



Eighth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
31 March - 1 April 2011

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 Eighth Meeting.

Artesunate (AS) – Amodiaquine (AQ): analysis of adverse drug reaction (ADR) reports

The Committee agreed that based on the UMC data, there is clearly a 'Signal' associating extrapyramidal reactions with the combination of AS-AQ, most likely due to the amodiaquine. More work is needed to understand the incidence and predisposing factors. The Committee was of the opinion that the regular inclusion of the full details of product, dose, dose frequency and concomitant drugs would permit further analysis, including dose/reaction associations and drug interactions.

The mechanism is currently unknown, and may not be directly related to the dose. There have been some patients on very high doses who have not experienced these reactions.

This 'Signal' is more or less the first from African data. The Committee recommended publishing this Signal and sharing the details with the manufacturer for a possible update of the Summary of Product Characteristics. The committee also suggested that the manufacturer should be contacted, to design a follow up study, to substantiate the present evidence and Signal of extrapyramidal symptoms with AS-AQ.

Pharmacovigilance (PV) Toolkit

The Pharmacovigilance Toolkit is being developed as a Pharmacovigilance resource repository for low and middle income countries looking to develop a good quality, standard pharmacovigilance system. The WHO Collaborating Centre (CC) for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from the WHO, the Uppsala Monitoring Centre (UMC) and the Global Fund.

A Malaria 'chapter' has been added, funded by the Roll Back Malaria partnership. Discussions are ongoing for developing a HIV chapter and perhaps, a TB chapter within the Toolkit. Multiple partners will be involved in the overall content development.

The Committee recommended that WHO would oversee the development; a technical/governance committee will be drawn from within the ACSoMP, to critically review and approve specific toolkit contents. But the WHO CC in Ghana will retain responsibility for the everyday maintenance of the Toolkit with technical overview from the UMC.

Training activities and PV training modules

A comprehensive pharmacovigilance curriculum is being developed as a collaborative effort between the International Society of Pharmacovigilance (ISoP), WHO and the UMC. There is a small writing group. The course structure will be hierarchical, with different levels, consisting of modules that are compact and defined, and reflect the complete field of pharmacovigilance, to be taught as separately, as individual modules, or as a combination of two or more modules. A set of tasks for practical hands-on training will accompany the teaching modules.

The Committee approved the ongoing work on pharmacovigilance curriculum development as timely and of universal value; and recommended that there should be a review process similar to the one for the pharmacovigilance toolkit. A working group made of representatives from the UMC, WHO and ISoP should be established, to outline what should be incorporated into trainings for different focus groups. WHO will

coordinate the project, with ACSoMP members invited to review and advice on specific aspects.

Council for International Organizations of Medical Sciences (CIOMS)' Activities

Update on the working groups:

- Working Group IX – this is a working group to discuss a harmonised view on risk management and specifically risk minimisation. The goal is to develop a risk minimisation toolkit, similar to the pharmacovigilance toolkit but more as a complement than an overlap.
- Working Group X – this is a new working group, to focus on systematic reviews and meta-analysis as good practices in regulatory medicine. The goal is not to produce guidelines but to discuss the interpretation of meta-analysis and develop a consensus on scientific and methodological criteria that represent good practices. These criteria would be used by both industry and regulators.
- CIOMS-WHO joint working group on vaccine pharmacovigilance: the group has been working on a draft report which is now being reviewed by the members. A close relationship has been maintained with the Brighton Collaboration with the purpose of disseminating the case definitions by the Brighton Collaboration. The draft report proposes some standardized definitions for the monitoring of safety of vaccines. The goal is to publish the report this year, through the WHO publication system.

Caveat document for SIGNAL and other data from Vigibase

When requested, the UMC provides data from the WHO global individual case safety reports (ICSR), database (Vigibase) along with a Caveat document, to make sure that the recipient will have a basic idea of what needs to be considered when reviewing the data. The document has not been updated since 1992, when it was first compiled. The UMC has now revised the Caveat document which was then approved by the Committee.

Making some Vigibase data publicly available: a concrete proposal

The Committee discussed issues around increasing public access to the data in Vigibase. This would need to be done in a responsible, stepwise fashion. Some extensions will be made to the current data retrieval interface being used by national centres, a new search tool. Those who are not members of the national centres will be able to log on but with a different level of access, for example, to some summary tables. The UMC is preparing to make these summaries available and the necessary search tool. The data presentation will be modelled on that used by the MHRA in the U.K. A dry run will be carried out with all national centres to test their reaction to the search tool and summary tables.

ACSoMP agreed that increasing public access to the data will raise overall awareness, to the importance of the work carried out by the UMC and would also give access to a valuable source of information.

Antibiotic resistance - pointers from pharmacovigilance data

One of the work packages within the Monitoring Medicines project (<http://monitoringmedicines.org/>) involves methodological development in investigating reports of therapeutic ineffectiveness. It may be possible to use this methodology to identify cases of antimicrobial resistance within the data base. The UMC had invited representatives from STRAMA (The Swedish Strategic Programme Against Antibiotic Resistance) and ReAct (Action on Antibiotic Resistance) to a meeting to discuss possible areas of collaboration. Using the global database and the methodology developed within the Monitoring Medicines project, the UMC has identified a list of possible cases of antibiotic resistance, but this needs to be verified on a national level to ensure that the right signals are being detected.

Health professionals should be encouraged to submit cases of suspected resistance to their local pharmacovigilance centre. The Committee suggested developing a policy on reporting recommendations for national centres, to submit cases of lack of therapeutic effectiveness, particularly in relation to antimicrobials.

Creating a quorum for publishing in pharmacovigilance

There are very few pharmacovigilance papers coming from national centres, especially from developing countries. ACSoMP proposes that technical support and assistance are provided to increase the number of publications. The first endpoint of this is to increase the strategic visibility of pharmacovigilance as well as its advocacy. The second endpoint is to improve the sharing of pharmacovigilance information to a wider community, as a form of outreach service. A reviewer group will be formed consisting of senior experts and scientists in pharmacovigilance, who are willing to providing assistance on a voluntary basis. National centres will be notified upon the creation of the reviewer's group and its purpose.

The Vaccines Blueprint Project

There are 71 developing countries where monitoring of adverse events following immunization (AEFI) is not implemented. In many of these countries, there is no AEFI monitoring at all, meaning that many vaccines are used with little to no feedback regarding vaccine reactions. There is huge variation in the way vaccine reactions are detected in the world.

The purpose of the global vaccine blueprint project is to provide a global support platform for capacity building in low and middle income countries. A concept of minimal capacity at country level that will involve immunization programmes, regulatory authorities and other supporting bodies like national pharmacovigilance centres and national AEFI review committees is being proposed.

The discussions at the meeting of the ACSoMP focused on the model for a global AEFI database. The group concluded that a global vaccine database is needed but this already exists, in Vigibase. However some improvements are needed, to accommodate the uniqueness and specificities of vaccines, with certain data fields included in the reporting format in order to maintain a functional database and for efficient and effective signal detection.

Collaborating Centres and Centres of Excellence for improving outreach and country support in pharmacovigilance

The landscape of pharmacovigilance is changing, donor agencies are promoting better access to medicines. The challenge now is to promote pharmacovigilance. Resources are limited within WHO, thus work needs to be directed more through collaborating and national centres, with the view to developing, sustaining and promoting pharmacovigilance in settings where it is most needed. Strategically, WHO is reaching out to countries through collaborating centres and other centres of excellence in pharmacovigilance. However clear guidelines are needed, in establishing these centres and how to work with them. A working paper will be drafted, to describe the terms of reference for satellite centres. This paper will be shared with the Committee, for review and further advise.

Medicines Patent Pool Initiative

UNITAID established the medicines patent pool in 2009, to improve access to patents and facilitate the development and production of life-saving, more affordable, and more suitable medicines. Many pharmaceutical companies want to be involved as it strengthens their position and image as a leader in improving access to medicines. The initiative will collaborate with the WHO prequalification programme, to ensure that good quality generic medicines are available through this scheme. With regard to responsibilities of safety monitoring, the Committee recommended forming a working group, to include and strengthen pharmacovigilance within the scheme of work of the Medicines Patent Pool.

Chagas disease, HIV/AIDS, TB, Monitoring Medicines Project: updates

Chagas disease: pharmacovigilance updates

WHO established a procurement and global distribution system for nifurtimox and benznidazole in 2009. Organizations such as MSF are involved in providing treatment in resource limited settings. However, pharmacovigilance systems are not present in these settings. There is a need for PV to assure the safety of these medicines.

The Committee recommended developing a plan to assist the integration of pharmacovigilance into Chagas disease programme. A small working was appointed to follow up this topic.

HIV/AIDS: pharmacovigilance updates

Tanzania Cohort Event Monitoring (CEM) Project – six sentinel sites , all based in Dar Es Salaam, will implement this method for the safety monitoring of medicines in HIV treatment programmes. The aim is for 250 enrolments per month of patients starting treatment for the first time, including pregnant women and children. The project is currently being implemented.

WHO partnership for 'targeted spontaneous reporting' with the Academic Model Providing Access to Healthcare (AMPATH) programme in Kenya: the objective is to test a feasible and sustainable method for documenting antiretroviral toxicity in a resource-constrained clinical setting, directly linked to the national pharmacovigilance programme. A subset of 1000 patients will be interviewed about experiences and perceptions of adverse effects.

TB: pharmacovigilance updates

Approximately nine million cases of TB are reported each year, with 1.7 million of these resulting in death, 400,000 of which are HIV associated. These are cases that are demonstrating resistance to the usual drugs.

Not only there is no provision for routine pharmacovigilance reporting, many MDR cases do not get reported either. A 'practical handbook on the pharmacovigilance of antituberculosis medication' is being developed. The current work on updating the Stop TB Strategy needs to include pharmacovigilance. The Committee recommended that this and issues related to pharmacovigilance of TB medicines in Global Fund Grants should be discussed at the next meeting.

Monitoring Medicines: project update

The EC-funded Monitoring Medicines project was developed by WHO and is currently being implemented as a partnership of 11 countries and coordinated by the UMC. The key objectives are to:

- support and strengthen consumer reporting;
- expand the role and scope of pharmacovigilance centres (medication errors);
- promote better and broader use of existing pharmacovigilance data (dependence and substandard quality);
- develop additional pharmacovigilance methods to complement spontaneous reporting systems; and
- develop a learning tool for the management adverse events with ARVs.

Pharmacovigilance Indicators: update

A set of core and complementary indicators have been developed. There are three classes of indicators:

- Structural.
- Process.
- Impact/outcome indicators.

The indicators are being validated.