Recommendations of the third meeting of the
WHO Advisory Committee on Safety of Medicinal Products
5-7 December 2005

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), constituted to provide advice on pharmacovigilance policy, and issues related to the safety and effectiveness of medicinal products, held its third meeting in December 2005. The following is a summary of the minutes of the meeting.

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

Two current important issues of *the* UMC are: (1) sustainability and (2) the funding of resources. Ninety per cent of the budget of *the* UMC is income from sales of UMC commercial products. *The* UMC runs the programme for least developed nations with the resources generated by marketing UMC products to well-developed, research-based industries. Concern was raised that *the* UMC is becoming too commercial in its operations and it was strongly suggested that a better budget allocation be obtained at the highest level of WHO.

Pharmacovigilance for antiretrovirals (ARVs)

ACSoMP has been asked to propose recommendations for safety systems within the HIV/AIDS programme and design specific studies with an action plan. This is a follow up of discussions on the need for pharmacovigilance in public health programmes, at the Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring. Encouragement is sought on how to collect adverse drug reaction (ADR) reports. Some sites are looking at toxicities and the consequences of combinations. Issues around guidelines for use of ARVs in paediatrics, use of drugs in pregnancy (registers) and in patients with co-morbidities were also raised.

Action points:

- A small working group will deliver a pharmacovigilance action plan for a pilot project in a few sites in Africa, to work with the WHO HIV/AIDS programme and strengthen spontaneous ADR reporting, monitoring of specific toxicities and using a pregnancy register. The proposal will also include a suggested budget and will be prepared by the end of January 2006, at which stage the HIV/AIDS programme will be consulted for their input.
- The HIV/AIDS programme will be asked to help identify individuals within the target countries in executing the approved version of the action plan. In writing the proposal, the working group would need access to the following information: pregnancy monitoring programme, other drugs being used in the HIV/AIDS programme.
- The methodology for monitoring pregnancy should be as in other WHO programmes, to avoid confusion in the field.
- The HIV/AIDS programme should be supplied with the new publication in the Safety Monitoring of Medicines series, '*The safety of medicines in public health programmes: pharmacovigilance an essential tool*'.

Patient Safety initiatives

1) Patient safety pilot project
ACSoMP members were presented with a four-year pilot project to incorporate the collection of medication errors into pharmacovigilance programmes. ACSoMP strongly supported this initiative but expressed concern that this was an ambitious project that would require additional resources.

Action points:
ACSoMP requested that the following principles be applied in furthering the project:

- Activities should serve to strengthen the principle objective of the national pharmacovigilance centres, which is the promotion of the science-based practice of pharmacovigilance.
- It should strengthen the capacity and self-sufficiency of the National Centres (financial sustainability in the short and long term).
- The principal focus should be on developing countries.
- There must be a clear cut WHO/QSM and UMC leadership on this programme.
- There must be a clear system for intelligence sharing and the translation of lessons learnt into policy.

2) WHO draft guidelines for adverse event reporting and learning systems
ACSoMP noted the draft manuscript recently published by the Patient Safety department in WHO. This had been issued without the normal consultative process within WHO. ACSoMP members expressed their disappointment that no mention was made of the work done by WHO/QSM and *the* UMC in the areas of pharmacovigilance and drug safety. They suggested that the department of Patient Safety should seriously consider including a section on the work of WHO/QSM and *the* UMC into this draft. Furthermore, they requested that their comments would be taken into account in revising this manuscript.

Action point:
- A section describing the work of *the* UMC should be drafted for immediate insertion into the draft document. ACSoMP members will provide extensive comments on the manuscript by end of January.

3) Advocacy
A draft of a pharmacovigilance advocacy paper was discussed. The paper outlines the strategic directions for medicine safety and the WHO Programme for International Drug Monitoring in the next few decades. It suggests developing 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.

Action points:
- To initiate discussions on pharmacovigilance at the political level and at WHO higher offices; to submit a proposal to the World Alliance for Patient Safety to integrate pharmacovigilance into the Alliance; to suggest yearly pharmacovigilance themes targeted at specific population groups; to introduce the concept of a worldwide Pharmacovigilance day.
- WHO may need to have some high level endorsements from ministries of health so that pharmacovigilance centres can move forward in promoting safety of medicines and find ways to integrate pharmacovigilance into the health policy of the country.

- A paper will be prepared and submitted to the World Alliance for Patient Safety.

WHO International Classification and Taxonomy

The International Classification of Diseases (ICD) team, from the WHO Family of International Classifications presented their work to ACSoMP members and showed how it related to pharmacovigilance. The ICD-11 is under preparation and the department needs the input of experts in the area of safety monitoring to review its section on *Drugs, medicaments and biological substances causing adverse effects in therapeutic use*. The team highlighted the need to harmonize terminologies throughout WHO.

Action point:
- WHO/QSM and *the* UMC will collaborate with the WHO Family of International Classifications.

Safety of medicines in children
ACSoMP has recommended that WHO address the issue of safety of medicines in children and that a guideline be prepared. The actions taken so far include approaching Karolinska Institute for preparing the first draft manuscript on the safety of medicines in children This project is currently in the development phase. A document prepared by one of ACSoMP members was presented. ACSoMP decided that the document needs to be strengthened with additional input.

Action point:
- Members to convey any comments on the presented document by the end of the year. The revised document will be an internal document to guide National Centres and can be posted in the new UMC website under the section on *Practical Pharmacovigilance*.

Report on kava
In the previous meeting, ACSoMP had commissioned an investigation on reports of hepatotoxicity with kava. The resulting report contains extensive analysis of various available literature (case reports, clinical trials, etc). The conclusions and recommendations were presented to ACSoMP.

Action points:
- ACSoMP to endorse this research and use the inquiry team's recommendations in drafting a WHO position paper. Drug regulatory authorities should be consulted for their views on the recommendations, for additional input to the WHO position paper. More time is needed for ACSoMP members to review specific documents used in the investigation; comments from members of ACSoMP should be sent to the authors by the end of January 2006; a revised document will be produced by the end of March, to be followed by six weeks of consultations and a final teleconference in mid-June 2006.

Safety of specific products

Oseltamivir
The WHO background work on the efficacy and safety of antiviral drugs during influenza pandemics was presented. As a consequence of the work started in 2002 and carried out by 30 experts, a WHO guideline was produced. However, data for 2004 is not included in the guideline. In August 2005, the pharmaceutical company Roche donated three million treatment courses of the medicine oseltamivir

towards a WHO international antiviral stockpile. It is necessary that the efficacy and safety of this medicine is adequately documented, both prior to, and during the possible flu pandemic.

Action points:

- Roche should be asked by WHO to assist with the development of a system of active surveillance for countries using oseltamivir in mass treatment during influenza pandemics. Particular attention should be given to pregnant women taking this drug.
- Reports and documents should be reviewed with the addition of a section on intensive monitoring of at least 10 000 patients as part of the pharmacovigilance assessment.
- Issues of counterfeit products should also be considered. The company should be asked to take part in the intensive monitoring programme, as part of the product stewardship.

Amodiaquine/artesunate

Ghana has switched to using amodiaquine and artesunate combinations in the treatment of malaria in the light of resistance to chloroquine and sulfadoxine/pyrimethamine. Reports of ADRs to this combination are emerging from Ghana and also verbal reports from Nigeria and Sierra Leone. These reports include dystonic reactions. A letter to The Lancet was drafted describing the situation. ACSoMP wished to have more information on the reports.

Action point:

- The reports should be investigated further. Risk minimization plans should be put in place so that situations such as the present crisis do not have a negative impact on the malaria programme.

Moxifloxacin

There has been some discussion on E-drug (electronic discussion group) about introducing moxifloxacin as a suggested treatment for resistant tuberculosis (TB) in the directly observed treatment short-course-plus (DOTS-plus) programme since the drug could potentially lower the treatment duration to four months. There is lack of data on the long-term safety with moxifloxacin. There are 4200 case reports in the WHO (UMC) database from 30 countries. These ADR reports are probably from short-term use. There are concerns that the drug is expensive, and that the drug on long-term use can lead to resistance of other bacteria. However, ADR data from short-term use should not be extrapolated to reflect effects from long-term use. Additionally, there is a need to make a statement about contraindications for use in pregnancy and in children.

Action point:

- Information must be sought from available clinical trials on the efficacy and safety from long-term use of moxifloxacin before any risk/benefit recommendations can be made.

Tenofovir and emtricitabine

Information was presented that a new combination of these two drugs is being reviewed. The concerns include the need to have renal effects in the safety profile. This drug is being promoted as first-line treatment in the HIV/AIDS programme; hence, this safety concern.

Action point:

- The Advisory Committee will be kept informed of further developments.

Levamisole
This medicine was discussed at the Twenty-eighth Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring. Concerns were raised by China that leukoencephalopathy followed the use of levamisole. This had resulted in the removal of this medicine from the national formulary by the Chinese government. This drug is in the WHO Model Formulary; but since many countries have withdrawn levamisole, the overwhelming data on toxicity should be communicated to the Essential Medicines Programme. However, it was noted that the WHO Expert Committee on Essential Medicines will not meet until 2007.

Action point:

- A member country (i.e. China) will communicate to the WHO Essential Medicines Programme about this new finding and apply for a formal de-listing of the drug from the Essential Medicines List (EML). The information regarding levamisole-induced leukoencephalopathy will be sent out to WHO Member States as a WHO Information Note. For those years when the Expert Committee do not meet, the WHO Essential Medicines Programme should introduce a process of interim consultation for the rapid suspension and de-listing of medicines from the EML.