PHARMACOVIGILANCE
NEWSLETTER

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Inspections to ensure Quality Pharmacovigilance

Content

Health professionals and patients are encouraged to **report adverse events** or **quality problems** experienced with the use of **vaccines and medicines** to the nearest NAFDAC office or via pharmacovigilance@nafdac.gov.ng or via eReporting platform available on the NAFDAC website www.nafdac.gov.ng or via Med Safety Application available for download on Android and IOS stores.

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EDITOR'S NOTE...

We wish to thank our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out the quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote reporting of Adverse Drugs Reactions (ADRs) and AEFIs. This edition of the newsletter focuses on: **Inspections to ensure Quality Pharmacovigilance**

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions and AEFIs. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng, fdic@nafdac.gov.ng) would be most appreciated.

Thank you for your relentless efforts in strengthening Pharmacovigilance System in Nigeria.

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Introduction

The safety of medicines is of utmost importance in reference to patients & Healthcare professionals. The pharmaceutical companies have ethical responsibility to ensure that their marketed products will have appropriate safety and efficacy (Khurana et al, 2015). Pharmaceutical legislation provides a legal framework to ensure the safe and effective use of medicines. This framework requires national regulatory authorities (NRAs) to establish and maintain a pharmacovigilance system (PV system) stating and enforcing the regulatory commitments that key stakeholders, including Certificate of Registration Holders (CRHs), are required to fulfil. In recent years, national legislative bodies and NRAs across the world have issued a significant amount of legislation and guidance enforcing the obligation to perform pharmacovigilance activities.

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk ratio is judged to be positive for the target population. A typical medicinal product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post authorisation (NAFDAC Good Pharmacovigilance Practice Guidelines 2021). Pharmacovigilance (PV) is a critical discipline in the healthcare system, aimed at promoting the safe and rational use of medicines through the prevention, identification, analysis, management, and documentation of adverse effects and other drug-related problems including medication errors, therapeutic failure & drug misuse. Effective pharmacovigilance helps in the early identification of unexpected adverse reactions and their risk factors, thereby ensuring medicines are used with minimal harm.

Robust PV systems are critical to ensure delivery of safe and effective medicines to patients worldwide. However, setting up and maintaining a PV system can be a challenge, especially in countries in the process of building their expertise or when resources are scarce (Peters et al, 2021). The World Health Organization (WHO) supports the development of national PV systems by providing a Global Benchmarking Tool to support NRAs in objectively evaluating their own regulatory system according to a maturity scale ranging from 1 (lowest) to 4 (highest). Maturity level 1 is the "existence of some elements of regulatory system" and level 4 is "operating at advanced level of performance and continuous improvement". In addition, the WHO and the Global Fund have published guidance on the minimum requirements for a functional PV system. Conducting Pharmacovigilance Inspections as an NRA is a critical step in achieving the WHO Maturity Level 4 Global Benchmarking Tool (ML4 GBT) Status. In addition, regulatory reliance, the concept of relying on other NRAs' outputs, work-sharing and joint assessments may support regulators as they evolve and refine their national PV systems.

An effective pharmacovigilance system requires partnership between multiple stakeholders, including national regulatory authorities (NRAs), healthcare providers and Certificate of Registration Holders (CRHs), to achieve public health goals. As countries further enhance their pharmacovigilance systems, consideration needs to be given to the development of requirements that benefit patients and are practical to implement (Peters et al, 2021).

NAFDAC is obliged to ensure compliance with PV obligations as stipulated in the Good Pharmacovigilance Practice Regulations 2021; pursuant to this, relevant guidelines have been developed to facilitate compliance by MAHs. NRAs can assess the quality and performance of a PV system through a variety of methods. Examples include the monitoring of the timely submission of ICSRs, PBRERs, RMPs and safety variations, and the review of the PV system description. In addition, inspections of the CRH's PV system and inspections of any pharmacovigilance service provider working on behalf of a CRH are useful to check compliance with applicable regulatory requirements. Inspections are commonly conducted face to face at the CRH or service provider site but can also be managed remotely. Inspection guidances, sharing of inspection findings as well as the joint inspection trainings, will likely support raising the standards of the PV systems of MAHs and service providers and consequently contribute to improved protection of patient safety (Peters et al, 2021).

Establishing "Effective Pharmacovigilance Systems"

The NAFDAC Good Pharmacovigilance Practice Guidelines 2021, expounds on what an effective pharmacovigilance system entails. A pharmacovigilance (PV) system is defined as a quality system used by the Certificate of Registration Holder (CRH) to fulfil its regulatory responsibilities in relation to pharmacovigilance. It is designed to monitor the safety of authorized medical products and detect any change to their benefit-risk balance. The PV system consists of structures, processes and outcomes; it covers organizational structure, responsibilities, procedures, processes & resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management. The pharmacovigilance system master file provides an overview of the pharmacovigilance system put in place by the Certificate of Registration Holder (CRH) and contributes to the appropriate management of and improvement(s) to the pharmacovigilance system. The ultimate responsibility for the operation and effectiveness of the PV system resides with the CRHs. Although the CRH may subcontract certain activities of the pharmacovigilance system to third parties, it retains the full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF).

As part of the pharmacovigilance system, the Certificate of Registration holder should have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance (QPPV). A QPPV may be employed by more than one CRH, for a shared or for separate pharmacovigilance

systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same Certificate of Registration holder, provided that the QPPV is able to fulfil all obligations. The CRH should ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the organisation; the QPPV should have access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it.

Mechanisms should be in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on the following:

- Safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;
- Ongoing or completed clinical trials and other studies the CRH is aware of, and which may be relevant to the safety of the medicinal products;
- Information from sources other than from the specific CRH, e.g. from those with whom the CRH has contractual arrangements; and
- The procedures relevant to pharmacovigilance which the CRH has in place at every level to ensure consistency and compliance across the organisation.

In relation to risk management of its medicinal products, a CRH is responsible for ensuring that it constantly monitors the risks of its medicinal products and reports the results of this, as required, to the Agency; The CRH is also responsible for taking all appropriate actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available.

A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. This includes studies that may have commenced prior to registration that are on-going after the product has been registered. A PASS may be initiated, managed or financed by a CRH voluntarily, or pursuant to an obligation imposed by the Agency.

Pharmacovigilance Inspections

In 2003, a statutory national pharmacovigilance inspection programme

was initiated by the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK; this mandates the MHRA to inspect marketing authorization holders (MAH) with centrally authorized products that had located the pharmacovigilance system master file (PSMF) in the UK (Adams & Trevett, 2019).

There has been significant increase in pharmacovigilance inspections by the USFDA to ensure that industry is complying with its responsibilities to safeguard human interest. The USFDA, carries out PV Audit before an Authority inspection as well as the USFDA PV Inspection in detail. Post marketing safety data collection and adverse event reporting is a critical element of the post marketing safety surveillance program for USFDA regulated drug products; the major pharmacovigilance activities include compliance with post-market requirements under the relevant regulations and USFDA implementing regulations pertaining to post-marketing surveillance and risk assessment. The PV plan includes various procedures apart from routine post-marketing ADR reporting and is aimed to enhance the sponsor's acquisition of safety data. To ensure compliance, CRHs should align with best practices in industry. It includes timely awareness of all appropriate regulatory obligations to identify any gaps and risk in routine PV activities. The concept of timely internal audits or mock inspections can play a vital role in understanding of current position in comparison to best practices. The CRHs are expected to provide complete and accurate responses within specified time to queries from authorities or findings in audits/ inspections (Khurana et al, 2015).

The Pharmacovigilance Inspection Guidelines for Nigeria Regulated Drugs explains that pharmacovigilance inspections are designed to review systems, personnel, procedures, and facilities put in place to comply with pharmacovigilance regulatory requirements and facilitate compliance. Inspections will be routine as well as targeted to Local Representatives and Marketing Authorization Holders suspected of being non-compliant. The results will be used to help Local Representatives and Manufacturers improve compliance and may also be used as a basis for enforcement of regulatory action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria. The inspection will be conducted where pharmacovigilance activities of the Local representatives or Marketing Authorization Holders are located.

The objectives of Pharmacovigilance Inspection include the following:

- To ascertain that the pharmacovigilance system established by Local Representatives and CRHs has personnel, systems, and facilities in place to meet their pharmacovigilance obligations,
- To ensure compliance with the pharmacovigilance obligations of the local representative and MAH to protect public health and safety,
- To improve the pharmacovigilance system established by local representatives/MAHs,
- To identify, record, and address non-compliance that may pose a public health risk and

• To use the inspection results as a basis for enforcement action, where considered necessary.

A risk-based approach to scheduling entails that, most of the inspections conducted are of high-risk pharmacovigilance systems that are large or complex in nature or include high-risk products with additional pharmacovigilance activities and additional risk minimization measures in place to manage known risks (Adams & Trevett, 2019)

During an inspection, inspectors can review source documentation and data to verify the completeness and accuracy of data submitted to authorities to support decisions made in benefit/risk assessments. This is critical for ensuring that patients are protected through sound decision making by the competent authorities. Inspections give the Regulator, the opportunity to educate MAHs with less mature pharmacovigilance systems and help them better understand the requirements. From their position, inspectors can identify areas where further guidance or changes to legislation may be required. The common goal is a collaborative approach with the organizations inspected and working together with organizations during inspection closure, to agree on corrective and preventative action plans that will effectively address the non-compliances observed and bring the pharmacovigilance system into compliance. One factor that affects the number of inspections the Good Pharmacovigilance Practice (GPvP) inspectorate can conduct in a year is the availability of inspectors (Adams & Trevett, 2019).

NAFDAC carried out (4) Pharmacovigilance inspections in the last quarter of 2024. The Agency has planned to carry out 9 or more new inspections by July 2025.

NAFDAC Pharmacovigilance Inspection Training for QPPVs & others

The National Agency for Food and Drug Administration and Control organized Pharmacovigilance Inspection Training for Qualified Persons responsible for Pharmacovigilance (QPPVs) in 2024. The training is crucial for QPPVs to maintain compliance with pharmacovigilance regulations and ensure the highest standards of drug safety. This QPPV training will prepare Marketing Authorization Holders (MAH) for Pharmacovigilance Inspections. The training is targeted at QPPVs & other company PV staff and designed to ensure that QPPVs are well-versed in their roles & responsibilities, thereby enhancing the company's ability to manage and mitigate risks associated with their products effectively. A total of 62 QPPVs were trained in 2024. In addition, a pharmacovigilance training session for healthcare professionals was held in Abuja from 21-22 October 2024; it covered ten (10) health facilities. Each facility nominated nine participants including the Facility PV Focal persons, Members of

the PV committee, doctors, pharmacists, nurses, and other healthcare practitioners who are involved in PV activities.

Conclusion

The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities as well as the quality and integrity of the pharmacovigilance system always remains with the Certificate of Registration Holder. The foremost aim of National Regulatory Authorities is to ensure patient safety by evaluating the activities of responsible companies for compliance with PV obligations. Therefore, an effective PV system is a condition for an organization to maintain the registration of its product(s) and it is also very essential for safety of people worldwide (Khurana et al, 2015). The QPPV training program kick started in 2024 by NAFDAC contributes to our collective efforts to ensure the safety and efficacy of medical products in Nigeria. Pharmacovigilance Inspections are essential to monitor and ensure compliance with PV obligations.

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