Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Pharmacovigilance Inspection Metrics Report

April 2017 – March 2018

1. Introduction

During the period 01 April 2017 to 31 March 2018, the MHRA's Good Pharmacovigilance Practice (GPvP) inspectorate conducted 22 inspections of marketing authorisation holders (MAHs). The purpose of these inspections was to examine compliance with existing EU and national pharmacovigilance regulations and guidelines. This report contains data relating to all 22 inspections conducted during the period.

Findings identified during inspections were graded as critical, major or minor; the definitions for which are included in Appendix 1.

The number of inspections conducted during the period 01 April 2017 to 31 March 2018 was fewer than in previous years with an overall increase in duration of each inspection. The increasing days spent per inspection can be attributed to the risk factors considered to compile the inspection programme for the reporting period.

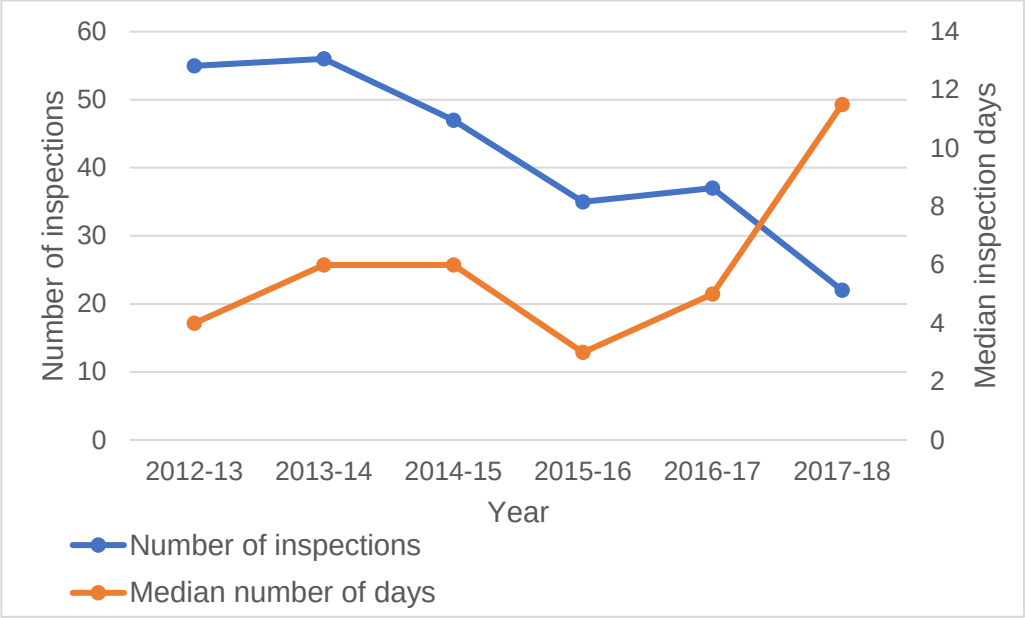

Figure 1 - Number of inspections per year compared with median days spent per inspection over the years*

*Days per inspection represent each day multiplied by each inspector, i.e. a six-day inspection could represent three days of inspection conducted by two inspectors.

2. Risk-based inspection planning

The MHRA GPvP inspection schedule is developed using a risk-based approach in accordance with Good Vigilance Practice (GVP) Module III. The national programme for each year also takes into account the EMA's programme of routine pharmacovigilance inspections of organisations with centrally authorised products.

Key risk factors reviewed during the development of the inspection programme for 2017/18 were product risk, the complexity of the pharmacovigilance system, the complexity and size of the organisation(s) involved in the pharmacovigilance system and the compliance and inspection history of an organisation, as illustrated in the figure below.

Figure 2 - Risk-factors influencing inspection planning

The increasing complexity of the higher risk pharmacovigilance systems we inspect has led to an increasing number of days spent per inspection, which has reduced the overall number of pharmacovigilance systems that have been inspected. Factors that contribute to increased complexity of the pharmacovigilance system include:

- Products that have unique and detailed requirements, such as additional pharmacovigilance activities including PASS and/or additional risk minimisation measures such as educational materials for patients and prescribers.
- Organisations that have undergone significant mergers or acquisitions or acquired licences for significant numbers of products. This can expand the scope of the inspection to cover aspects such as data migration and complex arrangements with global partners.
- Large organisations where it can take time to navigate the pharmacovigilance system and understand the processes in place, especially where the MHRA is the supervisory authority. In most larger organisations, irrespective of whether the MHRA is the supervisory authority, there are often complex processes spanning multiple global sites and functions which must be reviewed and understood by inspectors.

3. Types of inspection

Of the 22 inspections conducted during the period between 01 April 2017 to 31 March 2018:

- Sixteen inspections were conducted as a result of the periodic risk-based inspection planning process. Two of these were MAHs who had not previously undergone an MHRA GPvP inspection.
- Six inspections were triggered due to known or suspected compliance issues, or product safety concerns. Four of these were due to previous critical findings, one requested by CHMP and one was triggered due to specific risk information.

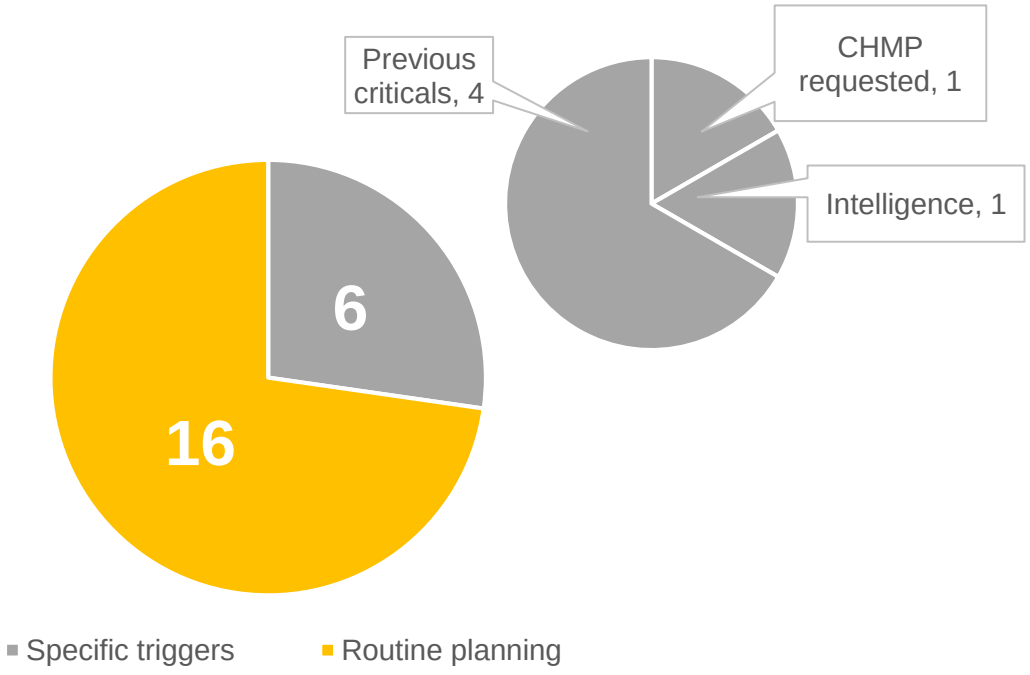

Figure 3 – Number of inspections conducted by type during 2017/18, small chart displaying inspection triggers

4. Summary of findings

A total of four critical, 89 major and 69 minor findings were identified during this period. A reported finding is often comprised of multiple separate findings, grouped according to a high level legislative requirement or according to a cumulative pharmacovigilance impact (under which many breaches of legislation could have been identified).

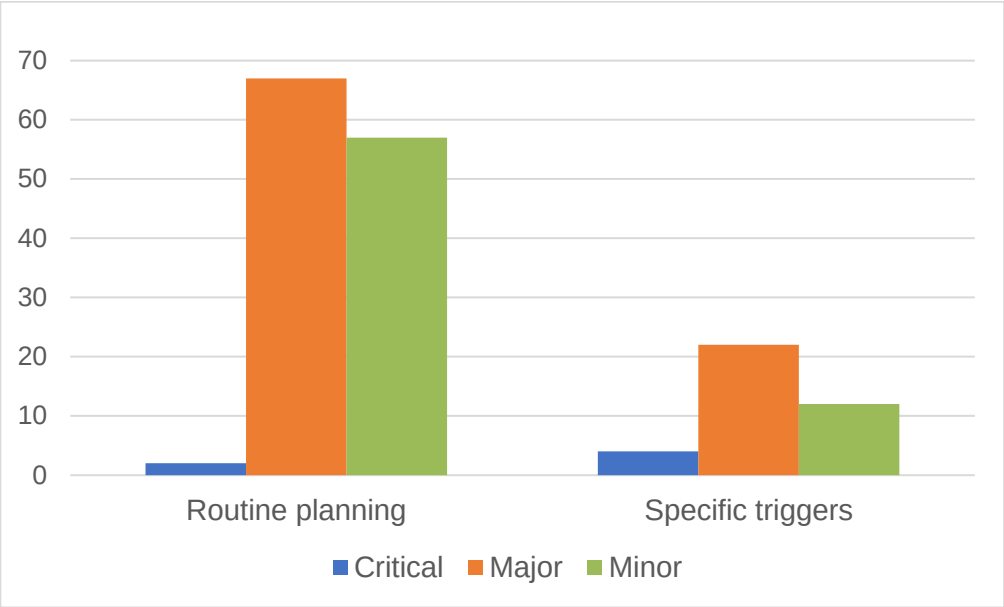

Figure 4 - Findings reported by inspection type

4.1 Critical findings

Four critical findings were issued during the reporting period from three inspections. Representing approximately one critical finding in every six inspections, this is similar to the previous period. Critical findings typically represent complex and significant deficiencies in a pharmacovigilance system, but broadly the critical findings reported in the 2017/18 period were categorised into the following topic areas:

- **2** Risk management
- **1** Quality management system
- **1** Ongoing safety evaluation

An anonymous summary of each critical finding is presented below.

Risk management systems
Significant deficiencies were identified across the risk management system for products reviewed during the inspection.

There were specific failings in relation to commitments within risk management plans (RMPs) including a failure to implement additional risk minimisation measures (aRMMs) for important identified and potential risks in accordance with the approved RMP, a failure to fulfil a request from a national competent authority (NCA) for specific data monitoring in lieu of a PASS, a failure to undertake targeted follow-up of events of special interest and a failure to analyse and report on the effectiveness of risk minimisation measures.

In addition, the MAH had not maintained RMPs in line with the known safety concerns and the current risk management system for certain products.

The MAH lacked documentation for the implementation of aRMMs and adequate oversight and monitoring by the EU QPPV of the adherence to RMP commitments.

This was graded as a critical finding due to the potential impact on the rights, safety or well-being of patients and the serious violations of applicable legislation and guidelines.

Additional risk minimisation measures, provision of information to national competent authorities and management of non-compliance

There were failures in the implementation of an electronic risk management system linked to a condition of specific marketing authorisations. These failures meant that reports submitted to the MHRA on the effectiveness of and adherence to additional risk minimisation measures were inaccurate.

The MAH's commitments to promote healthcare professional adherence to the measures and collect associated adherence data were not properly undertaken, and where deficiencies and compliance failures had become known to the MAH they had not been fully disclosed to the MHRA or properly handled.

Both of these aspects pose a risk to the rights, safety or well-being of patients; the seriousness of the finding was underpinned by the MAH's failures to disclose, fully investigate and take appropriate action when data management issues had arisen.

Quality management system for pharmacovigilance

The inspection reported widespread failures in the delivery of pharmacovigilance across critical pharmacovigilance processes. Specific critical processes that were not being fulfilled according to the legislative requirements included risk minimisation, submission and preparation of PSURs, submission of ICSRs and the maintenance of product information.

The MAH was aware of several failures within the pharmacovigilance system, however had not addressed these deficiencies.

The MAH had failed to ensure appropriate oversight of the pharmacovigilance system. The system was not fully represented in the pharmacovigilance system master file (PSMF) and this had an impact on the planning and conduct of the inspection.

The failure to deliver compliant activity across a number of critical pharmacovigilance processes, and in the context of the deficiencies being known to the MAH, was a serious breach of legislation.

Ongoing safety evaluation – Signal management
The MAH did not have the appropriate mechanisms and systems in place to allow for adequate ongoing safety monitoring, including signal detection. Signal detection was not being conducted for a large proportion of UK authorised products that were on the market. For the products for which signal detection had been conducted, the output reports contained incorrect statements and included inaccurate data, and the signal tracker in use at the time of the inspection did not provide traceability of all steps of the signal management process. There were examples of safety signals that had been identified by a previous pharmacovigilance service provider but had not been further evaluated, and there was a failure to maintain records of ongoing safety monitoring activities conducted by the previous service provider. The MAH had also failed to submit a safety variation application by the deadline following a published PRAC recommendation. This was graded as a critical finding due to serious violations of applicable legislation and guidelines.

In the three inspections where one or more critical findings were reported, it should be noted that there were also several major findings reported in other areas of the pharmacovigilance system as shown in the table below.

Inspection	Critical	Major	Minor
A	2	5	0
B	1	7	1
C	1	4	1

Table 1 - Numbers of major and minor findings reported alongside critical findings

4.2 Major findings

At least one major finding was reported in every inspection in the reporting period. The number of major findings reported ranged between one and eight. The typical number of major findings reported from an inspection was between three and five as shown in the graph below.

Figure 5 - Number of major findings reported per organisation

89 major findings were reported from inspections between 01 April 2017 and 31 March 2018. For the purposes of this report, findings have been grouped by overarching topics across the pharmacovigilance system, the nature of findings covered by each topic is provided in Appendix II. The topic with the highest proportion of major findings in the reporting period was risk management (25%). The next highest proportion of major findings was in relation to non-compliance in the quality management system (21%). These topics are discussed in more detail in the next section of this report (see focus topics in section 5).

Major findings for the provision of information for supervision by NCAs, including in the context of inspection, is an emerging trend, representing 16% of all major findings in this reporting period (see focus topic in section 5).

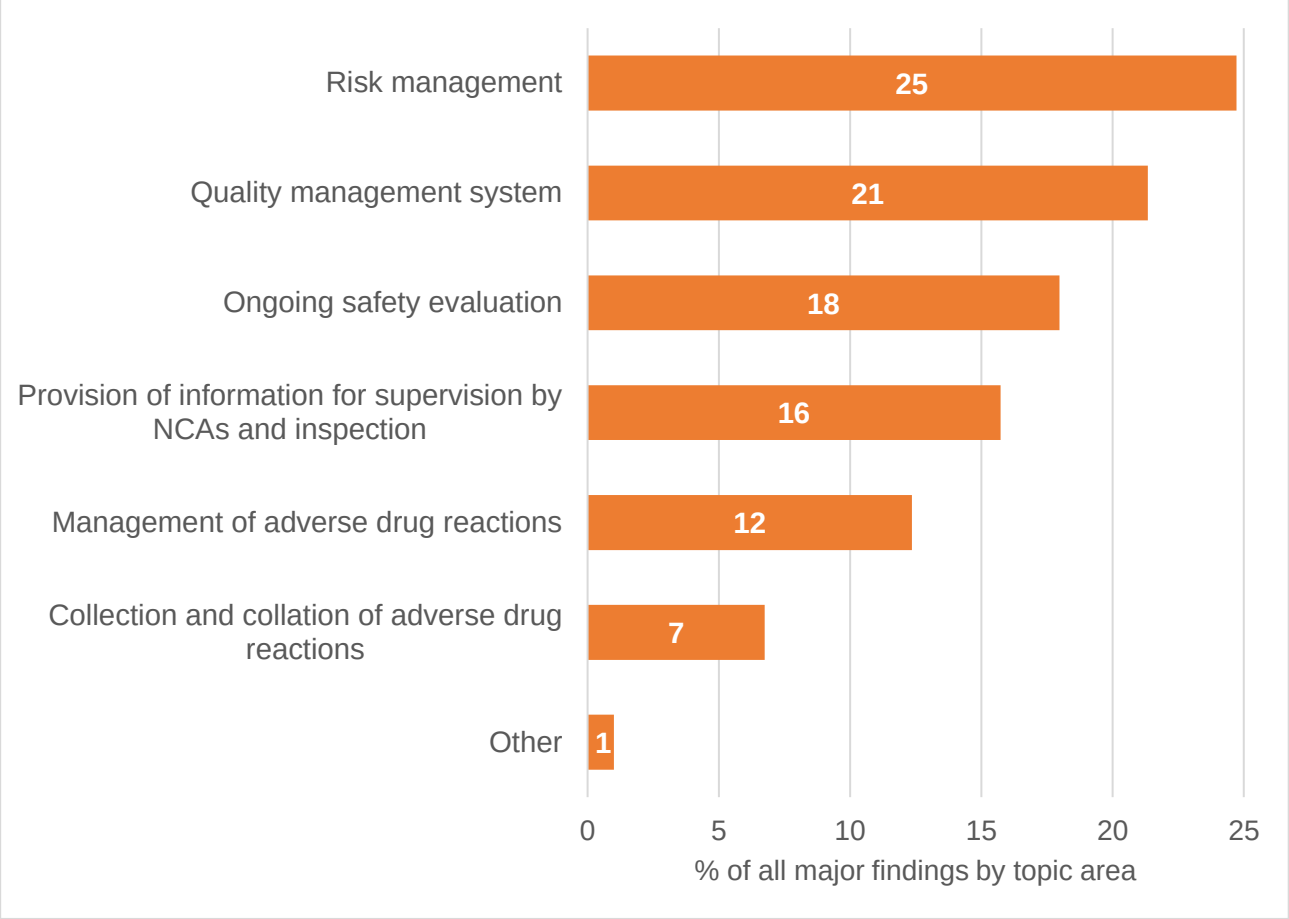

Figure 6 - Proportion of major findings reported for each topic area

There was a single major finding reported as 'other', which related to pharmacovigilance for biological medicines and resulted from failures to comply with the specific requirements in GVP Product- or population-specific considerations II: Biological medicinal products (GVP chapter PII) that spanned across multiple pharmacovigilance activities. This was not the only finding reported during the 2017/18 period against GVP chapter PII. Other findings in relation to breaches of GVP chapter PII have been reported under the specific area of failing, for example failure in meeting the requirements for ongoing safety evaluation for biological medicines.

Core pharmacovigilance activities such as ongoing safety evaluation and collection, collation and management of adverse drug reactions continue to be common areas of major findings consistent with previous years.

4.3 Minor findings

69 Minor findings were reported during the reporting period. The proportion of the findings by topic area is displayed in the graph below.

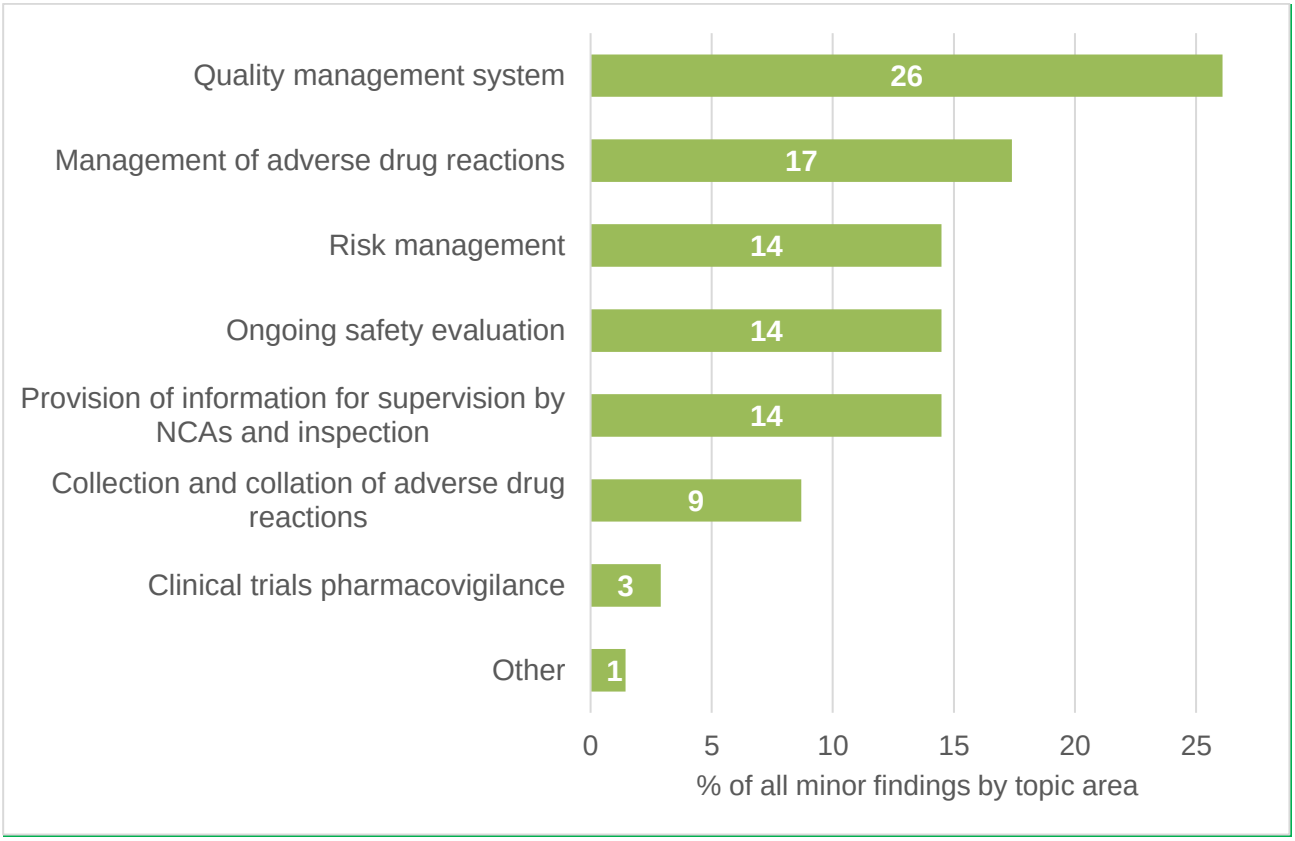

Figure 7 - Proportion of minor findings reported for each topic area

The quality management system was the largest proportion of minor findings. There was a single finding reported for a minor failing related to management of social media programmes which has been represented in the graph as 'other'.

5. Focus topics

5.1 Risk management

During this reporting period, findings in relation to risk management were reported against the more detailed topics shown in the graph below. Findings of any grading in relation to risk management were reported from 18 of the 22 inspections conducted from 01 April 2017 to 31 March 2018, including two critical findings and 22 major findings (25% of all major findings). This represents an increase from the previous reporting period during which no critical findings in this area were reported. Additionally, in the previous reporting period findings concerning reference safety information, risk management systems and post authorisation safety studies (PASS) collectively comprised 17% of all major findings.

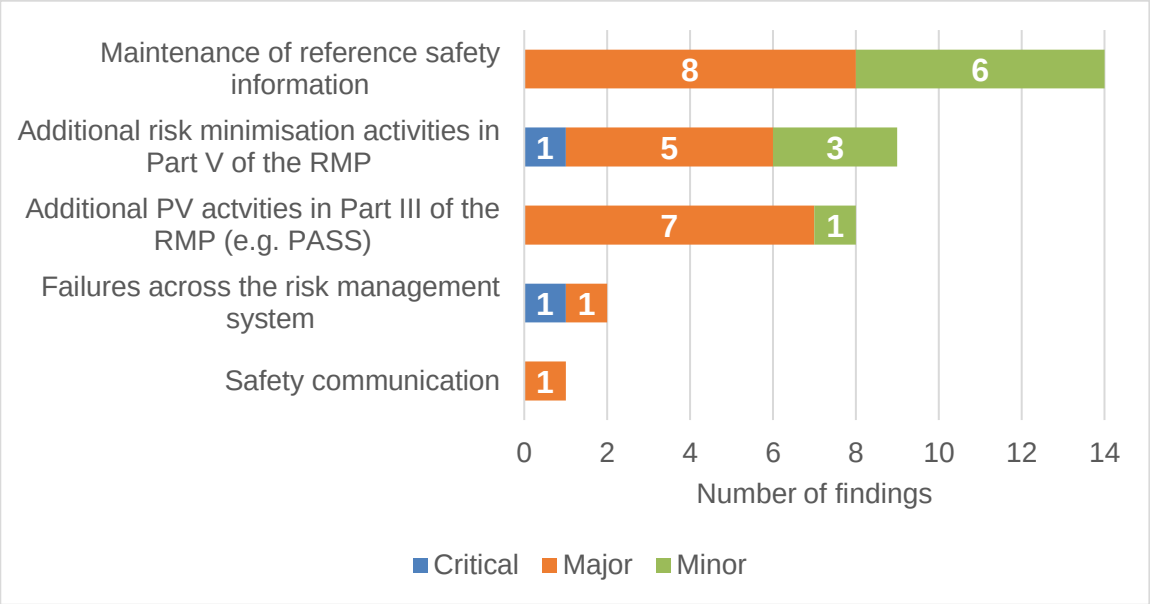

Figure 8 - Breakdown of all risk management findings

The topic of reference safety information continues to be a common area of non-compliance observed on inspection. There have been an increasing number of findings in relation to additional activities and measures required in parts III and V of the RMP respectively, including seven major findings reported for deficiencies with additional pharmacovigilance activities (e.g. PASS) compared with two in the previous reporting period.

5.2 Quality management

Findings of any grading relating to failings in quality management were reported from 18 of the 22 inspections conducted during the 2017/18 period, including a critical finding and 19 major findings (21% of all major findings). During 2016/17, this topic represented the largest proportion of major findings with a slightly higher proportion of 27% of all major findings.

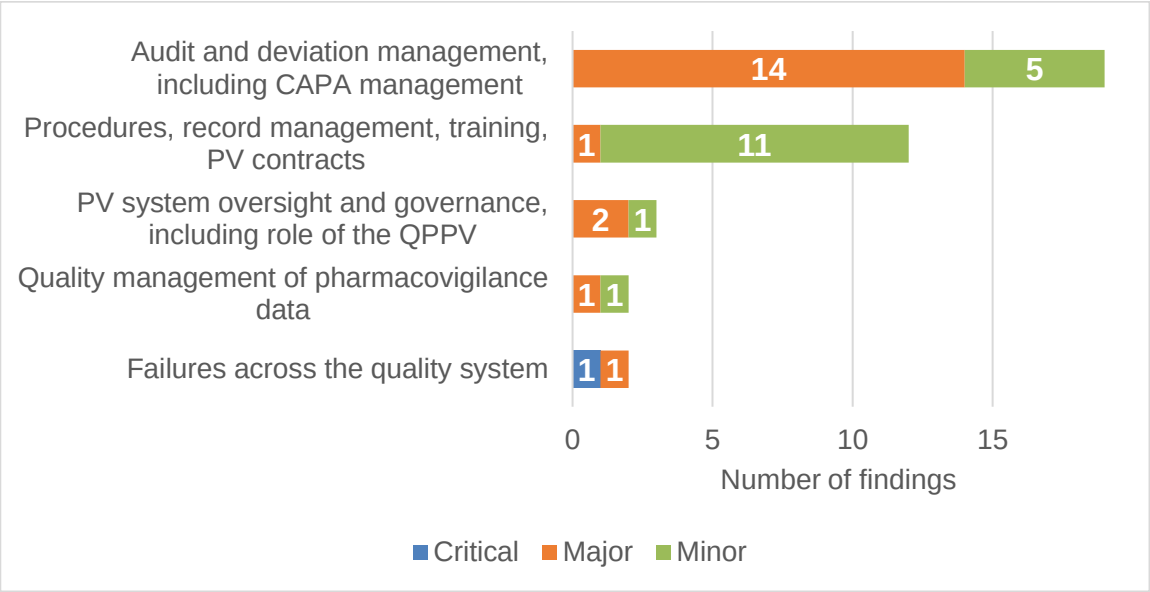

Figure 9 - Breakdown of all quality management findings

There is a clear legislative basis for establishing a quality management system for pharmacovigilance laid out in Commission Implementing Regulation (EU) No 520/2012 and detailed guidance described in Good Vigilance Practice (GVP) Modules I and IV. Findings arising from the quality management system can have an impact on any critical pharmacovigilance activity. The most common major findings reported in relation to quality management during the current reporting period were findings in relation to the management of audits and deviations including CAPA management. The ability for MAHs to identify non-compliance and effectively resolve it is essential to ensure that pharmacovigilance requirements are met and to uphold the safety of patients.

5.3 Provision of information for supervision by NCAs, including in the context of inspection

Although this was an area with fewer findings, it is a trend that has been emerging in contrast to recent years, with findings reported at 19 inspections during the 2017/18 period including 16% of all major findings. In light of the increasing number of days spent per inspection, issues with the provision of complete and accurate information, either pre-inspection (including in the PSMF and data in XEVMPD) or during the inspection can have the impact of increasing the duration of an inspection beyond that which was planned.

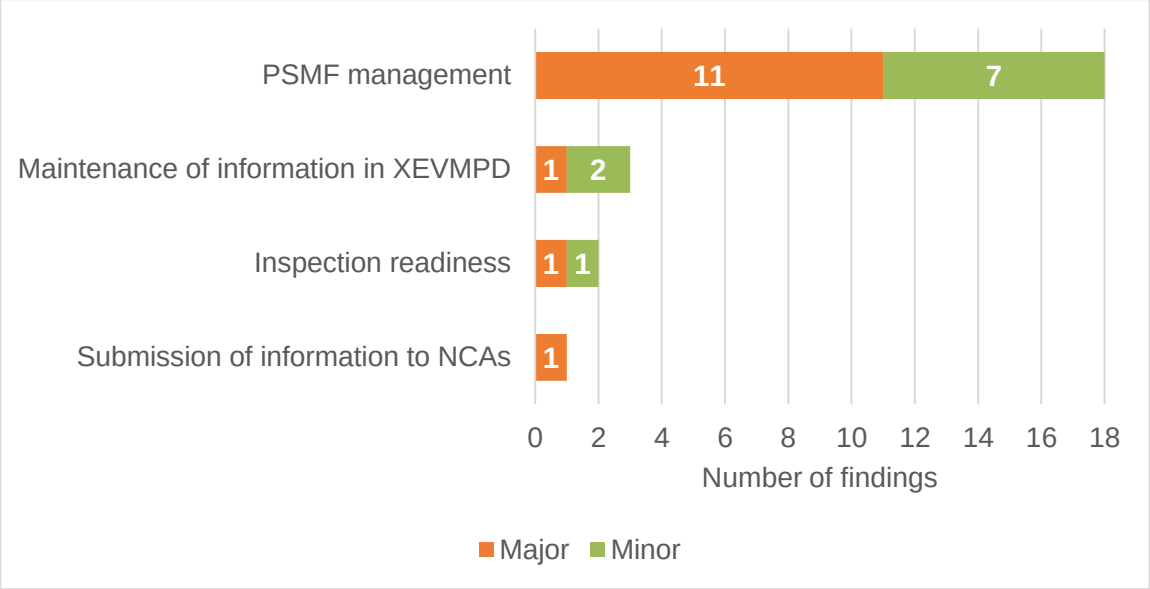

Figure 10 - Breakdown of all findings relating to provision of information for supervision

The most common subset of findings in this topic area was for the PSMF. This is again a subject for which there is clear and detailed guidance in Commission Implementing Regulation (EU) No 520/2012 and GVP Module II. Major findings reported for the PSMF are typically comprised of multiple deficiencies, either where the document contains inaccurate information, is missing required information or is non-compliant with the required format. It is a legal requirement for MAHs to maintain a PSMF and this document contributes to the planning and conduct of inspections by NCAs. Therefore, significant deficiencies in the PSMF can substantially impede the ability of inspectors to fulfil their role in verifying that the MAH is complying with its legal obligations.

6. Summary

From the outcomes of inspections conducted between 01 April 2017 to 31 March 2018, risk management is an area of specific concern. Findings relating to both routine and additional risk management activities comprised the highest proportion of critical (two out of four) and major findings (25%) reported from inspections conducted between 01 April 2017 to 31 March 2018. From the total 22 inspections conducted in this period, 18 reported at least one finding of any grading in relation to risk management.

Increasingly, products are being authorised with complex risk management systems and subject to specific conditions, particularly those with lower patient exposure prior to authorisation. The supervision of these systems through inspection is of importance to ensure that legal obligations are being met, that risks to patients are being managed appropriately and that assessors receive accurate and comprehensive information in order to make evidence-based decisions about the marketing authorisation.

MHRA GPvP risk-based inspection planning will continue to take product risk into account, with inspections in the programme that can be tailored to review product-specific aspects as well as pharmacovigilance systems. In addition to product risk, other aspects of risk outlined in section 2, such as organisational complexity and compliance history will continue to see that organisations with lower risk products are incorporated into the programme.

Appendix I – Inspection finding definitions

Critical: a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major: a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor: a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Appendix II – Categorisation of findings

Topic Area	Sub-topic of reported findings
Collection and collation of adverse drug reactions	Spontaneous sources of safety data, e.g. medical information, product quality complaints
	Literature searching
	Solicited sources of safety data (including patient support or market research programmes)
	Safety data exchange agreements
Management of adverse drug reactions	Case processing: data entry, coding, assessment, follow-up and reporting
	Data management, including migration of safety data
Ongoing safety evaluation	Signal management
	Periodic safety update reports
Risk management	Management of additional PV activities in Part III of the RMP (e.g. PASS, targeted follow-up questionnaires)
	Maintenance of reference safety information
	Additional risk minimisation activities in Part V of the RMP
	Safety communication
	RMP maintenance
Quality management system	Procedures, record management, training, PV contracts
	Audit and deviation management, including CAPA management
	PV system oversight and governance, including performance monitoring and role of the QPPV
	Information technology systems and applications
Provision of information for supervision by NCAs and inspection	Inspection readiness
	PSMF management
	Submission of information to NCAs
	Maintenance of information in XEVMPD
Clinical trials pharmacovigilance	Clinical trials pharmacovigilance (e.g. maintenance of RSI for clinical trials, SUSAR reporting)
Other	Other