Medicines & Healthcare products Regulatory Agency

MHRA

Pharmacovigilance Inspection Metrics Report

April 2019 – March 2020

1. Introduction

During the period 01 April 2019 to 31 March 2020, 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.

MAHs were selected for inspection using the risk-based methodology used by the GPvP inspectorate for a number of years. This risk-based methodology is in accordance with Good Vigilance Practice (GVP) Module III and considers factors such as 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. The UK's national inspection programme for this reporting year also took into account the European Medicines Agency's programme of routine pharmacovigilance inspections of organisations with centrally authorised products. Following the UK's departure from the EU on 31 January 2020, the UK entered a Transition Period where Union law continued to apply and therefore inspections continued to be conducted in accordance with EU regulations and guidance.

This report contains data relating to all 22 inspections conducted during the period 01 April 2019 to 31 March 2020 (2019/20). Information on the types of inspection, inspection findings and the amount of time spent on inspection have been examined, including analysis of specific technical topics where the highest number of findings were found.

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 22 inspections conducted in the period of 01 April 2019 to 31 March 2020, five inspections were triggered to assess the resolution of critical findings from previous inspections, one was triggered due to intelligence received and 16 inspections were scheduled and conducted in line with the routine national inspection schedule. As part of those routine inspections, four were of MAHs that had never been inspected by the MHRA, whilst the remaining 12 inspections were routine re-inspections of MAHs. Exactly half of the inspections completed were of innovative pharmaceutical companies and half were of generics organisations.

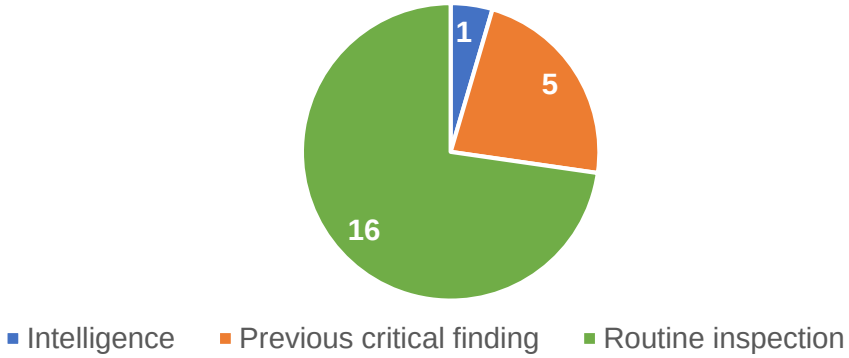

Figure 1 - Number of inspections conducted by type

As for the scope of inspections, whilst the majority included a review of the global pharmacovigilance system, several inspections covered specific targeted topics only. Two inspections focussed solely on maintenance of reference safety information, one inspection focussed on the management of non-interventional PASS and one inspection focussed on specific additional risk minimisation measures. One inspection was also dedicated to risk management systems, covering additional risk minimisation measures and maintenance of reference safety information. These targeted inspections allowed inspectors to focus on the areas of highest risk within the organisations' pharmacovigilance system.

15 onsite inspections included an element of office-based inspection (OBI) which is illustrated in Figure 2. For five of those inspections, OBI days were planned and conducted prior to the inspection onsite. For nine inspections, ad hoc OBI days were conducted after the onsite inspection[1]. 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 inspection was conducted entirely remotely as part of a project to develop an approach for remote GPvP inspections.

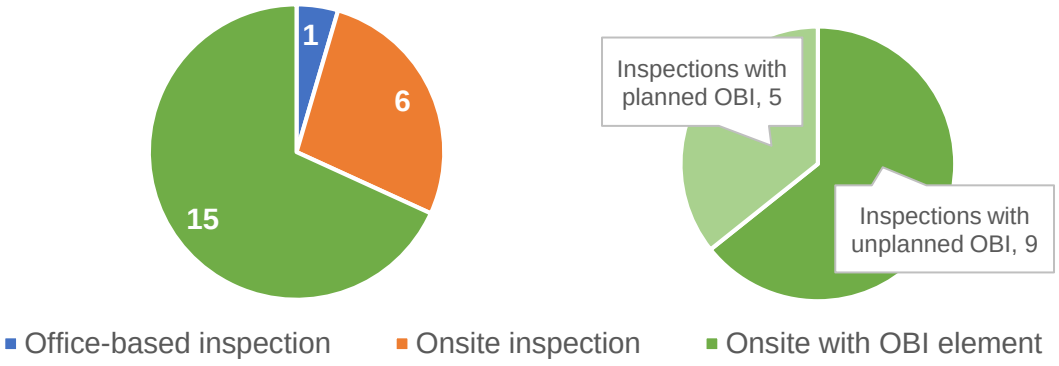

Figure 2 - Number of inspections conducted by inspection location, inset shows breakdown of onsite inspections with OBI element

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

3. Summary of findings

A total of five critical, 76 major and 46 minor findings were identified during this reporting period. A reported finding can often comprise of 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 presents the number and distribution of findings across the different inspection types. For the one inspection conducted due to intelligence received, no findings were raised.

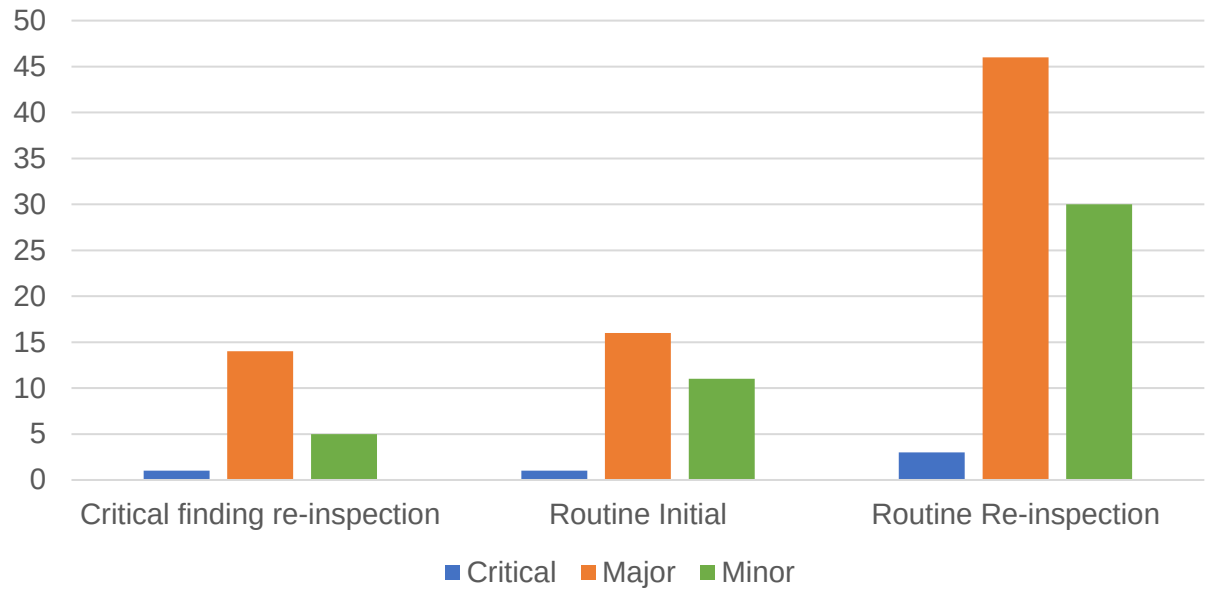

Figure 3 - Number of inspection findings by inspection type

When compared to the previous reporting periods, the average number of findings per inspection (irrespective of grading) over time has remained relatively stable at an average of just under six findings per inspection in 2019/20. This is demonstrated in Figure 4 below.

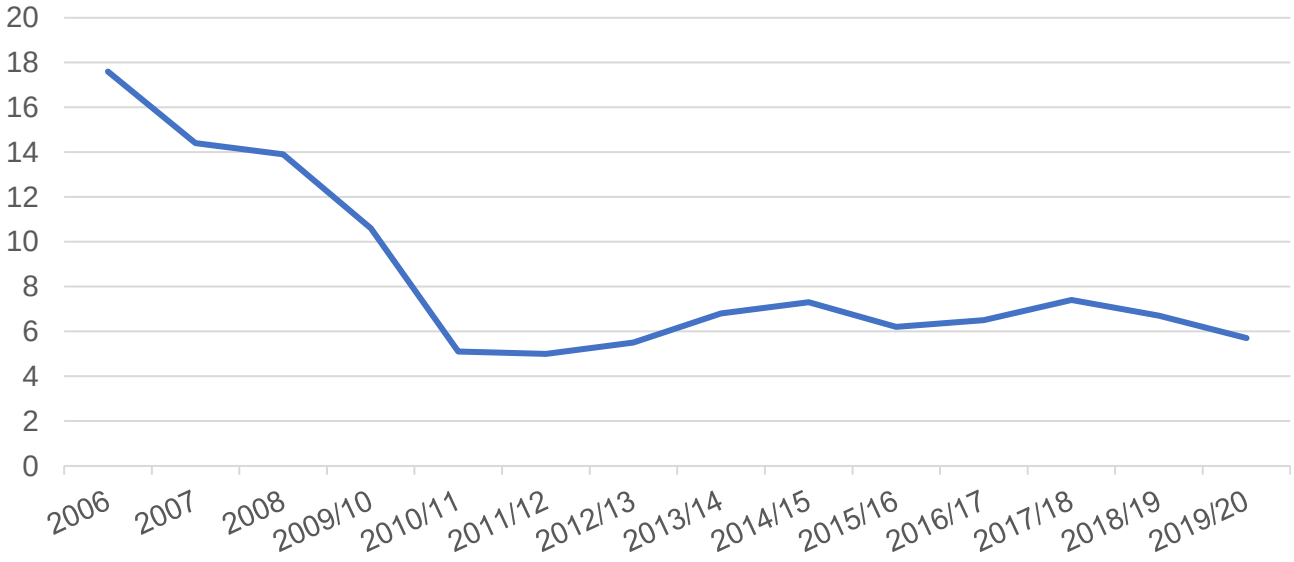

Figure 4 - Average number of findings reported per inspection over time

Figure 5 breaks this down further, presenting the average number of critical, major and minor findings reported per inspection over time. Over the years, the average number of critical findings has not changed significantly but the average number of major findings reported per inspection has increased, peaking at just over four in the last reporting period and dropping slightly to 3.5 for the current reporting period. For minor findings, the average number raised per inspection has decreased overall when compared to previous reporting periods yet there are clear fluctuations which prevent a general trend being confirmed.

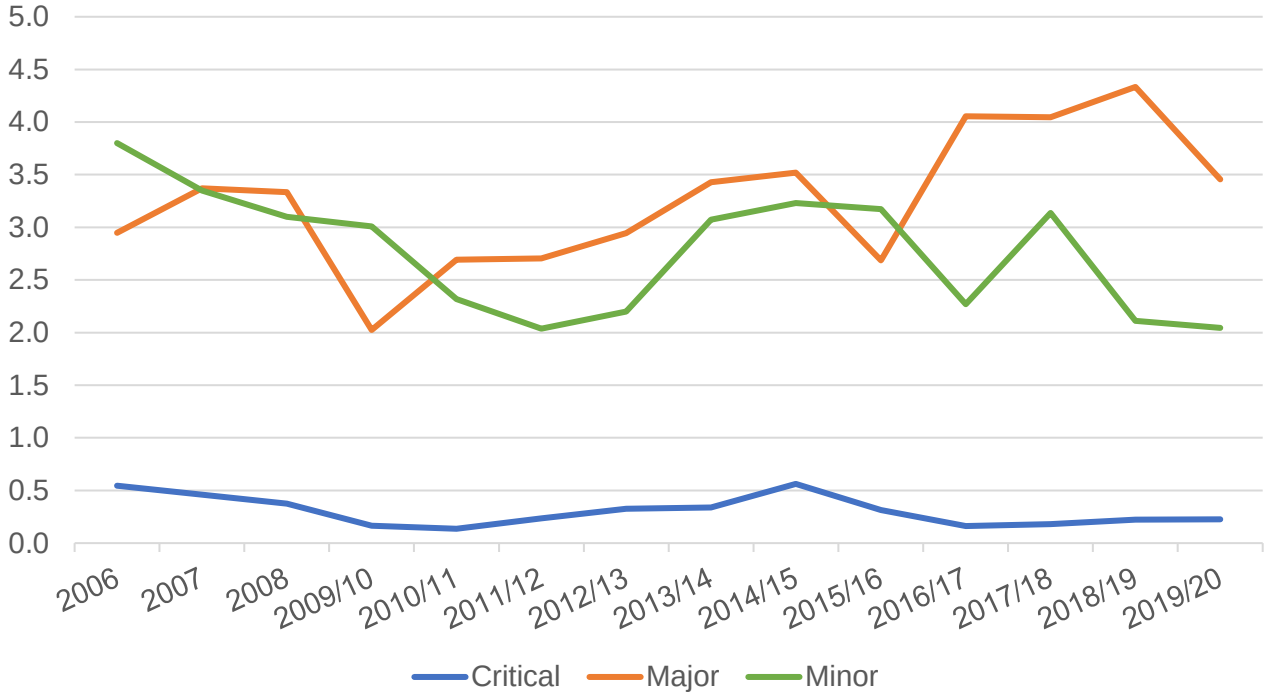

Figure 5 – Breakdown of average number of finding by type reported per inspection over time

3.1. Critical findings

3.1.1. Critical findings reported from 01 April 2019 to 31 March 2020

Five critical findings were identified from five inspections in the period of 01 April 2019 to 31 March 2020. This is approximately one critical finding reported from every 4.4 inspections which is consistent with the outcomes from the previous four reporting periods.

All five critical findings were in the area of risk management, specifically:

- three in relation to maintenance of reference safety information
- one in relation to implementation of additional risk minimisation measures
- one in relation to management of additional pharmacovigilance activities in Part III of the risk management plan (RMP)

Anonymous summaries of the critical findings are provided below by the relevant area.

Maintenance of reference safety information

For the three critical findings raised under this sub-topic, in each case the MAH had failed to ensure that patient information leaflets (PILs) with updated safety information had been packaged and released to market within the required timeframes.

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. However, a number of product batches were identified on each inspection which had been released with the out of date PIL beyond the maximum six months' timeframe following MHRA approval.

In addition, in one inspection there were examples of significant delays of up to a year to update product information published on the Electronic Medicines Compendium website (EMC) following regulatory approval of a safety update. The MHRA expectation is that following an update to product information the MAH should update EMC within 10 working days after regulatory approval.

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.

Implementation of additional risk minimisation measures

The MAH had not implemented the additional risk minimisation measures for a product which had been on the market for over two years and had a high percentage of the UK market share for the product.

The product's additional risk minimisation measures included educational materials to inform patients and healthcare professionals of important risks and potential overdose due to medication errors.

Failure to implement the educational material had been raised at a previous MHRA inspection as a critical finding. However, the MAH had still not fully implemented the additional risk minimisation measures at the subsequent re-inspection, and this was again graded as a critical finding.

Conduct of post-authorisation safety studies (PASS)

Significant breaches of the CHMP-approved study protocol for the MAH's non-interventional PASS were identified during inspection at a specific study site. These breaches impacted upon the collection of data related to the primary and secondary study end points and, as a result, there was no assurance that the data collected from this site could contribute meaningfully to the overall study objectives, resulting in a critical finding.

The breaches identified at the study site included:

- Information concerning the outcomes of interest for the study had not been collected during the six-month follow-up phase after last dose administration and the long-term follow-up phase of patients
- There were examples of where data entry into the electronic data capture system was inaccurate or incomplete
- There were adverse events recorded in the patients' electronic health records which had not been recorded in the adverse events page of the case report form and there was no evidence of a seriousness or causality assessment outside of the electronic data capture system to determine whether they met the protocol-defined criteria for inclusion in the study dataset
- There were examples of delays in reporting serious adverse events to the MAH
- There was no record of who performed the eligibility assessment for patients enrolled in the study at the inspected site and when they were performed
- Signed consent forms were missing for three patients

In each of these inspections, in addition to the critical finding, several major findings were also reported in other areas of the pharmacovigilance system, as shown in Table 1 below.

Inspection	Critical	Major	Minor
A	1	2	0
B	1	2	1
C	1	3	1
D	1	6	2
E	1	1	1

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 inspection topics since April 2012 is shown in Figure 6. A total of 94 critical findings were reported between 01 April 2012 and 31 March 2020.

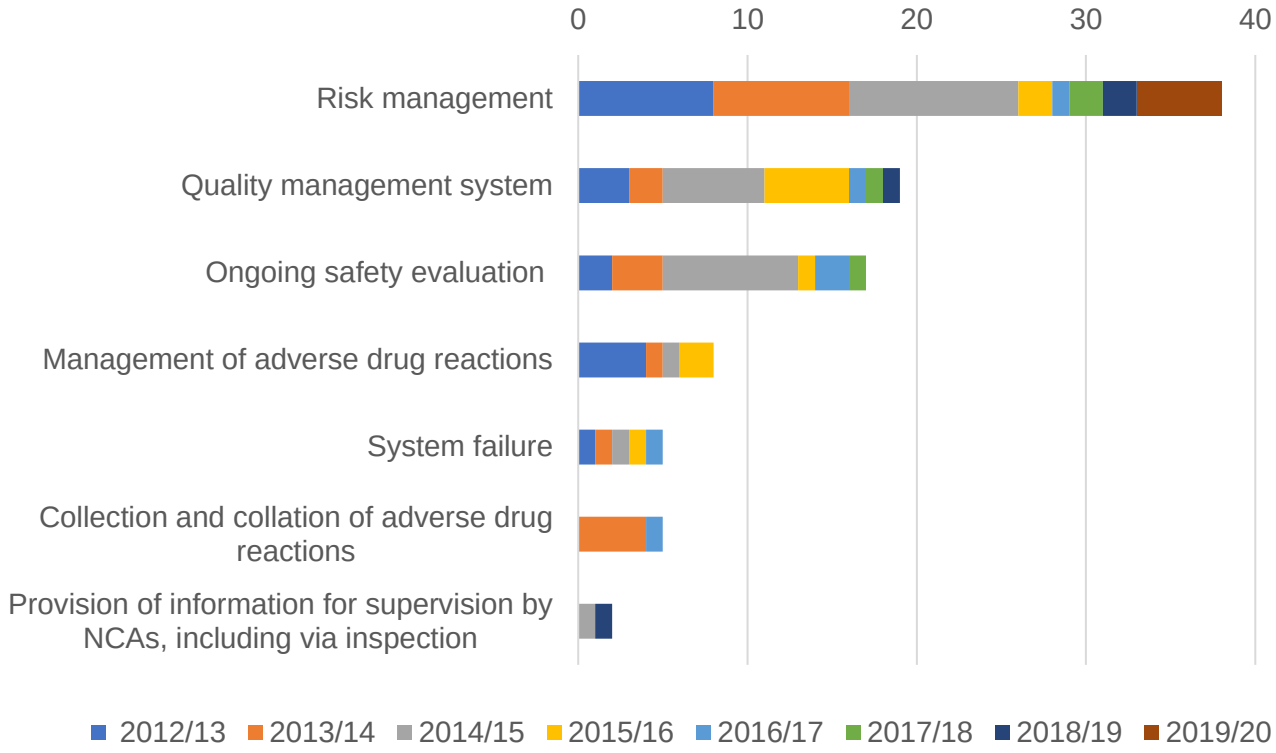

Figure 6 - Number and distribution of critical findings across topics

The number of critical findings has remained relatively stable for the last three years. In comparison to earlier reporting periods before 01 April 2016, the number of critical findings each year has decreased significantly.

Risk management remains the topic for which the largest number of critical findings has been reported over time. Findings in this area have historically related to routine risk management such as the maintenance of the reference safety information, which was the case for the current reporting period where three out of the five critical findings reported related to reference safety information. The two other critical findings raised during 2019/20 related to additional risk minimisation measures and additional pharmacovigilance activities, which follows the trend observed over recent years where critical findings have been more frequently raised under these topics.

3.2. Major findings

The number of major findings raised in this reporting period per inspection ranged between one and seven, with one inspection raising no findings at all. Out of the 22 inspections in 2019/20, the median number of major findings per inspection was three. Figure 7 displays the number of major findings by the number of inspections conducted.

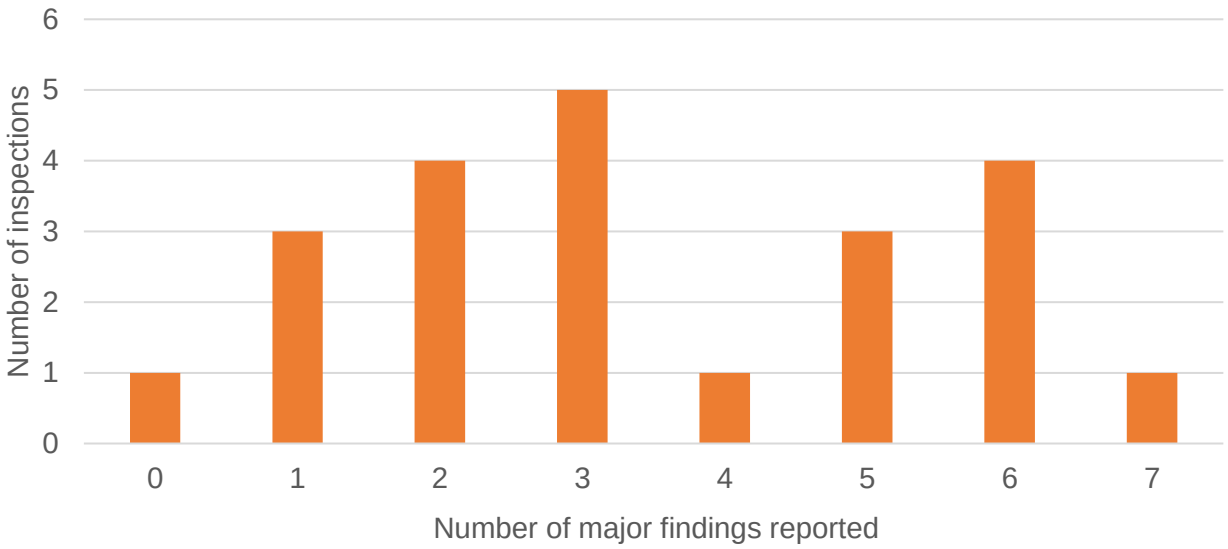

Figure 7 - Number of major findings reported by the number of inspections

In total, 76 major findings were identified in the period of 01 April 2019 to 31 March 2020. 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.

As shown in Figure 8, the highest proportion of major findings were reported in relation to risk management, with 23 findings (30%). This was followed by activities relating to the quality management system with 20 findings (26%), ongoing safety evaluation with 14 findings (18%) and management of adverse drug reactions with 13 findings (17%).

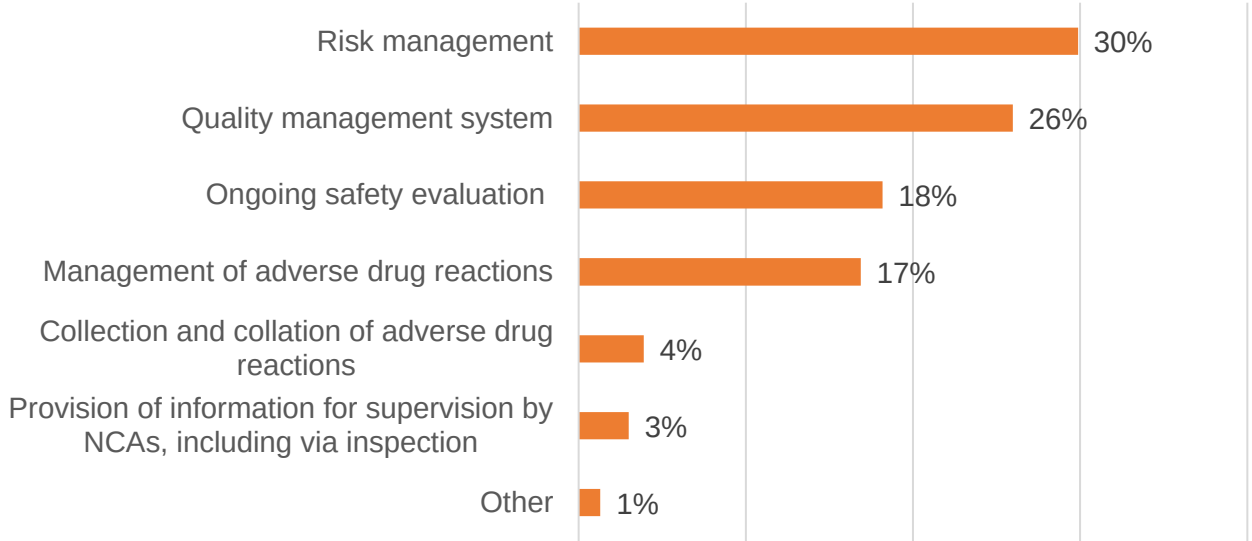

Figure 8 - Percentage of major findings reported for each topic area[2]

[2] Percentages rounded to the nearest integer and may not total 100%

In comparison to the previous reporting period from 01 April 2018 to 31 March 2019 (2018/19), the proportion of risk management major findings increased from 21% to 30% which can be seen in Figure 9 below.

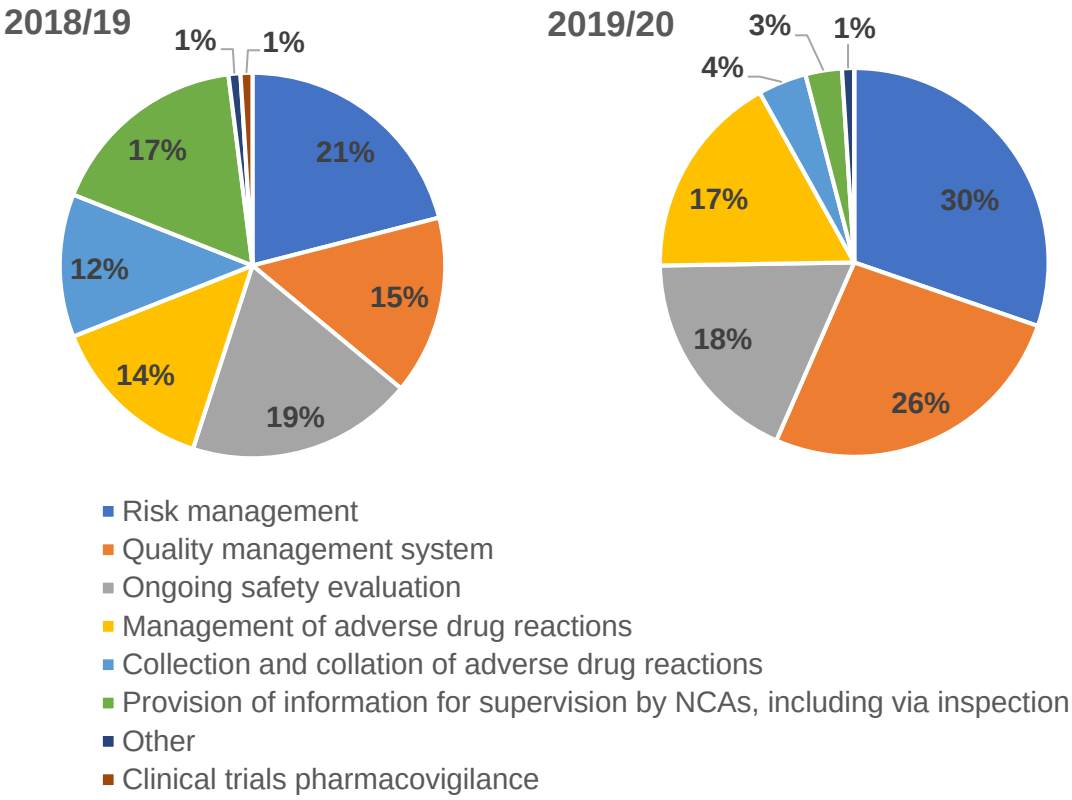

Figure 9 – Percentage change between inspection findings from 2018/19 and 2019/20 by topic area

Another topic which saw an increase in the proportion of major findings this reporting period compared to the last, was quality management systems which increased from 15% to 26%. The proportion of findings in the area of ongoing safety evaluation remained unchanged and there was a small increase in the proportion of major findings related to management of adverse drug reactions (14% to 17%).

There was considerable decrease in the proportion of major findings related to collection and collation of adverse drug reactions. In the previous period, this topic accounted for 12% of all major findings whereas the topic represented 4% in this reporting period.

A notable decrease was also seen in the proportion of major findings relating to the provision of information for supervision by the national competent authorities (NCA), including via inspection. In 2018/19, 17% of all major findings were raised against this topic whereas for 2019/20, this was only 3%.

Similar to the previous reporting period, one major finding reported as 'other' was raised due to non-compliance with pharmacovigilance requirements for biological medicines outlined in GVP *Product- or population-specific considerations II: Biological medicinal products* (GVP PII). This finding encompassed multiple deficiencies in pharmacovigilance activities for biological products, including signals and reference safety information. As was the case in 2018/19, another major finding also related to biological products and non-compliance with GVP PII, which was categorised under ongoing safety evaluation due to the nature of the finding.

3.3. Minor findings

46 minor findings were identified in the period of 01 April 2019 to 31 March 2020. In comparison to the previous reporting period, this was an increase of eight findings. Figure 10 presents the proportion of minor findings by topic area for the reporting period 2019/20.

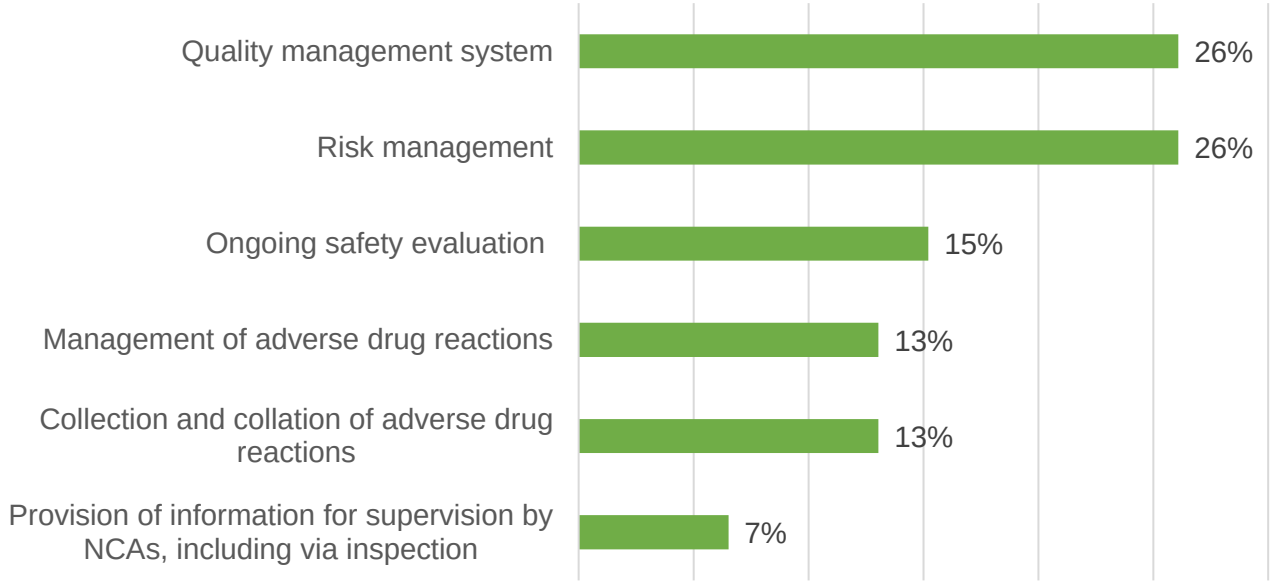

Figure 10 - Proportion of minor findings reported for each topic area

The largest proportion of minor findings was composed of non-compliances in relation to the quality management system and risk management, followed by findings in relation to ongoing safety evaluation, management of adverse drug reactions and collection and collation of adverse drug reactions. This was the same trend as for the major findings reported in 2019/20.

In comparison with the previous reporting period, collection and collation of adverse drug reactions had a much lower proportion of minor findings in this reporting period – a change from 21% to 13%. Risk management and the quality management system had a larger proportion of minor findings raised in 2019/20 than 2018/2019, an increase from 16% to 26% and 18% to 26% respectively. The proportion of minor findings in the area of management of adverse drug reactions and provision of information for supervision by NCAs, including via inspection, remained relatively unchanged since 2018/19.

4. Focus topics

The highest number of all findings in the reporting period (irrespective of the grading of the finding) related to risk management followed by quality management systems. This is depicted in Figure 11 below which demonstrates the spread of findings by grading and the number of findings raised against each inspection topic.

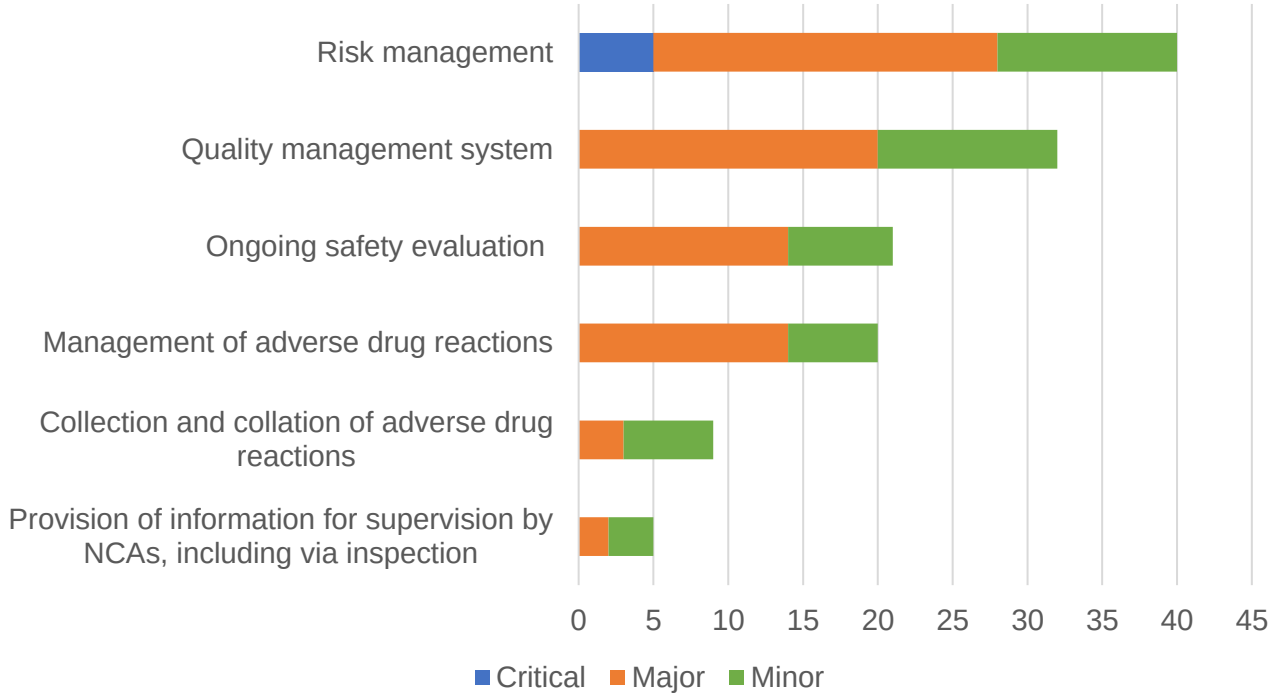

Figure 11 - Proportion of all findings reported for each topic area

4.1. Risk management

Risk management has remained the topic with the highest number of findings overall, which was the same for the previous two reporting periods. Findings in this area constituted 31% of all findings (40 out of a total of 127 findings) and were reported from 20 out of the 22 inspections. A breakdown of the 40 findings in this topic area by sub-topic is shown in Figure 92.

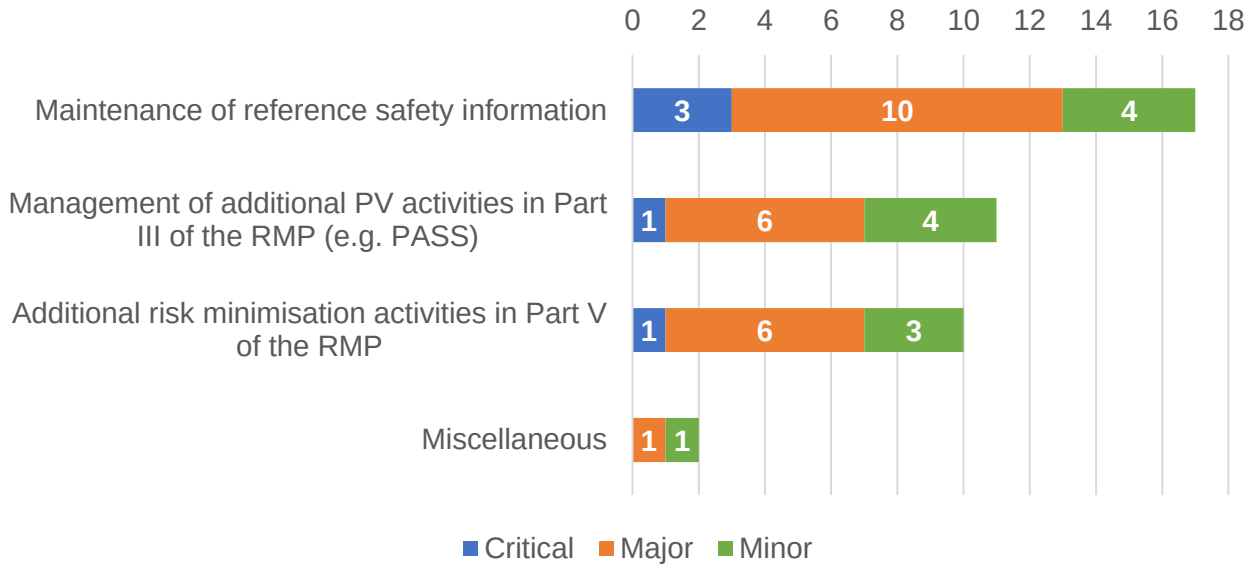

Figure 92 - Breakdown of all risk management findings

The majority of risk management findings related to failures in routine risk minimisation measures, specifically maintenance of reference safety information, such as the summary of product characteristics (SmPC) and the PIL, for which there were 17 findings. As discussed under the three critical findings, the most common non-compliance seen in this area was the release of outdated PILs in product packs, but other findings concerned failures to maintain the product information in line with the current scientific knowledge, delays in the submission of safety variations and delays in publishing updated product information on the EMC following approval of safety variations.

The second-largest number of risk management findings related to failures associated with additional pharmacovigilance activities, specifically PASS in the 11 findings identified, one of which has already been described as a critical finding above. Other findings relating to PASS were given for failures in the management of adverse events and serious adverse events, failure of the Qualified Person responsible for Pharmacovigilance (QPPV) to review and sign-off study protocols, lack of governing procedural documents to support the management of PASS and maintenance of the study record in the EU PAS Register.

There were also 10 findings relating to failures in implementing additional risk minimisation measures. The most common finding in this sub-topic related to deficiencies in the control and implementation of educational materials. This included failure to submit materials to the MHRA for approval and deficiencies in the tracking of receipt of educational materials by the target population.

Miscellaneous findings for risk management were reported in two inspections, which related to the maintenance of the RMP. For example, in one of these findings, the MAH had not submitted an updated RMP for a product to the MHRA for approval following a significant update.

4.2. Quality management systems

The second-highest proportion of all findings reported between 01 April 2019 to 31 March 2020 related to quality management systems. Findings in this topic made up 25% of all findings (32 out of a total of 127 findings) and were reported from 16 out of the 22 inspections. A breakdown of the 32 findings in this topic area by sub-topic is shown in Figure 3.

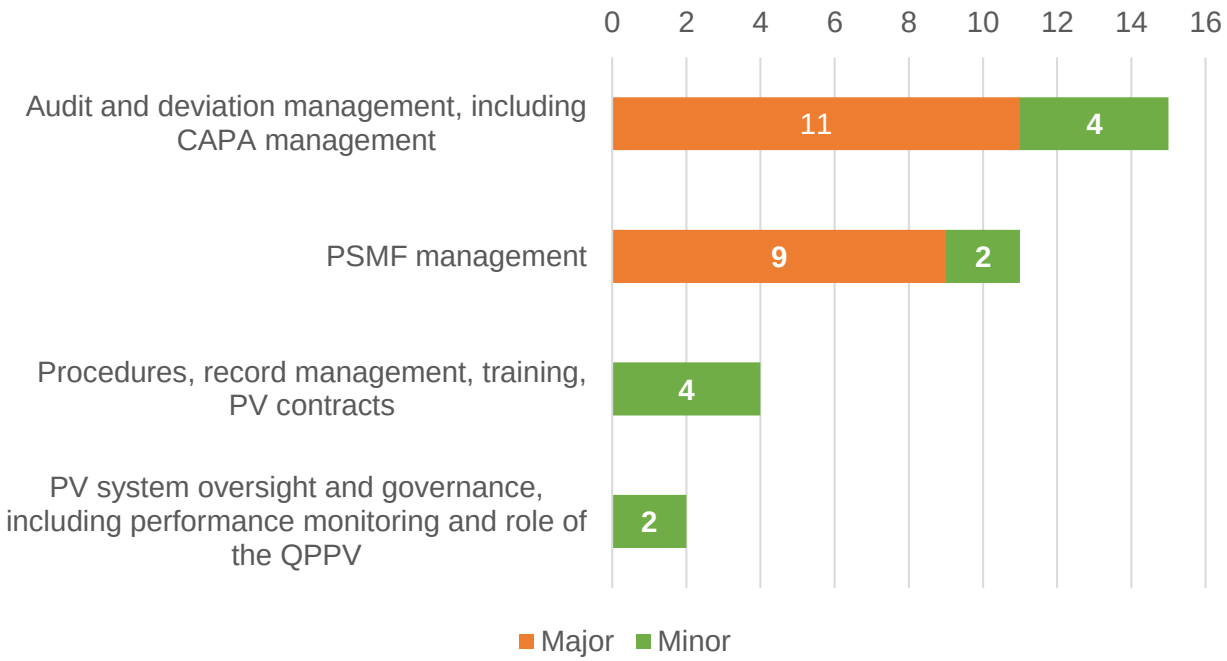

Figure 13 – Breakdown of all findings reported for quality management systems

The highest number of findings for quality management systems related to failings associated with audit and deviation management, including corrective and preventative action (CAPA) management, with 15 findings in total for this sub-topic. This was then followed by 11 findings related to failures in Pharmacovigilance System Master File (PSMF) management. Each of these sub-topics comprised of both major and minor findings.

Due to the nature of quality management systems spanning across the pharmacovigilance system, findings related to quality management systems may have arisen from direct review of the quality management system as a standalone topic or may have been raised during review of other technical topics where specific quality requirements for those pharmacovigilance activities were not fulfilled.

Out of the 11 major findings for audit and deviation management, nine of these were due to deficiencies in the management of CAPA including:

- Delays to CAPA development
- CAPA that did not address the root cause and impact analysis for the identified non-compliance
- Open CAPA which were significantly past their due date
- CAPA raised from a previous critical finding raised at an earlier MHRA inspection had not been addressed

The further two major findings under this sub-topic related to auditing of the pharmacovigilance system as not all relevant entities (such as internal pharmacovigilance activities, vendors/partners etc.) had been considered as part of the pharmacovigilance audit strategy.

For the nine major findings reported for deficient PSMF management, six of these findings were due to incomplete or incorrect information presented in the annexes to the PSMF, most notably for

annexes B (lists of contracts and agreements) and H (list of products covered by the pharmacovigilance system). Other findings also related to incomplete information provided in the PSMF, such as missing information for open deviations impacting the pharmacovigilance system and also missing information on audits with significant findings, along with the associated corrective and preventative actions.

5. Inspections over time

The number of inspections and the average time spent on inspection were reviewed since 2012/13. There is a clear change observed in Figure 14 between the approach used before and after 2016/17.

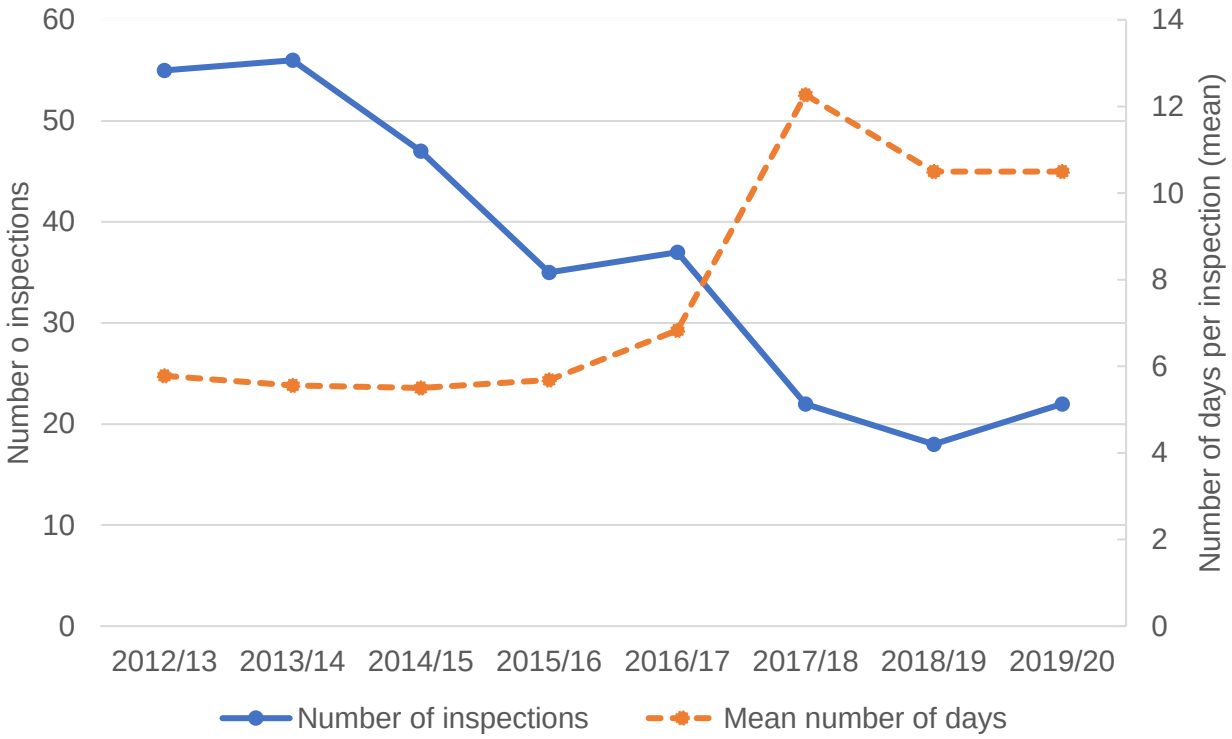

Figure 14 – Number of inspections per reporting period against the mean number of inspection days per inspection

From 2012/13 to 2017/18, as the number of inspections completed for each reporting period decreased, the time spent on each inspection increased. This increase can be attributed to the increasing complexity of pharmacovigilance systems operated by MAHs, such as global organisations with complex networks of affiliates and partners, and those which include products with complicated risk management systems. For 2019/20, a slight increase was seen in the number of inspections which likely reflected the increase in the size of the inspection team as more inspections could be conducted. The mean number of inspection days per inspection has reduced since 2017/18, which may relate to a more tailored approach to inspection planning where areas of highest risk for specific pharmacovigilance systems were the focus of the inspection scope, requiring fewer inspection days as a result. In 2019/20, five inspections used this targeted approach covering only one or two topics rather than a full pharmacovigilance systems inspection.

Although the number of inspections and the number of inspection days per inspection have changed considerably since 2016/17, the number of inspection findings remained stable in comparison at around six findings in total per inspection.

6. Summary

In the report period from 01 April 2019 to 31 March 2020, 22 inspections were conducted of which 16 were planned as part of the routine inspection scheduling, five were triggered due to previous critical findings and one was completed due to intelligence. A total of 127 findings were reported in this period. These comprised five critical, 76 major and 46 minor findings. The average number of findings issued in this reporting period was consistent with that of recent years, with only a small decrease in the number of major and minor findings.

All five critical findings were reported in relation to deficiencies in the management of known product risk, with three of these findings issued where safety updates to PILs had not been implemented as required.

With the exception of one inspection where no findings were raised, at least one major finding was reported in all inspections with the majority of inspections resulting in three major findings. The largest proportion of major findings was reported in relation to failures in risk management (30%). This was followed by deficiencies in quality management systems (26%) and failures associated with the ongoing safety evaluation of products (18%).

The largest proportion of minor findings was comprised of non-compliances in relation to the quality management system (26%) and risk management (26%), followed by findings in relation to ongoing safety evaluation (15%) and management of adverse drug reactions (13%).

Risk management was a clear area of significance when reviewing the metrics from this reporting period, 2019/2020. Not only was this the only area where critical findings were reported but it also had the largest number of major and minor findings. Through the risk-based inspection scheduling approach, information on products with additional risk minimisation measures and additional pharmacovigilance activities is used to help prioritise pharmacovigilance systems for inspection, which may lead to this area being a topic of focus on inspection and hence more findings are raised under this topic. However, from the detailed review of risk management findings, the majority of these findings actually related to routine aspects of risk minimisation, specifically ensuring that the information that is available to patients and healthcare professionals is kept up-to-date with the known safety profile of the product. This is relevant for any product throughout its lifecycle. To promote compliance in this area and raise awareness of requirements and expectations, maintenance of reference safety information was covered as a topic of focus at the GPvP Symposium 2020 and also discussed under the MHRA Inspectorate Blog[3].

As the MHRA GPvP Inspectorate continues to follow a risk-based approach to inspection scheduling, inspections will be prioritised based on the risk profile of products, the complexity of pharmacovigilance systems and intelligence received from external and internal sources. This will ensure that high risk areas are prioritised for inspection to ensure regulatory compliance, working towards the protection of public health.

[3] https://mhrainspectorate.blog.gov.uk/2019/12/17/passing-the-baton-from-gpvp-to-gmp-three-top-tips-for-protecting-patients-and-staying-compliant/

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