of their submission for the Benchmarking of European Medicines Agencies (BEMA) assessment[11]. BEMA is a Heads of Medicines Agencies (HMA) initiative involving an assessment of the systems and processes in individual agencies against a set of indicators, to identify strengths and best practices and any opportunities for improvement. The initiative aims '*to contribute to the development of a world-class pharmaceutical regulatory system, based on a network of agencies, operating to best practice standards.*'

The BEMA methodology includes both self-assessment and peer review assessment by trained BEMA assessors against a questionnaire of set predefined performance indicators. A scoring system, based on the maturity levels described in ISO 9004 are applied in order to provide a benchmark against which to measure improvements. The outcome of each visit is an anonymised report produced by the assessment team and agreed with the visited agency. All results are uploaded to a database and a report is generated for the agencies to use as a tool for identification of best practices and for improvement. The third cycle of BEMA is based on visits to agencies between 2012 to 2014.

The BEMA database was analysed for the Key Performance Indicator (KPI) 10.3 from the third cycle of BEMA to compare with the results of this survey.

> **BEMA III KPIs 10.3 – Management of interfaces – Between clinical assessors and pharmacovigilance assessors and GCP, GMP and GLP inspectors as appropriate and between individual inspectorates**
>
> The existence and effectiveness of communication and co-operation between clinical assessors, PV assessors and relevant inspectors and between different inspection disciplines are essential in ensuring that inspection findings are made available in a timely fashion to clinical assessors and that any failures to comply with relevant good practices are brought to their attention. Effective communication ensures also that clinical assessors are aware of planned inspections so that they can ask inspectors to target issues for which they may have concerns.

[11] http://www.hma.eu/bema.html Accessed: [12/06/2015]

In comparison, analysis of assessor reports from the third cycle of BEMA support the results of the survey with examples of best practice including the involvement of PV inspectors in debriefing of PV committees, exchange of information between assessors and inspectors through a 'clinic club' and monthly meetings between assessors and inspectors to discuss 'hot topics'. In line with the results of the survey, the benefits of cross training and shadowing were also noted with examples in training such as the EPITT, the EudraVigilance Data Analysis System (EVDAS), the Medical Dictionary for Regulatory Activities (MedDRA) and new legislation. Furthermore, it is interesting to note that regular auditing of the interfaces between assessors and inspectors was also considered helpful in the continuous improvement of the PV systems at NCAs. In summary, the results from BEMA III support the reinforcement of the link between assessors and inspectors and the benefits of improved communication process within NCAs.

5. Conclusions and future work

In conclusion, these survey results highlight the success of inspections involving multidisciplinary teams in facilitating MAH compliance with PV obligations and fulfilling regulatory responsibilities. Sharing of information, effective communication and interactions are essential elements towards achieving an integrated approach. The benefits of such collaborative approaches were described by many MSs with improved NCA efficiencies. For assessors there is a greater understanding and context of the varied mechanisms used by MAHs to achieve their regulatory obligations and the challenges faced, which in turn can help inform their assessments. For inspectors, product specific knowledge and any ongoing historical regulatory and safety actions can be helpful when reviewing PV data. Additionally, PV inspections offer training opportunities for both assessors and inspectors.

Nevertheless, the survey results illustrate the diverse approaches used nationally. It is considered noteworthy that a proportion of MSs do not have formal procedures for interactions between PV departments and inspectors. Aiming to provide advice to MSs who want to improve interaction between PV department and inspectors, the report provides examples and recommendations as to how best to improve interactions and ensure efficient communications which may be adapted to national requirements. The specific topics of interest below have been identified in the survey that may be taken forward for development of recommendations under key headings, as part of the quality toolkit for WP7:

1. Recommendations for the exchange of information between PV departments and PV inspectors
2. Identify good practice in how to make accessible/share information regarding MAH non-compliance within NCAs
3. Identify examples of good practice in training through common initiatives for both assessors and inspectors through a case study.