

**Recommendations of fourth meeting of the WHO Advisory Committee
on Safety of Medicinal Products
26 and 27 February 2007**

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its fourth meeting in February 2007. Constituted to provide advice on pharmacovigilance policy, and issues related to the safety and effectiveness of medicinal products, the following is a summary of the minutes.

The WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre)

The financial situation in the UMC has stabilized. The WHO database (Vigibase) is updated on a daily basis. During the year a project was undertaken to eliminate duplicate reports and so-called 'foreign' reports (reports received by a national centre from another country), which can also constitute duplicate reports in the WHO database. Almost 4 million cases are stored in Vigibase. The search tool VigiSearch was slightly modified to allow for a better retrieval of drug names and better performance in complex queries. A new tool was developed that allows for a semi-automatic data entry into WHO Drug Dictionary. This tool significantly decreases the time needed for data entry, while still allowing for manual quality control.

In co-operation with the MedDRA MSSO, links from WHO-ART to MedDRA have been created. A bridge has been created between MedDRA and WHO-ART.

The links with IMS Health have been strengthened and broadened. A long-term project to develop and produce methods and software for analysing IMS's longitudinal patient records is now in the pilot phase.

WHO Strategy for Medicine Safety

A strategy for safety of medicines in WHO is under preparation. This is intended to be used for assisting in fund raising. A plan is needed for capacity building in countries. The strategy outlines the initiatives which WHO Headquarters intends to undertake in the area of strengthening the safety of medicines during the next 5 years. It will be complementary to the 4-year plan of the Collaborating Centre for International Drug Monitoring and the strategic plans of the member countries participating in the Programme

It was agreed that a small group should be convened to take this forward.

Promoting Safety of Medicines in Children

The manuscript on monitoring the safety of medicines in children was discussed. The objective was to finalize the text for publication before the meeting on paediatric medicines in July. Following implementation of legislation applicable across the EU with respect to medicinal products for paediatric use, the EMEA has recently published guidelines on the conduct of pharmacovigilance in paediatric populations. This legislation and guidelines should be considered in reviewing the text, but the WHO manuscript is broader in its concept. However, information on the regulatory aspects of the text need to be expanded and there is a need for a section on medication errors. It was

agreed that several members of the Committee should provide input to the manuscript by the middle of April.

Training Programmes for Pharmacovigilance

A briefing on the courses, which had been conducted by WHO was given.

1. Intensive follow-up course in pharmacovigilance for African countries introducing artemisinin-based combination therapies (ACTs) 5-7 February, Zambia. Several problems were identified: spontaneous reporting had not been very successful over the 4 year period since the first training course; few pharmacovigilance centres had been set up, few personnel had been appointed and there was a lack of funding. Outcome: there was a clearer understanding of Vigiflow as a mechanism for providing a locally owned database for spontaneous reports but the problem of internet connection remains. A core protocol for cohort event monitoring (CEM) was developed. An adaptation of Vigiflow for use with CEM was requested. This will be taken forward at the forthcoming training course for CEM in Ghana at the end of June.
2. A basic pharmacovigilance course for French-speaking countries was held in Morocco from 12 - 23 February 2007. This was hosted by the Moroccan Pharmacovigilance Centre, with support from WHO and USAID.
3. A training course introducing pharmacovigilance into HIV/AIDS programmes was held in Barbados from 11-16 September 2006. An important aspect of this training course was a day devoted to discussion on the clinical management of HIV/AIDS.
4. A national training course for pharmacovigilance was held in Botswana from 11-15 September 2006. The advantage of teaching in one specific country was that the local problems as possible barriers to reporting could be discussed and possible solutions considered.

Social Marketing of Medicine Safety

The manuscript on the Social Marketing of Medicine safety was discussed. This script is intended to:

- outline the strategic directions for medicine safety within the WHO Programme in the next decades;
- to develop a strategy for the promotion of medicine safety around the world through a network of dedicated advocates, such as the WHO partners and national centres and
- to provide suggestions on broad tactics, creative ideas and materials which can be used as the basis for promoting drug safety to a wide range of audiences.

It was agreed that the text should be discussed and promoted during the Annual meetings of national centres.

Global Networking

A demonstration was made on the use of Mednet, the WHO site for linking partners and projects in WHO programmes. MedNet is hosting over 20 scientific communities. Documents can be shared and revised more easily than by using email. Shared networks are available with security and collaborative e-workspaces. Different countries or subjects can be associated. Membership of communities is controlled by the community. A pharmacovigilance community could be created. Exchange, share and communicate

are the essentials. It was agreed that Vigimed could be elaborated using this system. A community for ACSoMP should be set up.

Vaccine collaboration

Recommendations from a global consultation were presented. The aim is to get all adverse events following immunization (AEFIs) to the UMC, including from units outside the national pharmacovigilance centres. A person to act as a vaccine focal point is to be recruited to UMC. AEFI programmes should have access to Vigiflow. Improved advocacy and communication is necessary. The ATC classification system for vaccines needs to be revised. A pilot project in several countries for post marketing surveillance to improve reporting and signalling is to be developed. There is a working group on safety monitoring needs in an emergency e.g. pandemic flu. A rapid alert system is needed for vaccines in a pandemic. Potential coordination with QSM for antivirals during a pandemic is to be discussed. It is planned that a new reporting chain will be set up for use in a pandemic aimed at getting timely information.

Causality assessment

The discussion was introduced by outlining the history of development of the definitions. They were never meant to function as an algorithm. The system is used by over 70% of National Centres and needs to be refined for general use as such. There has been no validation of the system. The FDA does not use a single system, but does use the principles at times. Different situations need different approaches. For example, drug-induced liver injury has special criteria prepared by an interest group. The hepatologists' criteria were not designed for regulatory work, but to assist clinical understanding. There are situations where the 'WHO' criteria do not fit well. The primary purpose is to get a clear understanding of the report. When looking at groups of reports, other means need to be considered to establish causality. Some points in the definitions are not exclusive requirements. Reporters often want to know if an event is drug-related. It was pointed out that the initial part of the assessment of a report is a relationship assessment and that this needs to be done using criteria that are as objective as possible. Causality is better established later on clusters of events and looking at other factors such as pharmacology and epidemiology. The general opinion was that the 'WHO method' was valuable and should be retained and improved. It was suggested that ISoP would be a good forum for further discussion. CIOMS may also wish to discuss the issue.

Methodology for evidence of the need for pharmacovigilance

A protocol for collection of data on incidence in selected hospital departments has been developed. This could be used as a baseline for comparisons over several years. It could be undertaken by interns. A pilot project in a few hospitals will be undertaken and the results published at the Annual meeting of National Centres later this year.

Patient Safety pilot project

This is a collaborative project between the World Alliance for Patient Safety and medicine safety and should build upon the success of the WHO Programme for International Drug Monitoring. The problem, the approach and techniques were outlined. An advocacy role is important. One objective is to determine whether National Centres

can collect, identify and analyse reports with medication error. It is hoped that the UMC can analyse the pooled data. The future role of National Centres will be assessed. A tool kit needs to be developed. Early experience of the project in Morocco was described. The importance of assessing the preventability of adverse reactions was stressed. Cases already present in the WHO database will be analysed by the end of year. It was suggested that 'near misses' may not be identified and that these could provide valuable information. Those involved in rational use should be linked to this programme.

Specific Medicines

The Expert Committee on the Use and Selection of Essential Medicines have requested input from ACSoMP on questions on safety in relation to applications for listing on the EML. These need to be of a standard that can be posted on the website and should not contain information that cannot be verified. It is desirable that the assessments should contain:

- Critical review of submissions re safety
- Assessment of comparative safety
- Less emphasis on SPCs
- The use of the WHO database is seen as important.

In the future there will be an emphasis on safety of medicines in children. There is also a need to set up a mechanism for urgent additions and deletions to the EML on the grounds of safety.

Safety assessments and recommendations for the current applications for the EML were as follows:

Cefalexin

It was agreed that cefaloxin was acceptable in terms of safety.

Recommendation: Appropriate on the grounds of safety for inclusion in EML

Cefazolin

There are concerns over the number of reports of anaphylaxis associated with cefazolin

Recommendation: Include in EML with the proviso that it should be used only where rapid resuscitation can be undertaken in cases of anaphylaxis.

Emtricitabine

The recognized adverse reactions include lactic acidosis (usually associated with hepatic steatosis), fat redistribution, exacerbation of hepatitis B (HBV) in patients co-infected with HBV and HIV after emtricitabine withdrawal, immune reconstitution syndrome and osteonecrosis.

Recommendation: It is suggested that, should emtricitabine be included on the EML, the following points should be highlighted and addressed:

- Safety/efficacy concerns in patients with hepatitis B infection should be highlighted.
- The risks of lactic acidosis/mitochondrial toxicity should be mentioned as a class effect.

- The issue of osteonecrosis should be highlighted with specific advice to patients to seek medical advice if they experience joint stiffness, pain etc.

Emtricitabine + tenofovir

The main safety concern for tenofovir DF is renal toxicity, including renal failure, proximal tubulopathy (including Fanconi Syndrome), nephritis (including acute interstitial nephritis) and nephrogenic diabetes insipidus.

Recommendation: It is suggested that should emtricitabine/tenofovir DF be included in the EML, the following points should be highlighted and addressed:

- Recommendations for monitoring of renal function should be explicit and specified (including information in cases of patients at risk of or with pre-existing renal disease, i.e. elderly patients)
- Safety/efficacy concerns in patients with liver dysfunction, chronic hepatitis and in context of concomitant use with other antiretrovirals should be highlighted.

Fluoxetine

The adverse effect profile is well known and adequately described. Fluoxetine is better tolerated than TCAs considered as a group and is better tolerated in comparison with individual ADs, in particular amitriptyline. The relationship between SSRIs and suicide has been the focus for several investigations.

Recommendation:

Appropriate on the grounds of safety for inclusion in the EML.

Paromomycin

More data including from different settings like AIDS, paediatric populations and elderly people users is very important. It is desirable to have Phase IV studies to identify new safety and effectiveness issues [e.g., drug-drug and drug-food interactions] in real world situations related with the new indication and new settings.

Recommendation:

It is premature to include paromomycin in the EML. There is insufficient evidence of its safety in the treatment of visceral leishmaniasis.

Ribavirin

Medicine has not been evaluated in children and elderly. Precautions The drug has been shown to be teratogenic in animal at doses lower than therapeutic dose. Drug accumulates.

Recommendation:

The application is for ribavirin for treatment. There should be some comments / statement on use of ribavirin in post exposure prophylaxis. The drug is likely to be used / misused for prophylaxis where the benefit / risk could be quite different from when used for treatment.

Simvastatin

Increased risk of rhabdomyolysis with acute renal failure is associated with the use of simvastatin. As reversible increase in levels of serum aminotransferases may occur, liver function of the patient must be assessed before the start of the treatment with simvastatin.

Recommendation:

Simvastatin may be added to the complementary list of the EML. There needs to be careful monitoring.

Sumatriptan

Adverse reactions are common but the great majority are minor and evanescent. Although reactions are common, use of sumatriptan with the appropriate precautions is safe. There has been widespread use with few convincing serious reactions.

Recommendation: From the safety point of view, sumatriptan 50mg tablets can be recommended for inclusion in the EML.

Tenofovir

Recognized adverse reactions include lactic acidosis (usually associated with hepatic steatosis), fat redistribution, exacerbation of hepatitis B (HBV) in patients co-infected with HBV and HIV after tenofovir withdrawal, immune reconstitution syndrome and osteonecrosis.

Recommendation:

Tenofovir should initially be placed on the “Complementary List” in view of concerns regarding the feasibility of renal monitoring in developing environments.

Amodiaquine/artesunate

There have been reports on adverse events associated with the use of artesunate amodiaquine in several African countries, most reliably reported in Ghana. The review of these reactions suggested that once daily exposure to artesunate 200mg/amodiaquine 600mg was common to all events, making it plausible that these effects are dose dependent.

Recommendation:

It is premature to include amodiaquine-artesunate in the EML. An appropriate risk-management plan must be drawn up to address the dosage issues before contemplating inclusion of amodiaquine-artesunate in the EML.

Levamisole

In 1994-2003, 632 cases of imidazoles-induced demyelinating encephalopathy were reported in the domestic literature in China, of which 543 cases were levamisole induced. The causality of levamisole and demyelinating encephalopathy has been investigated and demonstrated by 6 pharmacoepidemiological studies.

The WHO global database contains 81 case reports of central nervous system disorder.

Recommendation: levamisole should be deleted from the EML because of the availability of safer products. However if resistance becomes a problem with the alternatives, it could be used as second line treatment.

Other specific medicines

Thalidomide

Foetal abnormalities with thalidomide are still being reported. The situation in Brazil is complicated by about 30 indications for use, mainly off-label and the difficulty in controlling its use. Clear messages about risk management and minimization are needed.

The Committee agreed that pressure should be put on governments to address this issue. If thalidomide is licensed adequate control measures must be in place.

Generic reporting form

A discussion took place on the pros and cons of developing a generic reporting form. The content and design need to be considered. Forms often need to be adapted to local situations. Another complication is the expanding nature of pharmacovigilance that requires new types of data e.g. medication error. Over the years all countries participating in the WHO Programme have developed their own forms to suit their own needs in spite of the existence of other models. Suggestion: that guidelines for designing a form be developed. Design and communication need to be included.

Any other matters

New Zealand Intensive Medicines Monitoring Programme (IMMP)

General concern was expressed about the threat to the future of the IMMP since the value of the methodology was considered important to worldwide pharmacovigilance.