REPORT OF FOLLOW-UP CONSULTANTS' TRAINING COURSE ON PHARMACOVIGILANCE

ACCRA 16 - 19 JUNE 2008

Executive summary
Fourteen representatives from nine countries met in Accra, Ghana to review and develop skills in the practice of pharmacovigilance. The objective was to train a pool of expert pharmacovigilantes to be competent in providing consultancy services on the establishment and effective operation of pharmacovigilance systems in public health programmes in Africa. This is particularly important for the assessment of medicine safety data particularly from new medicine being introduced in public health programmes. Concerted efforts should therefore be made to ensure that such systems are available and working. This Consultants' training was a follow-up to a first course held last year in Accra.

Background
Development of pharmacovigilance in resource poor settings of Africa faces several challenges. The biggest challenge is the acute lack of resources and political commitment resulting in a lack of qualified personnel to carry out pharmacovigilance work. Other problems include poor communication facilities, unbridled and uncontrolled supply of medicines and absence of functional national medicine regulatory authorities. Pharmacovigilance is a relatively underdeveloped activity in Africa with only 10 countries having national centers participating fully in the WHO Programme for International Drug Monitoring, a further 13 are associate members. These 23 countries of
which 19 are in sub-Saharan Africa, are at various levels of development and activity and their overall contribution in terms of reports to the global pharmacovigilance database is small. However, there are encouraging developments including the increasing collaboration between pharmacovigilance and public health programmes.

The integration of pharmacovigilance into public health programmes has the advantages that public health programmes are relatively well funded, circumscribed and provide a perfect setting for the treatment and follow-up of patients, most of whom are able to return to the treating practitioner for assessment of any unwanted adverse events. Some of the chemotherapeutic interventions in public health programmes are community-based and it is possible to obtain good quality adverse drug reaction reports from auxiliary health workers as shown by the successful pharmacovigilance programme linked to the intermittent preventive treatment of pregnant women with sulfadoxine-pyrimethamine in Ghana. Collaboration between pharmacovigilance and public health programmes is an opportunity to rationalize the limited resources in poor countries. It is also suggested that Pharmacovigilance Centres in resource limited countries should include intensive cohort event monitoring (CEM) of specific medicines and that, in the absence of a Pharmacovigilance Centre, a CEM programme could be undertaken on medicines that are vital in public health programmes.

**Country presentations**

Presentations were made by all the countries represented - Cameroon, Ghana, Kenya, Mozambique, Nigeria, Sierra Leone, Togo, United Republic of Tanzania and Zambia. They demonstrated the vast differences in the stages of development of pharmacovigilance. Nevertheless great progress had been achieved since the last training course.

In Nigeria a total of 672 reports of ADRs had been forwarded to the database. There is increasing interaction with the public health programmes and a cohort event monitoring study was on the point of starting. There was a discussion around the need for evidence of older medicines used in the African context. Metamizole was cited as an example of
the need for data specific to the populations in order that informed decisions can be made by the policy makers. It was suggested that new medicines should be registered only with a precondition that the pharmaceutical industry commit to conducting phase IV studies.

Much work had been accomplished in Kenya including the production of national ADR reporting guidelines and forms for reporting ADRs. Kenya has become an Associate Member of the Programme for International Drug Monitoring but to date no reports have been submitted to the global database.

In Ghana there has been a steady increase in the number of reports, a technical advisory Committee has been established, there is increasing collaboration with other stakeholders and the form for ADR reporting is now downloadable with plans to make it possible to complete on-line. There has also been an increase in training activities and there are research studies ongoing for antimalarials.

In Togo a national PV centre has been established and Togo has become a full member of the Programme for International Drug Monitoring. Legislation for reporting ADRs has been drafted and implemented. ADR reporting procedures and guidelines have been produced. Training activities have been initiated and preparation for cohort event monitoring is underway.

In Mozambique 201 ADR reports were received in the past year. Over half of these reports were from antimalarials, mainly from the Maputo Province. There has been an emphasis on training for PV across a wide range of stakeholders. Two crises were managed successfully, one in response to serious ADRs following use of albendazole and praziquantel for paediatric parasitosis and one resulting from ineffective anaesthesia because of confusing labelling of magnesium sulfate and lidocaine. There are safety research studies ongoing for antimalarials and antiretrovirals used during pregnancy.

Changes have occurred in the structure of the TFDA in United Republic of Tanzania. It has an established PV system and implementation of ADR monitoring is in the Clinical
trials and pharmacovigilance department. The ADR reporting form has been distributed widely and has been translated into local language—Swahili. Training manuals have been developed and used in training courses. There has been intense collaboration with public health programmes particularly HIV/AIDS, malaria and TB. Preliminary actions towards a cohort event monitoring study for antimalarials are being carried out and one is about to start for antiretrovirals.

Despite efforts by the Pharmacy Board to increase safety monitoring in Sierra Leone there is still no official pharmacovigilance centre in the country. However, regulations for PV have been developed and have been incorporated into the legislation. Also drug safety has been incorporated into the curricula of pharmacy students and that for medical students is pending. As counterfeit and substandard drugs are seen as a huge problem in the country, spontaneous reporting is being promoted as a tool for reporting suspected therapeutic failures and counterfeit or substandard drugs.

Although the formal pharmacovigilance activities are located in the DPM, most of the activities are being carried out in one hospital in Cameroon. This hospital has made great advances in distributing the ADR monitoring form, developing a brochure on a Guide to PV in Cameroon and forging links with public health programmes. It was suggested that some senior staff in the Ministry are invited to WHO for the Technical Briefing Seminar.

New legislation in Zambia, which came into effect in November 2004, provides for post-marketing surveillance and monitoring of ADRs. The original plan was centred on antimalarials but now includes all medicines on the market. A technical Working Group has been established, which has developed reporting forms and manuals for training the trainers. Some 120 ADR/AE reports are received annually and each one is acknowledged. As there is no PV coordinator as yet no causality assessment has been carried out.

**Action points**

- There is a need for more evidence to advise policy makers on the registration status of medicines.
• Pharmacovigilance should be a part of the legislative framework.
• More partners should be engaged to improve spontaneous reporting.
• Pharmacovigilance should be incorporated in the total health care delivery system.
• Links should be forged with rational use of medicines particularly to contribute to minimizing medication errors and there should be a PV representative on Drugs and Therapeutics Committees.
• Consistent feedback and short publications in bulletins should be done whenever possible since this promotes reporting.
• Each report should be acknowledged.

**Spontaneous reporting problem session**

This session highlighted a large number of concerns with spontaneous reporting. These formed four categories:

• Actual reports including design of form, multiplicity of forms, availability of the form and quality of the report.
• Reporters which included motivation of the reporters, ability of reporter to recognize ADRs and to follow-up patients
• PV centre including capacity of the Centre to handle reports and to perform causality assessment, to conduct advocacy campaigns and funding of the centre
• Political support and ownership.

The discussion on how to tackle these problems included a focus on encouraging manufacturers to report by developing a dialogue between the manufacturers, the regulatory bodies and the PV centre. It was agreed that excellent communication skills are needed in PV. To assist in this it was suggested that the PV centre could enlist students in the media and graphic arts to work closely with the PV centre. Public Health programmes are an opportunity for introducing PV but PV can only be sustained if it is linked to the regulatory authority. Advocacy at the highest level was encouraged.

**Action points**

• Automated notification/acknowledgement should be developed as part of Vigiflow
• Publication of case reports in PV/medicine bulletins is encouraged.
• A collaborative relationship should be developed between PV centres/regulatory authorities and the medicine manufacturers.
• Regulatory functions should include PV activities.
• Students should be seen as a useful source of (wo)manpower.

CEM session
The principles of cohort event monitoring were presented. It was agreed that spontaneous reporting is required for long-term follow-up. Pregnancy registers are also very valuable when following exposures in pregnancy. A protocol for a pregnancy register for antimalarials has been finalized and will shortly be piloted in a few countries.
It was also discussed that it was not necessary for all countries to conduct CEM studies. If CEM is to be developed in a country, the budget should reflect the pay scale of the country, the activities planned and the timelines envisaged.

Action points
• Each country should decide whether cohort event monitoring is an option for their settings. If so, the existing CEM manual should be used for guiding principles. The protocol developed by TDR should be posted on PVSF.
• Pregnancy registers should be used when following exposures in pregnancy. The TDR protocol should be accessed.

Medication error session
A presentation on the pilot project to expand the scope of the WHO Programme for International Drug Monitoring was given. The challenge is to extend the role of the National PV Centres to include the collection of information (such as on adverse incidences related to Medication Errors) that may be used to improve patient safety. The objective of the study conducted by the Moroccan pharmacovigilance centre was to determine the ability of the National PV centre to detect medication errors in order to improve reporting. The study found that there was a high percentage of non-assessable reports due to design of the form and/or incomplete information. It was agreed that
feedback to prescribers on medication errors should be increased and there is consensus that a no-blame policy should be implemented in order to improve confidence in reporting.

**Action Points**
- The scope of PV centres should be expanded to place more emphasis on patient safety in order to capture medication errors

**Crisis and communication session**
The crisis and communication session highlighted the importance of maintaining good contact with the media at all times and establishing a strategic planning programme. It was also emphasized that when a crisis occurs it was critical to gather independent and scientific facts of the case. Two cases of crises illustrated these points: one in response to serious ADRs after use of albendazole and praziquantel for paediatric parasitosis, and one resulting from ineffective anaesthesia because of confusing labelling of magnesium sulfate and lidocaine.

**Action points**
- A communication officer should be designated to the PV/regulatory organization.
- Students of media and graphic arts should be enlisted to assist with communication and design issues.
- Specific country recall guidelines should be posted on PVSF
- An assessment should be made of major potential risks, and plans made for preventing their occurrence or for managing scares or crises should they emerge.

**Fundraising session**
Features that are important to potential donors are: milestones, deliverables, monitoring and evaluation, partners in implementation, dissemination of results and sustainability. It is particularly important to consider the influence of delays and inflation rate on deliverables when negotiating with donors. Other issues that need to be considered when developing a proposal are partners at the national and international levels and liaison with
other disease programme activities. A non-exhaustive list of potential donors is as follows: GFATM, BMGF, World Bank, USAID, PEPFAR, PMI, EDCTP and MSH

**Action points**
- Existing funding templates are to be posted on the PVSF network site.

**SOP development**
A protocol itemizing issues to be observed during a mission to a country is needed. The protocol should be adapted to the country situation after a SWOT analysis. It is necessary to have two sets of SOPs: one for the consultant's own country and one for the country to be visited. A first chapter was drafted as annex1. An excel sheet was also shared with the group consisting of sections on personnel, literature, recurrent expenditure, activities and issues to consider.

**Action points**
- A protocol for Standard Operating procedure will be developed from these materials.
- Technical support will be provided to selected countries.

**Indicators**
Specific indicators are needed to capture baseline information. These should be rigorously reviewed and field tested.

**Action points**
- PV indicators should be developed in time for the Annual meeting of National Centres in October 2008.

**Networking**
The PVSF network is active and the new members will be invited to join. This network is considered a very useful source of information.
**Action points**

- Each country should submit a message at least once a month.

**Database issues**

Three sessions were held including hands-on practice with the database and Vigiflow.

Vigibase, which holds more than 4,000,000 individual case safety reports (ICSRs) is the core of the UMC operation. It is a repository for spontaneous reports and is freely available for all member countries in the WHO program for International Drug Monitoring.

Vigisearch is the search interface for VigiBase data. It is web-based and produces statistics based on substances and ADRs. It is also freely available for all members in the WHO Program for International Drug Monitoring.

Vigimine is an internal tool for analysis of VigiBase, which produces IC (information component) values for reaction/substance pairs according to the BCPNN (Bayesian Confidence Propagation Neural Network) algorithm. It is capable of producing a time scan showing how the IC values changes over time.

Clinical Insights is an ongoing project for analysis of longitudinal data. It is based on patient record data - developed on one dataset but can be adapted for more generalized datasets. There is a prototype already in use in the UMC research and signal departments.

During these session it was emphasized that VigiFlow is a web-based report management tool that simplifies management of national ICSRs. It is not a tool for reporting to the UMC (and the VigiBase database) but it can export reports to the UMC. VigiFlow can be used by any authority or company for management and storage of their reports. The advantages of using Vigiflow are...
• less delay in ADR reporting, faster feedback to the reporters and quicker detection of potential problems.
• Better quality by mandatory fields, error checks at entry and usage of standard lexicons for data entry.
• Live access to updated terminologies including WHO Drug Dictionary and WHO-ART.

**Action points**
• It was recommended that an offline version of Vigiflow be developed as Internet connectivity is an issue in some African countries.

**Policy Update**
A short presentation updating the group on the policy implementation of ACTs was given. This showed that to date, 41/42 malaria endemic countries have adopted an ACT treatment policy and currently 36 are implementing compared to 25 as at the end of 2007. At the end of 2007, 20 of them reported countrywide implementation. This indicates that the gap between adoption of the policy and implementation is narrowing and the challenge is to ensure country-wide coverage implementing of this policy and making sure that there are no stock-outs of the medicines (ACTs). However, in children less than 5 years the median proportion of children accessing ACTs was 2% (range <1 to 13). The reasons for this low ACT coverage include having ACTs only in the health facility and yet half of the population in Sub-Saharan Africa first seek treatment outside the health sector. Secondly, procurement and supply chain management systems are still very weak in most Sub-Saharan Africa countries. This further highlights the need to introduce ACT treatment closer to the home including Home Medicine Management (HMM) hence the importance of monitoring the safety of these medicines at all levels.

**Recommendations**
• WHO will prepare a briefing note on this group of inter-country consultants, which will outline the objective in creating such a group and the results of their
work so far. This briefing note will be distributed to all WRs in Sub-Saharan Africa, to Regional Offices and Regulatory authorities.

- The SOPs will be finalized and posted on PVSF for discussion prior to field testing.

- A long-term plan to sustain and expand this group should be developed by WHO and the Regional and Country Office.

- *A Follow-up meeting will be convened in one year; the Action points as identified in this report are to be pursued by the consultants and results reported at this time.*

The meeting was officially closed and appreciation was expressed to the University of Ghana Medical School, Accra, Ghana who were the prime organizers of the meeting.
Annex 1

Guidelines and advice on the diplomatic niceties, communications and practical problems of consulting in other countries

I. Mission principle:
   1. A consultant’s mission is one of enquiry and support in the facilitation of the host country’s aims and objectives, and the building of local capacity. It is an offer of help and advice appropriate to the country, not delivery of predetermined or established ideas or plans, even when they exist and are successful elsewhere.

II. Before the mission: preparatory stage
   A. Background research
      2. Find out as much about the country as you can (politics, economy, population, primary language(s), social and religious customs, etiquette, etc)
      3. Find out about its health policies and systems, disease patterns, immunisation and other public health programmes, drug regulation, infant and peri-natal mortality, life expectancy, etc
      4. Find out what you can about the performance of healthcare personnel, prescribing and dispensing patterns, medical and medication error, etc
      5. Try to discover where the power lies in the health system, and in PV in particular, and where your individual host stands in the structure
      6. Ask for a statement of the country’s objectives and aspirations for the mission

   B. Making preliminary contacts
      7. For WHO missions, you should be in touch with WHO HQ or WHO Afro who will inform the WR in the host country of your plans and the rationale for the visit
      8. Check to ensure that the visit has local approval, at whatever level might be necessary beyond your direct host
      9. Share your mission plan and objectives with WR and focal person in the host country
10. Clarify who the sponsors/funders for the trip are and how you obtain travel authorization and tickets, what the financial arrangements are and how and when you will be reimbursed

11. Check that you are able to conduct your mission in the appropriate language for the audiences in the host country.

C. Anticipating, preventing and dealing with potential barriers

12. People do sometimes have expectations about what ‘consultants’ will be like, in terms of age, gender, race, amongst others, and you may find your reception is cooler than you had expected

13. Your credentials or experience may be doubted or questioned

14. You may find that there is resistance to change or new ideas

15. Some people may feel that your presence is an implicit criticism of their country or its way of doing things

16. Check in advance that practical arrangements (such as accommodation, transport, meeting rooms, and so on) have been made

17. Check in advance that all essential personnel have been notified of the mission, and are available for parts of it relevant to them (e.g. partners essential for your to meet, members of training or briefing groups, and so on)

D. Medical and security clearance

18. The WR in your own country will advise you as to what needs to be done. These issues may take some time to sort out, so advance planning is necessary.

III. During the mission

19. A careful situational analysis needs to be done in the early stages, encompassing both the professional and the personal, social, and diplomatic issues, to review aims and objectives, to assess what is realistically possible, levels of readiness and willingness to co-operate, and the level of local capacity to meet objectives. Over-ambitious plans may need negotiating or moderating
20. Careful, unprejudiced attention and listening to the wishes and aspirations of the host country are needed so that their situation is understood, with full recognition of the (maybe enormous) differences from the experience and values of the consultant’s home country.

21. A consultant’s mission is not to carry out activities on behalf of the host country, but to facilitate and train personnel in the host country in carrying out their own activities (training or sensitization meetings, writing guidelines, for example) and to build their capacity and independence. Sharing similar experiences that could be interesting for the host countries could be a good starting point.

22. Be prepared for the unexpected: bookings not made, people not notified, facilities ill-equipped, and so on. In some situations computers and electronic projection may not be available, so check in advance, and have contingency plans.

23. In some situations the first day or two may need to be devoted to making and agreeing the work-plan, finalizing practical arrangements, making contacts and appointments.

24. At the end of the mission, achievements and next steps need to be reviewed and agreed, including future contact and possible follow-up.

III. After the mission

25. Prepare a report outlining the work of the mission and recording the agreed next steps.

26. Share report with focal person and WR.

27. Keep in contact and review progress against agreed objectives and timelines.

28. Discuss and agree further support or resources needed and negotiate delivery.

29. Share experience and lessons of the mission with other consultants to help in their development.

IV. Essential knowledge and skills which may be called upon

30. Planning training activities; preparing materials and setting up facilities; delivery.
31. Communications: planning and writing guidelines, leaflets, forms, news releases, bulletins; marketing and promotion of PV including at the highest political level; motivating and sustaining collaborative relationships

32. Data collection and management: manual and electronic means; available resources (such as Vigiflow)

33. PV systems: planning, management and development

34. The international dimension: WHO/UMC resources and support; the WHO Programme; WHO Afro and local WRs

35. Sources of funding and application processes and materials.
Annex 2

List of participants for Follow-up Consultants' Training on Pharmacovigilance in Accra

Participants

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