

**Seventh Meeting of the WHO Advisory Committee on Safety of Medicinal Products**  
**Geneva, Switzerland**  
**26 - 28 April 2010**

*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 Seventh Meeting.*

**WHO strategy for promoting best practices in Pharmacovigilance**

Any pharmacovigilance (PV) strategy should be aligned with the Millennium Development Goals.<sup>1</sup> It should be both health systems and primary healthcare based, focusing on priority medicines in areas where they are most needed. At the same time, this strategy should be aligned and consistent with the WHO Medicines Strategy<sup>2</sup>, which is currently within the 2008-2013 cycle. The strategy, currently under development, aims for best practices in PV, through activities that involve the WHO, its Collaborating Centres, the ACSoMP members, national PV centres, health professionals and professional organizations, academia, the public, industry, civil societies and other national and international experts. The primary focus will be on low and middle income Member States.

The draft WHO PV strategy will be presented at the thirty-third Annual Meeting of National Pharmacovigilance Centres in November 2010, at Accra, Ghana.

**Serious AEs in preventive chemotherapy interventions for the control of neglected tropical diseases**

An overview of the document entitled "Assuring Safety of Preventive Chemotherapy Interventions for the Control of Neglected Tropical Disease- Rev7" was presented and discussed. When finalized, it will be field-tested at national level. WHO is focusing on 5 Neglected Tropical Diseases (NTDs) for large-scale interventions; Lymphatic filariasis; Onchocerciasis; Schistosomiasis; Soil-transmitted Helminthiasis; Trachoma. 6 medicines are prioritized for the large-scale interventions albendazole, azithromycin, diethylcarbamazine, ivermectin, mebendazole, & praziquantel. The document aims to help NTD programme managers to address specific questions related to adverse events

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<sup>1</sup> <http://www.who.int/medicines/mdg/en/index.html>

<sup>2</sup> [http://whqlibdoc.who.int/hq/2009/WHO\\_EMP\\_2009.1\\_eng.pdf](http://whqlibdoc.who.int/hq/2009/WHO_EMP_2009.1_eng.pdf)

(AEs) and to establish a safety surveillance system. An inadequate management of serious adverse events (SAEs) may lead to damage of public health programmes,

ACSoMP members will provide written input to the current draft. Specific committee members will provide introduction between WHO NTD, local public health program managers and PV officials for effective collaborations between national NTD programme managers and the PV/drug regulatory authority.

### **Leveraging collaborations with Global Health Initiatives for building minimum standards for Pharmacovigilance in countries**

The Global Fund to fight AIDS, Tuberculosis and Malaria (GF) is an independent public-private partnership that aims to raise and disburse substantial new funds for these three high burden diseases. Principal recipients of these funds are the ministers of health of countries. This financing institution collaborates with the technical programmes within WHO. In October 2002, the GF board made a decision to strongly recommend recipients to implement pharmacovigilance, however the implementation by countries has been lacking. To address this gap, WHO technical guidance is sought to develop the GF PV strategy

2 parallel work-streams have been identified

- a. in immediate term, stimulate inclusion of PV in GF proposal submissions, and
- b. in the medium and long term – identify and field test effective PV processes and tools

### **Minimum PV requirements and tool kit for Resource Limited Settings (RLS)**

A consultation meeting was held in January 2010 to determine the minimum functional standards for PV systems for resource limited countries.<sup>3</sup> The minimum requirements include a national PV center with designated staff, with clear mandates, a national spontaneous reporting system, a national database (or a system for collating and managing adverse drug reaction (ADR) reports), a national PV advisory committee, and a clear communication strategy for routine information exchange or for communication in crises. A 'PV Toolkit' is defined as a set of practical tools to facilitate country PV processes. The user-friendly kit will carry standard operating procedures (SOPs), generic templates and forms for PV and will guide and assist countries in RLS, to set up and operate PV systems, and to assist in proposal submissions to donors. The toolkit is being developed by a PV consultant; Committee members will help populate this PV tool kit with SOPs and other PV resources.

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<sup>3</sup> [www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/PV\\_Minimum\\_Requirements\\_2010\\_2.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf)

The toolkit will be presented at a Stakeholders meeting in August or September 2010, followed by its field testing in some 10 to 20 Phase 1 countries.

### **Procedures for reviewing safety concerns by ACSoMP**

Proposed procedures for the review of safety concerns were presented. There is a need to develop a committee governance manual to reflect the current activities. The benefits for this include standardization of process, institutional memory, legacy and an audit trail (a chronological database of activity, output and outcome) of action points taken by the committee. A manual outline was proposed reflecting procedures such as organization of committee, duties and responsibilities of members, relationship with media and industry and conflict of interest. The WHO secretariat was tasked to develop a technical paper on the kind of issues that the committee could address, and the committee process for dealing with the same.

A writing group will draft the broad governance principles, to be reviewed in Nov 2010 at the Annual Meeting of National Centres in Accra, Ghana.

### **Guidelines on presenting evidence of safety in applications to the WHO Essential Medicines List (EML)**

At the last ACSoMP in March 2009, the first draft of the new guideline on procedures to assess safety aspects in EML applications raised two observations: first, procedures were too demanding for applications for new drugs, in particular if effectiveness-driven, and second, comparative risk and risk assessment of new vs. old drugs should be more structured. At the EML Committee meeting in March 2009, it was recommended that a short version of the extensive proposed guideline be produced, as a substitute of the 4-bullet-point section 11 of the current comprehensive EML guideline for applicants.

The new short bullet point version (largely an abstract of the long version) provides guidance on how to present safety claims supporting any application, various comparators and their justification, different studies and data, demographics of investigated patients with their risk factors, administration of candidate drugs, ADRs and risk.

The bullet point version will be posted on the WHO website along with the long explanatory version by the beginning of November 2010 for consultation and comments.

### **Access to Signals and Data**

Four different data sets had been considered for access outside the WHO Programme: summary statistics; limited database excerpt; complete database extract; and signals. Issues on whether data should be made available free of charge or for a nominal fee were discussed; a caveat and interpretation guidance on how to use these documents will be helpful in preventing misuse and misunderstandings.

WHO will continue to publish Signals in the WHO Pharmaceuticals Newsletter. National Pharmacovigilance Centres will have first access to the Signals, prior to publishing. A working group will prepare a position paper, on data access; the paper will draw upon the 1991 WHA resolution on exchange of information among Member States and the ICDRA resolutions on public access to data.

### **Strategic (PV) methodological choices and innovations to address current needs and priorities in disease control programmes**

The characteristics and value of Spontaneous reporting, Cohort Event Monitoring (CEM), targeted spontaneous reporting, Pregnancy registers, Patient records and Observational studies were discussed. The practical Pharmacovigilance challenge is to consider relevant methods that support a prescriber in making therapeutic decisions. Pharmacovigilance tools are present. However these need to be integrated to address the needs of policy makers and clinicians. This is a complex topic which will need committee guidelines on tools and interpretation of results.

### **Data management tools: Paniflow and CemFlow**

*PaniFlow* was originally built with Swissmedic collaboration for managing AE data related to Avian flu H5N1, but was later also taken up by WHO for the H1N1. The tool has a built in 'search and statistics'. Proposed next steps will be to integrate Swissmedic and international PaniFlow versions and finalize ongoing translations, evaluate the system and make appropriate corrections.

In CEM, a group of patients are monitored while treated with a specific medicine or group of medicines. *CemFlow* is the data management tool for CEM. All events in a control period before and during treatment are recorded. CEM terminology has been developed to collect and code these events. This tool is considerably versatile because of the potential for automated search and stratification. The next steps include pregnancy data entry, export tool to Excel format, extraction of ICSRs on E2B format as well as providing technological solutions for countries with poor internet connectivity.

### **Guidelines for consumer reporting of adverse drug reactions and adverse events due to medicines**

The Committee reviewed a draft guideline for setting up a consumer reporting system. Various suggestions were made, to replace 'consumer reporting' in the title: Public reporting; reporting by medicine users; etc. The Committee discussed content issues: additional information that could be requested (eg, source of medicines, unexpected benefits), barriers to reporting, reporting methods (by telephone, Internet, phone/text messages); seriousness of AEs; central versus de-central reporting systems; how to

stimulate reporting; data processing and data management (identification of duplicate reports; coding, storage and analysis of reports); interactions with other parties (industry, media, professional organizations, medicines regulatory agencies and others) There are several reasons for encouraging public to report ADRs, including: under-reporting by health care providers (HCP), new ADRs are detected (and probably earlier if public would report), possible to get ADR information on non-prescription products etc.

The Committee will review the document further and provide comments to the lead person of the relevant work package in the Medicines Monitoring Project (<http://www.monitoringmedicines.org/>)

### **Review of safety of specific medicines: AS-AQ**

A review of AE reports from Africa involving amodiaquine, artesunate or the combination as suspected drug in the WHO/UMC concludes that there is little evidence of ongoing major problems in Africa with the combination product. However, it is not known whether there are reactions not being reported or if reports are being submitted with delay to the UMC. There are reports implicating combination products in children but those implicating amodiaquine alone and artesunate alone still have to be analysed. Many reports seem to demonstrate typical extrapyramidal reactions and movement disorders. There may be pharmacogenetic reasons and new information has been published about drug-drug interactions with amodiaquine. There is an observed strong correlation of movement disorder AEs with these products in the reports to UMC. But current SPCs do not mention observed side effects like dystonia and extrapyramidal reactions and how HCP should manage them when they occur.

A recent survey of antimalarial drugs undertaken by the United States Pharmacopoeia reported sizeable rates of failure in tests of quality of antimalarial drugs in three African countries. A global review of various investigations being undertaken or available literature would be useful. The WHO secretariat will convene a meeting with various stakeholders, including industry, to review current scientific evidence and assess next steps.

### **Collaborations with other WHO Programmes**

#### *WHO Vaccines programme*

A global network for post-marketing surveillance (PMS) of newly pre-qualified vaccines aims to support PMS of newly prequalified vaccines with a standardized approach in adverse events (AE) reports submissions, tools development and assessments. With the Uppsala Monitoring Centre (UMC) playing a pivotal role, 12 member countries are currently involved in this project, with the latest member being China. The expected output is an improvement of reporting, causality assessment, and data analysis at the

global level using tools developed at the UMC. In a group meeting held earlier in 2009, a core set of minimum data for collecting AEFI and denominator data were proposed. Vaccine specific modifications have been made to fields within UMC database that were previously missing.

#### *Pandemic H1N1 vaccine safety*

There are more than 30 pandemic vaccines licensed globally and over 350 M doses distributed with over 300 M doses administered to date. Due to the pandemic situation, with only one identified antigen, there was an underestimation of product variability and diverse preparations, variation of use and safety profiles. Active surveillance for adverse events following immunization (AEFI) with accurate utilization figures may be of value to the programme. The AEFI reports from countries who received WHO donated vaccines are not proportional as expected. Officially, reporting serious AEFI has been made a precondition to receiving donations.

PaniFlow, the AEFI data management tool during the pandemic, was made available to 95 countries but only 9 countries have expressed interest. There was hesitation to embrace a new software. In part, there was wrong perception that this software was to provide a one time data entry system rather than capacity building for data management.

#### *HIV/AIDS programme – PV for antiretroviral medicines (ARVs)*

The ARV Pharmacovigilance Project is being implemented by WHO in collaboration with the UMC. The Project has four key components: 1) development of common tools and definitions; 2) national capacity building; 3) research agenda; and 4) coordination.

The common tools and definitions developed include practical handbook on PV, coded definitions, reporting tools, peer reviewed clinical management guidelines, and ARV PV training modules. Some of the new research agenda are studies on d4T toxicity, the safety of NNRTIs in women of childbearing age, tenofovir safety in patient with unmonitored renal status and follow up among patients, like pregnant women, in resource limited settings. Constructive engagement with Pharma industry, assisting countries with treatment guidelines, and helping them meet GFATM requirements with inclusion of PV systems for round 10 proposal submissions are points for immediate and future considerations.

#### *Tuberculosis and key features relating to PV*

Some of the drugs used in the treatment of TB are associated with very severe ADRs. These ADRs affect adherence to treatment. Two aspects of the TB control which are making PV more relevant today are scale up in the use of drugs for patients with drug-resistant TB and/or with HIV associated TB. The likelihood of drug toxicity from such regimens is increased. As yet there is no specific mention of PV in the Stop TB Strategy and no WHO handbook dedicated to PV in TB programmes. The immediate work plan

includes literature review, collaborative work with UMC for analysis of TB drug database, developing interim advice on Global Fund application, creating a handbook on PV for TB by September 2010, and briefing WHO representatives.

#### *Chagas disease*

WHO established a procurement and global distribution system for nifurtimox and benznidazole in 2009 and there is a need for PV to assure the safety of these medicines. WHO has initiated a project to collate and review all available information, to characterize adverse effects associated with nifurtimox and benznidazole. An algorithm was established with well-defined inclusion and exclusion criteria to search and select scientific publications on Chagas disease treatment; to conduct literature review on adverse effects associated with nifurtimox and benznidazole in the treatment of Chagas disease; to summarize available information as a review paper in an indexed journal. Key findings will be presented at the Annual Meeting of National PV Centres in November 2010.

#### *Traditional Medicines*

The International Regulatory Cooperation for Herbal Medicines (IRCH) meeting is held annually with working groups tasked to address various issues, including, vigilance of herbal medicines adulteration of products, quality of herbal materials and products, evidence for health based claims, consumer and practitioner awareness and education. Maintaining monographs, regulatory information database and meetings are the main activities. A WHO technical review document on clinical studies on traditional medicines is being developed. Identified top priority area of regulatory concern is the interaction of herbal medicines with other medicines for which a proposed new WHO technical document is in progress. Collaboration should be strengthened between PV programme at WHO HQ, UMC and the new traditional medicine programme on the vigilance of herbal medicines, with a view to information sharing, planning, and to avoid duplication of work

#### *WHO Family of International Classifications*

WHO Family of International Classifications includes the International Classification of Diseases (ICD), International Classification of Functioning, Disability and Health (ICF) and International Classification of Health Interventions (ICHI); the International Classification of Traditional Medicine (ICTM) is being developed. There are many arguments in favor of creating ICTM. Traditional medicines (TM) are used around the world but the current information systems in TM are not adequate. While local knowledge exists, there is a gap in international harmonization. The collaboration at the international level includes linking the TM classifications with a global norms and standards development activity, ensuring equal access to global public goods and developing a linguistic platform for adequate representation of TM concepts in different cultures and languages. Historically some work has been done. In the WPRO region, the WHO international standard terminology of traditional medicines (IST) was initiated about 4 years ago. ICTM will be all inclusive, and will attempt to accommodate all the terms and languages from

countries using TM into one system. The project is In progress, in collaboration with TRM, the Essential Medicines Programme in WHO, and the UMC, with a projected time frame of 3.5 years.

## **Updates**

### *Developing a set of indicators for pharmacovigilance*

Indicators are broadly classified into 4 groups: indicators on background information in the country, structural indicators, process indicators and outcome/impact indicators. 'Candidate indicators' within these groups have been classified as core, complementary and optional indicators following consultations with national centers, PV experts, and ACSoMP members. With this set of indicators, robust performance evaluation & comparison of level of maturity and self-improvement of centers will be possible.

The Indicator based Performance Assessment Tool (IPAT) has been developed by Management Sciences for Health (MSH). But WHO has not had an opportunity to provide input in developing this tool. ACSoMP will review IPAT, to find areas for developing a common tool.

### *CEM in Nigeria*

CEM was piloted in 6 geopolitical zones, as a method to capture and characterize the safety profile of ACTs, mainly artemether-lumefantrine and artesunate amodiaquine. The main adverse events (AEs) (body weakness and dizziness, loss of appetite, vomiting and abdominal pain) were similar to ADR profile of ACTs reported in literature. Severe AEs were not common. Patients treated with artesunate- amodiaquine had more AEs but had better treatment outcomes. An important observation was that physicians were splitting the dose of artesunate amodiaquine; all data elements were not always reported, leading to poor quality data; The future plan is to complete data analysis, enter data into CemFlow and scale up to reach 10,000 patients in the cohort.

On the question of ethical clearance, it was noted that, like spontaneous reporting, CEM is part of the routine PV monitoring of patients for adverse events and reactions and should therefore require no special ethical clearance. Patients should be informed but since it is impractical to get individual patient consent in a CEM programme, other ways of dealing with informed patient consent need to be followed eg the 'opt out principle'. The CIOMS document on International Ethical Guidelines for Epidemiological Studies (last updated in 2009) notes that requirement of a signed consent form may be waived if there is no more than minimal risk than that attached to routine medical or psychological examination.

The Committee will develop a guidance paper about obtaining ethical clearance in CEM as well as a clear guidance on the combined use of CEM and spontaneous reporting.



### *Medicines Monitoring project (FP7)*

This is a EC-funded project with 11 partners/beneficiaries and managed by UMC and WHO. This project will run for 3.5 years with a budget of (approximately) 2 million Euros. The project officially started in 1 Sept 2009.

A kick-off meeting was held for the partner beneficiaries in March 2010 in Uppsala. There are a number of work packages within the project: supporting ADR reporting by consumers; identifying problems related to irrational use of medicines and medication errors; broader use of pharmacovigilance data; developing new methods and tools to support safety monitoring of medicines; and develop learning tools and information database to support healthcare workers in the management of AEs in HIV/AIDS patients.

A data mining method for detecting drug dependence and the CemFlow version 2.0 are two of the project deliverables that have been completed to date. More information can be found on the project website [www.monitoringmedicines.org](http://www.monitoringmedicines.org)

### **HOT TOPICS**

The Committee agreed that the purpose of a session on hot topics is a good tradition to uphold and part of ACSoMP procedures, adding value to discussions and debates, and form part of developing the PV toolkit to address these issues. Many of these topics are of regulatory concern, and often involve discussions of complex signals, problems of benefit risk assessment, and of public and political concerns. At the seventh meeting, there were 4 broad items under this session: Medicines of current interest, role of PV in identifying counterfeit products, PV in Africa, PV in India.

*Medicines of current interest:* Typically, the Committee should select the topics from current issues and provide advice proactively, for example, regarding EML, drugs with important /serious AE, of public health consequence. The topics should be relevant to WHO's work, or topics referred from countries. But the role of the Committee will be to provide a summary of its evaluation of evidence, not a recommendation. and not a decision or criticism of an action made by some countries. Some examples of medicines of current interest include the following:

- Codeine containing OTC analgesics causing addiction and have led to access restriction and warning information to patients
- Sibutramine, with cardiovascular risk, led to product withdrawal
- Varenicline for smoking cessation, but with drug induced psychiatric disorders, offering a communication challenge.
- Rosiglitazone and CVS safety issue was placed under close review

National PV centres can request the Committee directly to provide advice on ongoing specific issues of global importance. The WHO secretariat will develop a guidance document for national centres, on procedures for initiating requests to ACSoMP.

*Strategies for combating counterfeit medicines and illicit medicines market: the role of PV:* It was argued that in the absence of any other system, PV centres should receive and investigate reports related to counterfeit medicines. A few terms will need to be added in the ADR reporting forms, in order to capture information on counterfeit products. The Medical Products Agency in Sweden (responsible for PV in the country) undertook a campaign in 2008, which raised public awareness about counterfeit issues. It is conceivable that reports from consumers could help reveal the presence of counterfeit products in the market. But there will be challenges, for example, the difficulty in ascertaining if the observed lack of effect is due to a counterfeit product or due to a lack of clinical effectiveness. Guidance for national centres will be of value and data mining protocols could help. The Committee agreed that the PV system has a role to play in dealing with product quality issues, and that tools should be developed with a view to collecting information on poor quality and substandard products.

*PV in Africa: Landscape assessment, needs evaluation*

An assessment of the true state of PV within Africa was conducted through a questionnaire survey with subsequent telephone interviews. The results reveal that very few PV systems exist and that they are not strong. The common need appears to be related to training, with a specific request for help with either establishing or re-starting a dormant PV programme. There are 14 countries with no known PV activity. Seven countries have specifically requested for IT support, four have requested twinning arrangements. There is a need for targeted intervention by the newly established UMC-Africa and the WHO Collaborating Centre for Advocacy and Training in PV, based at the University of Ghana Medical School. The ultimate aim is to have a harmonized PV system for various public health programmes. West Africa Health Organization (WAHO) is initiating a PV agenda with 17 countries. One focus of this initiative is using PV systems to combat counterfeits.

ACSoMP will communicate the results of this landscape assessment and the needs of Africa to the Global Fund with the objective of exploring further collaborations.

*Pharmacovigilance in India*

A brief history of the Indian PV system was presented. India joined the WHO-ADR monitoring programme in 1997 and the National PV programme was established through World Bank (WB) funding in 2004. In 2010, a new structure from the Ministry of Health and Family Welfare and Central Drugs Standards Control Organisation has led to the formation of several peripheral PV centers with reporting structures, with the involvement of academic institutions and formation of 3 panels : signal review; core training; and quality review panels. There will also be an ADR watch-list, based on the the following criteria: monitoring restrictions and withdrawals elsewhere in the world; AEs published in WHO Newsletter; diseases of public health importance; monitoring epidemics/pandemics; signals generated from spontaneous reports; and reports from the media. ACSoMP was requested for inputs to the PV activities in India.