Recommendations from the 5th Advisory Committee on Safety of Medicinal Products (ACSoMP), 25 - 27 February 2008, WHO Headquarters, Geneva

Summary of Recommendations

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its fifth meeting in February 2008. Constituted to provide advice on pharmacovigilance (PV) policy, and issues related to the safety and effectiveness of medicinal products, the following is a summary of the Committee's recommendations:

Current and future trends of consumer reporting: how can WHO prepare itself or maximize this utility?

This session examined the lessons and perspectives learned from the United States of America (USA) and the European Union (EU), to see how WHO could prepare itself and develop a strategy to manage consumer reporting.

The experience of the US FDA which has always accepted consumer reporting of adverse events was presented. The underlying principle here is that a single responsible agency (US FDA) should deal with reports from consumers and that these reports receive equal weight during initial evaluation, regardless of source. The value of consumer reporting is that they are an important source of information that US FDA may not have otherwise received. They often contain relevant medical detail (although in lay terms). When needed, US FDA follows up with heath professionals for additional information on key cases. SSRIs and suicide and non-prescription products such as naproxen and oesophageal injury were cited as examples of medicines for which consumer reports had provided important additional information.

Current EU legislation does not include provisions for adverse event (AE) reporting by patients, but, since December 2007, the EU commission has a new legislative proposal for strengthening pharmacovigilance allowing patients to report AEs. Some Member States in the European Union (EU) have taken the initiative in favour of patient reporting - Denmark, France, Netherlands, Sweden, UK. The quality of patient reports was noted to be often very good. The percentage of serious reports appear to be comparable with health-care professional reports. A pilot study in Sweden during 2005-2007 was presented; there appears to be some indication that consumer reports may be an additional source of information on adverse drug reactions (ADRs), in particular AEs due to misuse of over-the-counter (OTC) drugs, and problems due to inadequate information in product leaflets.

Recommendations/action points:

It was emphasized that caution must be exercised with consumer reporting and that it should neither remove nor replace reporting by health-care professionals.

WHO will consider the elements that need to be in a consumer reporting form allowing some flexibility to permit consumers to narrate their story as this is helpful in making assessments. Countries with consumer reporting should send their reports to the WHO Collaborating Centre in Sweden, the Uppsala monitoring Centre (UMC).

A small working group will focus on this project development and the value of using data from consumer reporting; the ethics of managing the data should be developed into a guidance document. Consumer AE reporting project should liaise with the patient safety pilot project.

Developing a set of impact indicators specific to pharmacovigilance

This session dealt with a proposal for specific objective measures that will address the state of pharmacovigilance (PV) activities at three levels: characterizing PV in a country, the measures that assess the
impact of PV interventions, and supervisory tools in detecting problems in implementation of those interventions. There is a need for a practical set of indicators for PV centres that will allow inter-country comparisons and will serve as a tool to leverage resource allocation for improvement.

Recommendations/action points:

ACSoMP is requested to define principles around developing a set of core and complementary indicators and to guide a process for arriving at a useful PV evaluation instrument. EU Framework may be a useful benchmark. A working group to develop this project further needs to be convened with the objective of finalizing the tool by the end of 2008.

Patient safety pilot project
The one-year patient safety pilot project has identified patient safety as an integral and existing part of the work of national pharmacovigilance centres. Vigibase, the WHO Individual Case Safety Reports (ICSR) database already contains much useful information on medication errors. An analysis of this data identified that interactions were especially important for medication errors and incidents were identified where medicines causing serious allergy had been re-administered. The pilot has also identified many functions that may be carried out by national PV centres: analysing their own databases for potential preventable medication errors, providing training in root cause analysis and educational seminars**.**

Recommendations/action points:
The committee recognizes the need to strengthen pharmacovigilance systems to detect, analyse, manage and prevent medication errors. Guidelines and training are recommended. Reporting of medication errors should be made as objective as possible. Consultations with World Alliance on Patient Safety on definitions and terminologies should be initiated.

Cohort event monitoring (CEM) studies
This session discussed CEM in Africa to collect data on medicines used in malaria. Cohort studies are based on observations in normal clinical practice when using available approved drugs in the market. Based on a training course held in Ghana two protocols have been submitted from Nigeria and the United Republic of Tanzania.

Recommendations:
Because sources of drug supplies and their quality have great variance, product identifiers (lot nos.) should be included in these study protocols. Lessons from practical problems encountered in CEM will be evaluated in these two pilot countries.

The Chinese challenge: project to incorporate Chinese data
A lot of quality ADR data is available in the national Chinese ADR database but stored in Chinese characters. The challenge the UMC is faced with is to make these case reports accessible in the global database for signalling purposes. A related challenge is to represent Chinese drug names in the WHO Drug Dictionary. If incorporated, these would benefit the research based pharmaceutical industry carrying out clinical trials in China. A WHO official letter has been sent to the Chinese State Food and Drug Administration (SFDA) calling for collaboration in the adaptation of Chinese ADR reports to the international standard format. The multinational pharmaceutical industry in China has also approached the UMC for a solution on compatibility of data. It is anticipated that these arrangements may take some time to be fully resolved. The current challenge in China includes time-consuming technical translation work and resolutions on resource mobilization and sharing. It is anticipated that resources may be generated collectively from health insurance agencies as well as drug industry associations.

Leishmaniasis
Visceral Leishmaniasis (VL) is a major public health problem in Bangladesh, India and Nepal. A description of a Leishmaniasis elimination project in these countries was presented. Until recently the antimonials and amphotericin B were the sole medicines available for the treatment of the disease. Oral miltefosine has now been found to be effective in hospital-based studies for the treatment of VL. However**,** a major concern with the medicine miltefosine is that it has been shown to be teratogenic in animal studies. It is contraindicated in pregnant women.

A project proposal has been initiated to identify the research needs to define the gaps and to generate appropriate tools that will help the disease control programmes to introduce pharmacovigilance for these medicines in their programmes. The Committee was informed of the progress that had been made in this area. Currently the full risk benefit profile of miltefosine is unknown. A risk management and minimization plan is being developed for the preventable adverse events.

Recommendation/action points:
Two committee members will assist in reviewing the Risk Management Planning framework of this project.

Parasitic disease: ensuring safer use of drugs in preventive chemotherapy public health campaigns
In both lymphatic filariasis (LF) and Schistosomiasis, mass treatment is undertaken with the help of non-health professionals (e.g. community volunteers and school teachers) without the benefit of a proper diagnosis. These programme managers need some guidance to detect drug reactions, report, manage and refer cases to a higher level. Safety of mass drug administration in loaisis and LF co-endemic areas was raised. Oversight committees to monitor serious ADRs are planned to better handle public health

programmes including responding to crisis situation. These programmes asked ACSoMP for guidance and advice.

Recommendations/action points:
The publication 'Safety of Medicines in Public Health Programmes: pharmacovigilance an essential tool' should be used as the starting point for any guidance to the public health programmes. Mass drug administration programme managers are encouraged to communicate with their in-country national PV centres (where available) for assistance.

Updates on HIV/AIDS programme: introducing PV in public health programmes
While PV for antiretroviral (ARV) medicines in public health has achievements, PV needs to be integrated in the training and daily work of service providers. Moreover, there is need to harmonize terms and definitions, reporting and analysis of AEs linked to ARVs, and addressing gaps to transfer PV knowledge from industrialized/middle income countries to low income settings. The ARV/PV project aims to establish a process to develop regional and country capacity to manage and report AEs linked to ARV, and to stimulate collection of spontaneous reports by PV centres and promote active surveillance. This is an area where the HIV programme is asking ACSoMP for advice. The ACSoMP publication on ARV PV served as a good basis for developing the HIV/AIDs proposal.

Recommendations:
The UMC is to be asked to study how to manage ARV/AE data, including the use of definitions.

Vaccines collaboration updates
There is a need for improving the tools and services for the identification of vaccine related safety signals. This can be addressed by the appointment of a proposed officer for vaccine signal detection. The evaluation of signal detection is an ongoing process. Global network for safety surveillance for pandemic drugs and vaccines was discussed because during pandemics, there may be many other concomitant drug use that potentially interact with vaccines. There is a plan to establish a network of sentinel sites to monitor newly pre-qualified vaccines in the post marketing phase. The objectives are to ensure standardized approaches to monitor serious AEs, identify and address potential safety signals in a timely manner, and to ensure that the safety information is adequate to support immunization policy.

Recommendation/action points:
The 'Adverse Events Following Immunization (AEFI)' subgroup and the 'safety of vaccine formulation' subgroup of the Global Advisory Committee on Vaccine Safety (GACVS) will be working with the UMC for the improvement of AEFI detection and reporting, increasing the pool of vaccine signal reviews, and establishing methodologies for evaluating vaccine signals and evaluating excipients of vaccines causing AEFI.

Preparedness for pandemic 'flu
WHO is providing guidelines on regulatory preparedness for human pandemic influenza vaccines and generic operational guidelines. Because of many unknown facts, there is a need for safety assessments in practice that take into account time and work load constraints, role of different stakeholders and coordination. The activities at the national level will strengthen existing post-marketing surveillance systems.

Recommendations:
The Committee recommended that there should be a session at the thirty-first annual meeting of national PV centres.

Hot topics of current interest

Human papilloma virus (HPV) vaccine
A brief description on cervical cancer and HPV infection was presented. The link between HPV and cervical cancer provides the basis for vaccine development. There have been some reports of fatalities with the vaccine. Media attention of the fatal cases has confounded perception of the safety of the HPV vaccine (Gardasil). There was no identified pattern in the causes of death or in the time of these deaths. In six cases, causes of death were reported as pulmonary embolism, myocarditis, sepsis, meningitis. In three of these six cases, another vaccine was concomitantly given. In summary, the association between death and vaccination could not be assessed. 35 cases of Guillain Barré Syndrome (GBS) including Miller-Fisher variant were reported. Some were hearsay and were unconfirmed. The observed cases have confounding factors such as co-administration of Menactra. This issue is under further observation and assessment.

Discussion:
When this new vaccine is used more widely, there will be new unexpected adverse events. Good exposure data in real time is needed but this is an anticipated challenge. Background medical conditions of the subset of women population that will receive these vaccines should be known beforeheand, in order to assess attributable risk from vaccine exposure. This is also a current interest of GACVS. Coincidental use of oral contraceptives in this group might be confounders to the proper assessment of this vaccine safety.

Recommendations:
Committee awaits more data to make more conclusive statements.

Thiazolidinediones (pioglitazone and rosiglitazone)
Rosiglitazone has been shown to cause fluid retention and cardiac failure, myocardial ischemia, infarction and mortality. Early clinical trials showed that rosiglitazone and insulin are associated with increased risk of cardiac failure. In 2006, WHO published an analysis of spontaneous adverse drug reaction (ADR) reports from the UMC database that revealed a disproportionate increase in cardiac failure. There was a higher incidence of myocardial ischaemia (hazard ratio of 1.31) relative to comparator regimens. The information has since been added to the SPC. The US FDA meta-analysis showed increased total ischemic risk by 1.4, but the specific myocardial ischemia risk was not elevated. Significantly more women who received rosiglitazone experienced fractures of the upper arm, and or foot than women who received other drugs (this was consistent with 'A Diabetes Outcome Progression Trial (ADOPT) study results).

Pioglitazone taken for durations of up to 3.5 years has also demonstrated an excess risk of 0.8 fractures per 100 patient years of use for women. However, the limitations of these studies were inconsistencies on mortality, the absence of increased risk of MI with combination therapy. There were other confounding issues such as control selection, selection bias. Long-term studies with pioglitazone showed a protective effect on the heart. While rosiglitazone raises blood lipids, pioglitazone increases blood lipids to a lesser extent. There may be also some hint of drug interactions between angiotensin converting enzyme (ACE) inhibitors and rosiglitazone.

There are no long-term evidence of oral hypoglycaemic agents showing real efficacy and prevention of complications. Because of the equivocal and uncertain findings from the US meta-analysis, a box warning citing uncertainty in the findings has been added. But no clear update to prescribing advice has been made.

The challenge is deciding the hierarchy of information needed to make sound regulatory decisions. There is criticism on the absence of complete efficacy-risk comparison. Regulatory decisions to allow these products in the market are based on the evidence of efficacy on lowering glycosylated haemoglobin, but long-term studies are needed to assess safety.

Recommendations:
Committee to consider reviewing all the evidence for further deliberations and evaluation.

Abacavir: risk of myocardial infarction (MI)
This issue is currently under evaluation in the EU. There seems to be an increase in risk of MI with recent use of abacavir (that is, in patients currently using or who used abacavir in the past 6 months). There is strong evidence for an emerging new signal.

A prospective study running for nine years is looking into this. But it appears that the phenomenon is also seen with didanosine. But the Glaxo post-marketing safety data appear not to have picked up this signal. A postulate is that one of the metabolites of abacavir is pro-inflammatory hence perhaps some biologic and vasculitic mechanisms are likely and should be further investigated.

Recommendations:
To closely follow EU decisions about this new signal.

Biosimilars
This session attempted to answer if drug safety profile should be linked more to the product than to the substance. The existing INN (International Nonproprietary Name) nomenclature policy will need to be changed when it comes to naming biosimilars because biologicals are not homogeneous products. For instance, Thailand has 10 epoetin alpha biosimilars, all with the INN epoetin-alfa. Eprex is an innovative epoetin, also with the INN epoetin-alpha. As a result, Eprex and the other biosimilars with the same INN are often substituted for one another at hospital pharmacies. But these have different effects. So giving a common name to all epoeitins can be a big challenge in pharmacovigilance when it comes to tracing back to a substance that actually caused an adverse reaction. Some of the factors in the discussion included the

dependence on the legal system of each country for classification but at the same time, encouraging the assurance of traceability of biosimilars.

Recommendations:
A sub-committee should make clarification of this issue with some proposal for clear principles of biosimilar nomenclature and the consequences of their application to PV to be taken up at the International Conference of Drug Regulatory Authorities (ICDRA).
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How to integrate vaccine definitions into the WHO Programme
Vaccine pharmacovigilance and other related terms used were discussed. Brighton Collaboration definitions were considered for adoption. There is a need to review the WHO adverse reaction terminologies (WHO─ART), to facilitate reporting of AEFIs at national centres, and in the causality assessment of AEFIs. Some countries have separate forms for AEFI reporting and it might be useful to integrate these forms with the ADR reporting forms.

Recommendations:
Cooperation between ACSoMP and the CIOMS Vaccine pharmacovigilance working group is to be encouraged. Integration of national immunization programs with the national PV programs to be supported and strengthened. Proposal made to integrate vaccine AEFI data collection into drug ADR reporting forms and expanding UMC data fields as needed.

How to initiate revision of existing definitions
This session explored the context and the process for revising PV definitions; some of the definitions are old, there are emerging new terms and concepts. Examples for review are “adverse reactions”, “adverse events”, “signal”, “incidents”, “warning” and “alert.” How can patient safety be defined? Is medical error a term that needs a definition in relation to drug misuse or abuse? The session called for views and suggestions on the way forward.

There are regulatory and legal implications when revising definitions. Responsible agency to do this task needs to be identified. The Family of international Classification (FIC) or UMC could lead this initiative.

Recommendations:
The Committee agrees that definitions of terms and concepts should be reviewed. The Committee recommends that WHO takes the lead while delegating work to technical bodies.

Optimizing use of Vigibase
At present there are no guidelines for reporting to the Vigibase. National pharmacovigilance centres choose different criteria for submission of reports. As a consequence the database is not very consistent. All individual case safety reports collected by national pharmacovigilance centres, irrespective of the national criteria for data collection may be included in the database. Different categories of reports could be flagged and stored in a common database or separate databases could be kept for different types of reports. There may be a need to define if adverse events from food supplements and cosmetics could also be sent to the database

Recommendations:
The UMC needs to review their existing advise to national pharmacovigilance centres on what they may report to the database. An all-inclusive principle for reporting is proposed: if it affects the health of the patient, then it should be reported. UMC should draft a message to advise people on reporting requirements for drug reactions.

Indicator-terms of drug dependence
A project in the UMC is investigating the use of Vigibase as a resource for patient safety in areas of medication errors, interactions and drug dependence potential. Various permutations of ADR terms and cluster terms have been examined to determine if dependence signals could be picked up. There seems to be a distinction in the reporting pattern between benzodiazepines (and benzodiazepine derivatives) and other drugs known to cause dependence. For these latter drugs, it is very rare for psychiatric and other nervous system related ADR terms to be quantitatively highlighted before the term "drug dependence" in the database. It is not clear whether these terms are predictors of drug dependence or are independent adverse events associated with benzodiazepines. Nevertheless these are clearly candidate predictors of benzodiazepine-dependence. And there are other terms which on their own may not be of predictive value but in a cluster of terms, when taken together, would predict drug dependence. Proposals are requested to find more sophisticated patterns, or other reporting trends in identifying drugs of dependence. Another approach would be a clinical review of case reports related to drug dependence. The committee is requested to advise on how to proceed.

Recommendation/action points:
The UMC internal report is to be circulated to committee members for comments. The definition of dependence/withdrawal needs to be made clear.