



Pharmacovigilance Inspection Metrics Report

April 2018 – March 2019

1. Introduction

During the period 01 April 2018 to 31 March 2019, the MHRA's Good Pharmacovigilance Practice (GPvP) inspectorate conducted 18 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 18 inspections conducted during the period.

As in previous years, MAHs were selected for inspection using a risk-based methodology in accordance with Good Vigilance Practice (GVP) Module III. The national inspection programme for this reporting year also took into account the EMA's programme of routine pharmacovigilance inspections of organisations with centrally authorised products. Factors considered in the risk-based approach include product-specific risks (e.g. new active substances or new biological products), the complexity of the pharmacovigilance system, the complexity and size of the organisation(s) involved in the pharmacovigilance system, including service providers, and the compliance and inspection history of an organisation.

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



2. Types of inspection

Of the 18 inspections conducted in the period of 01 April 2018 to 31 March 2019, two inspections were triggered by critical findings from previous inspections and 16 inspections were scheduled and conducted in line with the routine national or EMA inspection schedule. Nine of those were inspections of MAHs that had never been inspected by the MHRA. The remaining seven inspections were routine re-inspections of MAHs.

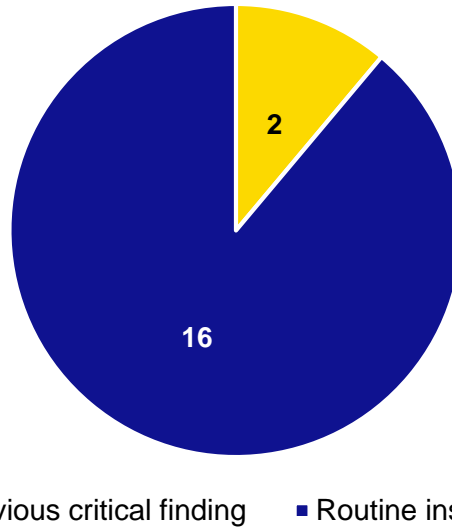


Figure 1 - Number of inspections conducted by type

Figure 2 illustrates that nine inspections included a remote inspection element. For four of those inspections, office-based inspection (OBI) days were planned and conducted prior to the inspection onsite. For six inspections ad hoc OBI days were conducted after the onsite inspection¹. Ad hoc OBI days may be conducted post-inspection to review additional documentation for significant inspection findings or documentation that is not readily available during the onsite inspection. In addition, one of the 18 inspections was conducted entirely remotely as part of a pilot project on office-based GPvP inspections.

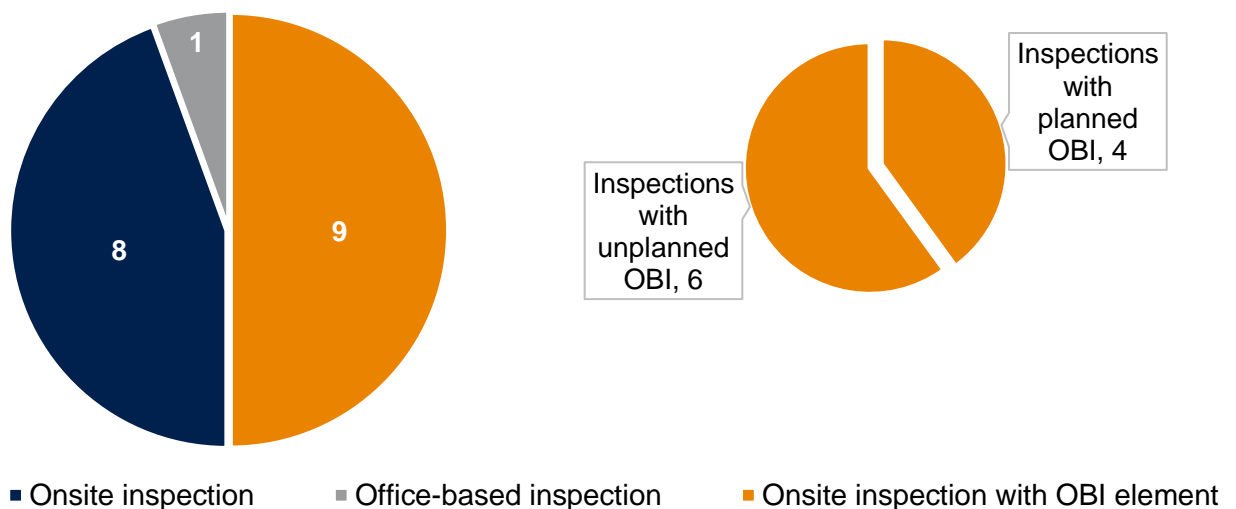


Figure 2 - Number of inspections conducted by inspection location, inset shows breakdown of onsite inspections with OBI element

¹ For one inspection, planned and unplanned OBI days were conducted



3. Summary of findings

A total of four critical, 78 major and 38 minor findings were identified during this period. A reported finding often comprises multiple separate findings, grouped according to a high-level legislative requirement or according to cumulative pharmacovigilance impact (under which many breaches of legislation could have been identified). Figure 3 shows the number and distribution of findings across the different inspection types.

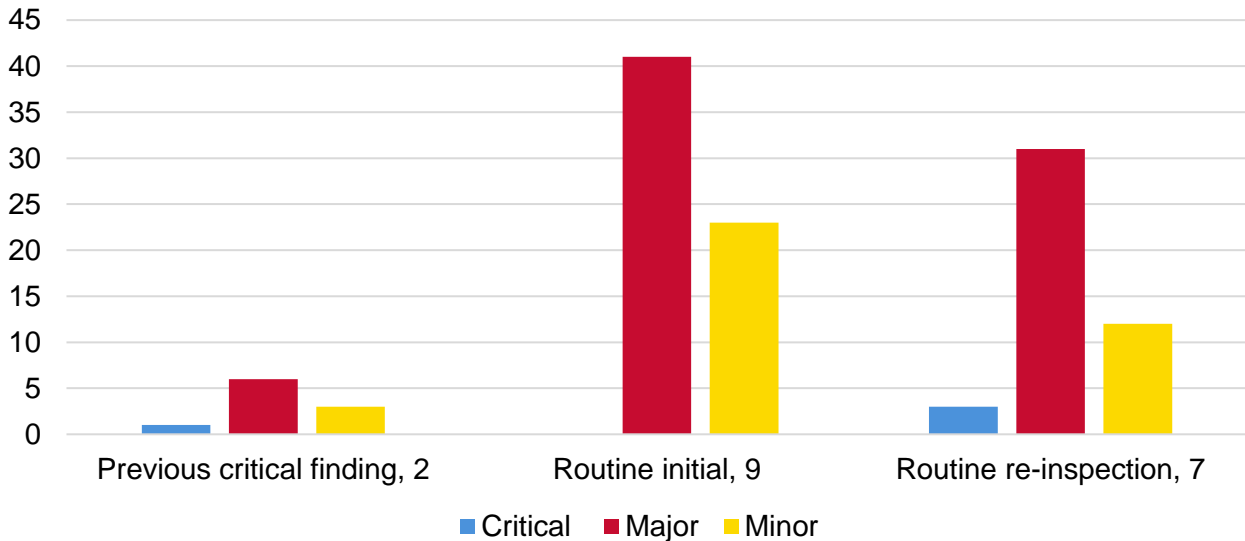


Figure 3 - Number of inspection findings by inspection type

As shown in Figure 4, the average number of findings issued per inspection (irrespective of grading) over time has remained relatively stable at an average of just under seven findings per inspection in the period from 01 April 2018 to 31 March 2019 when compared to the previous reporting periods.

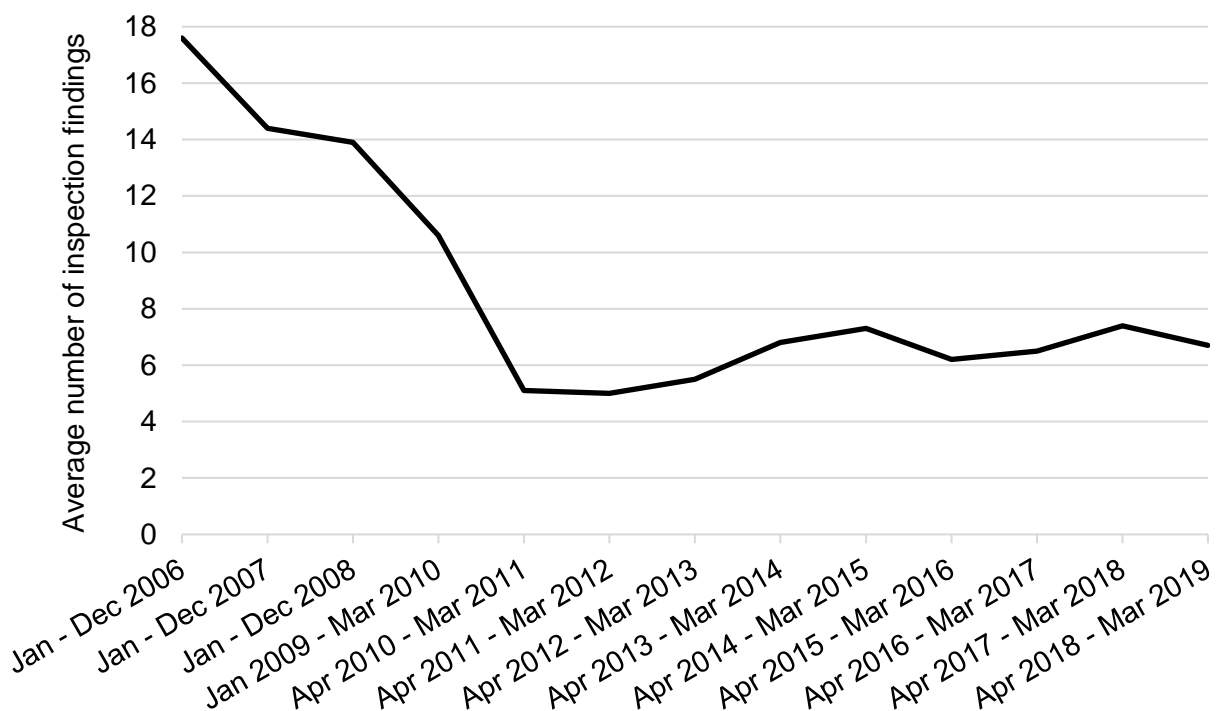


Figure 4 - Average number of findings reported per inspection over time



Figure 5 further illustrates the average number of critical, major and minor findings reported per inspection over time. Over the years, the average number of critical findings has remained relatively constant. In contrast, the average number of major findings reported per inspection has increased from two in the reporting period of January 2009 to March 2010 to just over four in the period of April 2018 to March 2019. An exception is the reporting period of April 2015 to March 2016 which saw a temporary drop in the average number of major findings reported per inspection. Despite fluctuations in the average number of minor findings reported per inspection between successive reporting periods, a slight decrease is noticeable over time.

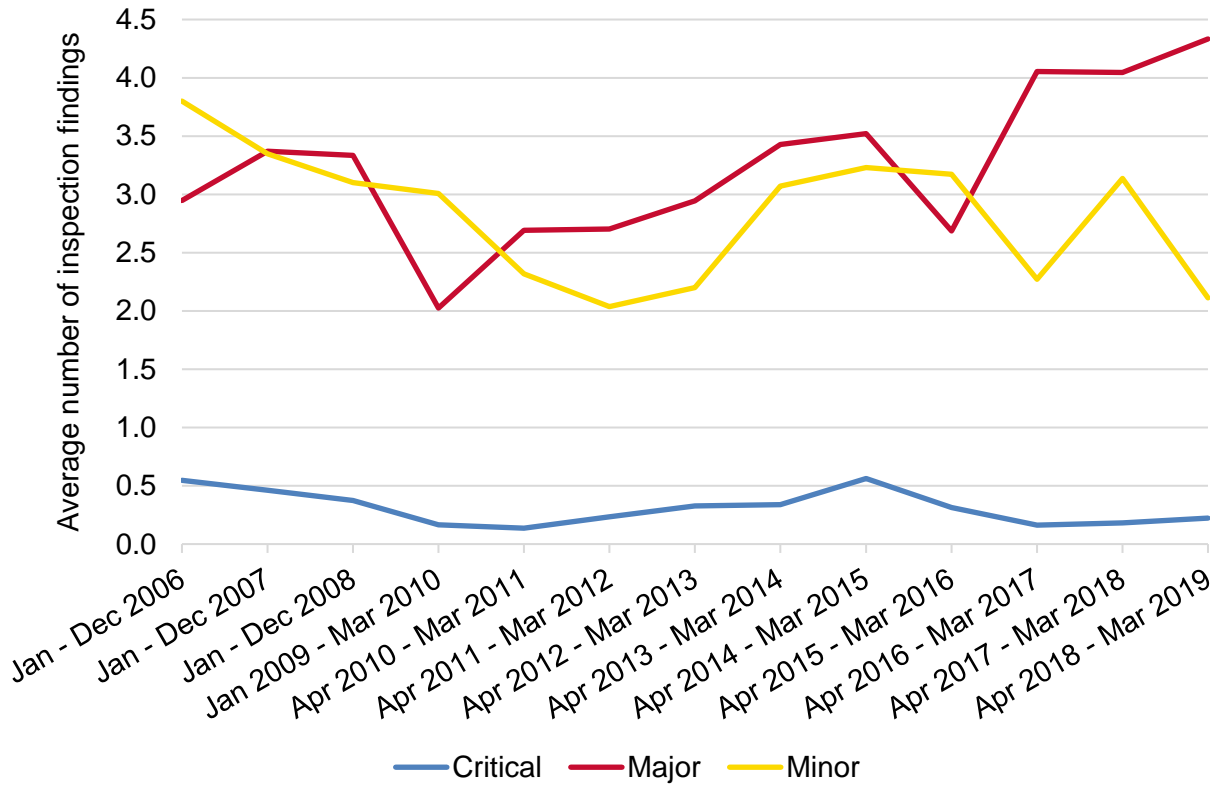


Figure 5 – Breakdown of average number of finding by type reported per inspection over time



3.1. Critical findings

3.1.1. Critical findings reported from 01 April 2018 to 31 March 2019

Four critical findings were identified from three inspections in the period of 01 April 2018 to 31 March 2019. This is approximately one critical finding reported from every five inspections which is a slight increase from the previous reporting period.

Two critical findings were issued in relation to risk management, one critical finding was reported in relation to the quality management system and a further critical finding was made regarding the provision of information for inspections.

An anonymous summary of each critical finding is presented below.

Risk management: implementation of updated patient information leaflets

The MAH had failed to ensure that patient information leaflets (PILs) containing updated safety information were being introduced to packaging in accordance with the guidance published by the MHRA. MHRA guidance states that once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months.

The data reviewed during the inspection indicated that a large number of batches had been QP certified with PILs which had been superseded by versions approved more than nine months prior, with many of these missing new warnings in section 2 *What you need to know before you take...* or serious adverse reactions in section 4 *Possible side effects*.

The delays in providing patients with up-to-date information on known product risks was considered to adversely affect the rights, safety or well-being of patients and posed a potential risk to public health.

Risk management: additional risk minimisation measures

The MAH had failed to take appropriate actions to ensure that all pharmacies dispensing the company's product were monitoring adherence with mandated additional risk minimisation measures (aRMM), in accordance with the effectiveness plan agreed with the MHRA.

As a result of this deficiency, the MAH had no information on the adherence to the conditions of the aRMM for a substantial number of exposed patients, representing about 15% of UK sales in a two-year period. This resulted in incomplete information being submitted to and reviewed by the MHRA in annual adherence reports to assess the effectiveness of the aRMM.

This critical finding was reported as the failures to fully meet the objectives of the aRMM in the UK posed a risk to the rights, safety and well-being of patients.

Quality management system: management of known non-compliance in the pharmacovigilance system, mechanisms for compliance management, written procedures

At the time of the inspection, inspectors were unable to verify compliance of critical pharmacovigilance activities due to a number of ongoing deficiencies in the pharmacovigilance system, some of which had been identified by the MAH either prior to inspection announcement or during inspection preparation activities.

Deficiencies concerned the integrity and management of pharmacovigilance data, the MAH's ability to systematically track and implement CAPA resulting from audits and inspections, the



oversight and compliance management of a key pharmacovigilance service provider, key performance indicators and written procedures.

Collectively, these deficiencies represented a failure to implement an adequate quality system as described in Chapter II of the Commission Implementing Regulation (EU) No. 520/2012.

This finding was graded as critical, not only due to a serious violation of legislation and guidelines pertaining to the operation of a quality system for pharmacovigilance, but due to a failure by the company to address known issues which may pose a risk to patients.

Provision of information for inspections

Data provided to inspectors in the form of line listings from the safety database was incomplete and contradictory. Without the ability to verify the data in the database, inspectors were unable to satisfactorily assess compliance of other critical pharmacovigilance activities in accordance with the obligations laid out in Article 111 of Directive 2001/83/EC.

This finding was graded as critical as the compliance with EU legislation and guidance for the management, assessment and reporting of individual case safety reports, the completeness and accuracy of periodic safety update reports (PSURs), and ongoing safety evaluation activities could not be reviewed. Therefore, inspectors were unable to verify compliance with EU legal obligations and fulfil the supervisory remit of the national competent authority.

In two of the three inspections where one or more critical findings were reported, several major findings were also reported in other areas of the pharmacovigilance system as shown in Table 1 below.

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

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



3.1.2. Distribution of critical findings over time

The number and distribution of critical inspection findings across different topics since April 2012 is shown in Figure 6. A total of 89 critical findings were reported between 01 April 2012 and 31 March 2019.

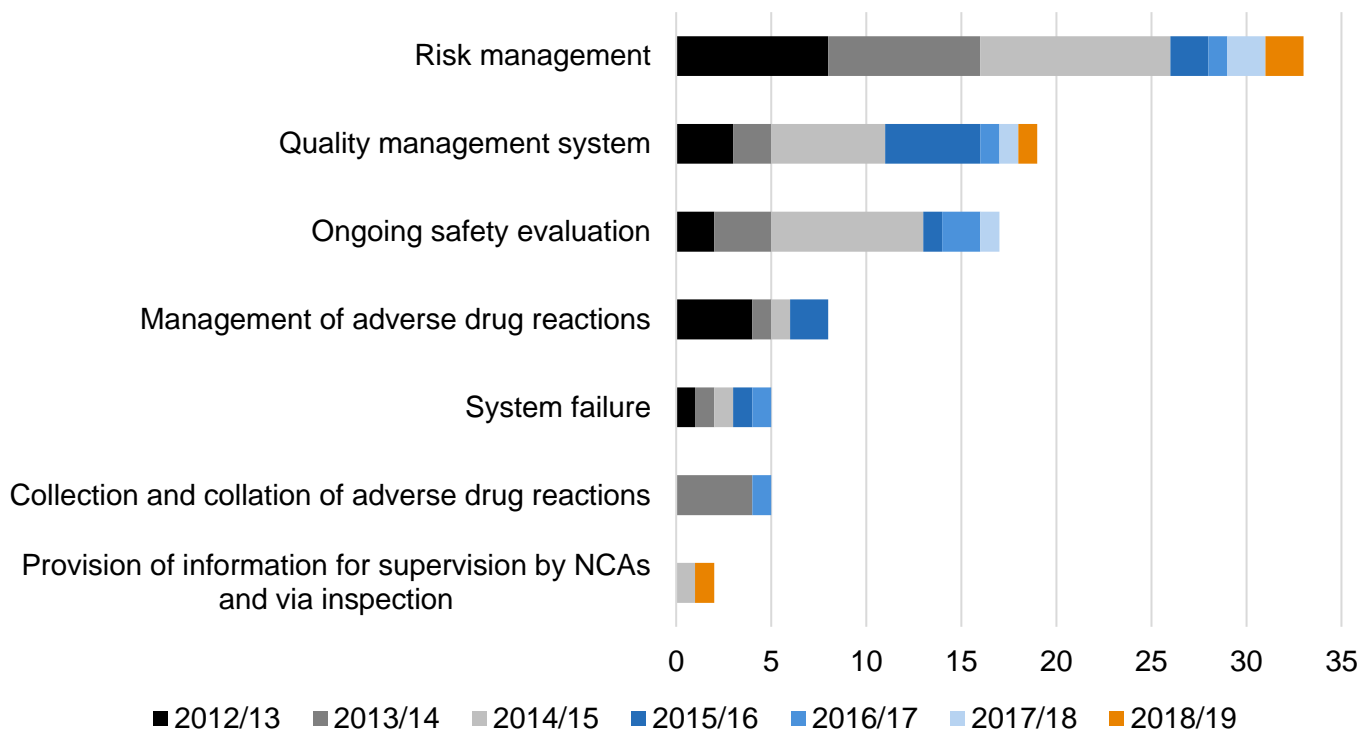


Figure 6 - Number and distribution of critical findings across topics

The number of critical findings decreased in recent years, but certain topics are more often associated with critical findings than others.

Risk management is a topic for which the largest number of critical findings has been reported over time. Traditionally, findings in this area related to routine risk management such as the maintenance of the reference safety information. In recent years, an increased number of critical findings in this area related to additional risk minimisation measures, such as educational materials or pregnancy prevention programmes, or additional pharmacovigilance activities.

Quality management system remains a topic of interest in critical findings with one finding reported in each of the last three years.

Ongoing safety evaluation is another topic in which historically a lot of critical findings were reported. The majority of those findings related to signal management activities and it is noteworthy that in the period of 01 April 2018 to 31 March 2019 no critical finding was reported in this area. This was the first time since 2012.



3.2. 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 majority of inspections reported between four and five major findings.

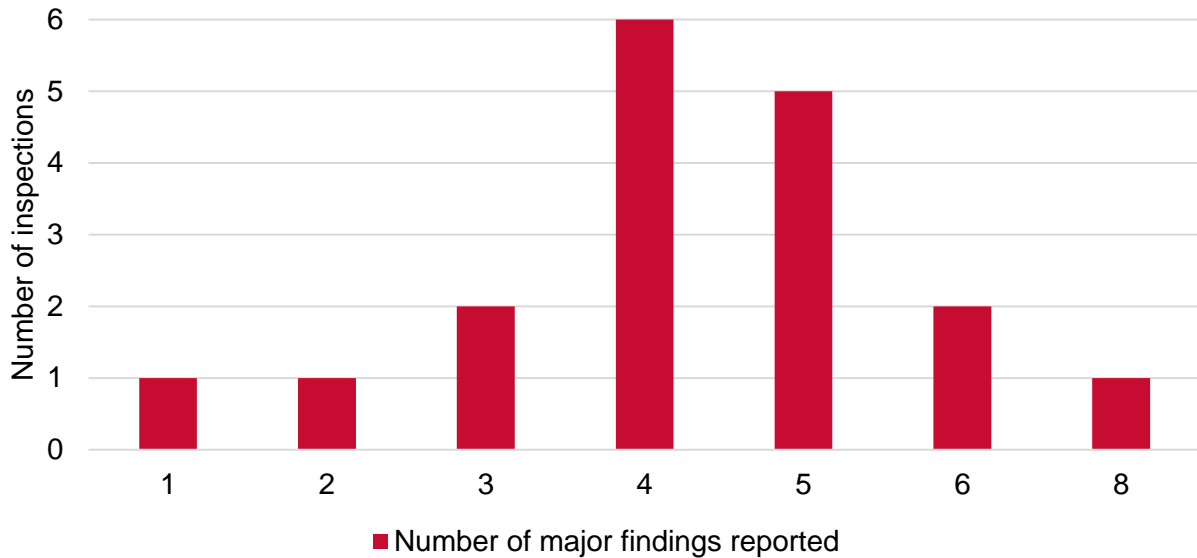


Figure 7 - Number of major findings reported at organisations

78 major findings were identified in the period of 01 April 2018 to 31 March 2019. 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.

21% of all major findings were reported in relation to risk management. This was followed by activities relating to ongoing safety evaluation (19%) and the provision of information for supervision by national competent authorities (NCAs) including via inspection (17%).

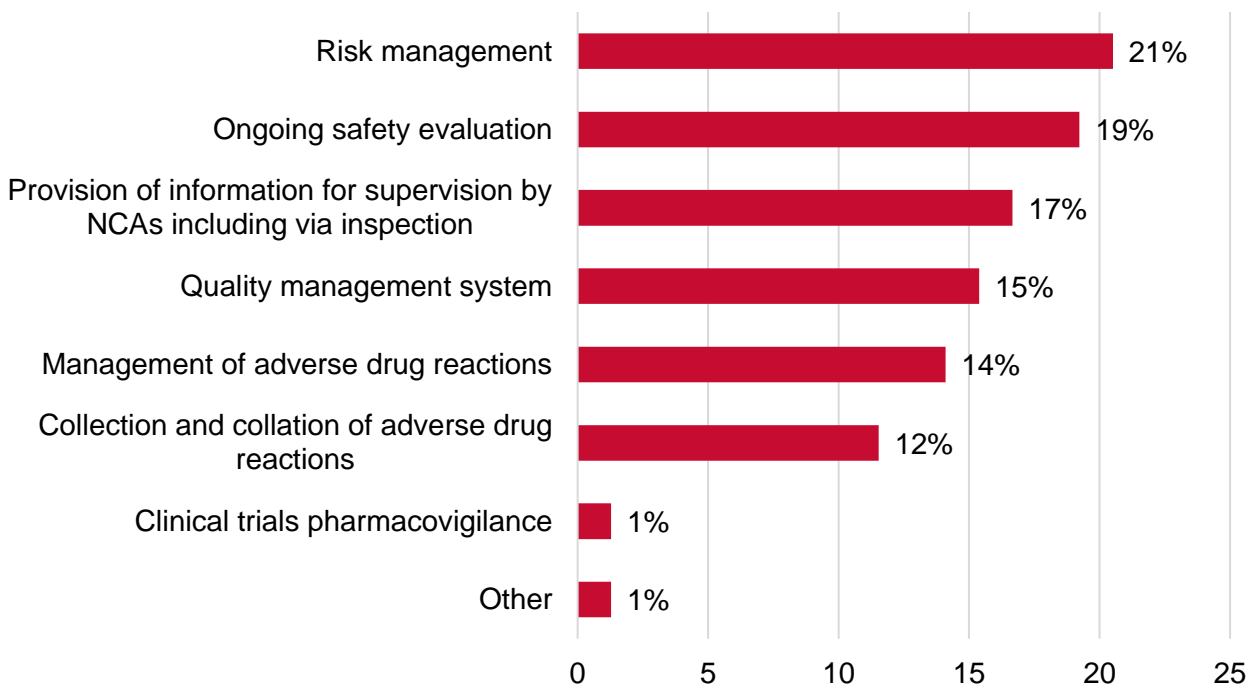


Figure 8 - Proportion of major findings reported for each topic area



In comparison to the previous reporting period from 01 April 2017 to 31 March 2018, the proportion of risk management major findings has decreased from 25% to 21% but remained unchanged in the area of ongoing safety evaluation (18% vs 19%) and the provision of information to NCAs (16% vs 17%).

A marked drop was seen in the proportion of non-compliances related to the quality management system. In the previous period, this topic accounted for 21% of all major findings whereas the topic represented 15% of major findings in this report period.

An increase was seen in major findings issued for core pharmacovigilance activities such as the collection and collation of adverse drug reactions (7% vs 12%) and the management of adverse drug reactions (12% vs 14%).

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 PII) that spanned across multiple pharmacovigilance activities. This was not the only finding reported during the 2018/19 period against GVP PII. Other findings in relation to breaches of GVP PII have been reported under the specific area of failing, for example failure in meeting the requirements for ongoing safety evaluation for biological medicines. A more detailed breakdown of findings issued for breaches against the requirements in GVP PII is provided in section 4.3 of this report.



3.3. Minor findings

38 minor findings were identified in the period of 01 April 2018 to 31 March 2019. In comparison to the previous reporting period, about 45% fewer minor findings were reported. The proportion of minor findings by topic area is displayed in the graph below.

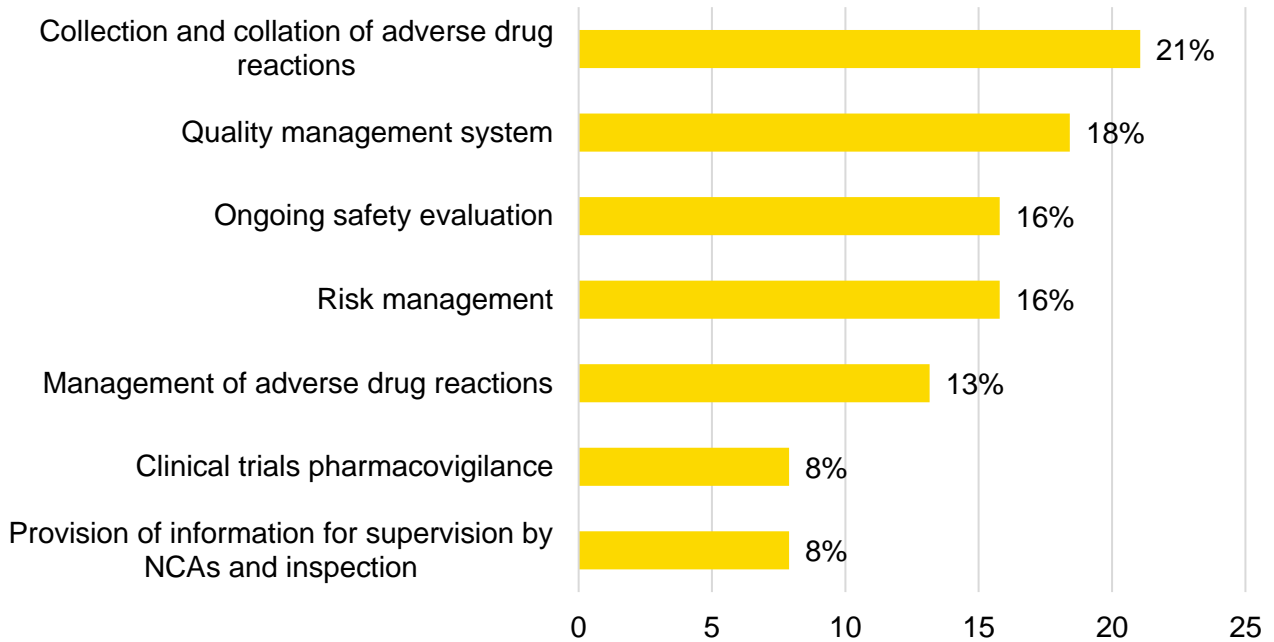


Figure 9 - Proportion of minor findings reported for each topic area

The largest proportion of minor findings was composed of non-compliances in relation to the collection and collation of adverse drug reactions, followed by findings in relation to the quality management system and ongoing safety evaluation.



4. Focus topics

4.1. Risk management

The highest proportion of findings in the reporting period related to risk management. Findings in this area constituted 20% of all findings (i.e. 24 findings) and were reported from 13 out of 18 inspections. A breakdown of the 24 findings in this topic area is shown in Figure 10.

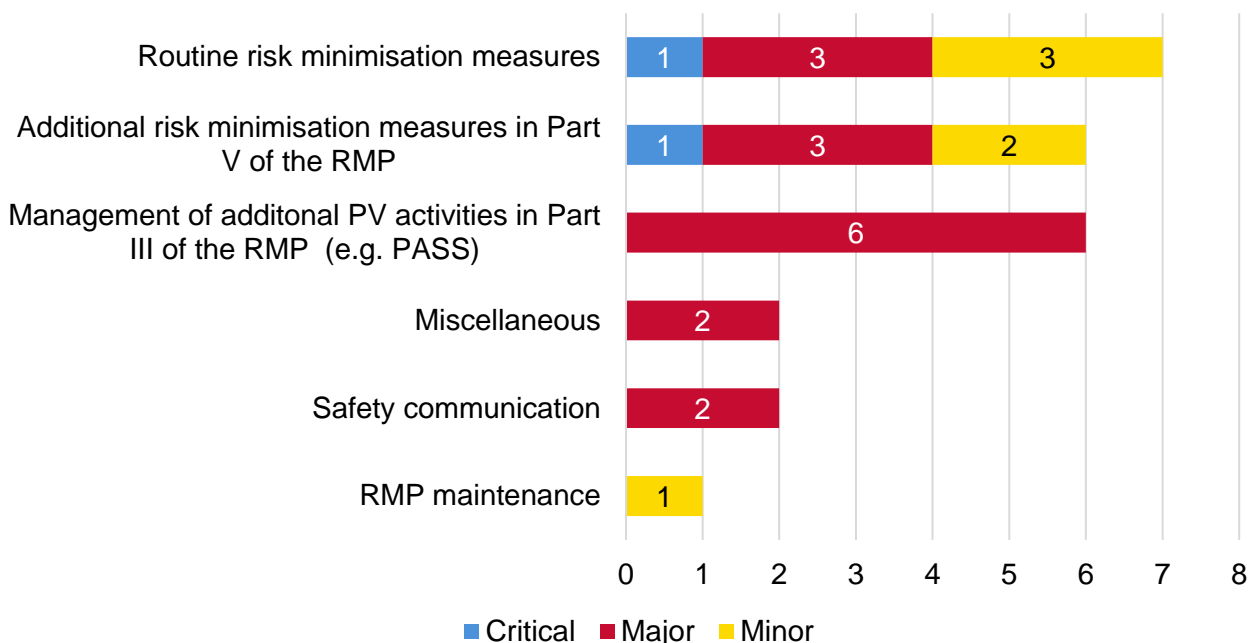


Figure 10 - Breakdown of all risk management findings

The majority of risk management findings related to routine risk minimisation measures, specifically the maintenance and communication of safety information in the authorised product information, i.e. the summary of product characteristics (SmPC) and the PIL (seven findings). In addition to the previously discussed critical finding relating to the release of outdated PILs in packs, other findings concerned failures to submit safety variations to update the product information in line with the current scientific knowledge and delays in publishing the updated product information on external websites following approval of safety variations.

Findings in relation to additional risk minimisation measures and additional pharmacovigilance activities made up the second-largest number of findings in this category with six findings each. The most common finding regarding additional risk minimisation measures related to failures in distributing educational materials to the target population as per the MHRA-agreed implementation plan. Common findings in relation to post-authorisation safety studies (PASS) included deficiencies in the content and submission of aggregate study reports, management of adverse events (AE) and serious AEs, failure of the QPPV to review and sign-off study protocols and maintenance of the study record in the EU PAS Register.

In two inspections, major findings for risk management were reported which grouped various aspects of this topic, e.g. implementation of additional risk minimisation measures, maintenance of the RMP, and oversight of additional risk minimisation measures and additional PV activities, under one overarching finding. These are included as 'miscellaneous' in the graph above.



4.2. Ongoing safety evaluation

The second-highest proportion of all findings reported between 01 April 2018 to 31 March 2019 related to ongoing safety evaluation. Findings in this topic made up 18% of all findings (i.e. 22 findings) and were reported from 14 out of 18 inspections. A breakdown of the 22 findings in this topic area is shown in Figure 11.

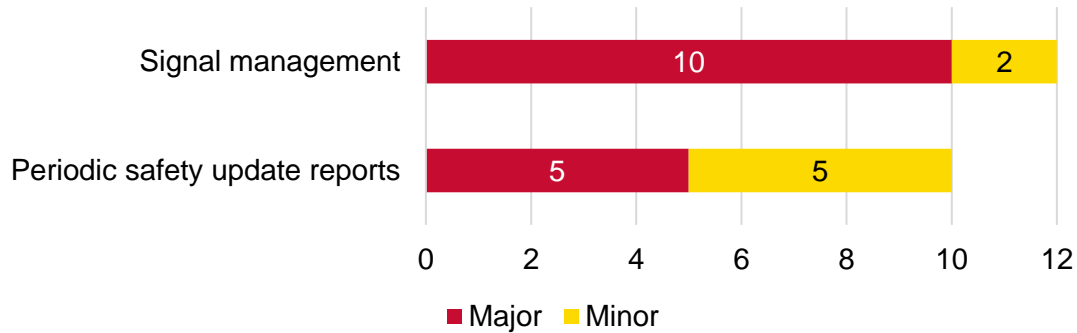


Figure 11 – Breakdown of all findings reported for ongoing safety evaluation

The distribution of findings between signal management and PSURs was almost equal; however, more major findings were reported for signal management.

It should be noted that findings in signal management may be reported for deficiencies associated with more than one aspect of this critical pharmacovigilance process. In this reporting period, six out of the twelve findings related to more to than one aspect of signal management.

Out of the ten major findings, six related to deficiencies in the conduct of signal management activities such as failures to include all sources for signal detection or to maintain records supporting the rationale and traceability of decisions taken. Other findings reported significant delays between the individual steps in the signal management process.

Three major findings related to deficiencies in the documentation of the signal management system, signal detection methodology, timelines and corresponding processes in written procedures.

Three major findings related to failures in conducting signal detection in EudraVigilance for products that were part of the EMA pilot and/or to the lack of procedural documentation for this activity.

Five findings also related to the requirements for signal detection as described in *GVP Product- or Population Specific Considerations II: Biological medicinal products* and these are described in more detail in section 4.3 of this report.

The findings reported for PSURs often related to different aspects. The most commonly reported aspects in major and minor findings were associated with inaccurate sales and patient exposure figures, the inclusion of unrelated adverse event reports in the interval and cumulative summary tabulations of adverse reactions and failures to consider or include relevant cases in the PSUR sections evaluating the benefits and risks of the medicinal product.



4.3. Biological medicinal products

In accordance with the risk-based approach to inspection scheduling, nine out of the 18 inspections in this report period were conducted of MAHs which held at least one marketing authorisation for a biological medicinal product or a biosimilar. Biologicals are high-risk products due to their complex nature and the greater potential for variability of the quality, safety and efficacy between different batches of the same product based on changes in the manufacturing process.

In five of the nine inspections², major findings were reported for signal management activities as the MAH had not incorporated the specific requirements for biologicals as described in *GVP Product- or Population Specific Considerations II: Biological medicinal products (GVP PII)* into signal management activities for these products. Such deficiencies related to a lack of mechanisms to detect any acute and serious new risks that may emerge following a change in the manufacturing process in line with the guidance in GVP PII. In addition, findings were reported for failures to evaluate signals for biologicals in the context of batch-specific exposure data to identify any changes in product safety and quality over time.

In two of the five inspections reporting a finding in signal management, deficiencies were also identified in relation to the SmPC and PIL of the biological medicine as they did not include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file. Such wording is important to improve the traceability of biological medicines.

² It should be noted that the four inspections of MAHs with biological medicines that did not report findings in relation to the requirements of GVP PII did not include a review of signal management activities in their scope.



5. Summary

In the report period from 01 April 2018 to 31 March 2019, 18 inspections were conducted of which 16 were planned as part of the routine inspection scheduling and two were triggered due to previous critical findings. A total of 120 findings were reported in this period. These comprised four critical, 78 major and 38 minor findings. The average number of findings issued in the report period is consistent with that of previous years, albeit a significant decrease was seen in the number of minor findings issued.

The four critical findings were reported in relation to risk management, the quality management system and the provision of information for inspections.

At least one major finding was reported in all inspections with the majority of inspections resulting in four to five major findings. The largest proportion of major findings was reported in relation to risk management (21%). This was followed by activities relating to ongoing safety evaluation (19%) and the provision of information for supervision by national competent authorities, including via inspection (17%).

The largest proportion of minor findings was composed of non-compliances in relation to the collection and collation of adverse drug reactions (21%), followed by findings in relation to the quality management system (18%) and ongoing safety evaluation (16%).

Product-specific risks such as additional risk minimisation measures, additional pharmacovigilance activities or product type are considered during inspection scheduling. In the reporting period a high proportion of findings was made in relation to product-specific requirements. For example, the highest proportion of all findings was reported in relation to risk management (20%, 24 findings), which continues to be an area of specific concern. Two out of the four critical findings related to routine and additional risk management measures, and the highest proportion of major findings (21%) were also issued in this area. Findings reported for ongoing safety evaluation activities such as signal management and PSURs comprised the second-highest proportion of all findings. In addition, non-compliances in relation to product-specific requirements for biologicals as described in *GVP Product- or Population-Specific Considerations II: Biological medicinal products* were identified for all MAHs of biologicals or biosimilars where signal management activities were reviewed during the inspection.

The MHRA continues to fulfil its legal obligation to conduct inspections to examine compliance with existing EU and national pharmacovigilance regulations and guidelines, with a focus on high risk products and systems in order to best protect patients. Consideration of other aspects of risk such as organisational complexity and the compliance and inspection history will continue to ensure that organisations with lower risk products are incorporated into the inspection 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 authorised product information |
| | Additional risk minimisation measures 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, including via 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 |