

This briefing note is for policy-makers and traditional medicine practitioners. It introduces the concept of pharmacovigilance (PV), and explains its importance as part of monitoring the safety of traditional medicines. It is intended to help Member States to think about what to do about traditional medicine safety. It is prepared in question and answer format, and avoids lengthy technical explanations on pharmacovigilance.

Many Member States of the WHO South-East Asia Region have a long and rich heritage of traditional medicines. They have integrated it into their national health-care delivery systems to varying degrees. One of the common challenges that Member States face is monitoring the safety of traditional medicine products, especially setting up systems of pharmacovigilance for traditional medicine products. This challenge was highlighted in a Regional Workshop on Appropriate Integration of Traditional Medicine into National Health-Care Systems in 2015. This document provides information with regard to establishing an adverse events reporting system for traditional medicines.

Q1. Why is safety monitoring of traditional/herbal medicines important?

- Safety is always a fundamental principle in the provision of any health-care treatment and procedures. Given the reality of wide use of traditional medicine worldwide, monitoring safety of traditional medicines becomes important and a priority area of work among Member States.
- Contrary to popular belief, traditional medicine products are not always “safe”, particularly when used in combination with other medicines, and result in negative health consequences.

Facts

- 67.7% of the population used traditional and complementary medicine in the USA in 2000.
- 80% of the developing world’s population use a certain form of traditional medicine.
- In the South-East Asia Region, 10%–45% OPD visits in the public health sector were related to traditional medicine services in 2015. *Source: WHO.*

Q2. How to monitor and report the safety of traditional medicines?

- The safety of a traditional medicine can be monitored through a national pharmacovigilance (PV) system. A PV system is the network between all stakeholders including national and regional pharmacovigilance centres, health facilities (public and private), drug stores/pharmacies, patients/consumers and manufacturers. It means that all stakeholders should participate in the reporting.

Pharmacovigilance (PV) is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

- Monitoring can be done through three possible channels: i.e. (a) **spontaneous-voluntary reporting system** (SRS) for all health products; (b) **intensive monitoring programme** (IMP) for specific products; and (c) **active surveillance** for particular products for a specific period. For instance, two-year intensive monitoring programme for single herbal ingredient formulation after its inclusion in the National Essential Drug List (NEDL)-cohort study in Thailand.
- A standard single reporting form in a printed or electronic form/online reporting system or telephone can be used for reporting. (Web-based database consisting of reporting tool, data entry/correction, searches, statistics and log of the report, etc.)

Q 3. What is to be monitored ?

- Adverse reactions
- Medication errors
- Case reports of acute and chronic poisoning (toxicity)

- Abuse and misuse of medicines
- Adverse interactions of medicines with chemicals, other medicines and food.

An adverse drug reaction (ADR) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or treatment of disease, or for the modification of physiological function.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Q 4 What information should be in the report?

Any suspected adverse drug reactions (ADRs)/adverse events (AEs) associated with the use of herbal/traditional medicines and other factors affecting product safety should be reported. The report should contain information on the following elements:

Patient information:

- Identification of the patient/consumer with appropriate confidentiality needs to be provided in order to avoid duplications and to facilitate follow-up.
- Age, sex and a brief medical history.
- Risk factors, e.g. age, impaired renal function, previous exposure to the herbal medicine(s) concerned, previous allergies, drug misuse or abuse.

Product information:

- Details of suspected herbal/traditional medicine products if known: species name (Latin binomial name and common vernacular name of medicinal plant) and/or brand or ingredient name(s), part of medicinal plant used, preparation methods; manufacturer, country of origin, batch number, expiry date and provider;
- Administration details: dose and quantity supplied, dosage form, route, start/stop dates, and indication or reason for use; and
- All other medicines used (including self-medication), with administration details.

Adverse drug reaction/adverse events information:

- Date of onset (or duration from first administration to onset of event), description with symptoms and signs, severity and seriousness, results of clinical investigations and tests, course and outcome, and

Reporter information:

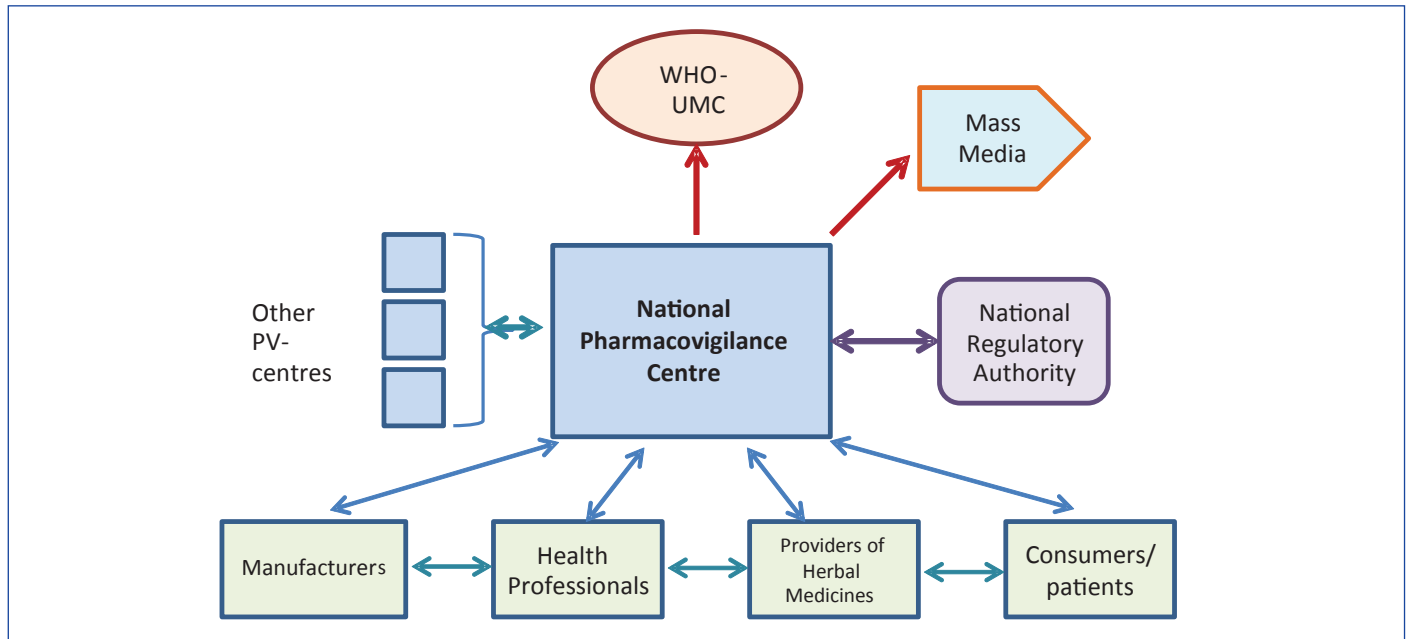
- Name and address (to be considered confidential and to be used only for data verification, completion and case follow-up)

Q 5. What does PV centre do after receiving the report?

- Conduct individual case safety report (ICSRs) assessment while classifying its severity and suggesting regulatory actions and feedback to the reporter.
- Conduct signal detection by analysing and assessing the case report in its database and assessment (case series).
- Propose risk minimization tools, if needed.
- Do risk communication at national and international level, when signal is detected.
- The causality assessment can be carried out using any appropriate assessment method for herbal and traditional medicine products.
- Categorize ICSRs into non-serious and serious categories. The serious adverse drug reactions (ADRs) and adverse events (AEs) will be further subcategorized such as death, life-threatening, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect.

- After detecting signal, PV centre has to inform the concerned National Regulatory Authority (NRA) to take appropriate regulatory action including risk management and communication such as withdrawing products from the market, adding warnings, amending labelling or packaging, restricting prescribing criteria or use as per the evidences received.

Communication network of pharmacovigilance (PV)



Q 6. Why is it challenging to do pharmacovigilance for traditional medicine products?

- **Complexity of herbal product:**
 - (1) **Lack of clinical trial data:** Unlike conventional medicines, systematic clinical trial data for many herbal and traditional medicine products is not always available. A licence can be issued based on the history of medicinal use. It is difficult to obtain safety and efficacy data on the herbal product.
 - (2) **Chemical complexity:** Herbal and traditional medicine remedies and preparations are chemically rich complex mixtures comprising several hundreds of constituents. The effects are likely to be attributed to a group of related constituents rather than a single constituent.
 - (3) **Non-uniformity (products not standardized):** The profile of constituents is often not uniform throughout a plant and certain parts of the plant can be toxic. The precise profile of constituents is likely to vary between different batches of herbal materials, and factors such as environment, time of harvesting, storage, processing and drying can affect their variability. This makes it difficult to determine pharmacokinetics, pharmacodynamics and toxicology, and to establish which ingredient causes a safety concern.
 - (4) **Quality assurance and control:** Unlike conventional pharmaceutical products, herbal and traditional medicines are prepared from materials of herbal origin which are often obtained from various geographical and commercial sources, resulting in uncertain condition. Furthermore, procedures and techniques used in its manufacturing and quality control measure are often very different from those used for conventional medicines.
 - (5) **Lack of technical expertise and facilities** and manpower to analyse the problem, particularly in identifying substandard, adulterated and contaminated, wrong medicinal plants, which is a common problem with traditional medicine products.
 - (6) **Possible interaction** between different traditional medicine products and with allopathic medicines and foodstuffs.
- **Difference in product regulation** on categorizations of herbal/traditional medicine. For instance, a herbal product in one country can be classified as a dietary/food supplement in another without any health claim.
- **Insufficient information and lack of access to reliable information** support such as product name, part use, etc., for analysing the products concerned.

- **Botanical nomenclature:** The nomenclature of crude plants is not consistent. In many texts the names are in Latin, consisting of two parts, one related to the scientific name and the other indicating the plant part, e.g. digitalis folium. Misleading and inconsistent names are commonly used.
- **Safety monitoring:** Many health-care providers are not trained on safety monitoring of medicines including traditional medicine (pharmacovigilance methods), which results in underreporting or zero report.

Q 7. How can pharmacovigilance for herbal and traditional medicine be improved?

- Networking should cover health facilities (traditional medicine practitioners), manufacturer, drug store (pharmacists) and consumer.
- Harmonize regulations for herbal/traditional medicine products among Member States.
- Proactive pharmacovigilance through the product life cycle is the way forward and the future direction for drug safety. For instance, the regulatory system should have a mechanism to collect safety data before marketing approval and after marketing.
- TRM practitioners should participate in causality assessment process and they should be trained on causality assessment.
- PV should be integrated into curriculum of medical education.
- PV should be integrated into good pharmacy practices (GPP) in community pharmacy.
- Use of modern technology and its development through IT facilities and mobile application tools should be encouraged.
- The exact scientific name of the plant, the plant part used and the name of the manufacturer should be included in the ADR report on herbal medicines.
- Regular training programmes for strengthening national capacity in monitoring the safety of traditional medicine products and for promoting awareness should be encouraged.
- It would be better to start early with the professional training of health-care students to create a culture of reporting ADRs.
- National quality specification and standard for herbal materials (selection, sampling, testing of plant material, stability studies), GMP, labelling, and licensing schemes for manufacturing, imports and marketing should be mandatory.

Q 8. How has international pharmacovigilance evolved?

- 1961: The disaster caused by thalidomide, resulting in many thousands of congenitally deformed infants due to exposure in utero to an unsafe medicine promoted for use by pregnant women.
- 1963: The Sixteenth World Health Assembly adopted a resolution (WHA 16.36) that reaffirmed the need for early action in regard to rapid dissemination of information on ADRs.
- 1968: The First WHO Pilot Research Project for International Drug Monitoring (WHO PIDM) created to develop a system, applicable internationally, for detecting previously unknown or poorly understood AEs of medicines, which started collecting international ADR reports in a central database (VigiBase™).
- The WHO PIDM aims are – (1) To enhance patient care and patient safety in relation to the use of medicines, and (2) to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.
- WHO promotes pharmacovigilance at the country level. Initially, the WHO PIDM members consisted of 10 Member States. As of May 2016, 126 countries have joined the WHO PIDM, and 29 associate members are awaiting full membership

Uppsala Monitoring Centre (UMC): At the global level, Uppsala Monitoring Centre (UMC) in Sweden plays the role of a WHO collaborating centre -WHO international database (WHO VigiBase). UMC has undertaken a project with the aim of attaining global standardization for herbal medicines. For the therapeutic classification of herbal/traditional medicine products, the herbal anatomical-therapeutic-chemical (HATC) classification is proposed to be used. WHO Drug Dictionary (WHO-DD) is proposed to be used for recording and coding the identity of herbal/traditional medicine products, as it has been developed to store structured, classified information on the names of herbal/traditional medicine products and their ingredients.