الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Pharmacovigilance Inspections Report

Jan 1st, 2022 to Dec 31, 2022

Contents

1 Introduction

During the period 01 Jan 2022 to 31 Dec 2022, the national pharmacovigilance center (NPC) in the Saudi food and drug authority (SFDA) conducted fifty inspections of marketing authorization holders (MAHs) in the Saudi market. Inspections mainly aimed to examine and ensure compliance with existing Saudi pharmacovigilance regulations and guidelines. Therefore, MAHs were selected for inspection using the risk-based methodology. This risk-based methodology follows GVP Module III and considers multiple factors. These factors are:

- Product-specific risks (e.g., new active substances or new biological products)
- The complexity of the pharmacovigilance system
- The complexity and size of the organization(s) involved in the pharmacovigilance system, including service providers and the number of products
- The compliance and inspection history of an organization
- All pharmacovigilance documents of the MAHs reporting and their rate, if applicable, to SFDA.

This report contains data relating to eighteen inspections either routine or for cause (trigger) inspections conducted from 01 Jan 2022 to 31 Dec 2022. Information on types of inspection and inspection findings have been examined, including analysis of specific topics where the inspection team found the highest number of findings among the visits.

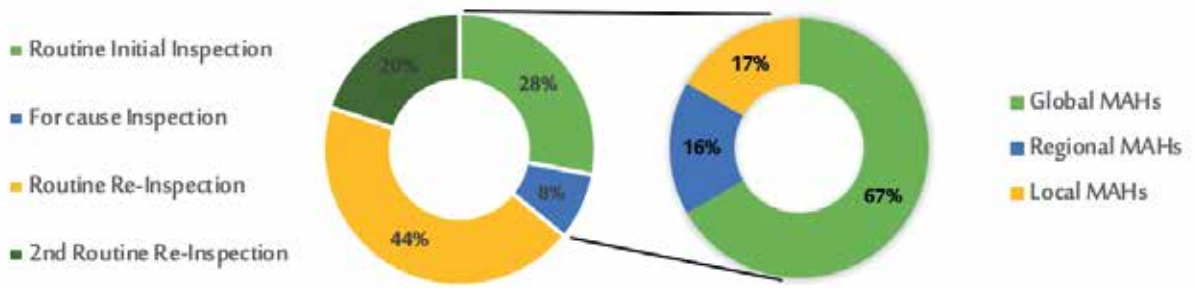
Selection of the inspection types were identified by the inspection team in Appendix I. The inspection findings identified as critical, major, or minor are the definitions for which are included in Appendix II.

2 Overview of Inspection Department activities

Out of fifty inspections visits conducted in 2022 (including all inspection types), fourteen were scheduled and conducted as a routine initial inspection based on risk-based methodology. One MAH of the fourteen routine inspection was not fully inspected due to significant malpractice in applying pharmacovigilance requirements and this case was directed to the legal department to take the required action. Twenty-two re-inspections were scheduled and completed as follow-ups based on the CAPA provided in the previous routine inspections. The inspection team conducted ten inspections as a second re-inspection to follow up the feedback re-inspection finding. Out of ten second re-inspections, nine MAHs closed the provided CAPAs, and one MAH needed to be closed to the CAPA properly and it was considered a non-compliant MAH. The executive directorate for pharmacovigilance triggered four inspections based on MAHs performance in 2022.

Out of eighteen routine and trigger inspections, twelve were global MAHs, three were regional MAHs, and three were local MAH. Local distributors handled eight MAHs that were inspected out of 18 Routine initial and trigger inspections.

Figure 1 - Number of inspections conducted by type during 2022



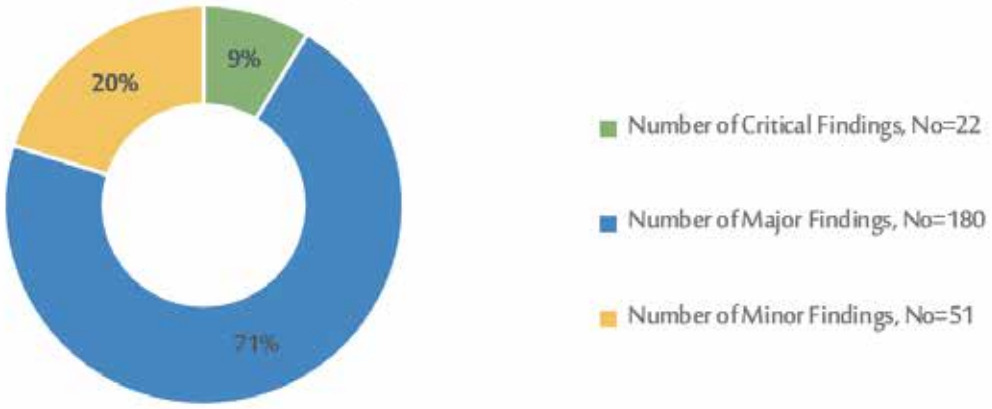
For non-compliant MAH, the inspection team allow for two inspection attempts to correct the observation. Suppose the MAH cannot close the CAPA after the second re-inspection. In that case, the inspection team will take the necessary action, which may include suspending of the activities of the non-compliant MAH and issuing of a penalty according to the non-compliance status until resolving the compliance matter.

On December 28, 2020, SFDA released new legislation, "Implementing Regulations of the Law of Pharmaceutical and Herbal Establishments and Products." Through that document, there was a major change in reporting time frame and classification of reports. Indeed, that change did affect MAHs compliance during 2021 and 2022.

3 Summary of findings during the reported period 2022

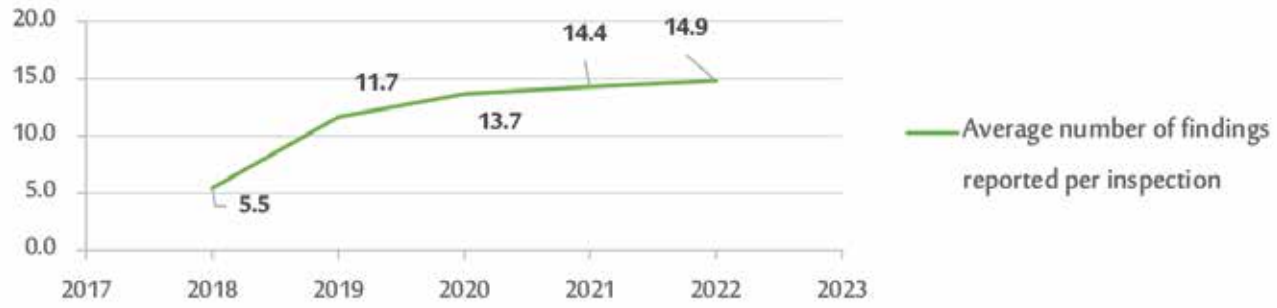
Twenty-two critical findings, hundred-eighty major findings, and fifty-one minor findings were identified during this reporting period year (2022). The reported finding can often comprise multiple non-compliances according to Saudi GVP requirements or cumulative pharmacovigilance impact (under which many guideline violation have been identified). The inspection that had a targeted scope (Triggered) focused on one specific technical area triggered by the technical team at SFDA.

Figure 2 - Number of over all inspection findings for Routine initial and for cause inspections



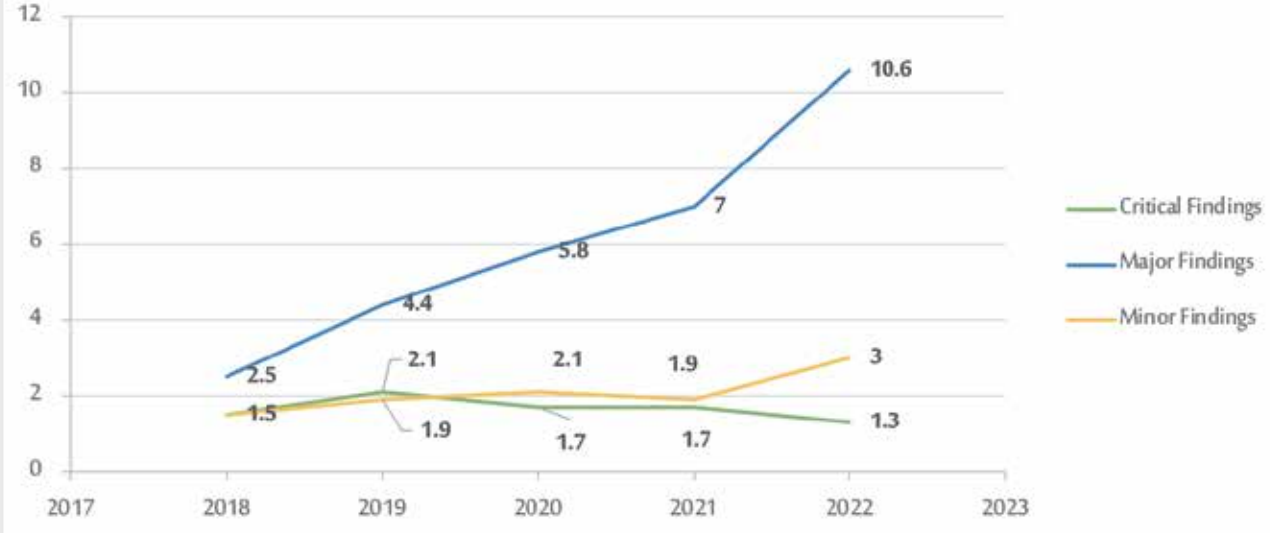
Compared to previous reporting periods, average number of findings per inspection (irrespective of grading) has increased. The average number of findings reported per inspection in 2022 increased from 14.4 and to 14.9 (3.5 % increased), as demonstrated in Figure 3 below.

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



A review of the average findings reported each year by grading was completed and is presented in Figure 4.

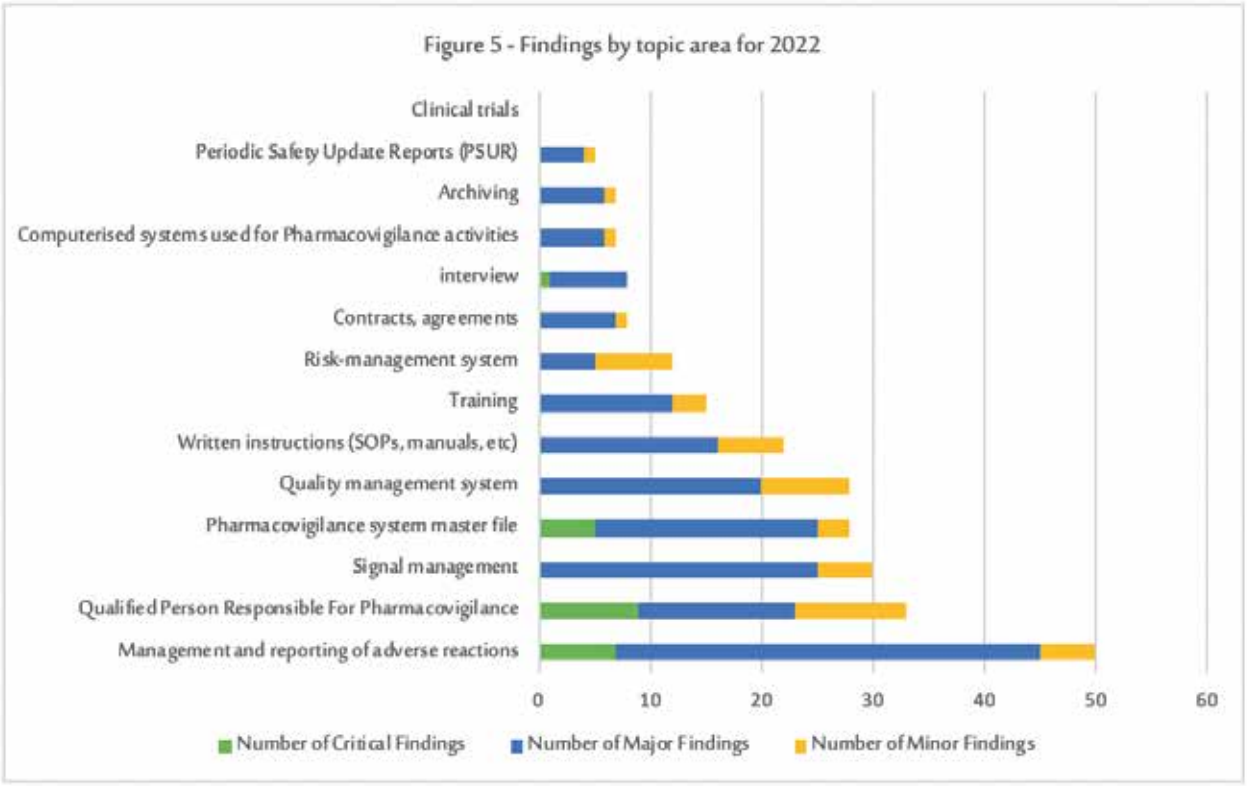
Figure 4 - Average Number of Findings by Grading Reported Per Inspection Over Time



Over the years, the average number of critical findings has remained between 1.3 to 2.1 reported findings per inspection, but the average number of major findings reported per inspection has significantly increased. The increased number of major findings over time could be attributed to the fact that the inspections conducted during this period were:

- Local distributors handled PV activities with improper data safety exchange agreements that do not cover all required activities needed to be conducted in Saudi Arabia.
- The inspected MAHs had limited knowledge about Saudi GVP.
- There is an improper implementation of the guideline locally compared to the well-established MAHs globally, which were inspected during the past years.
- The limitation of the pharmacovigilance system harmonization between Saudi Arabia and regional countries. The reason behind that was the difference between the local regulatory requirements and Arab countries.

The average number of minor findings reported per inspection has fluctuated, but the average number in 2022 was the highest value among all previous years.



By breaking down the inspection findings by topic area, as presented in Figure 5, the highest proportion of findings regardless of grading was about the management of adverse drug reactions, comprising 19.8%, or 50 of 253 findings. That was followed by the qualified person responsible for pharmacovigilance with 13% (33 out of 253) of all findings reported, and the Signal management with 11.9% (30 out of 253). These three topics almost had the highest proportion of findings in 2021 too.

4 Critical findings

4.1 Critical findings reported during 2022

Twenty-two critical findings were identified from nine inspections in 2022. The average of reporting finding was approximately 1.3 critical findings reported per inspection. All twenty-two critical findings were in the area of Qualified Person Responsible for Pharmacovigilance, Pharmacovigilance system master file, Management and reporting of adverse reactions, and Interviewee knowledge; specifically:

- The Qualifications of the QPPV.
- System oversight of the local QPPV.
- Back-up process and delegation between the local QPPV and deputy during the absence events.
- The availability of the Organizational structure in the provided documents.
- Pharmacovigilance system that is implemented within the MAH locally.
- Maintenance and submission of Pharmacovigilance system master file (PSMF).
- Data collection methods for adverse reactions.
- Interviewee's knowledge about the pharmacovigilance concepts.

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

Qualifications of the local QPPV

- For the 4 critical findings raised under this sub-topic, in each case, the MAH had failed to ensure that the local QPPV was full-time dedicated to handling the pharmacovigilance activities.
- As Saudi GVP stated in (I.C.1.1. Qualifications of the qualified person responsible for pharmacovigilance in KSA) that "As part of the pharmacovigilance system, the marketing authorization holder shall have permanently and continuously at its disposal A full-time qualified person responsible for pharmacovigilance (QPPV) reside in KSA.". NPC represented by the inspection team expected to assign a fully dedicated personal qualified and responsible for pharmacovigilance activities.

System oversight of the local QPPV

- For the 4 critical findings raised under this sub-topic, in each case the QPPV was not fully aware or involved in the pharmacovigilance system, had a minimal role in the system oversight, or not aware of the updated pharmacovigilance requirements in Saudi Arabia. Besides, one of the MAHs did not have a qualified person responsible for pharmacovigilance (QPPV) to handle pharmacovigilance activities.
- As Saudi GVP stated in (I.C.1.3. Role of the qualified person responsible for pharmacovigilance in KSA) that "The QPPV shall be responsible for the establishment and maintenance of the marketing authorization holder's pharmacovigilance system and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements." NPC represented by the inspection team, expected the local QPPV to know the PV system fully and had a significant role in the local implemented system.

Back-up process and delegation between the local QPPV and deputy during the absence events

- For the critical findings raised under this sub-topic, the MAH failed to ensure a local standard to describe the backup process and delegation in each case.
- As Saudi GVP stated in (I.C.1.3. Role of the qualified person responsible for pharmacovigilance in KSA) that "The QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.". Therefore, NPC, represented by the inspection team, expected the MAHs to implement a (documented) delegation process that ensures accurate transfer of responsibilities.

Organizational structure

- For the 2 critical finding raised under this sub-topic, the MAH had not provided an organizational structure that described the role of the local QPPV within the MAH. In addition, there was no documentation supporting the connection between the local QPPV and the global team.
- As Saudi GVP stated in (II.B.4.2. PSMF section on the organizational structure of the marketing authorization holder) that "A description of the organizational structure of the marketing authorization holder relevant to the pharmacovigilance system must be provided." Based on that, NPC represented by the inspection team expected the MAH to provide an organizational structure that describes the role of the local QPPV within the MAH.

Pharmacovigilance system

- For the 2 critical findings raised under this sub-topic, one of the MAHs had failed to ensure the availability of local PV system. The other one, their local QPPV were unaware of the implemented Pharmacovigilance system in the MAH global office.
- As Saudi GVP stated in (I.C.1.3. Role of the qualified person responsible for pharmacovigilance in KSA) that "The QPPV shall be responsible for the establishment and maintenance of the marketing authorization holder's pharmacovigilance system and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements." Based on that, NPC, represented by the inspection team, is expected to implement a local PV system and assure a local QPPV to be fully aware of the PV system and have a significant role in the local implemented system.

Maintenance and submission of Pharmacovigilance system master file (PSMF)

- For the critical finding raised under this sub-topic, the MAH failed to ensure the availability of a local PSSF owned by the local QPPV. Besides, the local Saudi QPPV is unaware of the last updating PSMF. In one case, the provided PSSF is not compatible with the required
- template mentioned in the guideline of Saudi GVP and there was no SOP describing the maintenance of local PSSF and its updating frequency.

  As Saudi GVP stated in (II.B.2. Registration and maintenance) that "however, they are required to prepare and maintain a pharmacovigilance system master file. In all circumstances, an appropriate pharmacovigilance system must be in place, described in a PSMF, with the location and QPPV details entered and maintained". Therefore, NPC represented by the inspection team expected the MAHs to have a local PSSF that was compatible with the required template mentioned in the guideline of Saudi GVP.

Data collection methods of adverse reactions

- For the 7 critical findings raised under this sub-topic, the limited channels are used to receive adverse drug event reports in each case. There was no direct communication channel (phone number) or Arabic website for reporting adverse events from the public. Besides, the local QPPV has no access to the MAH database to handle the local ICSRs. In addition, The local QPPV has no access to medical representatives in the Saudi Market to collect the AE reports. There was no database or excel sheet for documentation local cases.
- As Saudi GVP stated in (VI.B.1. Collection of reports) that "Marketing authorization holders should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources. For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports". Therefore, the NPC inspection team expected the MAHs to receive adverse drug event reports with appropriate channels.

Interviewee knowledge about the pharmacovigilance concepts

- For the critical finding raised under this sub-topic, the interviewed medical representatives had limited pharmacovigilance knowledge. Besides, the availability of medical representatives during the inspection time.
- The NPC represented by the inspection team expected the MAHs to have well-educated medical representatives about pharmacovigilance.

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

Inspection	Critical Findings	Major Findings	Minor Findings
A	1	11	3
B	3	10	7
C	6	24	0
D	1	15	0
E	4	15	3
F	2	24	1
G	2	25	0
H	1	19	2
I	2	16	6

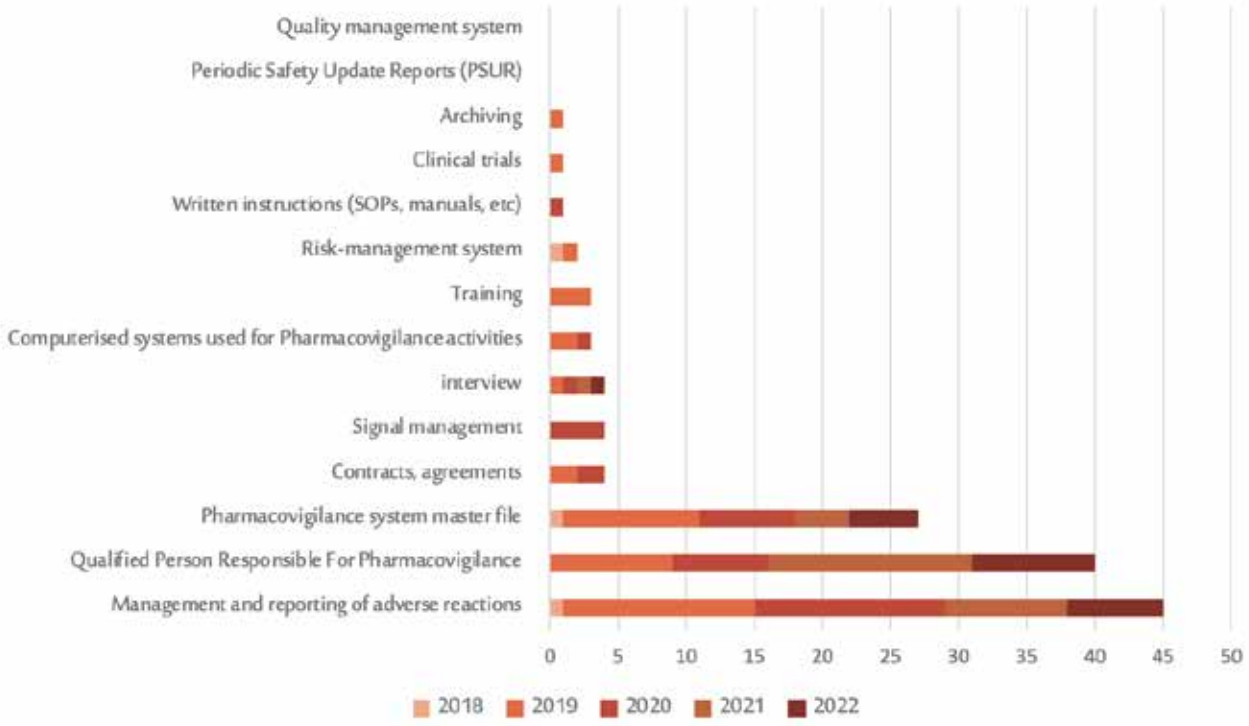
Table 1 - Numbers of major and minor findings reported alongside critical findings

4 Critical findings

4.2 Distribution of critical findings over time

Between November 2018 and December 31, 2022, 135 critical findings were reported. For the current reporting period, 22 critical findings were identified from 9 inspections out of 18 in 2022. That was decreased with the previous five reporting period's years, despite a higher overall number of inspections conducted during this reporting period compared to previous reporting periods. The number and distribution of critical inspection findings across different inspection topics since November 2018 is shown in Figure 6. Overarching topics across the pharmacovigilance system have grouped this report's findings. The nature of the findings covered by each topic is provided in Appendix III.

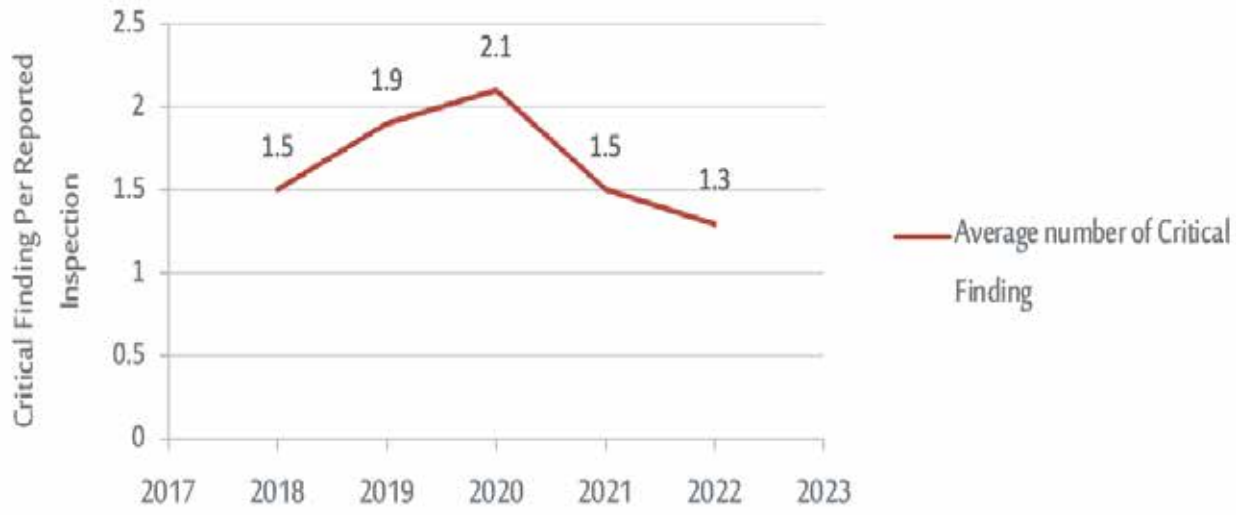
Figure 6 - Number and distribution of critical findings across topics



Management and reporting of adverse reactions remain the topic for which the most critical findings have been reported. The seven critical findings associated with this topic were reported in 2022 related to data collection methods. The qualified person responsible for Pharmacovigilance is another topic where critical findings have frequently been reported, nine critical findings reported during 2022 were in this area. The pharmacovigilance system master file is another topic where critical findings have frequently been reported in the past, and five of the critical findings reported during 2022 were in this area.

For this reporting period, a critical finding was also reported against MAHs medical representatives' interviews also noted in another inspection visit in 2022.

Figure 7 - Average Number of Critical Finding Per Reported Inspection Over Time

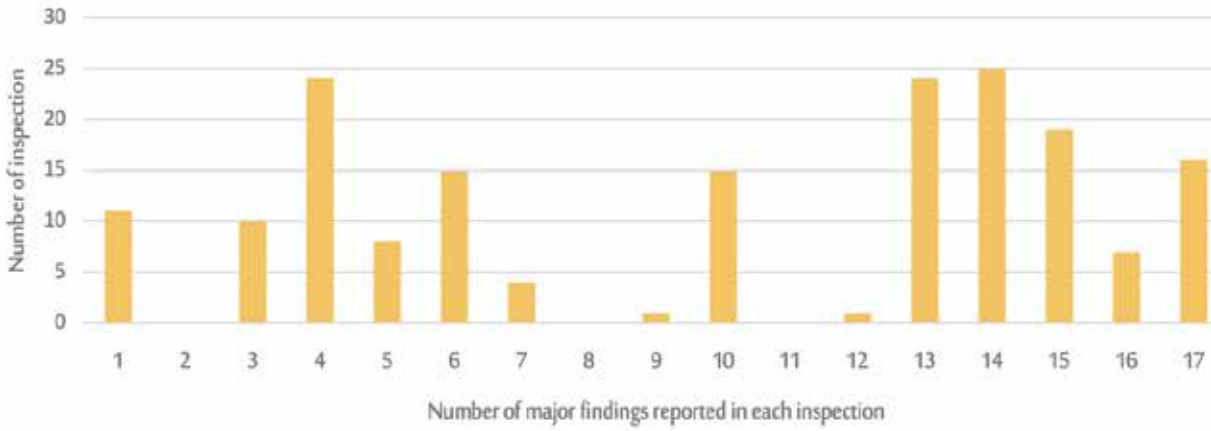


Approximately 1.3 critical findings were reported from every inspection, which decreased by 13.3% from the previous reporting period.

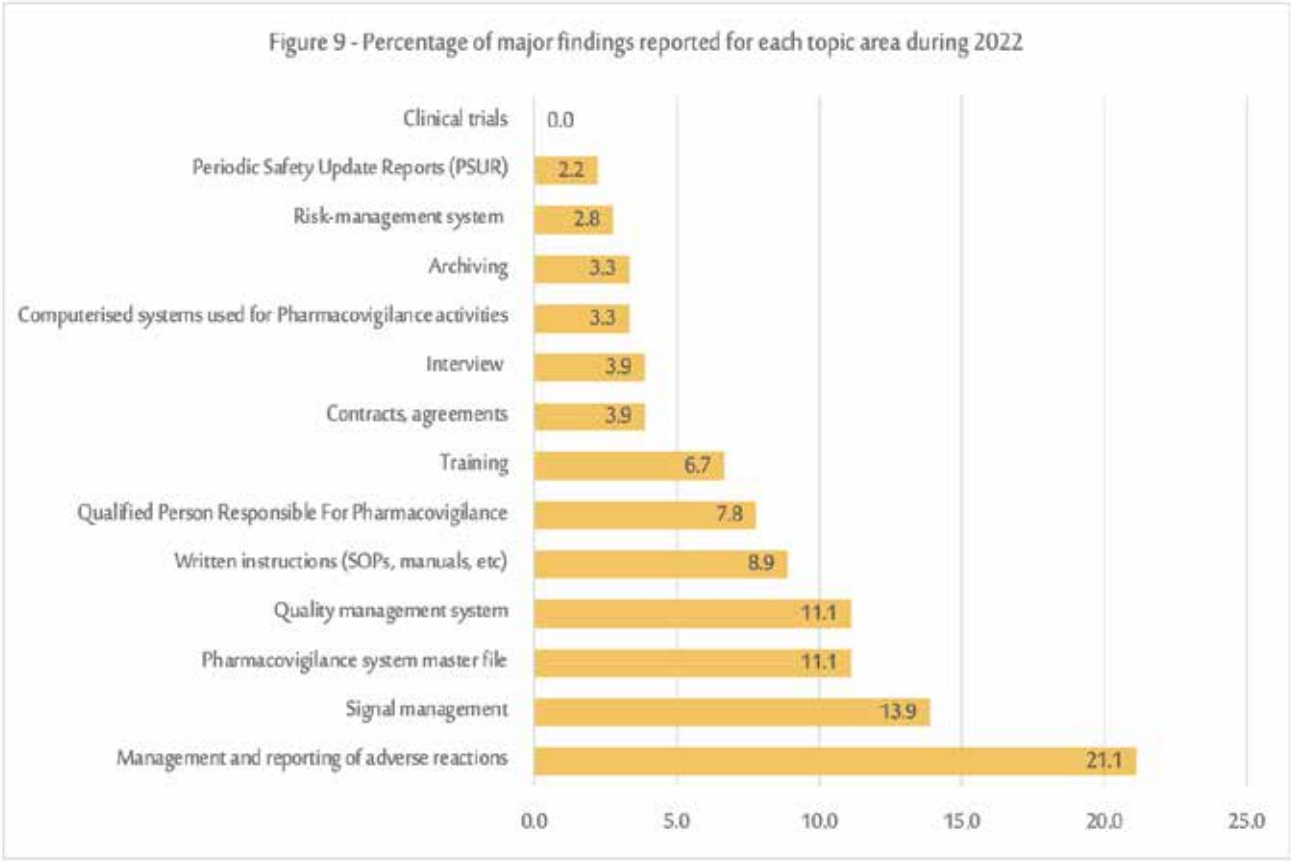
5 Major findings

The number of major findings raised in this reporting period per inspection ranged between 1 and 25, with three inspections raising no major findings. Out of the 18 inspections in 2022, the average number of major findings per inspection was 10.6. Figure 8 displays the number of major findings by the number of inspections conducted.

Figure 8 - Number of major findings reported by the number of inspections in 2022



In total, 180 major findings were identified in 2022. Overarching topics across the pharmacovigilance system have grouped this report's findings. The nature of the findings covered by each topic is provided in Appendix II.



As shown in Figure 9, the highest proportion of major findings was reported about Management and reporting adverse reactions, with 38 findings (21.1%). The signal management followed that with 25 findings (13.9%), and then the pharmacovigilance system master file and Quality management system followed that with 20 findings (11.1%) for each.

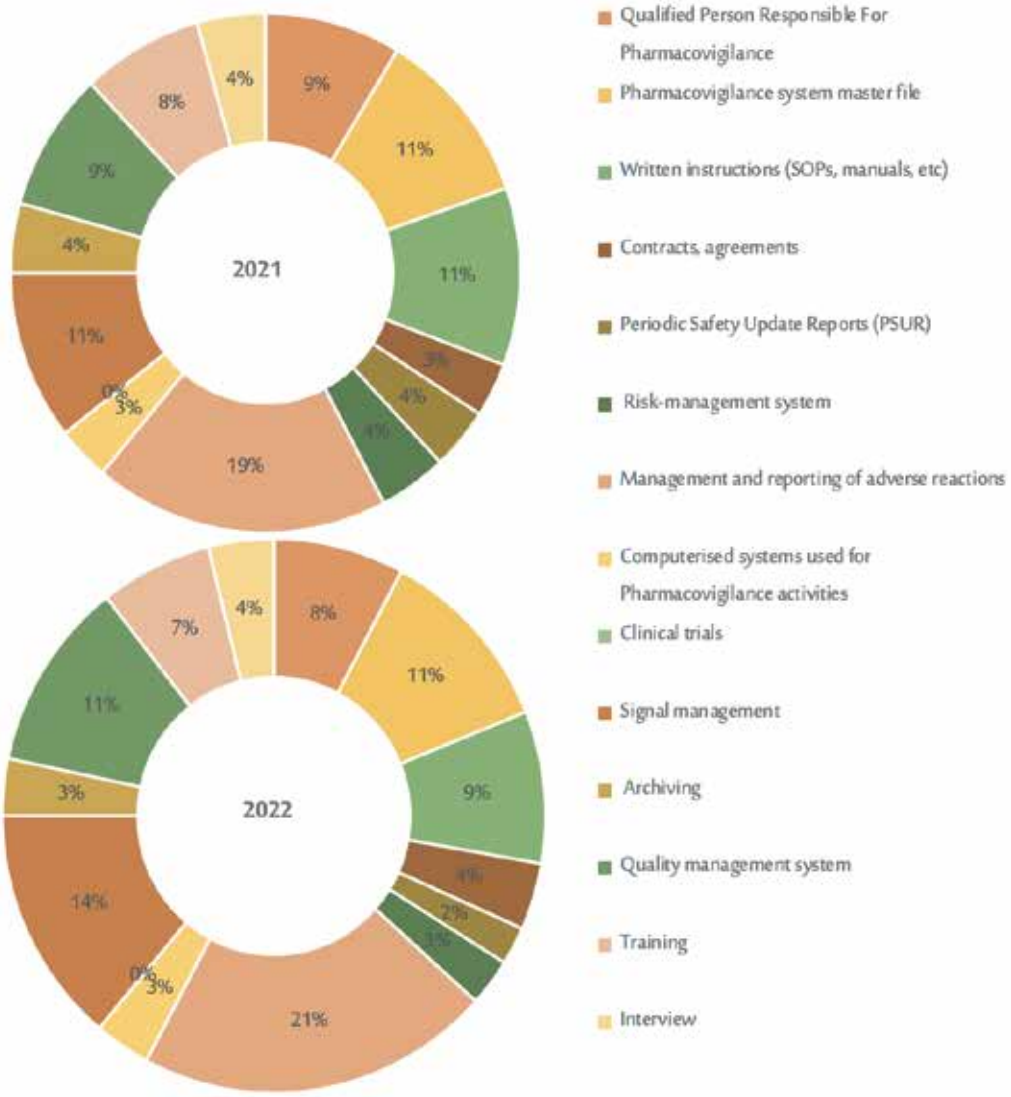
Between November 2018 and 31 December 2022, 704 Major findings were reported. One hundred eighty major findings were identified from 14 out of 18 inspections for the current reporting period. The number and distribution of major inspection findings across different inspection topics since November 2018 is shown in Figure 10.

Figure 10 - Number and distribution of major findings across topics over time

Compared to the previous reporting periods from 2021 until 2022, the overall percentage of the topics fluctuated between the topic areas. Management and reporting of adverse reaction findings increased by 10.5% at the top of overall findings from 2021 until 2022.

The proportion of Management and reporting of adverse reaction findings risen from 19% in 2021 to 21%, as shown in Figure 11 below.

Figure 11 – Percentage change in the major findings between inspection findings from 2021 to 2022 by topic area

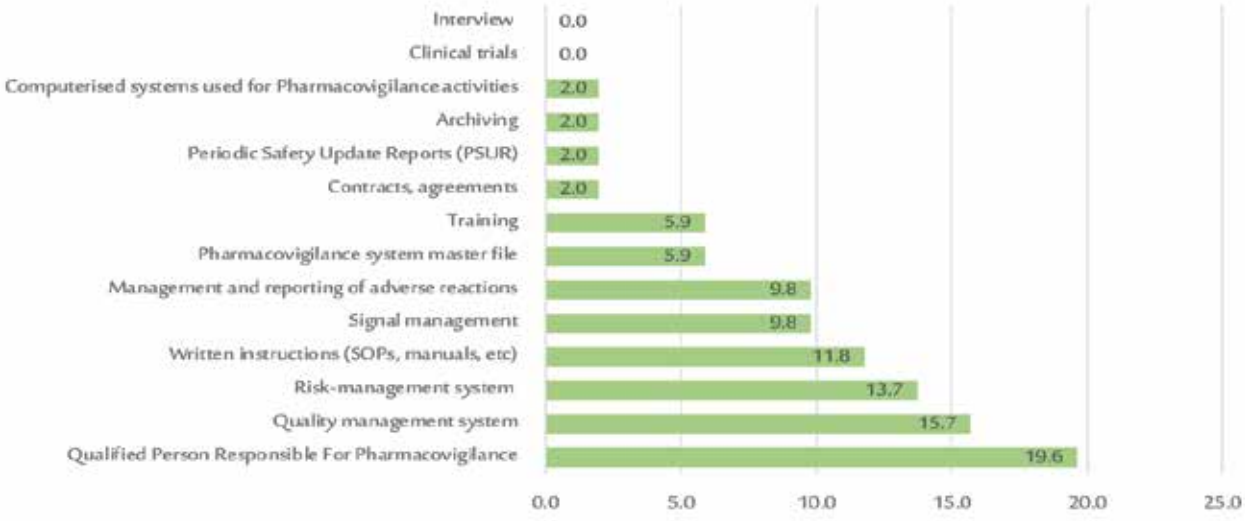


Another topic that shown an increase in the proportion of major findings this reporting period compared to the last period was signal management, which increased from 11% to 14%. The proportion of findings in the area of Pharmacovigilance system master file remains the same, and there was a slight decrease in the proportion of major findings related to the qualified person responsible for pharmacovigilance (9% to 8%). There was a considerable increase in the proportion of major findings related to quality management systems (9% to 11%).

6 Minor findings

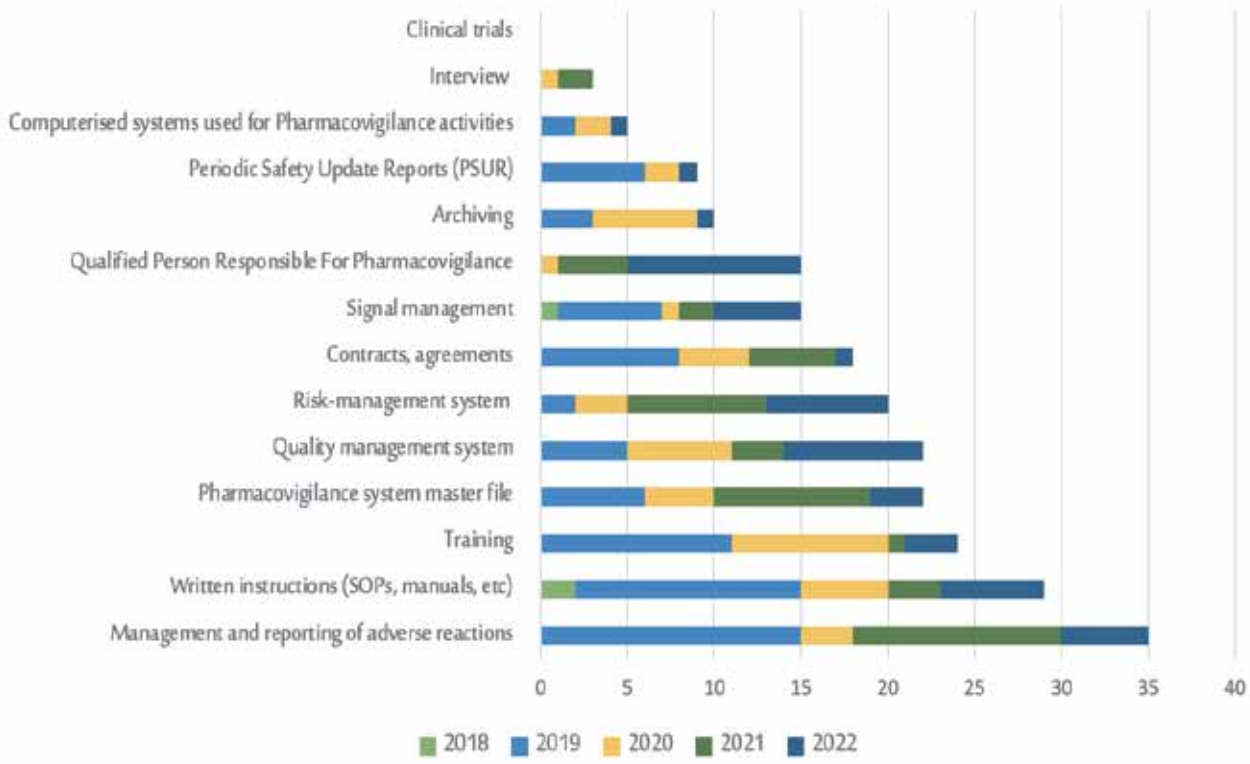
Fifty-one minor findings were identified in 2022. Compared to the previous reporting period, there were 49 findings reported in 2021 and 47 minor findings reported in 2019. Figure 12 presents the proportion of minor findings by topic area for the reporting period 2022.

Figure 12 - Proportion of minor findings reported for each topic area in 2022



The largest proportion of minor findings was composed of non-compliances in relation to the qualified person responsible for pharmacovigilance, followed by findings in relation to the quality management system, risk-management system, and written instructions (standard operating procedure (SOP), manuals, etc.)

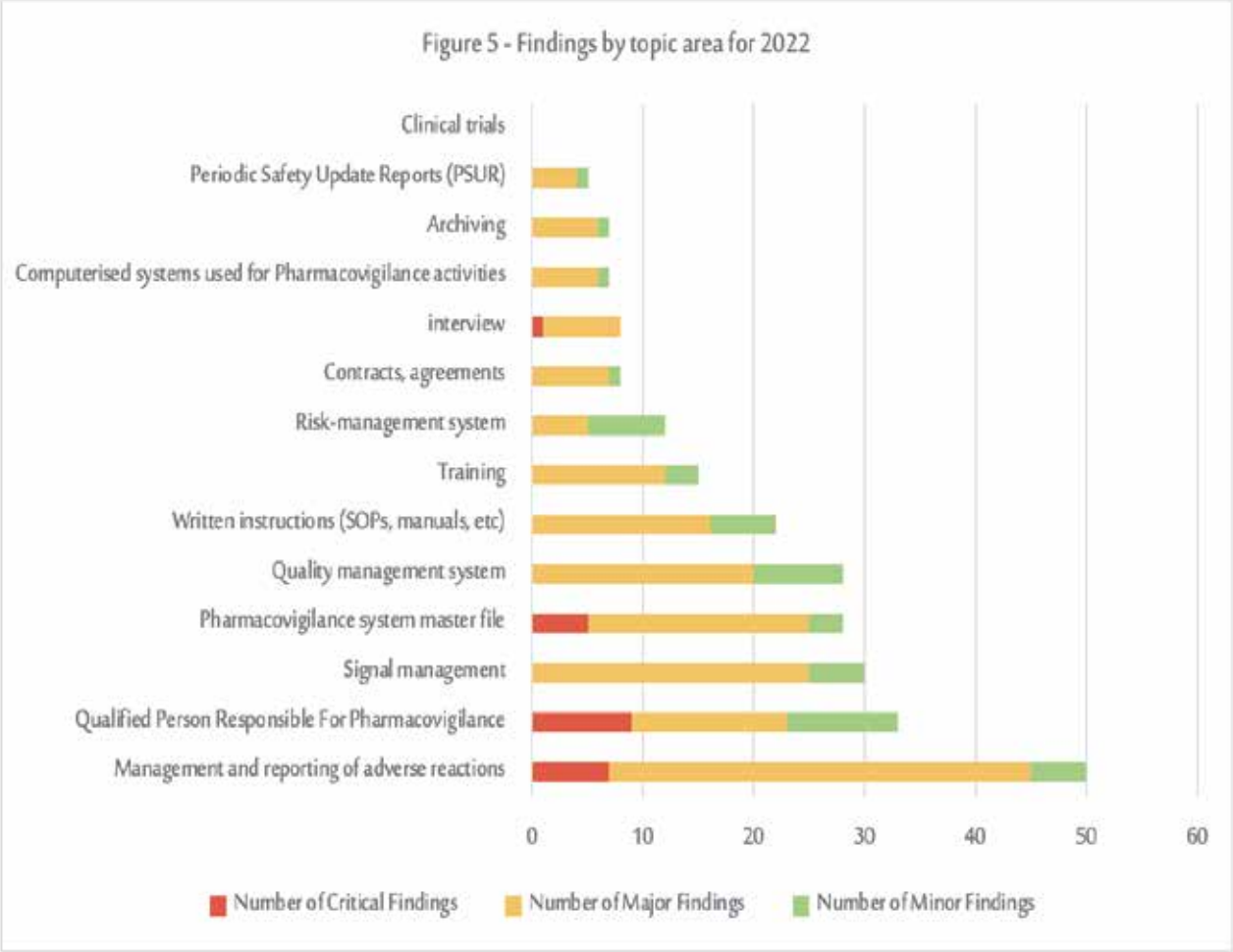
Figure 13 - Number and distribution of minor findings across topics



In comparison with the previous reporting period, the qualified person responsible for pharmacovigilance had a much high proportion of minor findings in this reporting periods – a change from 0%, 2%, 8%to 19.6% respectively (with respect to the number of findings 77 in 2019, 47 in 2020, 49 in 2021, and 51 in 2022). Quality management systems and written instructions (SOPs, manuals, etc.) had a larger proportion of minor findings raised in 2022 than in 2021, increasing from 6% to 15% and 6% to 11.8%, respectively. The risk-management system had a lower proportion of minor findings decreased in 2022 than 2021, from 16% to 13.7%.

7 Focus topics

The highest number of all findings in the reporting period (irrespective of the grading of the finding) related to Management and reporting of adverse reactions followed by the Pharmacovigilance system master file, then the qualified person responsible for pharmacovigilance.

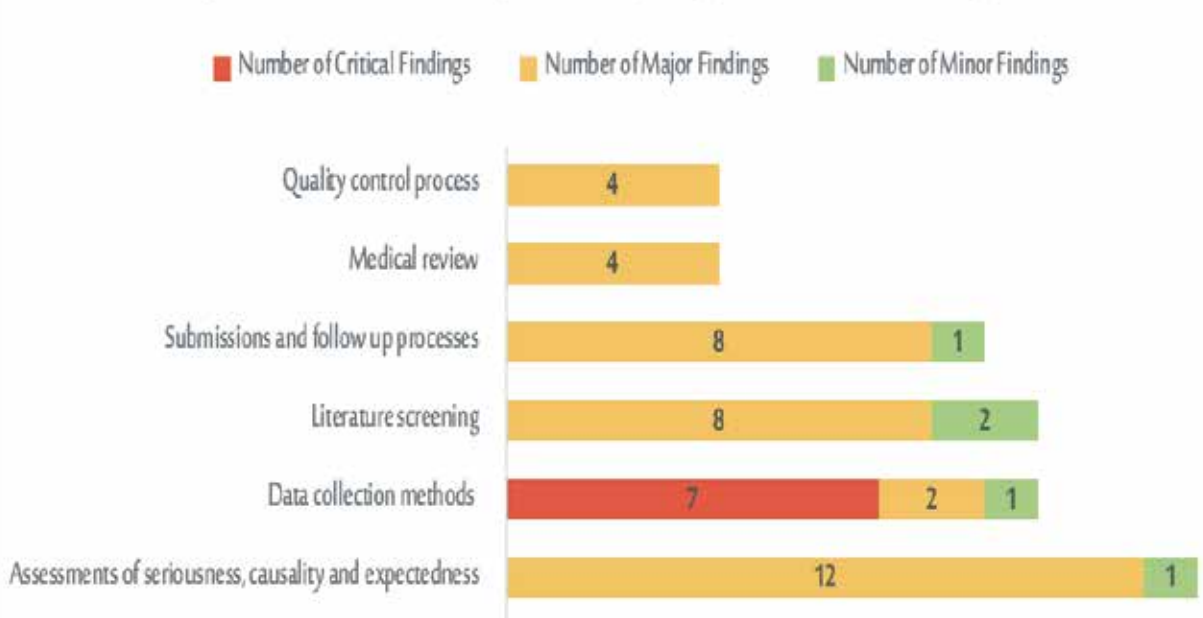


7 Focus topics

7.1 Management and reporting of adverse reactions

Management and reporting of adverse reactions have remained the topic with the highest findings overall, the same for the previous two reporting periods. Findings in this area constituted 19.8% of all findings (50 out of 253) and were reported from 16 out of the 18 inspections. A breakdown of the 50 findings in this topic area by sub-topic is shown in Figure 14.

Figure 14 - Breakdown of Management and reporting of adverse reactions findings in 2022



The majority of Management and reporting of adverse reactions related to failures in the assessments of seriousness, causality, and expectedness of the reported adverse events were 13 findings. The most common non-compliance seen in this area was the related to not involving the local QPPV in these processes or part of them.

The second-largest number of Management and reporting of adverse reactions findings sub-topic related to failures associated with the data collection method detected as limited channels used to receive adverse drug event reports, for which there were 10 findings. The most common non-compliance seen in this area was related to:

- No direct communication channel (phone number) or Arabic website for reporting adverse events from the public.
- No system to document and process the received local cases.
- The local QPPV cannot access to the MAH database to handle the local ICSRs.
- The local QPPV cannot access to Saudi market medical representatives to collect the AE reports.
- There was no database or excel sheet for documentation of local cases.

- The Saudi Arabia web page was not present in the global drop list.
- The connection between the available website and the important pharmacovigilance links is not available.

There were also ten findings relating to Literature screening. The most common non-compliance seen in this area was related to:

- Literature screening of the local journals was not performed in Saudi Arabia.
- There was no timeframe to conduct this Literature screening, and there needed documentation for the previous attempts.
- Neither the global team nor the local QPPV performed this process.
- No SOP was available to describe the process for Literature screening locally (periodicity of the screening, documentation, involvement of local QPPV in the process).
- No SOP was available to describe the process of handling vendor the Literature screening locally (periodicity of the screening, periodicity of the reconciliation between the MAH and the vendor, the periodicity of auditing captivity by the MAH on the vendor)

- The inconsistency between the provided SOP and real practice.

There were also nine findings relating to the Submissions and follow-up processes in Management and reporting of adverse reactions. The most common non-compliance seen in this area was related to:

- The local SOP of the MAHs was not updated with the new regulation of the new reporting periods of local ICSR and quality reports.
- MAHs have not created Policy of submission and follow up of ICSRs.

There were also four findings relating to the medical review. The Most common non-compliance seen in this area was related to:

- There was no SOP for medical review activities.
- No medical review for the local ICSRs provided.

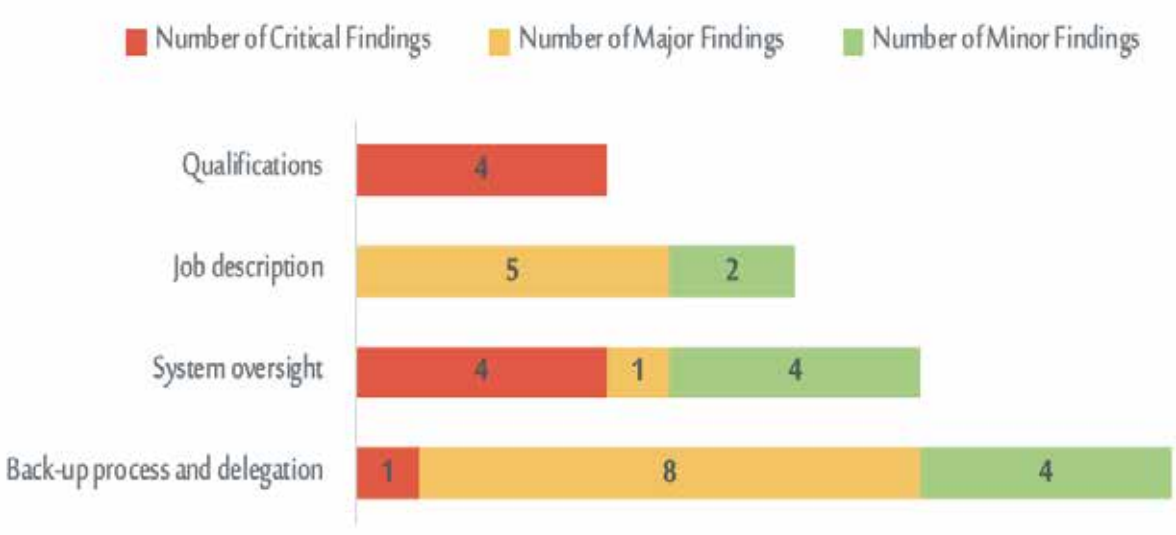
There were also four findings relating to the quality control process. The Most common non-compliance seen in this area was related to there was no SOP for the quality control process.

7 Focus topics

7.2 Qualified person responsible for pharmacovigilance

The second-highest proportion of all findings reported in 2022 related to the QPPV. Findings on this topic comprised 13% of all findings (33 out of 253) and were reported from 13 of the 18 inspections. A breakdown of the 33 findings in this topic area by sub-topic is shown in Figure 15.

Figure 15 - Breakdown of Qualified person responsible for pharmacovigilance findings in 2022



The highest number of findings for QPPV was associated with the backup process and delegation, with 13 findings for this sub-topic. That was followed by nine findings related to System oversight of the local QPPV and seven findings related to the job description of the local QPPV. Each of these sub-topics is comprised of critical, major, and minor findings.

Most common non-compliance seen in the backup process and delegation sub-topic:

- No clear written backup and delegation SOP or process during absence is available.
- No proper documentation and implementation of the backup and delegation process.

The common non-compliance seen in the System oversight sub-topic was that the local QPPV was unaware or not involved in the implemented PV activities or the delegated responsibilities locally or globally.

Most common non-compliance seen in the job description of local QPPV sub-topic:

- No Job description to handle pharmacovigilance activities locally.

- The responsibilities that local QPPV must do were not clear in the provided job description.
- The available job description was not appropriately implemented.
- Some responsibilities of the local QPPV were missed in the provided job description.
- The local QPPV did not sign the provided job description.

Lastly, the common non-compliance has been seen in the qualifications of local QPPV sub-topic:

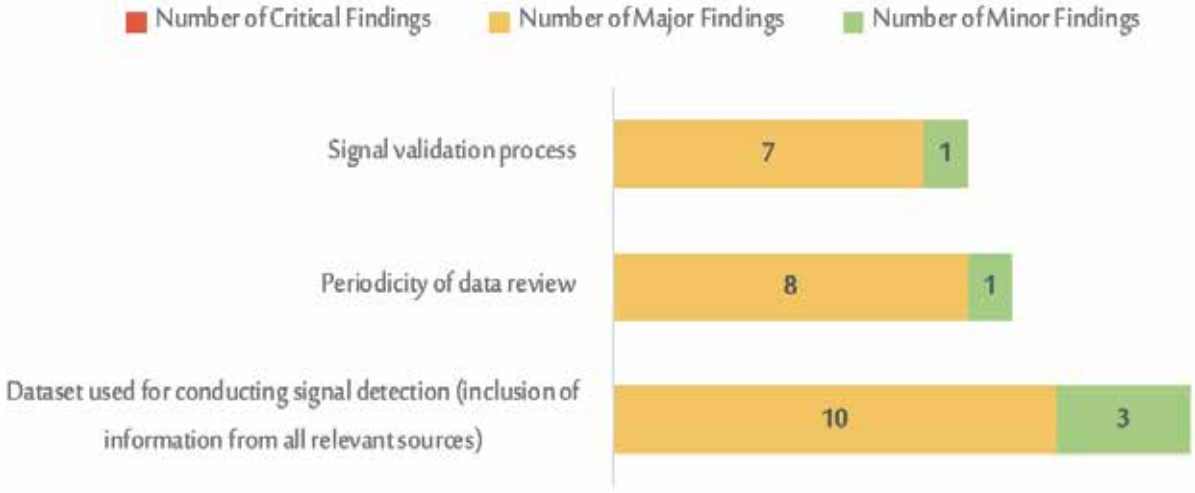
- The local QPPV did not dedicate full-time to handling the pharmacovigilance activities.
- Deputy-QPPV handled the inspection; there was no local QPPV in the MAH.

7 Focus topics

7.3 The signal management

The third-highest proportion of all findings reported in 2022 was signal management. Findings on this topic made up 11.9% of all findings (30 out of 253 findings) and were reported from 14 out of the 18 inspections. A breakdown of the 30 findings in this topic area by sub-topic is shown in Figure 16.

Figure 16 - Breakdown of The Signal Management findings in 2022



The highest number of findings for signal management is associated with the Dataset used for conducting signal detection (inclusion of information from all relevant sources), with 13 findings in total for this sub-topic.

This was followed by nine findings related to the periodicity of data review and eight findings related to signal validation process. Each of these sub-topics is comprised of major and minor findings.

Most common non-compliance seen in the dataset used for conducting the signal detection (inclusion of information from all relevant sources) sub-topic:

- No SOP was available to describe the process of handling the signal detection processes in Saudi Arabia.
- The available SOP for this process was not compatible with the guideline of Saudi GVP.
- There was no database or excel sheet for documentation of the conducted signal screening.
- No proof of screening for external signals.
- No involvement of local QPPV in the signal detection process.
- No periodical reconciliation process between the global team and local QPPV about the conducted signal screening outcome.

- No SOP was available to describe the process of handling vendor the signal detection process locally (periodicity of the screening, periodicity of the outcome reconciliation between the MAH and the vendor, the periodicity of auditing captivity by the MAH on the vendor).

The common non-compliance has been seen in the Periodicity of data review sub-topic:

- No periodic review of the data was stated in the provided SOP in Saudi Arabia or globally.
- No SOP was provided that described the periodicity of data review to detect the signals.

Lastly, the common non-compliance has been seen in the signal validation process sub-topic:

- No signal validation was performed in Saudi Arabia or globally.
- No SOP that described the Signal validation process.

8 Inspection Satisfaction

During 2022, the inspection team conducted an experience satisfaction survey for the inspected MAHs to measure the MAHs satisfaction with the NPC PV inspection and the understanding of the PV aspects after the inspection visits. The aim of that survey was to achieve excellence in pharmacovigilance inspection and improve performance.

This survey report contains three sections that mainly focus on measuring the satisfaction and the level of involvement of the local QPPV after the inspection, then adding any suggestions and notes to improve the service. The total number of participants was 70, and 42 completed the responses. The overall outcome of the survey ranged between satisfied and very satisfied.

The most important suggestion that received from the free text question was:

1 “I recommend having annual assessment in terms of the degree of compliance in the PV system of MAH in Saudi Arabia, So it helps to notice every company and their level in regards to others.”

2 “I suggest regular meetings between PV employees twice a year with the SFDA.”

3 “Expedite sending the report to MAH by email as soon as its signed as the clock starts for the CAPAs from the report signature date and not from the notification to the MAH , so to enable the MAH enough time to properly draft the CAPAs in addition in some situations we might only receive the report through regulatory affairs as hard copies and PV did not officially receive it by email.”

4 “Having the inspection report more detailed in describing the finding to be easily understood and correctly tackled.”

5 “Requesting the draft regulations to be in track changes format for the ease of identifying the changes in the document.”

The inspection team will put into consideration the provided suggestion in 2023.

9 Summary

In the report period from 01 January 2022 to 31 December 2022, fifty inspections were conducted, fourteen as a routine inspection based on risk-based methodology, four for-cause (trigger) inspections, twenty-two re-inspections, and ten inspections as a second re-inspection. A total of 253 findings were reported in this period. These comprised 22 critical, 180 major and 51 minor findings. The average number of findings issued in this reporting period was slightly increased from 14.4 and to 14.9 (3.5 % increased), with a small decrease in the number of critical findings and significant increase in major findings. The average number of minor findings reported per inspection has fluctuated, but the average number in 2022 was the highest value among all previous years.

All 22 critical findings were reported in relation to the qualified person responsible for pharmacovigilance, pharmacovigilance system master file, management and reporting of adverse reactions, and interviewee knowledge. With the exception of three inspection where no major findings were raised, at least one major finding was reported in all inspections with the majority of inspections resulting in 10.6 major findings. The largest proportion of major findings was reported in relation to failures in management and reporting adverse reactions (21.1%).

This was followed by deficiencies in signal management (13.9%) and failures associated with pharmacovigilance system master file and Quality management system (11.1%) for each.

The largest proportion of minor findings was comprised of non-compliances in relation to the qualified person responsible for pharmacovigilance (19.6%) and quality management system (15.7%), followed by findings in relation to risk-management system (13.7%) and written instructions (SOPs, manuals, etc) (11.8%).

The inspection team conducted an experience satisfaction survey on the inspected MAHs during the last period from 2018 to mid of 2022. The total number of participants was 70, and 42 completed the responses. The overall outcome of the survey ranged between satisfied and very satisfied.

As the pharmacovigilance inspection team in national pharmacovigilance center continues to follow a risk-based approach to inspection scheduling, inspections will be prioritized 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 prioritized for inspection to ensure regulatory compliance, working towards the protection of public health.

Appendix I: Inspection type definitions

*excerpt from page 100-105 of the Guideline on Good Pharmacovigilance Practices (GVP) (Version 2.0, September 2015).

Routine inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

'For cause' inspections

For-cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For-cause inspections are more likely to focus on specific

pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger.

Pre-authorisation inspections

Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorisation application. Pre-authorisation inspections are not mandatory, but may be requested in specific circumstances. Principles and procedures for requesting pre-authorisation inspections should be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorisation.

Announced and unannounced inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to

conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

Remote inspections

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorisation holder or firms employed by the marketing authorisation holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorisation holder.

Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

Appendix II: Inspection finding definitions

*excerpt from page 127-128 of the Guideline on Good Pharmacovigilance Practices (GVP) (Version 2.0, September 2015).

Critical deficiency

Is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.

Major deficiency

Is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.

Minor deficiency

A weakness in this part comes from one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

Deficiencies are classified by the assessed risk level and may vary depending on the nature of medicine. In some circumstances, an otherwise major deficiency may be categorized as critical. A deficiency reported after a previous inspection and not corrected may be given higher classification.

Appendix III: Categorization of findings

Table 2: Topics and sub-topics of inspection findings

Topic area	Sub-topic of reported findings
Qualified Person Responsible For Pharmacovigilance	Qualifications
	Job description
	System oversight
	Back-up process and delegation
Pharmacovigilance system master file	Organizational structure
	Pharmacovigilance system
	Maintenance and submission
Written instructions (SOPs, manuals, etc.)	Procedures
	Manuals
	Process for SOP training
Contracts, agreements	Contracts
	Agreements

Topic area	Sub-topic of reported findings
Periodic Safety Update Reports (PSUR)	PSUR scheduling
	Format and content
	Quality control of PSURs
	Timeliness of submission
	Assessment report comments
Risk-management system	Risk-management plan format and content
	Compliance with risk minimization measures which are beyond routine Pharmacovigilance
Management and reporting of adverse reactions	Data collection methods Assessments of seriousness,
	causality and expectedness
	Medical review
	Quality control process
	Submissions and follow up
	processes
	Literature screening

Topic area	Sub-topic of reported findings
Computerized systems used for Pharmacovigilance activities	Backup and disaster recovery process
Clinical trials	Adverse event reporting from clinical trials
	Consistency between the Investigator's Brochure and SPC when marketed products are used in CT
Signal management	Dataset used for conducting signal detection (inclusion of information from all relevant sources)
	Periodicity of data review
	Signal validation process
Archiving	Archiving facilities
Quality management system	Quality system and compliance management

Topic area	Sub-topic of reported findings
Quality management system	Facilities and equipment for pharmacovigilance
	Audit (internal- and external) and Corrective and Preventive Actions process
Training	Available trainings
	Evaluation of training
	Maintenance of training records
Interview	MAH employees interview

Appendix IV – Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
aRMM	Additional Risk Minimization Measure
CAPA	Corrective and Preventative Action
GVP	Good Pharmacovigilance Practice
ICSR	Individual Case Safety Report
MAH	Marketing Authorization Holder
NPC	National Pharmacovigilance Center
PSMF	Pharmacovigilance System Master File
PSSF	Pharmacovigilance Sub-System File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SFDA	Saudi Food & Drug Authority
SOP	Standard Operation Procedures