



Ninth meeting of the WHO Advisory Committee on Safety of Medicinal Products
Geneva, Switzerland
3 to 4 May 2012, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. Following is a summary of discussions and recommendations from the ninth meeting.

PV toolkit

The Pharmacovigilance Toolkit is intended as a pharmacovigilance (PV) resource repository for low and middle income countries. The WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from the WHO and the UMC. The toolkit has been presented to the Committee at its previous meetings and has received valuable comments and guidance from the members. The toolkit was launched on January 2012 and has generated wide interest globally, and feedback from users of the web toolkit has been positive. Both web accessible (www.pvtoolkit.org) and available in thumb drives, this resource also includes material from public health programmes.

At the ninth meeting, the ACSoMP advised that the toolkit should include links to other publications such as the European guideline on good pharmacovigilance practices as well as consider translating the toolkit content into other languages, for broader uptake and ease of use.

Procedures for reviewing safety concerns by ACSoMP

This topic was considered in the light of recent drug scares around the world when WHO was called upon to provide urgent technical and strategic assistance to the affected countries. The committee discussed a proposal that outlined the process by which safety concerns are channelled to WHO and action steps that follow this, including how members of the advisory committee can be engaged in the investigations. Communications, documentation and knowledge management protocols were suggested. It was agreed that WHO should put together a list of PV professionals highlighting their competent expertise; and that this list could be referred to when identifying relevant experts to handle and investigate the crises.

EU PV legislation and reports from EU Member States

The Committee discussed the new EU PV legislation and the potential impact on the WHO Programme for International Drug Monitoring. The WHO Programme was established in 1968, in response to the thalidomide disaster, to collect, analyse and share information on adverse drug events globally. The EU member states are important partners in this collaboration. The Committee reaffirmed the vital value of Vigibase, the WHO global Individual Case Safety Reports (ICSR) database as a global signal detection tool, and the need for all countries in the WHO Programme to ensure that the best possible data quality is

provided whilst adhering to applicable country laws and regulations for the protection of patient confidentiality. The Committee recommended that a working group should be established, to work with the EMA, to ensure and facilitate the continuing collaboration with EU Member States, for meaningful data exchange between WHO and EU states, to support WHO in its mandate of detecting signals and providing global information on drug safety in a timely fashion.

Detecting, analysing and preventing medication errors within PV centres

This session referred to one of the outputs of an ongoing WHO project with various partners under the Seventh Framework Programme of the European Union (EU-FP7). This aspect of the project aims to increase the capacity of PV centres in identifying and understanding the root causes of preventable ADRs. A draft publication 'Reporting and learning systems for medication errors: detecting, analysing and preventing within pharmacovigilance centres' has been prepared by WHO, together with the Morocco PV Centre, National Patient Safety Alliance, UK and the UMC. The broad elements of the draft were presented to ACSoMP at its ninth meeting.

In the US FDA, medication error (ME) prevention work is incorporated within drug development of the industry, which includes an assessment of proprietary names of the medicinal products, among others. In China, while MEs are in the purview of the ministry of health, the PV centres do receive reports. The Committee noted that off-label use of medicines leading to harmful outcomes must be responsibly reported but this is not undertaken currently and lessons are lost. Therefore, a proposal to map the impact of harm from MEs was made. WHO was advised to send the document for public comments.

PV of medicines supplied through international agencies

In assisting countries to treat priority diseases, international agencies often procure and supply medicines to countries with little or no functional PV systems; marketing authorization holders (MAH) with regulatory requirements to collect reports on these products are often unable to meet this responsibility in these settings. This is particularly true when the products are put to off-label use. The Committee reviewed a PV agreement that would be signed by countries as a condition to receiving cheaper medicines in a specific disease treatment programme. Obligations of each party in the drug procurement and supply chain are stipulated in the agreement with clearly defined responsibility for PV within this collaboration.

The Committee noted that the proposed agreement is not explicit on the accountability of the responsible agency within the recipient country for PV monitoring, responsibility for addressing serious drug reactions, nor the legal role of national regulatory authorities (NRAs). The Committee also advised that:

- risk communication needs to be included in the agreement because serious adverse events (SAE) like cardiac and hepatic deaths can damage the reputation and credibility of public health programmes
- roles of public health departments, the NRAs, the PV centres and the recipient organizations should be better clarified in the agreement.

The Committee recommended a coordinated effort, at a higher level within WHO, for a responsible, consistent, and standard plan with an organization-wide strategy to integrate PV within all its drug administration programmes.

Definitions in PV

The Committee discussed the normative role of WHO in establishing definitions and recommended that WHO should continue developing definitions in pharmacovigilance as the recognized authority in providing a common framework. But it is necessary to include the perspectives and inputs from industry as important stakeholders. The Committee approved that the Council for International Organizations of Medical Sciences (CIOMS) consultation meetings on PV definitions is a good model for facilitating discussions with industry.

Safety of medicines in sub-Saharan Africa: USAID- SPS

A recent survey of selected African countries by the USAID/Strengthening Pharmaceutical Systems (SPS) programme highlights the lack of capacity to monitor drug safety, the inadequate PV policies and their implementation in the region. Results show that although many countries have PV programs, the functionalities are quite variable, especially with respect to electronic information exchange, and the ability to take actions on Signals. While 70% of global population on anti-retroviral medicines live in Africa, only 6% of ADR reports come from Africa. The survey concluded with a number of policy recommendations related to infrastructure for strengthening PV, risk management planning, integration of PV into training and education, using safety data in regulatory decisions and treatment guidelines. The Committee noted the synergies with recommendations from similar surveys by WHO and suggested collaborations between WHO and SPS for joint strategies and solutions to the identified challenges, and their implementation in countries.

PV of TB

The global burden of TB is considerably high (9M cases in 2010, with 1M deaths, 650,000 cases of MDR TB). XDR TB cases have been reported worldwide. Some countries have no laboratory capacity to detect XDR which contributes to underreporting. While TB drugs have been in the market for long and ADRs are known, the extent of ADR related morbidities and mortalities are unknown. Part of the problem appears to be the long treatment and complex regimen, and the presence of co-morbidities; with the scale up of treatment and the introduction of new TB drugs worldwide, care must be taken to prevent resistance to the new TB drugs.

Targeted Spontaneous Reporting (TSR), WHO's approach for collecting ADR data in public health programmes, is well suited for PV in TB control programmes in low resource settings and builds on integrating safety monitoring as part of a national TB treatment programme. ADRs will be monitored as standard of care in DOTS (direct observed treatment), to collect information on specific adverse events and / or specific treatment regimens. The Committee noted that while TSR provides a practical tool, for integrating PV within a public health programme, it will be challenging to detect new and unexpected reactions with this approach.

Monitoring Medicines (MM) project

The EC-funded Monitoring Medicines project was developed by WHO and is currently being implemented as a partnership of 11 countries and coordinated by the UMC. The broad objectives are to support and strengthen consumer reporting and to expand the role and scope of work of PV centres to include MEs. This will lead to broader & efficient use of existing PV data. Analysis of VigiBase to provide better indicators for detecting dependence producing medicines and developing methods to detect incidence of substandard medicines are two such examples of this work. Moreover, the project also intends to develop additional PV methods to complement spontaneous reporting. There is a further component to develop learning tools for PV for HIV treatment managers. Various work packages, the activities and

products that were produced from the work packages were presented. The Project will be completed by Feb 2013.

The Committee recommended that the web based tool for ADR reporting by patients that has been developed under the MM project initiative should be shared with the EMA for further development of the tool and for its possible use within EU. The Committee advised the wider dissemination of the MM project results at the PV side event at the 65th World Health Assembly at Geneva, in May 2012.

Toxicity monitoring in routine antiretroviral therapy (ART) implementation

The key interest of PV monitoring in ART is to find local toxicity cases that can inform global and national treatment guidelines. TSR is being introduced in ART in Kenya, and Cote d'Ivoire, Vietnam and Laos, and Cohort Event Monitoring (CEM) is about to be launched in ART in Tanzania. The Committee discussed key toxicities related to ARVs: renal toxicity with tenofovir, risk of teratogenicity with efavirenz, hypersensitivity reactions to nevirapine.

Safety of antimalarials

Amodiaquine (AQ) was removed several years ago from the WHO Model List of Essential Medicines but was later re-introduced in combination with artesunate (AS), for the treatment of uncomplicated falciparum malaria. Following Zanzibar and Burundi, Ghana was among the first countries in Africa to introduce this combination as 1st-line treatment of malaria and adverse reactions were reported with this combination in the country through both hospital studies and spontaneous reports to the national pharmacovigilance centre. A review commissioned by WHO found a causal association between the drug combination and movement disorders, and concluded that this is a Signal. Based on these findings, the MAH was asked to review its Summary of Product Characteristics (SPC), to include the newly reported side effects.

In a revised SPC, the MAH proposes to include the observations of both dystonia and extra pyramidal symptoms. The committee recommended that in addition to withholding treatment in case of appearance of such reactions, proper guidance should be given to health workers for pro-active management of dystonic reactions and that advice on use of suitable alternative medicines to treat malaria should be provided. The Committee also recommended that the SPC should provide clarity on dosing in children and should be re-written, so that it is easily understood by laypersons. The Committee also made other recommendations with edits on specific sections of the SPC, to be conveyed to the MAH.

Piloting PV indicators in selected countries

The WHO PV indicators have been developed as quality assurance tools for the evaluation, comparison and trending of PV systems and practice in countries. The indicators cover core and complementary parameters as well as structure, process and outcome matrices and will support the collection of both quantitative and qualitative data. The WHO PV indicators will be implemented, in 2-3 countries per region; two health-care facilities and one public health program will be included per country in the pilot.

The Committee noted that there are currently no standards for PV centres which can be used as benchmark for objective comparisons. The Committee acknowledged that complete data collection will not be possible in certain settings, but at the very least, these PV indicators are educational tools for NCs to appreciate process, progress and outcomes. There is also a predictive value to the indicators, that allows NCs to prepare themselves for the future: for example, measurements of increasing ADR reports would alert NCs to practical

implications (of such trends) on human resources, staff training and funding of PV centres. The Committee recommended that the current version of the WHO PV indicators should be published on the WHO medicines website and included in the WHO PV toolkit; the Committee also recommended collaborating with the WHO Global Vaccine Safety initiative on the revision of the vaccine vigilance indicators.

Global Vaccine Safety (GVS) initiative

The GVS initiative was first presented to ACSoMP at its eighth meeting, in 2011. This initiative is to strengthen global capacity for vaccine PV, has been endorsed by the Strategic Advisory Group of Experts (SAGE) on Immunization and Global Advisory Committee on Vaccine Safety (GACVS) and is aligned with the Decade of Vaccines Collaboration that focuses on improving global vaccine strategies. There are 8 strategic objectives. WHO acts as the secretariat and there is a governance steering committee to ensure strategic execution of the objectives. The GVS initiative will be presented at the 65th World Health Assembly (WHA) for approval.

Initial implementation has been undertaken through existing mechanisms (vaccine PV networks, WHO Collaborating Centres and CIOMS, with progress reports to SAGE and GACVS), with diverse financing. The Committee also heard about present developments to VigiFlow, to make it more user friendly for AEFI (Adverse Events Following Immunization) data entry. The vaccine-friendly version of VigiFlow (the ADR data management tool) will be called VacciFlow. The Committee approved the initiative but cautioned that care is needed, to ensure that VigiFlow and VacciFlow are not perceived to be two different systems.

WHO SSFFC Global Surveillance and Monitoring Project

SSFFC stands for ‘Substandard, spurious, falsely labelled, falsified and counterfeit’ medicines. SSFFC case studies were presented by the relevant WHO team that is leading this project, to elucidate examples of:

- Commercial diversion and falsely labelled products
- Intention to deceive – with no active pharmaceutical ingredient (API) or ‘actives’ in products
- Substandard products with specific contaminants
- Reduced amount of API in products
- Quality problem with clear intention to deceive (for example, 99% ‘actives’ detected but failure to dissolve)
- Manufacturing error with contamination.

Raising awareness of the issue, whilst important, must be dealt with carefully to avoid the unintended consequence of assisting those engaged in this illicit activity to improve production of their dangerous products. There is much misleading information about the scale and scope of SSFFC medical products. The project will thus encourage Member States to report incidents to the WHO in a systematic manner providing a reliable body of evidence by which to make future decisions and arrive at an accurate assessment of threat. Pilot studies in two regions - Europe and Western Pacific - have been proposed. The pilot study aims to establish a system for rapid reporting, and assessment of SSFFCs and to issue alerts. The Committee discussed the role of the WHO Medicines Safety programme and the UMC and how existing processes and tools can be used to the advantage of the SSFFC project. As a first step in this collaboration, the UMC will develop a real-time algorithm to data-mine Vigibase (the WHO global database of Individual Case Safety Reports) to compare against products known to be vulnerable to falsification.

Reporting of drug ineffectiveness

As a follow up of the conclusions from the 8th ACSoMP meeting, a working group from within the ACSOMP has proposed recommendations on reporting and assessing drug ineffectiveness. The group presented the importance of reporting therapeutic failure, and the wider use of the term to describe this adverse event. There are several reasons and mechanisms why a drug may not be effective at all or not as effective as expected in a particular case or cases (disease and patient-related, primary or secondary drug ineffectiveness, medication error, biopharmaceutical problems, substandard or counterfeit products, or new characteristics of disease). For a better assessment of drug ineffectiveness, the report should include some specific information about the patient, disease, other medications and other aspects of treatment and the description of medicine ineffectiveness. Due to specific mechanisms and public health relevance of unexpected drug ineffectiveness, the reasons for therapeutic failure in those instances need to be captured. The Committee observed that a separate system for reporting therapeutic ineffectiveness should not be proposed, but available reporting formats should be optimized, together with a guideline for reporting this kind of information. The Committee recommended integrating the necessary information fields (for better identification of therapeutic failure) in the ADR reporting form; developing a guideline to encourage and improve the quality of reports; and advancing these efforts in the context of drug resistance or other public health challenges.