Conclusions and Recommendations from the Tenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
17 - 19 April 2013

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. The conclusions and recommendations from the Tenth meeting of ACSoMP are presented below.

Core support to the WHO Safety and Vigilance programmes:

The Uppsala Monitoring Centre (UMC) has supported WHO for more than 30 years as a WHO Collaborating Centre. The UMC handles the safety information management chain and focuses on multiple critical tasks such as signal detection, tools development, and trainings. Additional collaborating centres have come up more recently, to address specific areas of work such as Training and Advocacy for PV in Africa (Ghana, 2009), medication errors and the role of PV centres (Morocco, 2010), pharmacovigilance in education (Lareb, Netherlands, 2013). The WHO Collaborating Centre in Oslo supports by developing the normative tool, the ATC classification system for medicinal products and by assigning ‘Defined Daily Doses’ (DDD) to these products.

The Committee noted that in the coming years WHO and the Collaborating Centres should focus on a more enhanced interaction between the regulatory activities and the PV systems, for the use and implementation of the knowledge acquired through pharmacovigilance. The Committee also recommended strengthening links between PV Centres and Patient Safety programmes.

Pharmacovigilance of medicines in the elderly: how can WHO prepare for this challenge?

The Committee recommended that PV should be more present in a visible manner in the WHO initiative on ‘Ageing and Life Course’. WHO should develop a comprehensive paper on pharmacovigilance problems in the elderly, and solutions to address those problems. A small sub-group of the Committee should be created to:

1. Draft an explanatory document why elderly is a vulnerable group with respect to medicines use
2. Consolidate available information to help national PV centers create programmes and action plans for monitoring the safety of medicines in the elderly.

3. Support WHO to develop a policy document on the importance of monitoring the safety and safe use of medicines in the elderly.

**WHO Pharmacovigilance indicators**

WHO uses a three-tiered approach for monitoring country pharmaceutical situation: Level I indicators measure the existence and performance of core national pharmaceutical structures and processes. Level II indicators measure key outcomes of these structures and processes in the areas of access, product quality and rational use. Level III indicators assess specific components of the pharmaceutical sector, health system, or national medicines policy in more depth. Consistent with this approach, the WHO PV indicators are categorized into Level III. A global and stepwise consultative process has been followed in identifying the WHO PV indices.

The Committee noted the revisions to the document since its last meeting, in particular the section on indicators for public health programmes and recommended developing a framework for the implementation of the indicators. WHO HQ and UMC would work closely with countries in the assessment of PV in their settings, and establish a database to consolidate the PV situation worldwide. The WHO PV indicators manual will remain a work in progress, with each new version reflecting the lessons learnt in the course of implementation of the tool in the countries.

**Safety monitoring of medicines in malaria treatment**

The Committee discussed various initiatives to collect data on the safety and safe use of antimalarials and concluded that the principles of Cohort Event Monitoring (CEM) are sound; but the methodology needs to be standardized across various CEM efforts.

The Committee recommended that the experience to date with CEM should be reviewed, and the lessons learnt should be documented. A ‘WHO CEM protocol’ ‘tag’ could be used to identify studies that implement CEM in a manner consistent with the original WHO perspective of the method.

**Global Vaccine Safety Initiative (GVSI)**

The GVSI is WHO’s implementation mechanism for the Global Vaccine Safety Blueprint. The Committee acknowledged the rapid progress in implementing the GVSI and the efforts to create national data management systems that will facilitate access to AEFI (Adverse Events Following Immunization) information, for both the national programs and the regulatory authorities. The Committee encouraged efforts to align capacity building for pharmacovigilance of medicines and vaccines.
African Medicines Registration Harmonization

The African Medicines Registration Harmonization (AMRH) initiative was launched in 2009, to address serious gaps in regulatory capacity for this function in the African region. The New Partnership for Africa’s Development (NEPAD) is tasked with securing political support, the World Bank manages the budget, and WHO provides technical oversight and leadership for the initiative. The Committee expressed concern over the absence of any post-registration monitoring activities within the initiative and called on donors, governments and technical agencies to ensure that the AMRH is accompanied by schemes for post-market surveillance of the registered medicines. The Committee noted that post-market surveillance and pharmacovigilance require only modest investments, but will contribute to the overall benefit of governments, donors, the pharmaceutical industry and most importantly patients. The Committee called on all stakeholders to mobilize the needed resources to ensure that the AMRH is developed simultaneously with a robust, well-funded post-marketing programme. The Committee had the following comments:

Harmonization of safety data submission

The lack of harmonization of PV data submission in low and middle income countries (LMIC) has meant that companies have to comply with countless different reporting requirements; this results in inefficiency and, the loss or late submission of crucial safety information to the authorities. Countries outside the ICH region have started efforts for harmonization, however, regional harmonization that differs from ICH standards will not lead to a global solution unless the results achieved are at least “ICH-compatible”.

A seamless exchange of ICSRs between industry and Medicines Regulatory Authorities is possible with the implementation of tools such as the UMC data management tool VigiFlow. The committee recommended that use of such tools could be promoted, as part of a harmonization package for PV in LMIC. However it must be acknowledged that harmonizing the format is not enough: content, quality, adequate staffing and uniform timelines for reporting are also key.

PV training course on post marketing activities for regulators in low and middle income countries (LMIC)

The Committee advised that the basic PV courses need to include the principles of benefit/harm assessment, evaluation and enforcement of risk management plans, and the use of safety data for regulatory decision making. Resources to monitor medicine safety during all the different steps of its life need to be developed, linking this to the impact on public (and patient) safety. The Committee encouraged WHO to develop a training package on PV for regulators in LMIC and noted that any effort in this regard should build on the US FDA experience with its one week course on regulatory decision making in the post market setting.
WHO/ UMC proposal for public access to information from VigiBase

Based on previous ACSoMP recommendations, the UMC has been working on the steps towards the release of the WHO UMC (Vigibase) data to the public. The same level of access will be provided to all users. A simple, user friendly search mask will allow the user to obtain an overview on the whole VigiBase dataset and search for products/active ingredients. However, the data will be presented as statistics only. No line listings and no individual case safety reports (ICSRs) will be provided. A disclaimer with the explicit information that ‘patients should not discontinue their medication if they think they are suffering from an ADR, but should consult their HCP and report the suspected ADR’, as well as the UMC Caveat Document will precede the actual access to VigiBase. The Caveat Document will be rewritten in a language that is easily understood by the general public. The Committee approved these considerations and commended the progress in making VigiBase accessible to the public.

The Committee noted that the experience of other stringent regulatory authorities has shown the benefits of transparency to outweigh the potential problems associated with open access.

The impact of the new EU PV guidelines –definitions and technical procedures for ICSR reporting

The new EU legislation requires PV to go beyond the WHO definition of PV, to include also the management of benefits and risks of medicines on the market, powered by tools that help embrace the evidence hierarchy to benefit public health. A proposal for a recommendation on Medication errors and the scope of PV to address this was presented to the Committee and approved:

All aspects of medicines regulation may be relevant and the naming, labeling and information for users of products are particular areas impacting on the risk of medication errors. Risk management can play a critical role in ensuring evidence based planning of data collection and risk minimization and this has the potential to reduce the burden of harm from medication errors. Likewise, the collection of near-miss reports, and of reports of suspected adverse reactions due to medication errors, the collation and analysis of these reports, including coding, definitions and other data management issues are important and their optimization has major potential for reducing the harm from medication errors.

The Committee recommended that bridging between patient safety initiatives and pharmacovigilance (including naming and labeling issues) should be a priority for the WHO programme. The Committee further recommended to explore the development and harmonization of relevant terminology, event classification and technical work at the interface of pharmacovigilance and patient safety. Finally, the Committee recommended that national pharmacovigilance centres should include medication errors within their mandates.
The Committee also noted that reporting of ICSRs to UMC by the European Medicines Agency (EMA) is likely to start in 2016; until then national pharmacovigilance centres will continue reporting to UMC. It was agreed that a WHO-EMA joint communication on Member States continuing to report to UMC until notified of a change in reporting by EMA, should be prepared, posted publicly, and shared at the annual meeting of national pharmacovigilance centres.

**Pharmacovigilance for biotherapeutics:**

In a presentation to the Committee, representatives of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) noted that the complex production process and manufacturing chain, delayed adverse drug reactions (ADRs), immunogenicity, relative instability of the products and traceability are some of the aspects requiring special consideration in the PV of biotherapeutics. These problems are compounded by additional challenges such as inconsistent PV systems, naming and prescribing practices that vary across countries (for example, use of INN versus trade names), changes in manufacturing processes that may lead to a significant change in clinical effectiveness, inappropriate substitution (therapy switch) and prescription.

The IFPMA requested WHO to

- take action on clearer, harmonized and distinguishable naming of biotherapeutics
- advance guidance and training of stakeholders on processes and systems for PV of biotherapeutics

The Committee noted that similar problems exist also for small molecules. Even electronic record systems may not provide more information other than just the INN. Recording trade names is already recommended in ICSR reporting guidance, but might need to be further emphasized. Specific advice on these aspects could be added to the PV Toolkit.

**Anatomical Therapeutic and Chemical (ATC) classification and the Defined Daily Dose (DDD) for medicinal products**

ATC/DDD is a tool for coding medicinal products and for quantifying and comparing drug utilization within and across facilities, countries etc. It was first used to alert policy makers to the over-use of antibiotics. However the tool remains relatively unknown and under-utilized. ATC/DDD can help determine drugs / classes of drugs to monitor in a facility. Since DDD can provide information on volume of medicines used, together with ADR reports, it can help also determine ADR rates.

The Committee recommended inviting a member of the WHO International Working Group for Drug Statistics Methodology at the next ACSoMP and other relevant PV events, to discuss the utility of ATC DDD.
Adverse events reporting for medical devices

More than 20,000 different types of medical devices exist. However, there are few relevant regulations on medical devices. The need for training and capacity building in techno-vigilance/post marketing surveillance is very high, especially in LMIC. Another key problem is the absence of a well-recognized nomenclature for medical devices.

The Committee noted that medical devices are important in the diagnosis, prevention, and treatment of diseases. Monitoring adverse events, medical errors related to medical devices, and device malfunction are important for understanding the safety and safe use of medical devices in actual practice/ recommended the following: The Committee recommended the development of robust systems for monitoring the safety and safe use of medical devices and to consider the ADR reporting systems for medicines as useful models. The Committee also recommended developing a nomenclature on medical devices, collecting data on the burden of adverse events due to medical devices and the exchange of information between the pharmacovigilance and devices networks.

Strategies for monitoring the safety of new TB medicines

PV will be included in the revised international standards for TB care in the post 2015 strategy. Several anti-TB drugs are in the pipeline. Several countries are interested in registering bedaquiline (BDQ) for use in multidrug resistant TB (MDRTB) following its accelerated approval by the US FDA. BDQ presents some serious concerns, in part because its ½ life is in months. PV tools to study drug interaction would thus be very important. Active PV will be recommended for this drug with a need to follow-up safety aspects, including hepatotoxicity, cardiotoxicity and mortality.

The Committee welcomed the appearance of new TB drugs, acknowledged the willingness of Stop TB to carry on specific PV efforts, and emphasized the need for PV systems to accompany the roll-out of new TB medicines, building on existing systems and capacities.

Substandard and falsified medical products

Substandard/spurious/falsely labeled/falsified and counterfeit (SSFFC) medical products are a global threat. Inter-country collaboration is needed to tackle this threat. WHO has developed a simplified tool for reporting SSFFCs (Rapid Alert) and a database that stores the reports. The project started as a pilot with 10 countries trained in the use of these tools; more countries are now receiving training in the full roll out of the project. SSFFCs are difficult to identify, particularly if they have some (and not a complete absence of) therapeutic effect. SSFFC products that are toxic are detected more easily. Synergies do exist between the SSFFC and PV disciplines. PV can be another set of ‘eyes and ears’ for SSFFC, just as laboratory networks could be.
How can PV Centres contribute to drug quality surveillance systems?

Drug quality related issues may be due to manufacturing or post manufacturing issues. Standard ways of looking at ADR do not always help identify drug quality issues. PV does not include field investigation, and does not engage field epidemiologists who are able to analyze the information with a rapid turnaround. PV reporting requirements for non-serious ADRs can limit timely identification of these poor quality products. But in some countries the ADR monitoring system also monitors quality issues, with an automatic system to signal quality issues requiring laboratory testing. The UMC has developed an algorithm to detect poor quality and SSFFC products based on lack of efficacy reports in the pharmacovigilance database. The algorithm needs to be validated by countries, to see if these ‘clusters of potential SSFFCs’ detected by the UMC algorithm are real SSFFC cases.

The Committee recommended coordinating efforts between PV and SSFFC networks, to complement each other’s work. The Committee also recommended that WHO should send a letter to all PV centres, urging them to collect and share reports of decreased therapeutic effect with WHO.

Update on toxicity monitoring for ARVs

The HIV department is in the process of revising and publishing the WHO 2013 “Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - Recommendations for a Public Health Approach”. The department commissioned several systematic reviews on ARV toxicity to support and inform the Guidelines Development Committee’s review of evidence and recommendations, including reviews on toxicity with tenofovir, nevirapine and efavirenz.

ACSoMP emphasized a better role for PV in the update of guidelines, as it not only identifies, but also quantifies the risks (e.g. renal failure with TNF). The Committee encouraged WHO-HIV to consider on-going work of prospective cohorts such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D).

PV training modules

A sub group of ACSoMP has been developing a PV curriculum that considers the whole field of PV, and proposes theoretical chapters as well as practical hands-on exercises. The full Committee was presented with the table of contents and next steps, including plans for publishing the course content. The document will be completed in 2013. The Committee noted that this is an evolving document and its contents will reflect the expanding scope of PV as it develops. Monitoring and Evaluation (M&E) of PV is also included in the curriculum (with links to the WHO manual of PV indicators), to provide education and training on how to monitor and evaluate a PV system.
**Toolkit**

The Pharmacovigilance Toolkit has been developed as a PV resource repository for low and middle income countries, to support their efforts to develop a good quality, standard PV system. The WHO Collaborating Centre (CC) for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from WHO. A short update was presented focusing on progress and new features. In particular, a link with Vaccines is in the pipeline, a toolkit manager has been hired for everyday management of the toolkit and to respond to FAQs from countries, and promotional materials and a business plan are being developed, to advocate and improve the use and maintenance of the Toolkit.