Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Pharmacovigilance Inspection Metrics Report

April 2016 - March 2017

1. Introduction

During the period 01 April 2016 to 31 March 2017, the GPvP Inspectorate conducted 36 inspections of marketing authorisation holders (MAHs) and one inspection of a pharmacovigilance service provider. Of these:

- 13 inspections were of MAHs/ organisations who had not previously undergone an MHRA GPvP inspection.
- 15 inspections were routine re-inspections.
- 9 inspections were triggered due to critical findings identified at previous inspections or in response to a specific issue.[1]
- Of the 37 inspections conducted, 18 were performed to fulfil the EMA programme of inspections relating to centrally authorised products.

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 37 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.

A total of six critical, 150 major and 84 minor findings were identified during this period. It should be noted that 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).

[1] The majority of these inspections were triggered due to critical findings identified at previous inspections.

2. Findings by Inspection Type

The number of inspection findings based on the inspection type is displayed below. Definitions of the inspection type are included in Appendix II:

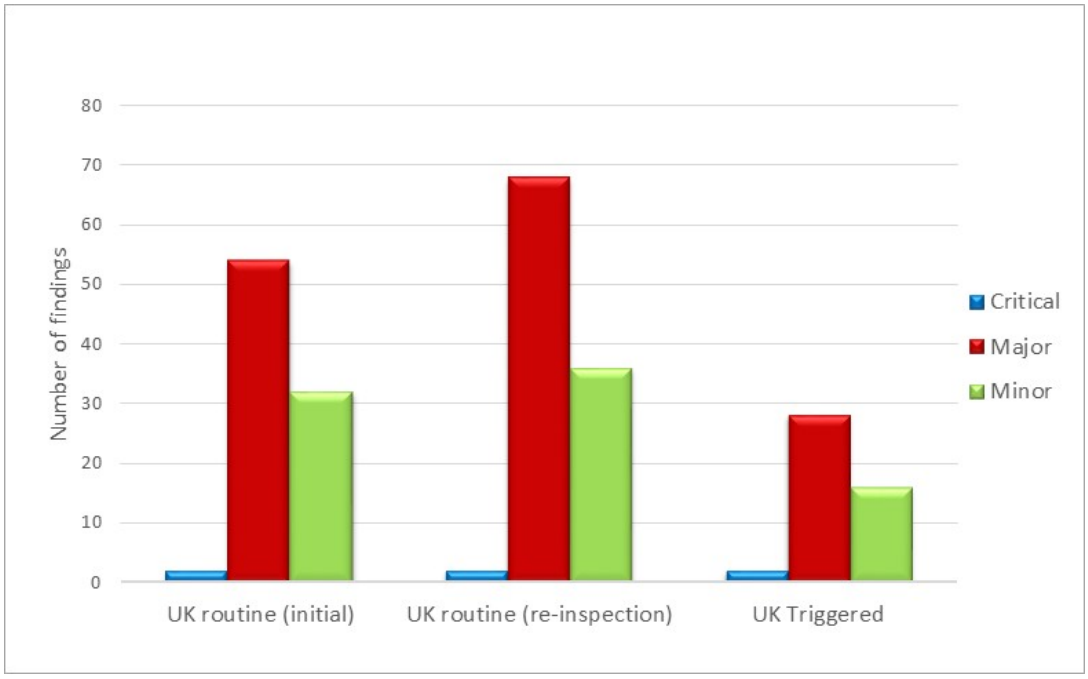

Fig. 1: Number of inspection findings by inspection type

The average number of findings reported by inspection type is displayed in the graph below:

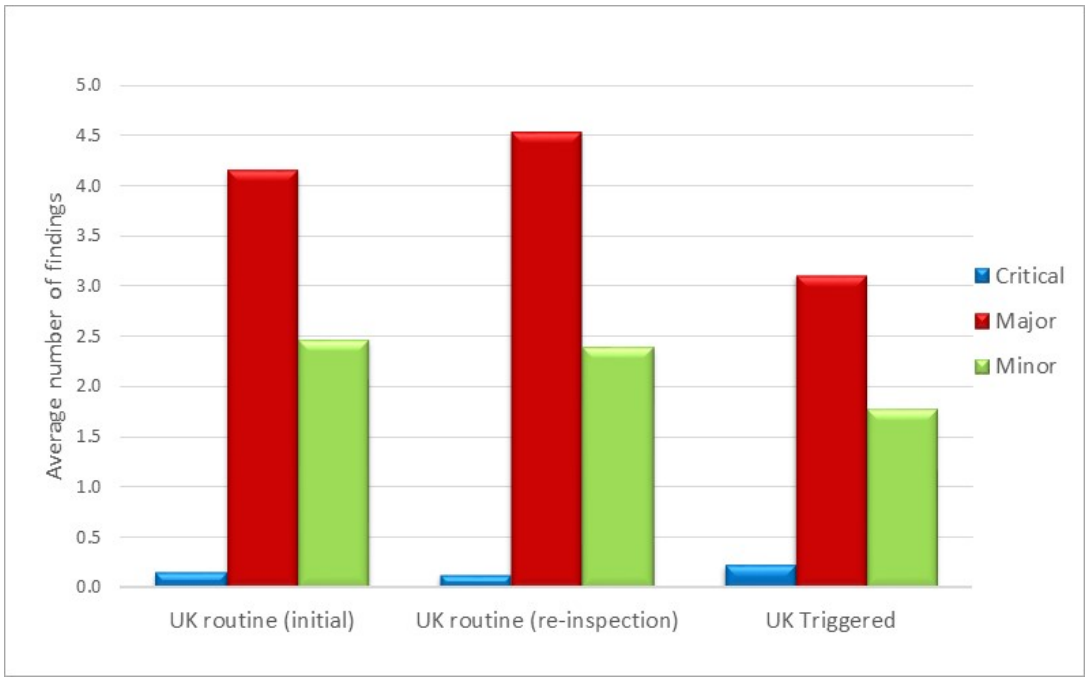

Fig. 2: Average number of inspection findings by inspection type

3. Critical Findings

The six critical findings reported were identified during six of the 37 inspections that were performed.

3.1 Critical findings by topic area

The chart below details the topic areas where critical findings were identified:

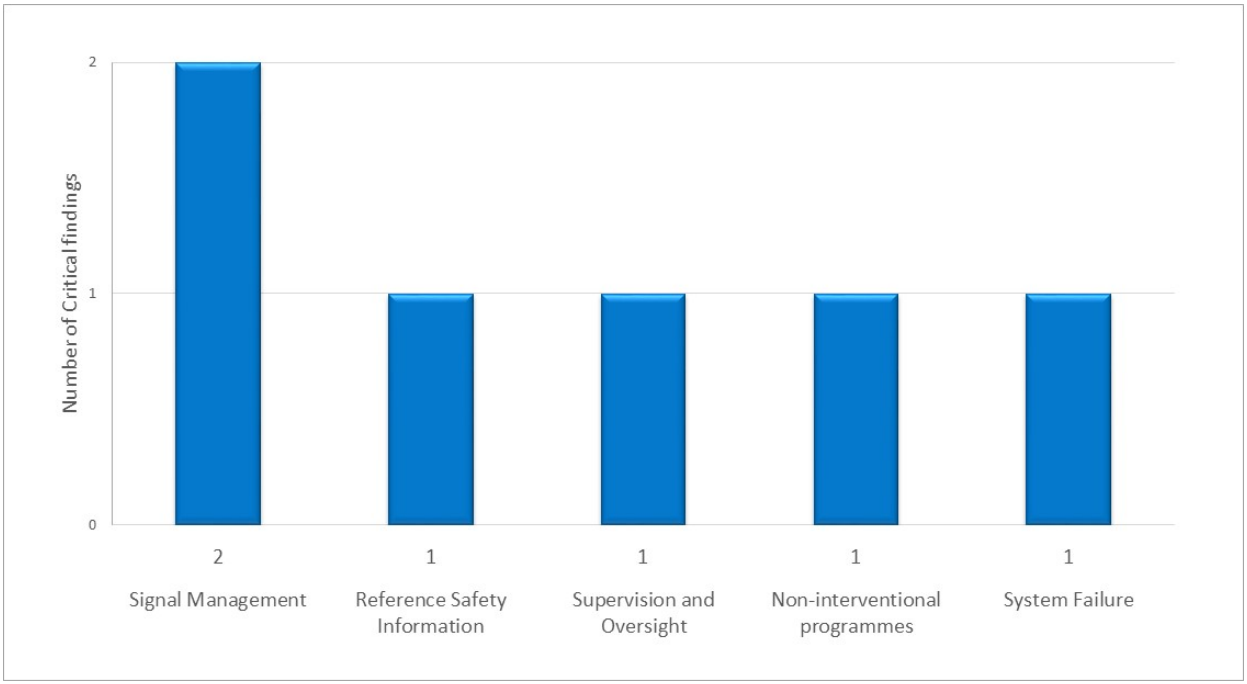

Fig. 3: Critical findings by topic area

The largest proportion of critical findings reported was in relation to signal management (two in total), representing 33% of all critical findings identified.

A single critical finding was identified in each of the following areas: maintenance of reference safety information, supervision and oversight of the pharmacovigilance system, non-interventional programmes and failure to establish a global pharmacovigilance system.

3.2 Current versus previous reporting period

The number of critical findings identified during this reporting period has continued to decrease from previous years, with six critical findings reported versus 11 in the previous reporting period. In the previous period, a critical finding was reported approximately every three inspections on average; however, in this reporting period, a critical finding was reported approximately every six inspections on average.

This reduction could indicate that significant issues identified at previous inspections were found to have been largely resolved during re-inspection or that there has been a positive trend toward compliance more generally. It could also be indicative of the fact that the inspection programme in April 2016 to March 2017 mainly included routine, rather than targeted, inspections.

3.3 Summary of critical findings reported during the period

Critical finding 1: Signal Management

A critical finding in relation to ongoing safety evaluation had been identified at a previous inspection and was not considered sufficiently resolved at the re-inspection. The specific deficiencies were in relation to a repeated failure to include all available safety data in signal detection activities, including cumulative ICSR data that resided in the global safety database and non-ICSR literature articles.

There were further methodological deficiencies identified with the MAH's approach to quantitative signal detection using adverse reaction data derived from ICSRs, and the MAH had not implemented a process to track safety signals in accordance with GVP Module IX.B.4.1.

Critical finding 2: Signal Management

A critical finding in relation to ongoing safety evaluation had been identified at previous inspections and was not considered sufficiently resolved at the re-inspection. A critical grading was given due to the recurrent nature of the finding and persistent breach of legislation by the MAH.

The specific deficiencies were in relation to incomplete evaluation of a safety signal, where the conclusions drawn (and consequent decisions) from the safety evaluation were not supported by appropriate scientific or clinical justification. There was inadequate document control for safety reviews, which resulted in a lack of accurate records to support when reviews had been conducted, whether appropriate clinical review had taken place and whether reports had been finalised in a timely manner. In addition, evaluations excluding relevant ICSRs and procedural deficiencies in relation to signal management processes existed.

Critical finding 3: Reference Safety Information

Significant deficiencies were identified with superseded versions of summaries of product characteristics (SmPCs) and patient information leaflets (PILs) being publically available on the MAH's corporate website. As a consequence of failing to update the website with updated product information, clinically important safety information, including contraindications and special warnings and precautions, was missing for many products and was therefore not available to patients and healthcare professionals via this route.

The MAH had also failed to maintain the authorised product information through submission of an appropriate variation application, following published recommendations from the PRAC and following internally confirmed signals.

Critical finding 4: Supervision and Oversight

A critical finding was reported due to significant failings in the resourcing, oversight and management of the pharmacovigilance system by the MAH and, collectively, the deficiencies represented a serious breach of legislation. The MAH had failed to ensure that safety data, records and documentation were available (including to inspectors), and that the pharmacovigilance system was functioning and supported though audit oversight and staff training. Specifically:

- The MAH failed to have a QPPV permanently and continuously available.

- The MAH was unable to gain access to the records, data or supporting documentation (e.g. written procedures for critical process) for the pharmacovigilance system, following transition of outsourcing arrangements from one pharmacovigilance service provider to another.

- There was no MAH oversight of pharmacovigilance activities still being undertaken by a service provider with whom contractual arrangements had been terminated.

- The MAH had failed to cooperate with inspectors regarding provision of relevant documentation.

- No internal audits of the pharmacovigilance system had been conducted by or commissioned by the MAH, and none were planned.

- There was no evidence of training for many staff working on pharmacovigilance activities, specifically case processing.

Critical finding 5: Non-interventional Programmes

A critical finding was reported in relation to the management of non-interventional programmes (NIPs), including patient support programmes (PSPs) and market research programmes (MRPs). A critical grading was given because the MAH had failed to address known deficiencies in the management of NIPs and, consequently, there was no assurance that suspected adverse reactions arising from NIPs would be collected and collated in the pharmacovigilance system. This resulted in the potential for a large amount of safety data to remain unreported. Specifically:

- There was no global policy or procedure(s) governing the set-up of PSPs, specifically in relation to the measures to collect suspected adverse reactions from these types of programmes.

- There was no mechanism for the global pharmacovigilance function to be aware of ongoing programmes for the purposes of complying with GVP Module II.B.4.3, i.e. for the MAH to be able to produce and make available a list of such programmes to support inspection, audit and QPPV oversight.

- There were issues with oversight of PSP vendors, including deficiencies with the pharmacovigilance audit programme and contractual agreements.

- There were no measures in place to ensure appropriate set-up of MRPs outside of specific regions, to ensure that suspected adverse reactions are collected from these types of programmes. This included deficiencies with procedural documentation, PSMF content and contractual agreements with third-parties.

Critical finding 6: System Failure

Significant deficiencies across the pharmacovigilance system were identified, which represented a failure by the MAH to implement and operate a global pharmacovigilance system that is compliant with EU and national legislation. This constituted a serious breach of legislation and consequently a critical finding was reported.

The MAH had failed to establish a system to collect and collate safety information from a variety of sources, to report serious suspected adverse reactions to the Agency, to undertake ongoing safety evaluation for UK authorised products, and to provide for adequate mechanisms of maintenance

and oversight of the pharmacovigilance system. In addition, the MAH had failed to implement specific quality system procedures and processes for critical pharmacovigilance activities.

3.4 Graphical summary of critical findings reported over time

The graph below displays the average number of critical findings reported per inspection over time:

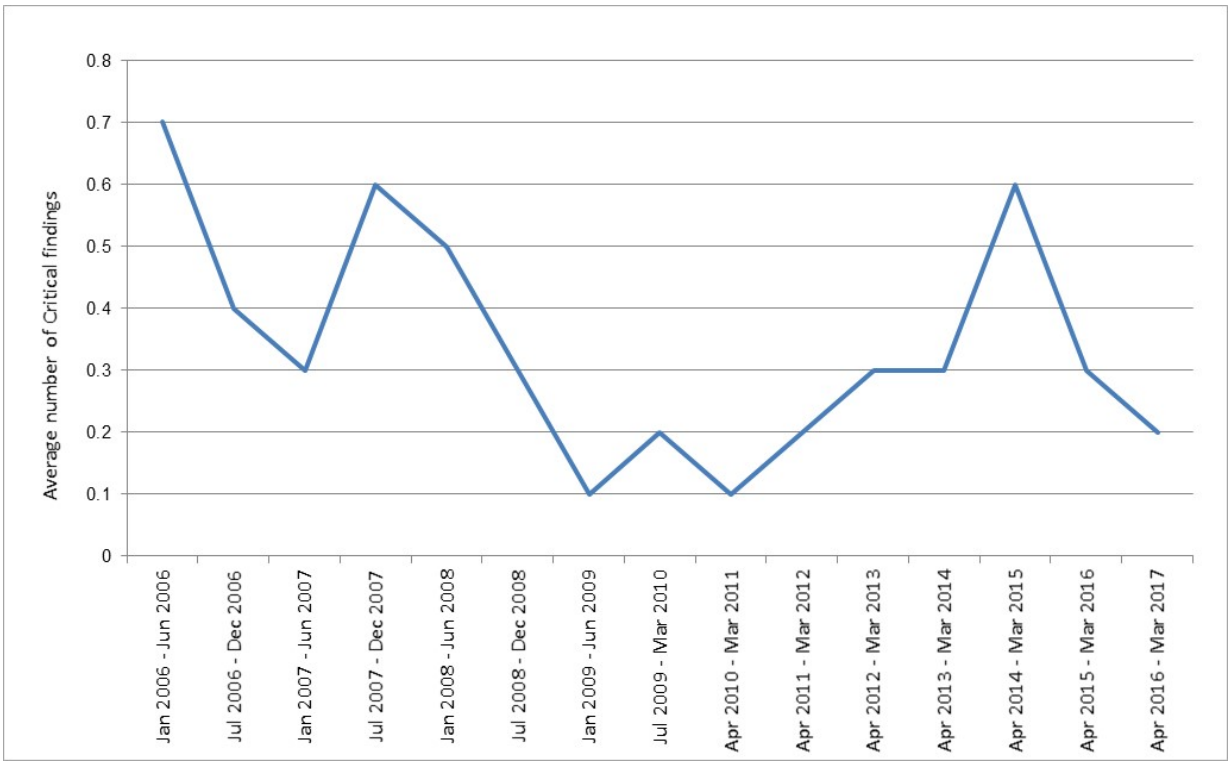

Fig. 4: Average number of critical findings reported per inspection over time

The average number of critical findings has decreased in the past two years. The average number of critical findings identified per inspection in this reporting period is 0.16 (rounded up to 0.2 in the graph), compared to 0.3 in the previous reporting period. This translates to a critical finding being reported approximately every six inspections on average, compared to every three inspections on average in the previous reporting period.

4. Major Findings

150 major findings were identified across 36 of the inspections performed in this reporting period.

4.1. Major findings by topic area

The chart below displays the distribution of major findings by topic area:

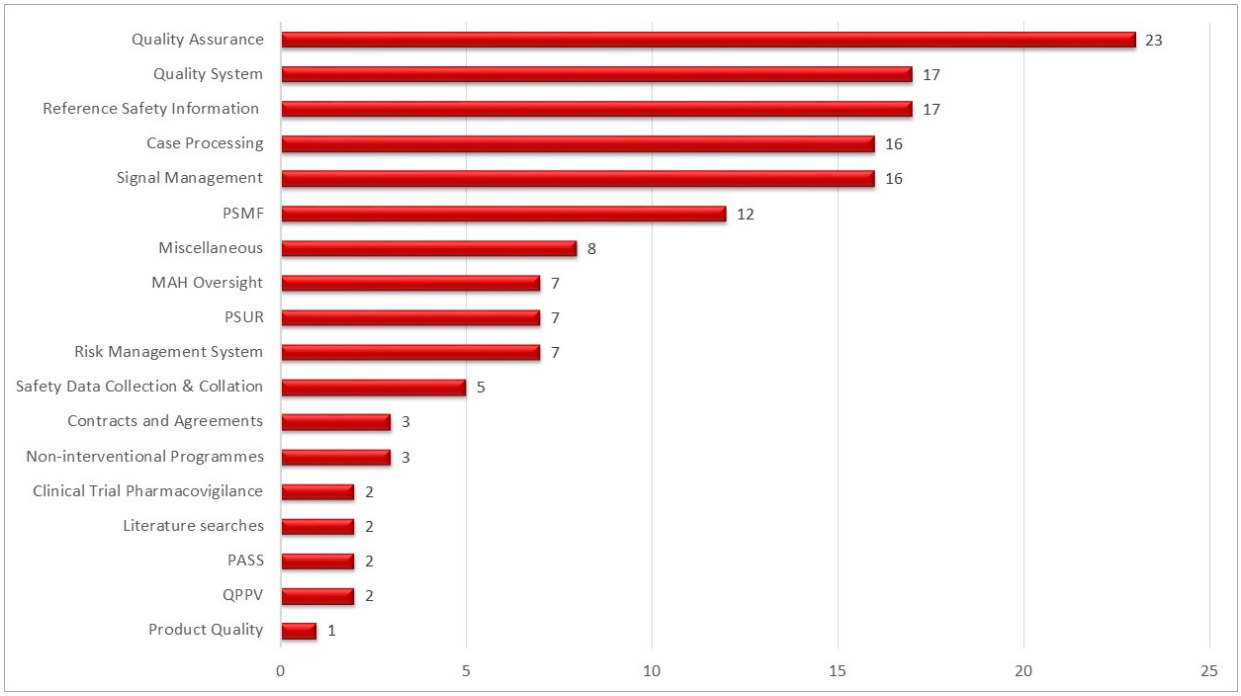

Fig. 5: Finding categories ranked by the number of major findings

Major findings were identified across 18 topic areas, as detailed in the chart above. The largest proportion of major findings for a specific topic area was identified in relation to the quality system and quality assurance activities[2]. Taken together, these findings represented 27% of all major findings identified.

Major deficiencies associated with the maintenance of reference safety information, case processing and signal management represented the next largest proportion, each representing approximately 11% of all major findings reported.

Miscellaneous findings included failures in safety data management, supply of unlicensed medicines, MAH responsibilities with regards to the maintenance of the Article 57 database, management of company-sponsored websites and public communication.

[2] Quality system findings include those associated with procedural documentation, training and pharmacovigilance record management. Quality assurance findings include those associated with audit and management of non-compliance, including corrective and preventative action (CAPA) management.

4.2. Current versus previous reporting period

The total number of major findings has increased from the previous period by approximately 60%. Outlined below are the topic areas that have largely contributed to this increase:

- Major findings associated with quality management have increased by 82% compared to the previous reporting period (40 major findings in this period compared with 22 in the previous period). The requirements for risk-based audits of the pharmacovigilance system and management of non-compliance (identified through audit or other mechanisms) have been poorly implemented by several MAHs. This includes failing to implement effective and timely CAPA following inspection findings.

- Major findings in relation to the maintenance of reference safety information increased significantly in the reporting period, with 17 findings reported between April 2016 and March 2017 compared to seven in the previous period. Major findings associated with reference safety information were characterised by failures and/or delays to submit safety variation applications to update the safety sections of SmPCs and PILs.

- Major findings in relation to signal management increased from 11 in the previous period to 16 in the current reporting period. This included examples of failures to comply with product-specific guidance (GVP Chapter P II) for biological medicinal products.

- Major findings in relation to oversight and supervision of the pharmacovigilance system increased significantly from one in the previous period to seven in this period. Several of these findings included failures in the oversight of pharmacovigilance service providers, with subsequent impact on a variety of pharmacovigilance activities. There were also examples of failures by the MAH to support the EU QPPV, particularly where this role had been outsourced to a third-party service provider. In one instance, there was no proactive notification to, or consultation with, the third-party QPPV at the time of significant licence acquisitions by the MAH or when critical pharmacovigilance activities had been outsourced to another independent service provider. Deficiencies in the maintenance of the PSMF and Article 57 database were also reported under this heading, where these were considered to have impacted the MAH's or national competent authority's ability to oversee and supervise the pharmacovigilance system.

4.3. Number of major findings reported per organisation

The chart below displays the number of organisations that received a specific number of major findings at a single inspection during the period 01 April 2016 to 31 March 2017. Overall, the average number of major findings reported per inspection was 4.1.

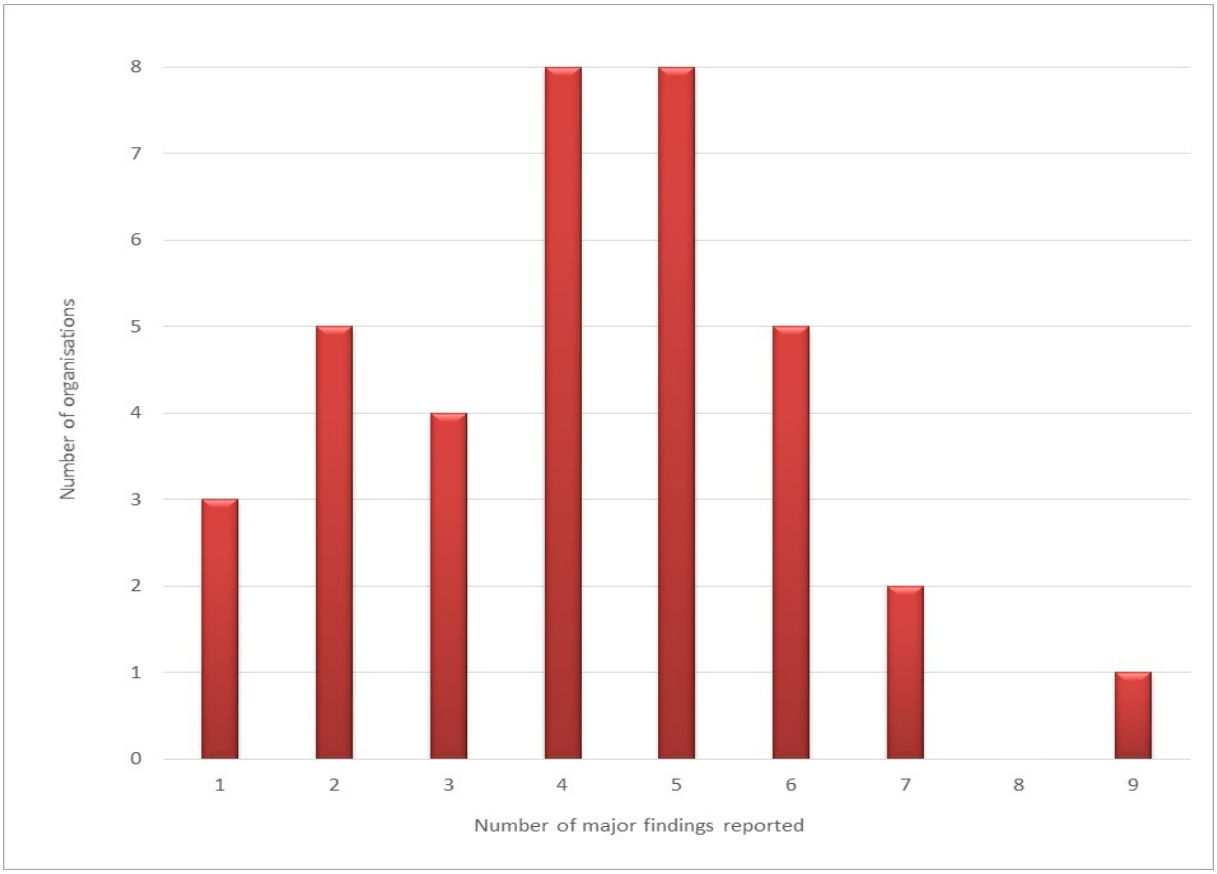

Fig. 6: Number of organisations that received a specific number of major findings at a single inspection

5. Minor Findings

84 minor findings were identified during the reporting period. The chart below displays the distribution of minor findings by topic area:

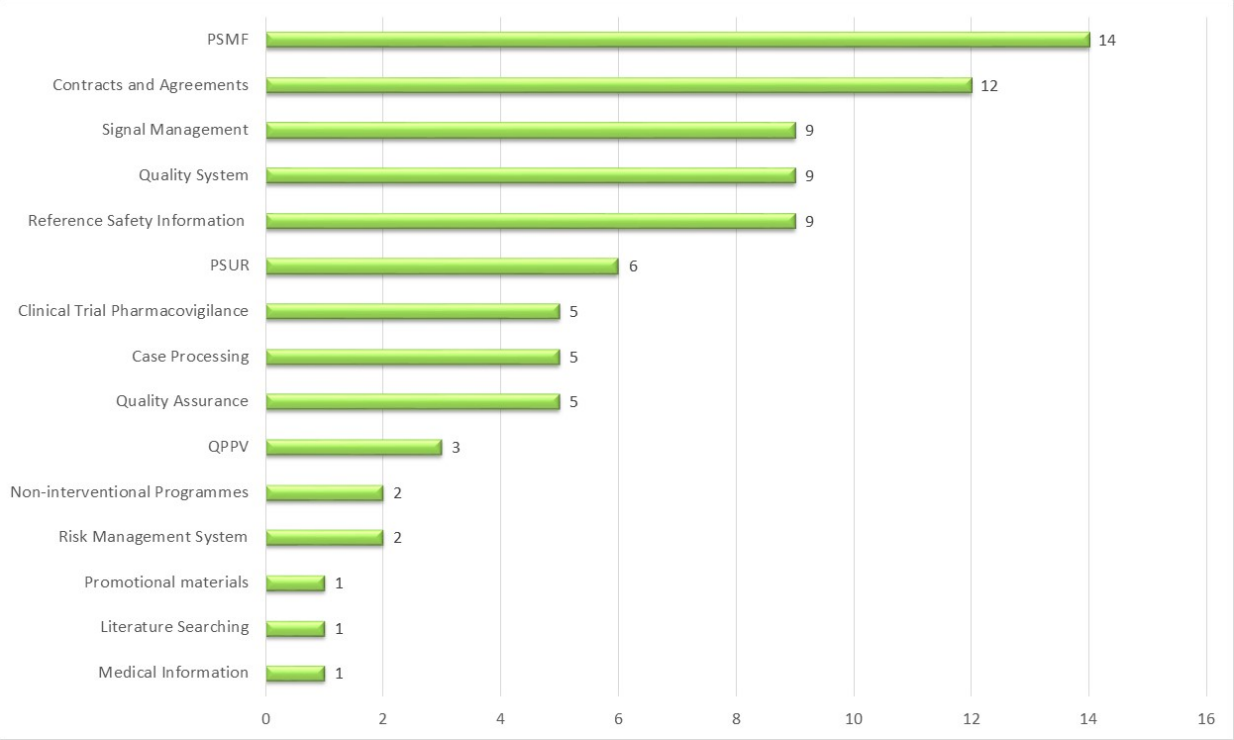

Fig. 7: Finding categories ranked by the number of minor findings

Minor findings were reported across 15 topic areas. The largest proportion of minor findings was in relation to the PSMF, followed by issues with pharmacovigilance contracts and agreements.

6. Average Number of Inspection Findings over Time

The graph below displays the average number of findings reported per inspection over time:

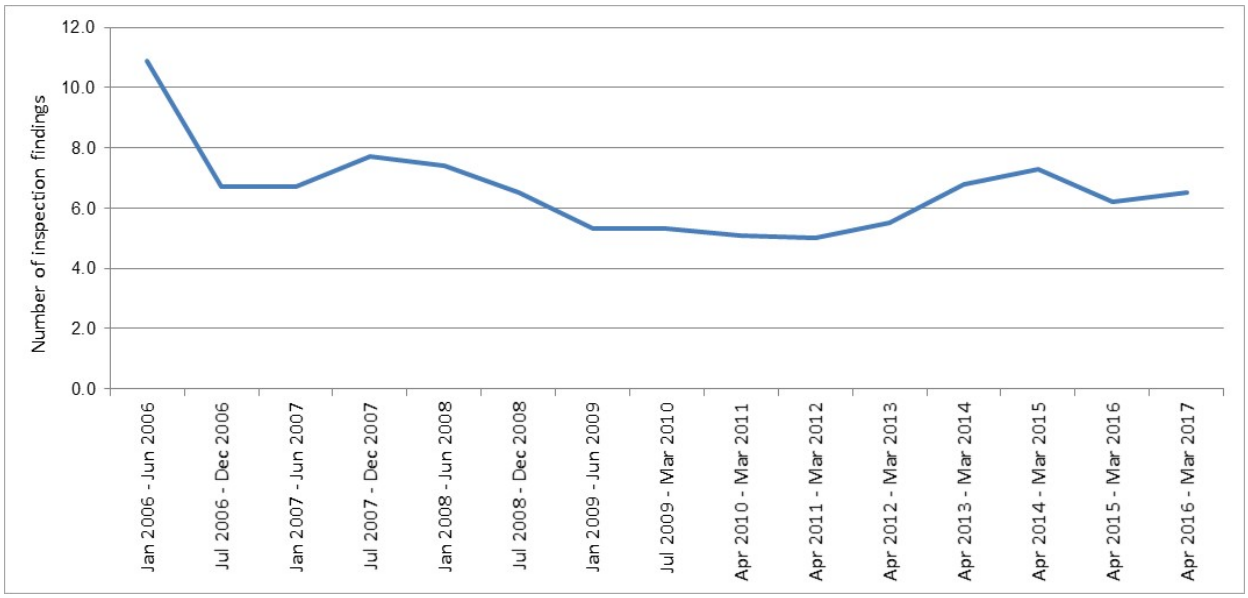

Fig. 8: Average number of findings reported per inspection over time

The average number of findings reported per inspection in this reporting period is similar to the previous period (6.5 in this period compared to 6.2 in the previous period).

7. Summary

In the period April 2016 to March 2017, the MHRA conducted a total of 37 pharmacovigilance inspections. This is a minor increase of two inspections compared to the previous year. Approximately 35% of these inspections were of MAHs/ organisations that had not previously undergone a MHRA pharmacovigilance inspection. The largest number of inspections were routine re-inspections (15 in total, 41%).

Six critical findings were reported during this period. The largest proportion of critical findings was in relation to signal management, representing 33% of all reported critical findings (two in total). Both critical findings related to significant issues that had been identified at previous inspections that were not considered sufficiently resolved at the re-inspection. A single critical finding was identified in each of the following areas: maintenance of reference safety information, supervision and oversight of the pharmacovigilance system, non-interventional programmes and failure to establish a global pharmacovigilance system; each of these representing approximately 17% of all critical findings identified. A summary of each of the critical findings is provided in section 3.3.

150 major findings were reported during this period, with 36 out of the 37 inspections conducted resulting in at least one major finding being reported. The largest proportion of major findings for a specific topic area was in relation to the quality system and quality assurance activities. Taken together, these quality management findings represented 27% of all major findings identified. It is worth emphasising that approximately three-quarters of major findings were therefore reported in relation to failings in critical pharmacovigilance processes.

Overall, the topic areas representing the largest proportion of inspection findings in this period are associated with the quality system and quality assurance activities, signal management, maintenance of the PSMF and maintenance of reference safety information. It is worth noting that there may be some variability in the assignment of a topic heading to specific findings, based on the information available at the time of the inspection. For example, where there is evidence that pharmacovigilance deficiencies are the direct result of quality management issues, consequently the finding will be classified as such. Alternatively, the finding may be classified to reflect the symptom of the issue(s), for example under a heading of signal management or aggregate reports.

GPvP Inspectorate, November 2017

8. 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.

9. Appendix II – Inspection type definitions

UK routine inspection (initial) – this comprises inspections performed according to the national inspection programme and where it is the first MHRA pharmacovigilance inspection of the MAH.

UK routine inspection (re-inspection) – this comprises routine re-inspections of MAHs under the national inspection programme.

UK triggered - these inspections are performed under the national inspection programme and are triggered by either previous critical findings, requests from other MHRA divisions or as a result of other intelligence.

CHMP triggered – inspections requested by the CHMP in response to a specific trigger.