Medicines & Healthcare products Regulatory Agency

Pharmacovigilance Inspection Metrics Report

April 2021 – March 2022

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Contents

1. Introduction

During the period 01 April 2021 to 31 March 2022 (2021/22), the MHRA's Good Pharmacovigilance Practice (GPvP) Compliance Team conducted 32 inspections of 30 marketing authorisation holders (MAHs). The purpose of these inspections was to examine compliance with currently applicable UK and EU pharmacovigilance regulations and guidelines.

The GPvP inspection model consists of four discrete inspection arms that each focus on specific pharmacovigilance activities: routine pharmacovigilance activities, routine risk management and safety communications, additional risk minimisation activities, and non-interventional post-authorisation safety studies (NI-PASS). MAHs are selected for inspection using a risk-based methodology which is aligned with the principles outlined in Good Vigilance Practice (GVP) Module III and takes into account the critical pharmacovigilance processes outlined in GVP Module I. The methodology identifies pharmacovigilance systems, products and NI-PASS that are considered to be of highest risk to patient safety and facilitates the decision on which inspection arm the required inspection should fall under. These routine inspections are included in an annual schedule, alongside inspections triggered due to previous critical findings or intelligence received by the GPvP Compliance Team ('for-cause' inspections). Section 3 of this report includes a breakdown of inspection outcomes for 2021/22 for each of the four inspection arms.

The coronavirus (COVID-19) pandemic has had a lasting impact on the way that the GPvP Compliance Team conducts inspections. The majority of inspections in the period 01 April 2021 to 31 March 2022 were conducted remotely, with only investigator site inspections associated with NI-PASS inspections being conducted onsite. Going forwards, a hybrid approach is being applied by the GPvP Compliance Team, whereby the location for inspections will be selected based on multiple factors, including inspection scope and company set-up.

This report contains data relating to all 32 inspections conducted during the 2021/22 period. Information on the types of inspection, inspection findings over time and the data from each inspection arm have been examined.

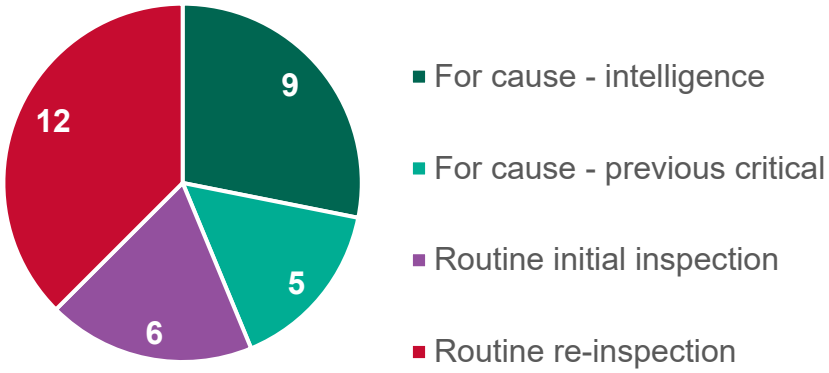
Findings identified during inspections were graded as critical, major or minor; the definitions for which are included in Appendix I. The topics under which findings can be categorised are explained in Appendix II.

A list of abbreviations used throughout this report is provided in Appendix III.

2. Overview of inspections conducted

Of the 32 inspections conducted in 2021/22, five inspections were triggered to assess the resolution of critical findings from previous inspections, nine were triggered due to intelligence received, and 18 were scheduled and conducted in accordance with the routine national inspection schedule. Of the 18 routine inspections, six inspections were of MAHs that had not previously been inspected by the MHRA GPvP Compliance Team (initial inspections), whilst the remaining 12 inspections were routine re-inspections of MAHs. Figure 1 provides a breakdown of the number of inspections conducted by type.

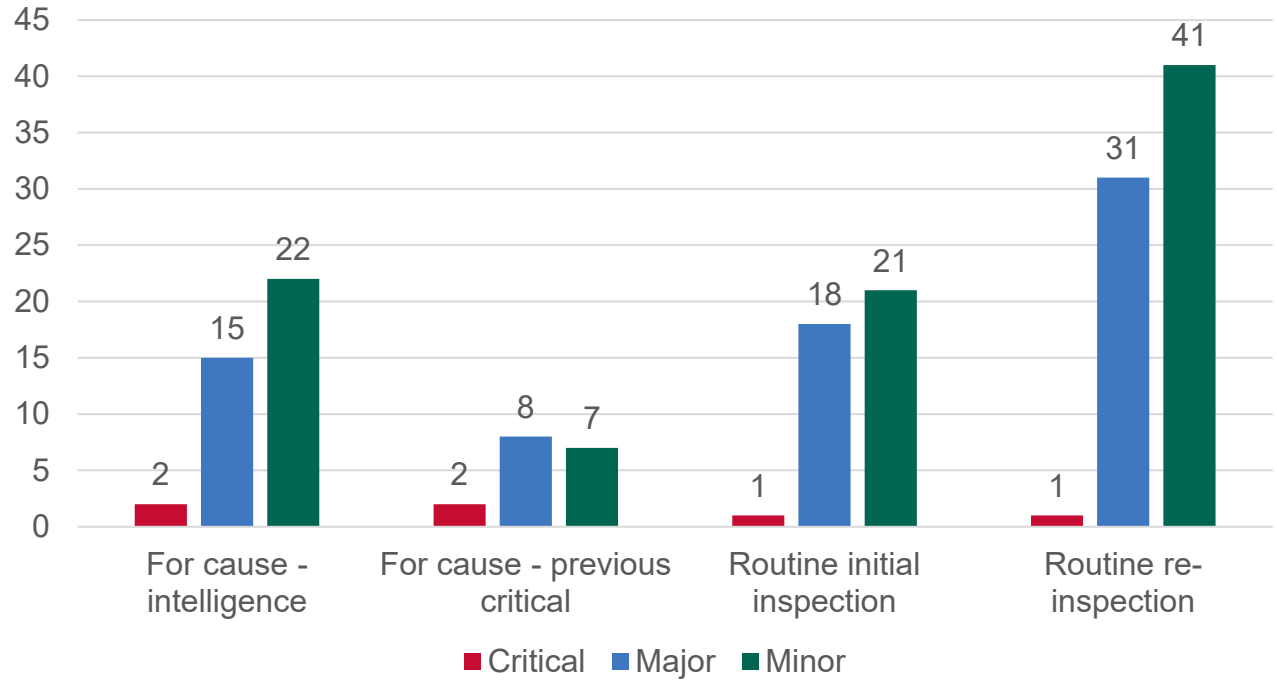
Figure 1 - Number of inspections conducted by type



There were 13 inspections of innovative pharmaceutical companies, 18 inspections of generics organisations and one inspection of a parallel import company.

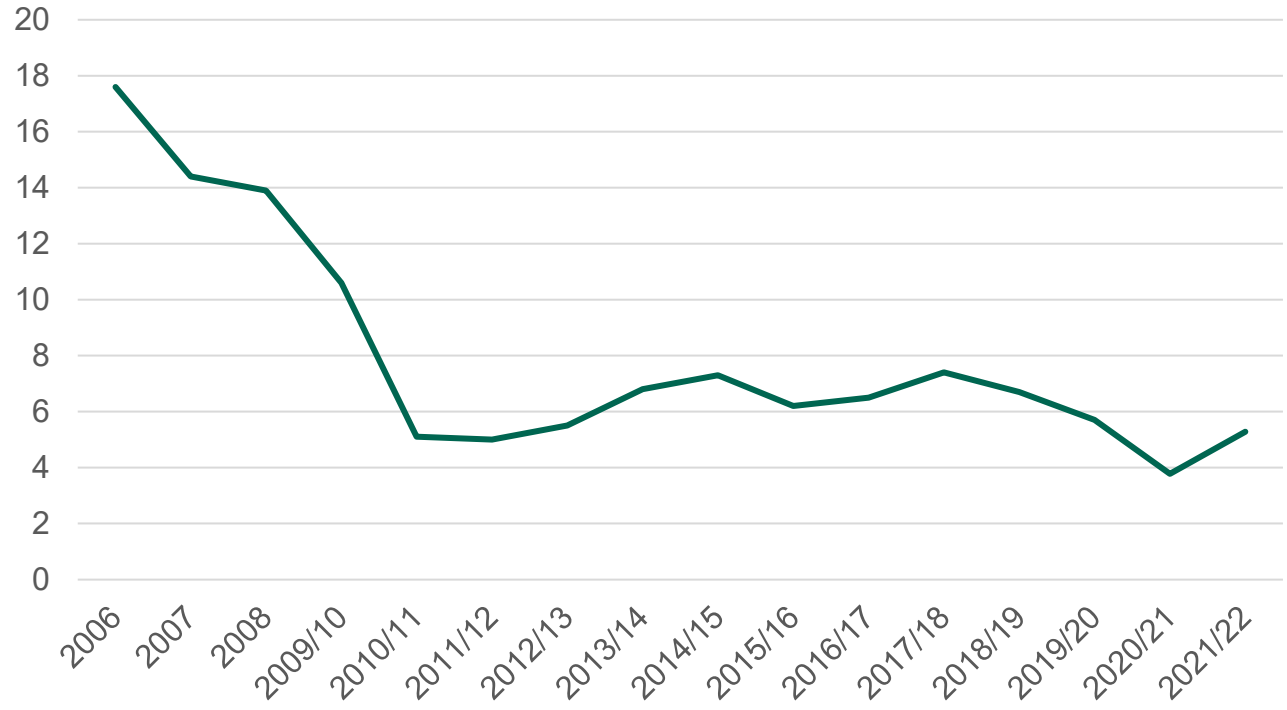
A total of six critical, 72 major and 91 minor findings were identified during this reporting period. A reported finding can often comprise multiple separate non-compliances, grouped according to a high-level legislative requirement or according to the area with resounding pharmacovigilance impact (under which various breaches of legislation could have been identified). Figure 2 provides a breakdown of the number and distribution of reported findings by grading for each inspection type.

Figure 2 - Number of inspection findings by inspection type



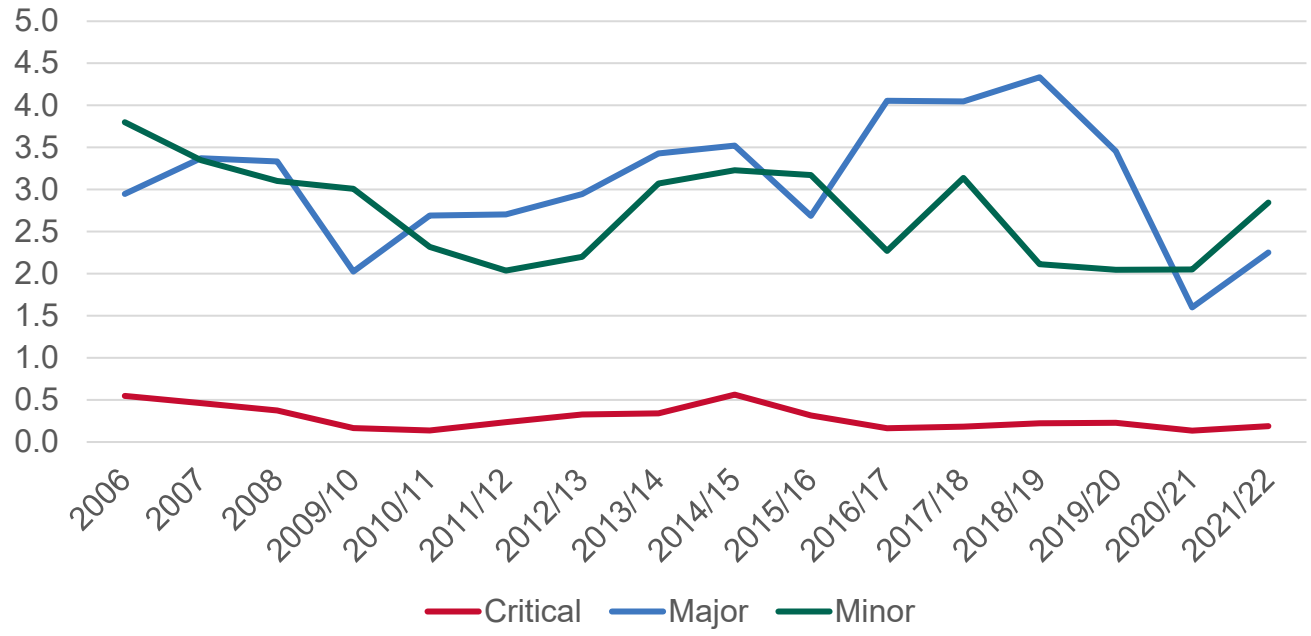
When compared with the previous reporting period (2020/21), the average number of findings, irrespective of grading, reported per inspection has slightly increased (5.3 in 2021/22 versus 3.8 in 2020/21), as demonstrated in Figure 3.

Figure 3 - Average number of findings reported per inspection over time



The average number of findings by grading reported per inspection over time is presented in Figure 4.

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

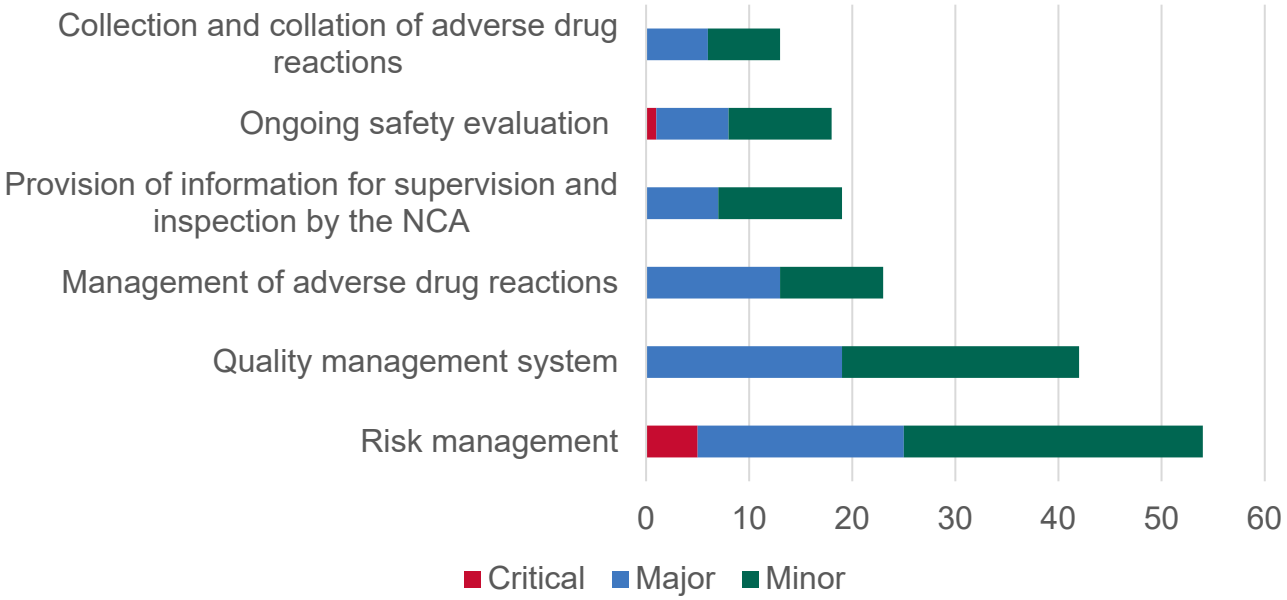


Overall, the average number of critical findings reported per inspection over time has remained stable, while the average number of major and minor findings reported per inspection has historically fluctuated. For the current reporting period, the average number of major findings reported per inspection was 2.3 and the average number of minor findings reported per inspection was 2.8; this is a slight increase from the previous reporting period which reported an average number of 1.6 major findings and 2.1 minor findings per inspection. At least two findings were reported from all 32 inspections conducted in 2021/22.

Figure 5 provides a breakdown of inspection findings reported in 2021/22 by topic area. 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 highest proportion of findings regardless of grading were related to risk management, comprising 32% (54/169 findings). This was followed by findings relating to the quality management system with 25% (42/169 findings) and the management of adverse drug reactions (ADRs) with 14% (23/169 findings). In the previous reporting period, the topics with the highest proportion of findings regardless of grading were the quality management system, risk management and ongoing safety evaluation. Risk management is a topic in which a high proportion of findings are routinely identified; however, the increase in the number of findings identified during the current reporting period is likely attributable to the increased number of inspections conducted under the NI-PASS and additional risk minimisation activities inspection arms. As NI-PASS inspections are a newer area for

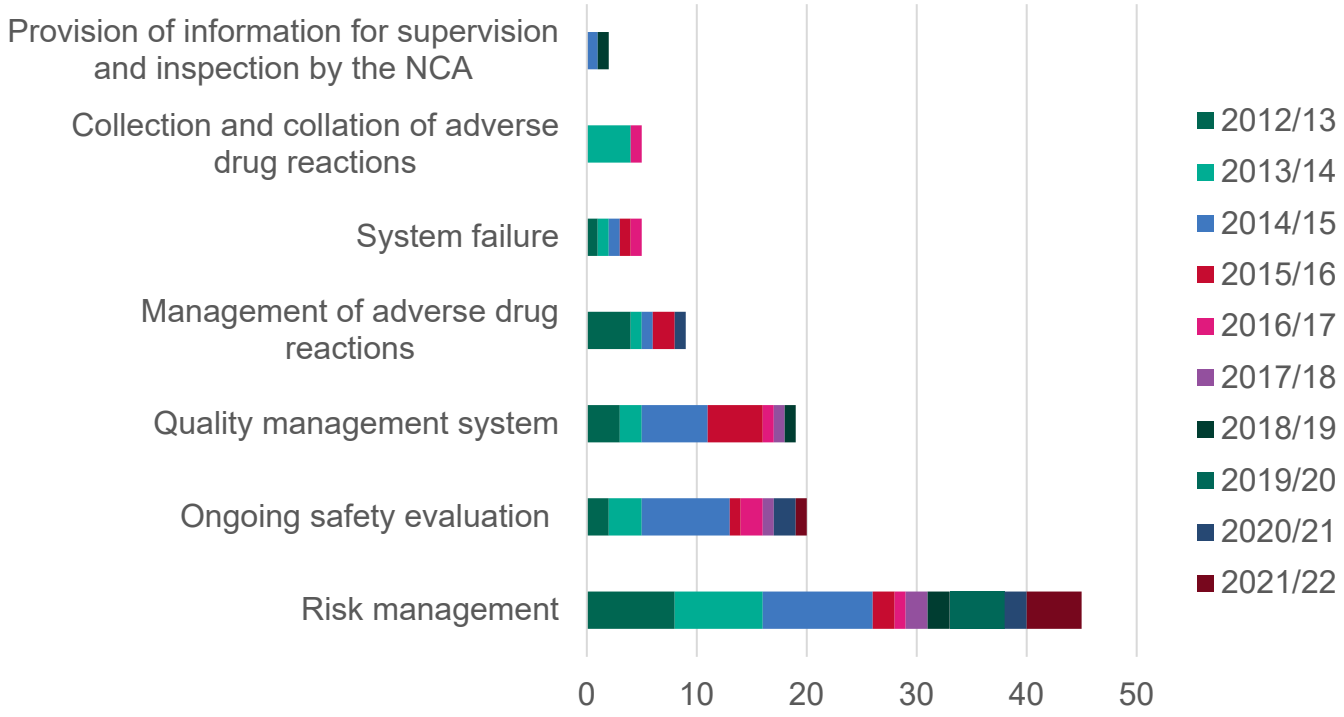
inspection, MAHs may be less familiar with the regulatory requirements to implement an NI-PASS and have less inspection experience in this topic. The aRMM inspection arm focuses on complex programmes which must precisely meet specific aRMM commitments to mitigate important identified risks. The greater number of findings in this reporting period may be due to limited experience of the inspected MAHs in operating complex risk management systems. No findings were reported under clinical trials pharmacovigilance and other categories.

Figure 5 - Findings by topic area



Since 01 April 2012, a total of 94 critical findings have been reported. For the current reporting period, six critical findings were identified from six inspections. This is consistent with previous reporting periods. The number and distribution of critical findings across inspection topics is presented in Figure 6.

Figure 6 - Number and distribution of critical findings across topics



Risk management remains the topic for which the largest number of critical findings has been reported overall. Five critical findings associated with this topic were reported in 2021/22; two of these related to the management of additional pharmacovigilance activities in Part III of the RMP (NI-PASS), two findings related to the maintenance of reference safety information and one finding related to additional risk minimisation measures (aRMMs) in Part V of the RMP. This is consistent with past reporting periods where critical findings have also been reported against these risk management subtopics.

The other critical finding identified in 2021/22 was reported under the topic ongoing safety evaluation, where a critical non-compliance was identified for the submission of PSURs. This topic has the second largest number of critical findings reported overall.

3. Inspection model and review of findings

The GPvP inspection programme consists of four discrete inspection arms. Routine risk-based inspections are scheduled under one these arms after applying tailored risk assessment methodologies. Each inspection arm has a specific objective and includes specific technical topics within its scope. Where appropriate, individual inspections can incorporate more than one inspection arm in order to make the best use of resources. An overview of the four inspection arms is outlined below.

Routine pharmacovigilance activities

Objective: To assess whether the MAH has the ability to identify, characterise and report new or changed risks for their medicinal products.

- Collection and collation of safety data
- Management of ICSRs (post-authorisation spontaneous and solicited sources)
- Periodic safety update reports
- Signal management and reporting of important identified risks
- Compliance management by the MAH (e.g. QPPV supervision, performance monitoring, audit)

Routine risk management and safety communication

Objective: To assess whether important safety updates have been communicated to patients and healthcare professionals in the UK, either through the authorised product information, direct healthcare professional communication (DHPC) or educational materials.

- Maintenance of reference safety information
- Implementation of approved changes to product information
- Safety communication, including DHPCs and educational materials

Additional risk minimisation activities

Objective: To assess whether aRMMs are being implemented in accordance with the agreed risk management plan (RMP).

- Tailored to individual risk management systems
- aRMMs can include controlled access programmes, controlled distribution systems and pregnancy prevention programmes, as examples.

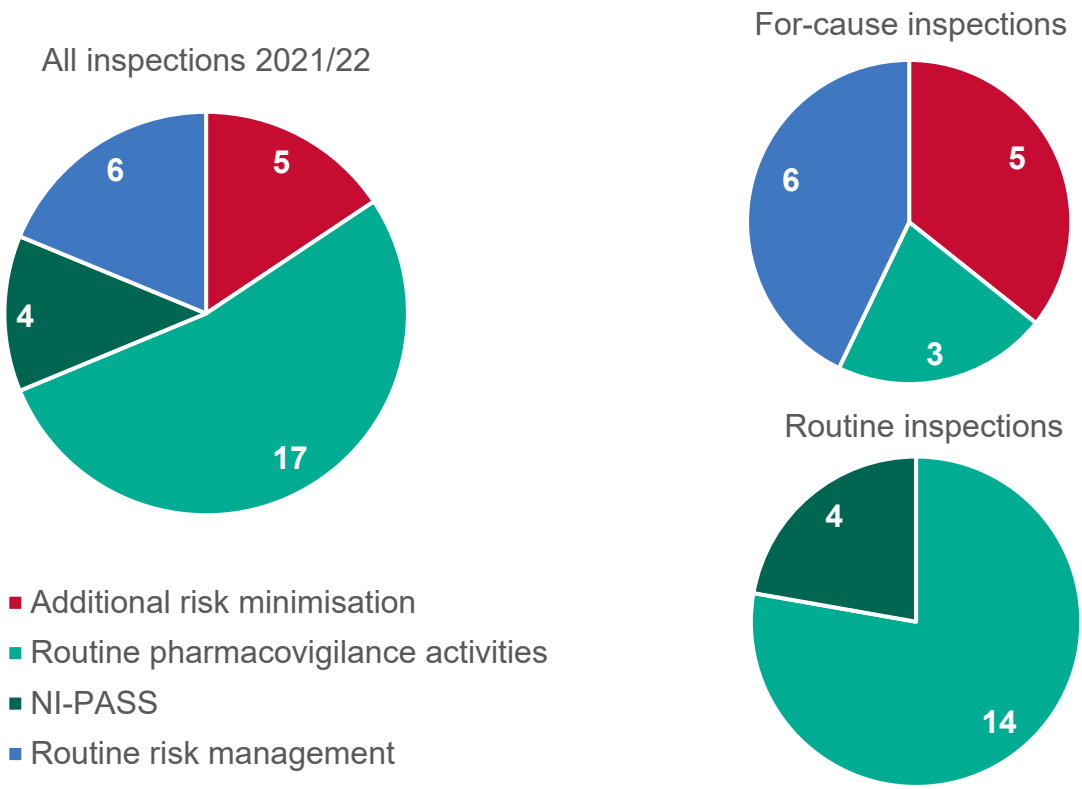
Non-interventional post authorisation safety studies (NI-PASS)

Objective: To assess whether NI-PASS are being conducted in accordance with the approved study protocol and that safety data is collected and reported appropriately.

- Study-specific inspections with visits to UK investigator sites as necessary

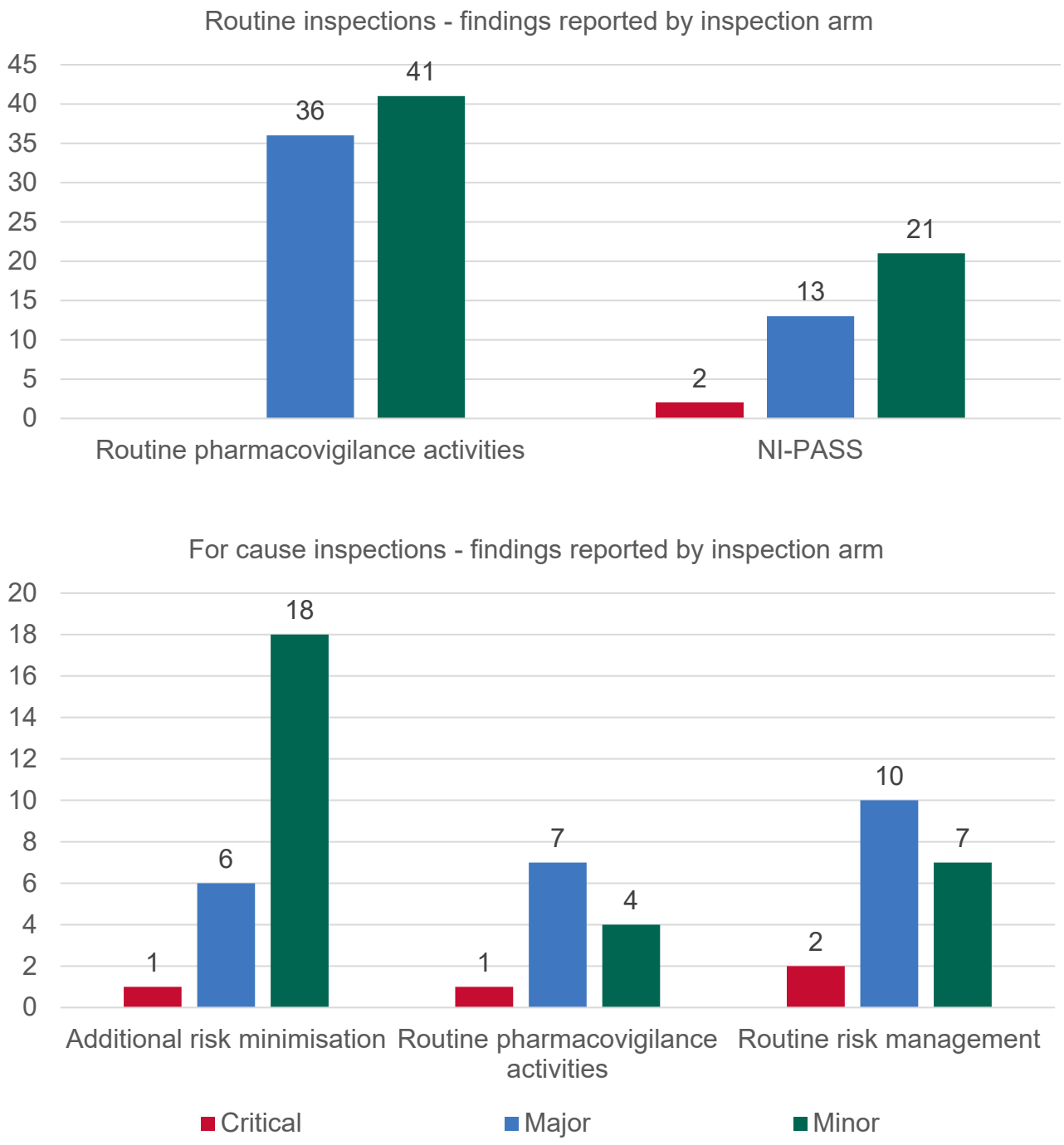
As shown in Figure 7, 17 inspections were conducted under the routine pharmacovigilance activities arm in 2021/22, six inspections were focused on routine risk management and safety communication, five inspections fell under the additional risk minimisation activities arm and four were focused on NI-PASS. When breaking it down by inspection type, of the 14 for-cause inspections, six inspections were focused on routine risk management and safety communication, five inspections were focused on additional risk minimisation activities and three inspections fell under the routine pharmacovigilance activities arm. Of the 18 routine inspections, 14 were routine pharmacovigilance activities inspections and four inspections focused on NI-PASS.

Figure 7 – Breakdown of inspections completed in 2021/22 by type and by inspection arm



Findings were reported across all inspection arms for both the for-cause and routine inspections conducted in 2021/22. Figure 8 presents the number of findings reported under each inspection arm for routine and for-cause inspections.

Figure 8 – Findings reported under each inspection arm for routine and for-cause inspections

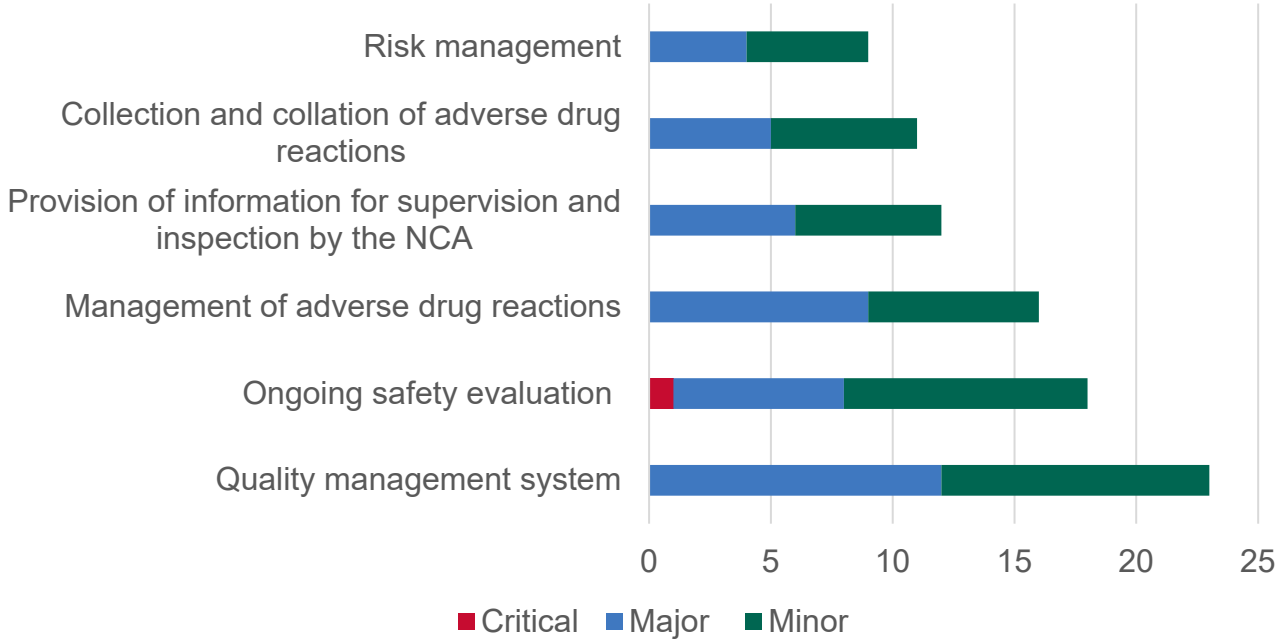


The inspections conducted under each inspection arm and the resulting findings are further reviewed and discussed in sections 3.1 to 3.4.

3.1 Routine pharmacovigilance activities

From the 17 inspections conducted under the routine pharmacovigilance activities arm in 2021/22, one critical, 43 major and 45 minor findings were reported. The split of inspection findings by grading across inspection topics is presented in Figure 9.

Figure 9 - Findings by topic area from routine pharmacovigilance activities inspections



The majority of findings reported under this inspection arm related to the quality management system, with 23 findings in total. Within this topic, most findings were reported under the subtopic of audit and deviation management, including corrective and preventative action (CAPA) management (12 in total). Such findings included:

- Failures to resolve identified non-compliance in a timely manner, including delays in implementing CAPA
- No documented audit strategy or risk assessment for audit planning
- A failure to consider all critical pharmacovigilance processes or internal pharmacovigilance processes in the audit strategy

A total of 18 findings, irrespective of grading, were reported against ongoing safety evaluation, including one critical finding. These findings were evenly spread across the subtopics, signal management and periodic safety update reports (PSURs). There were also 16 findings, irrespective of grading, reported against the management of ADRs. All but one of these findings related to case processing (data entry, coding, assessment, follow-up, and reporting).

3.1.1. Critical findings

One critical finding was reported in 2021/22 under the routine pharmacovigilance activities arm. The finding was reported in the area of ongoing safety evaluation and was identified from a for-cause inspection triggered due to a previous critical finding.

Ongoing safety evaluation – PSURs

The MAH failed to submit PSURs for four active substances to EU national competent authorities (which at the time of submission included the MHRA).

The previous MHRA GPvP inspection of the MAH identified that PSURs for two active substances had not been submitted to EU national competent authorities; this finding was graded as major.

On identification of the repeat finding, a critical finding was issued as the MAH failed to provide national competent authorities with the opportunity to assess the benefit risk profile through the review of PSURs, as required in legislation. Additionally, the MAH failed to successfully remediate the finding identified during the previous MHRA GPvP inspection.

3.2 Routine risk management and safety communication

A total of six inspections were conducted under the routine risk management and safety communication arm in 2021/22, from which two critical, 10 major and seven minor findings were reported. As to be expected, the majority of findings reported under this arm were in relation to risk management (12 in total), specifically the maintenance of authorised product information. These findings included:

- Delays in the submission of safety variations to national competent authorities
- Failure to keep the product information of generic medicines in line with the current scientific information presented in the product information of the reference medicinal product
- Delays in updating company websites and electronic medicines compendium (emc) website following a change to the product information

There were also a small number of findings reported against the quality management system and PSMF management.

3.2.1. Critical findings

Two critical findings were reported in 2021/22 under the routine risk management and safety communication arm. Both findings were reported in relation to the maintenance of reference safety information. They were both identified from for-cause inspections, one triggered due to a previous critical finding and the other triggered based on intelligence received by the GPvP Compliance Team.

Risk management – maintenance of reference safety information

A previous MHRA GPvP inspection of this MAH had reported a critical finding relating to the maintenance of reference safety information. Failures in the process had been identified, one of which included the certification of superseded patient information leaflets (PILs) in product batches well beyond the maximum timeframe for implementation of updated PILs into packs.

During the re-inspection conducted in 2021/22, it was identified that the MAH had continued to certify product batches containing a superseded PIL significantly beyond the maximum timeframe for implementation of updated PILs into packs. Additionally, the MAH had failed to update their company website with the most up-to-date version of the PIL.

The continued failure to ensure that the PIL in product packs and on the company website was up-to-date with the current scientific knowledge meant that patients and prescribers did not have the full and comprehensive information available to allow the safe use of the product. Due to the nature of patient impact and because the previous critical finding had not been addressed, this remained a critical deficiency.

Risk management – maintenance of reference safety information

The MAH had failed to implement updated PILs containing new safety information into product packs for two products, and as such, a large number of product packs containing superseded PILs had been released to market well beyond the six-month timeframe required for implementation of updated PILs into packs.

Due to the nature of the warnings and the medical significance of the safety information that was missing from the PIL, there was an impact on the safety and well-being of patients. The finding was graded as critical accordingly.

3.3 Additional risk minimisation activities

Five inspections were conducted under the additional risk minimisation activities inspection arm in 2021/22. Of these inspections, three were conducted prior to the commercialisation of the product on the UK market to determine whether the proposed risk management system for the product was fit for purpose and would operate in compliance with the conditions of the marketing authorisation. To note for two of these inspections, one involved a product for which the licence had been suspended and one incorporated both a pre- and post-commercialisation review of the risk management systems for two related products.

In total, one critical, six major and 18 minor findings were reported. As to be expected, the majority of findings reported under this arm were in relation to risk management (13 in total), specifically for aRMMs in Part V of the RMP. These findings included:

- A failure to adhere to the controlled distribution system in place for the product (post-commercialisation inspection), or the identification of deficiencies with the proposed controlled distribution process (pre-commercialisation inspections)
- Procedural documentation did not adequately describe processes associated with the risk management system

In addition, nine further findings were reported in relation to the quality management system. These findings were spread across all the subtopics under this overarching topic.

3.3.1. Critical findings

One critical finding was reported in 2021/22 under the additional risk minimisation activities arm. The finding was identified from a for-cause inspection triggered based on intelligence received by the GPvP Compliance Team.

Risk management – aRMMs

This inspection comprised a post-launch and pre-launch review of complex risk management systems for two related products that were subject to a controlled distribution system and pregnancy prevention programme.

The critical finding was issued as the procedures and processes that the MAH had in place were not robust enough to support the potential increase in workload following launch of the new product. The proposed risk management system for the pre-launch product was based on the existing risk management system of the product already launched. Significant non-compliances were identified during the review of the post-launch risk management system, for which the root cause given was a lack of resource. Additionally, there was a lack of

procedures in place describing how processes within the risk management system would be undertaken with increased demands and who would be the responsible party.

Based on the non-compliances identified in relation to the implementation of the risk management system for the product already launched on the UK market, and the forecasted increase in workload after the new product launch, there was no assurance that the system in place would function as required and the risks of the products would be adequately managed following product launch.

3.4 Non-interventional post-authorisation safety studies

Four inspections were conducted under the NI-PASS inspection arm in 2021/22, all of which had associated investigator site inspections. For two inspections, two investigator site inspections were conducted, while the remaining two inspections had one associated investigator site inspection.

In total, two critical, 13 major and 21 minor findings were reported from the four NI-PASS inspections. As to be expected, the majority of findings reported under this arm were in relation to risk management (20 in total), all of which were associated with the management of additional pharmacovigilance activities in Part III of the RMP. Common findings included:

- Data management issues, including a failure to enter all data required by the study protocol into the electronic data capture (EDC) system despite availability in source documentation, and the identification of discrepancies between information held in the EDC system and source documentation
- Data integrity issues, including inappropriate access control to the EDC system, and a failure to manage queries in the EDC system effectively (e.g., delays in opening and closing queries and inappropriate query handling)

Seven findings were also reported in relation to the quality management system, the majority of which concerned procedures and record management. In addition, six findings were reported in relation to the management of ADRs, all of which related to the case processing of ADR reports arising from NI-PASS.

3.4.1. Critical findings

Two critical findings were reported in 2021/22 under the NI-PASS inspection arm. Both findings were associated with conduct of NI-PASS and were identified from routine inspections.

Risk management – Additional pharmacovigilance activities

This critical finding related to the conduct of NI-PASS. During the investigator site inspection, it was identified that the inspected site had not been using a data collection tool which was required by the study protocol. It was subsequently identified that there was a lack of oversight by the MAH regarding the use of this data collection tool across all UK sites. The MAH had submitted an interim study report to the PRAC, upon which a decision had been made to terminate the study. However, the interim report did not transparently describe the use of the data collection tool and the associated limitations.

Additionally, examples of primary and secondary endpoints were identified in source documentation at the investigator site that had not been recorded in the EDC system and were therefore not included in the interim report.

As a result of these significant deficiencies associated with data collection, there was no assurance that all primary endpoint data had been recorded and was available in the final analysis of the study.

Risk management – Additional pharmacovigilance activities

This critical finding also related to the conduct of NI-PASS. There was a lack of study oversight by the MAH and a lack of robust processes to ensure that information was being collected by investigator sites in order to meet the study objectives.

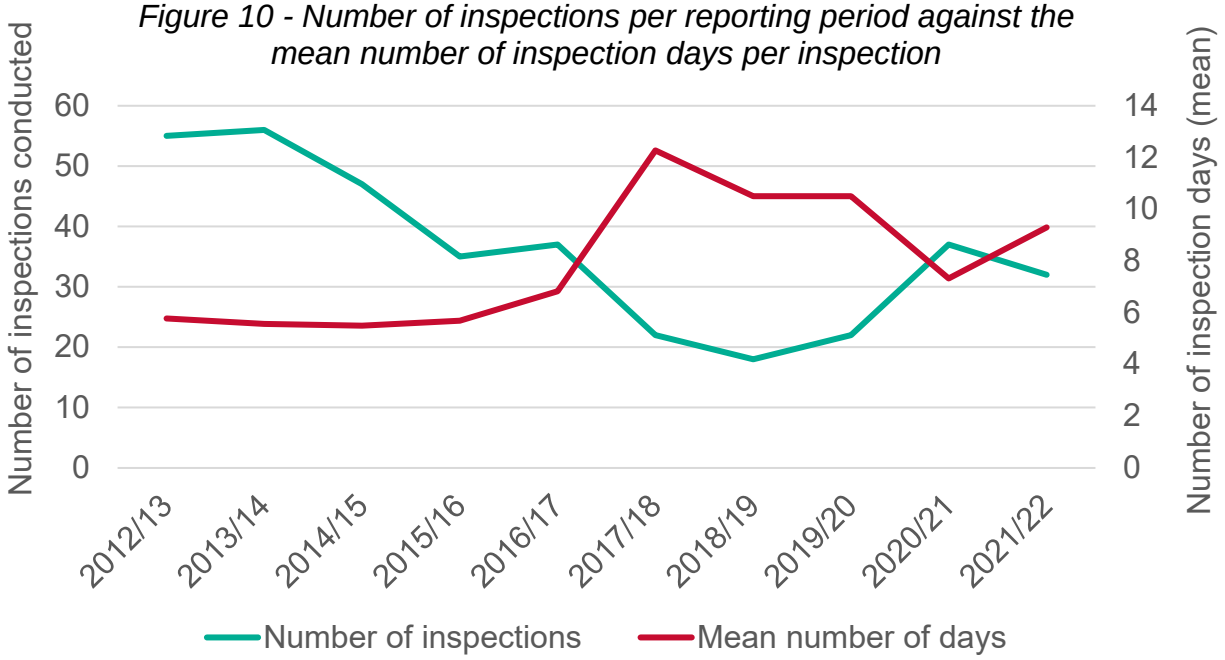
During the investigator site inspection, significant failures in detecting and reporting adverse events from the patient medical records were identified. A number of serious adverse events occurring during the study had not been entered into the EDC system, as well as examples of significant medical history and concomitant medications. Other than a site initiation visit and close-out visit, the MAH did not conduct any monitoring visits of the investigator sites. Additionally, the training provided during the site initiation visits did not include clear instructions regarding the identification and location of relevant source documentation (i.e. medical records and clinic notes) to obtain study-relevant information.

Ultimately this impacted on the completeness and accuracy of the information presented and analysed in the final study report, which had been submitted to competent authorities.

4. Inspections over time

The number of inspections per reporting period and the average time spent on inspection since 2012/13 is displayed in Figure 10.

Figure 10 - Number of inspections per reporting period against the mean number of inspection days per inspection



Between 2013/14 and 2017/18, the number of inspections completed for each reporting period decreased whilst the number of inspection days per inspection increased. As discussed in previous metrics reports, this increase in the mean number of inspection days was attributed to the increasing complexity of pharmacovigilance systems operated by MAHs, requiring additional inspection time. This posed a challenge for GPvP inspectors to address as there are many pharmacovigilance systems operated for UK authorised products that require supervision, and as such, the revised GPvP inspection model was developed in 2020/21.

Following the introduction of the revised GPvP inspection model, there was a significant increase in the number of inspections conducted and the mean number of inspection days per inspection decreased. This change was attributed to the move towards more targeted inspections with a tailored scope applied under one of the inspection arms.

As shown in Figure 10, when compared with the previous reporting period, the number of inspections conducted in 2021/22 decreased slightly, while the mean number of days per inspection increased slightly. This small change is likely due to the increased number of NI-PASS inspections that were conducted in 2021/22. NI-PASS inspections comprise of an inspection of the MAH and usually an inspection of one or two investigator sites.

Accordingly, these inspections require a greater number of days to complete, which also impacts the number of inspections that the GPvP Compliance Team can conduct.

All inspections were conducted remotely for the period 2021/22, with the exception of the investigator site inspections associated with NI-PASS inspections. In total, six investigator site inspections, associated with four NI-PASS inspections, were conducted at onsite facilities. Going forwards, the GPvP Compliance Team will continue to conduct remote and onsite inspections, taking a hybrid approach. The location for inspections will be decided on a case-by-case basis at the discretion of the lead inspector and will be based on multiple factors such as inspection scope and company set-up.

5. Summary

For the reporting period 01 April 2021 to 31 March 2022, 32 inspections of 30 organisations were conducted, of which 18 were planned as part of routine inspection scheduling, nine were conducted as a result of intelligence received and five were conducted due to a previous critical finding. The majority of inspections focused on routine pharmacovigilance activities (17 in total), whilst there were six inspections of routine risk management activities, five inspections of additional risk minimisation activities and four inspections of NI-PASS.

A total of 169 findings were reported, comprising six critical, 72 major and 91 minor findings. Findings were identified in all inspections conducted in 2021/22. Of the six critical findings reported in this period, five were reported in relation to risk management and one was reported in relation to ongoing safety evaluation. Critical findings were identified from inspections conducted under each of the inspection arms. With regards to the major findings reported in 2021/22, the largest proportion was reported in relation to risk management and the quality management system, followed by the management of ADRs. Similarly, for minor findings, the largest proportion of findings related to risk management and the quality management system.

It is clear that risk management was an area of significance when reviewing the metrics from the 2021/22 reporting period. With the introduction of the revised GPvP inspection model in 2020/21, three of the four inspection arms have a primary focus in the risk management area: management of additional pharmacovigilance activities (NI-PASS), maintenance of authorised product information and safety communication (routine risk management), and management of aRMMs in Part V of the RMP (additional risk minimisation activities). Accordingly, a large number of findings have been reported under this topic. Findings of all gradings were spread across each of the subtopics in risk management, highlighting the importance of managing risk to patients at all points of the product lifecycle and across critical pharmacovigilance processes.

The MHRA GPvP Compliance Team will continue to apply a risk-based approach to inspection scheduling under each of the four inspection arms. 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.

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	Subtopic 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)
	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 the MHRA, including via	Inspection readiness
	PSMF management[1]

[1] PSMF management was counted under the quality management system in previous metrics reports.

inspection	Submission of information to the MHRA
Clinical trials pharmacovigilance	Clinical trials pharmacovigilance (e.g., maintenance of reference safety information for clinical trials, SUSAR reporting)
Other	Other

Appendix III – Abbreviations

ADR	Adverse Drug Reaction
aRMM	Additional Risk Minimisation Measure
CAPA	Corrective and Preventative Action
DHPC	Direct Healthcare Professional Communication
EDC	Electronic Data Capture
emc	Electronic Medicines Compendium
GPvP	Good Pharmacovigilance Practice
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
NI-PASS	Non-interventional Post Authorisation Safety Studies
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan