37th Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring
Tianjin, China
14 - 17 October 2014

The thirty-seventh annual meeting of representatives of national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring was held 14 -17 October 2014, at Tianjin, China. The meeting included eight working groups that discussed various issues in pharmacovigilance. The summary of discussions from each working group is presented below.

WG1. Challenges and opportunities in facilitating collaboration between public health programmes and national pharmacovigilance (PV) centres

Objectives:

- To discuss the importance of collaboration between programmes (such as TB, Malaria, Immunization programmes etc.) and pharmacovigilance centres
- To discuss challenges to and opportunities for such a collaboration
- To share experiences on how countries have handled these challenges and examples of benefits of such collaborations.

Expected outcomes:

- To present a broad framework for collaboration between public health programmes and national PV centres:
  - What, when and how;
  - Roles and responsibilities
- To provide recommendations to countries, WHO Collaborating Centres (WHO CCs) and / or WHO for promoting collaborations between Public Health Programmes and PV centres.

Discussions: In general, there was agreement within the group that immunization and other public health programmes (PHPs) such as such as TB and HIV treatment programmes are set up as strong, well resourced, vertical programmes, with limited or no collaboration with the national Pharmacovigilance (PV) centres. The programmes usually do not collect and / or share pharmacovigilance data with the National PV Centre or with the WHO database, Vigibase.
PV centres could help integrate PV within the PHPs and also support the routine benefit/harm assessment of treatments within the PHPs. However PV centres are often under resourced or under developed and therefore unable to support PV within these PHPs. This has led to PV being set up programme by programme in many countries, taking away resources and the opportunity to invest in a National PV Centre that can support PV across different programmes. Having a central PV facility will not only remove biases in benefit-harm assessment of products used within the PHPs, but will also improve the public confidence and perception of such PHPs. A Central PV facility will also help

standardise PV tools and methodologies across the various programmes, thus ensuring best and consistent practices in safety monitoring in PHPs. In addition, by engaging with the PHPs, the PV centres could gain some visibility within donor communities that support PHPs. PV Centres could also leverage the patient cohorts within PHPs for proof of concept of PV methods and tools.

The group made the following recommendations:

National PV centres to:

- Adopt / further develop guidelines for integrating PV in PHPs, and develop their own competence • Collaborate with PHPs through joint activities, for example, to develop joint information materials on the safety and safe use of medicines used in in the PHPs; organize joint training materials and courses for PV; develop joint activity plan for PV etc.
- Develop proposals together with PHPs to mobilize funds for joint activities
- Support PHPs in the implementation, monitoring and evaluation of the PV function within the health programmes

WHO and WHO CCs to:

- Advocate and facilitate the integration of PV into PHPs
- Develop methodologies, guidelines and tools for PV in PHPs
- Assess training needs and develop training materials for PHP programme managers and staff in PV • Support regional data aggregation and analysis
- Negotiate with global donors and procurement agencies to include funds for PV for procured / donated medicines

WG2. Global information sharing during a medicinal product –related crisis

Objectives:

• To share various examples of medicinal product related crisis in recent times

- To reflect on the following, to understand how countries managed the crisis
- Data gathering
- Validation
- Communication
- Regulatory action
- To discuss information sharing, locally and internationally: what, when, how, value added, challenges, opportunities.

Expected Outcomes:

- To identify the core elements of a strategy for information sharing during a medicinal product-related crisis
- To define roles and responsibilities for various stakeholders (governments, public, media, NGOs, health professionals, industry, inter-government agencies, etc.) in information sharing during a medicinal product related crisis.

Discussions: The group agreed that a 'Signal' would rarely lead to a crisis. A rumour about an adverse drug event could easily result in panic and crisis unless there is a routine process for handling and investigating such rumours. It is often seen that countries with weak/no regulatory systems are at higher risk for crises. Every regulator needs a standard protocol that includes an up-to-date internal fact sheet with clear key points on what is known, what are rumours, what is under investigation etc. Communication and media handling are just as critical. Early and active communication of consistent information through a designated and credible spokesperson with established media relationships

are key features of an established drill. Media monitoring for rumour identification and prioritisation of communication based on cognitive factors and other findings from risk psychology research can be usefully exploited to mitigate and manage a crisis. Global information sources such as VigiBase and websites of stringent regulatory authorities should be leveraged, to supplement local information on an event. In some instances frameworks such as the International Health Regulations could be usefully employed to access confidential information from some settings.

The group made the following recommendations:

Countries to:

- Strengthen regulatory systems
- Establish credible media relationships
- Monitor media
- Identify and train a respected spokesperson
- Institute internal processes for communication preparedness
- Initiate stakeholder deliberation and health diplomacy to overcome anti-government sentiments
- Strengthen regional/global information exchange
- Raise awareness of global impact of local communication and local adaptation of global information

WHO / UMC to:

- Develop the definition of crisis and possibly the preferred term: critical incident
- Develop model SOPs for crisis and media management (cf. “Expecting the Worst”)
- Include crisis prevention and management exercises in training courses
- Coordinate urgent global information exchange through VigiMed
- Link pharmacovigilance, SSFFC surveillance and quality defect systems at global level

WG3. Evaluating benefit/risk assessment in drug regulatory decisions: adapting international decisions to local settings

Objectives:
To have a broad understanding of the influence of external factors on regulatory decisions in a country, Vis-à- Vis the:

- Influence of international decisions
- Availability and quality of local PV data
- Role of local needs (lack of availability of other treatment options), resources (e.g. lack of laboratory to monitor renal / liver functions); characteristics of population (e.g. G6PD deficiency)
- Factors that determine restrictions over suspension versus product withdrawal: when are these appropriate; how are these measures decided, implemented.

Expected Outcomes:

- To outline a broad framework for best practices in benefit-harm assessment
- To list the various factors that influence benefit-harm assessment and regulatory decisions in countries
- To propose recommendations for countries, WHO CCs and / or WHO for promoting best practices in benefit-harm assessment and regulatory decisions.

Discussions: The group noted that factors that influence regulatory decisions making are many and varied. In general, the approach to regulatory decision making needs to be consistent and stepwise. The approach should consider national needs, available data, local experience of data evaluation, and the possibility to generate additional data if needed. Factors that trigger a review and benefit-harm assessment include: the magnitude of risk, strength of evidence, maturity of the PV system and its sensitivity to detect and identify new and emerging issues, thresholds for review, and experience with a product and additional / new information that emerges.
The regulatory decision to withdraw, suspend or restrict the use of a product would also depend on population demographics such as genetic predisposition, disease burden, availability of alternative treatment option, capacity to implement the decisions and risk management measures.
Transparency and communication with the public, health professionals, media, industry and other international regulatory agencies throughout the decision making process would be essential to mitigate and manage perceptions of conflict of interest and improve compliance with the decisions.

The Group made the following recommendations:

WHO and UMC to:

- Develop a broad, generic framework with a template for benefit-harm assessment that
  - Links clinical trial (safety and efficacy) and post marketing (safety and effectiveness) data
  - Considers existing resources and publicly available assessment reports
- Link with other WHO CCs and Agencies to organize training in benefit-harm assessment for health-care professionals and regulators

National PV Centres and regulators to:

- Support the implementation of recommendations (restricted use, special monitoring etc.) through training and advocacy activities in health-care systems in the country
- Provide relevant platforms and communication channels to promote transparency and share information with public

WG4. Systematic data collection of drug exposure during pregnancy: "Is there a role for PV centres?"

Objectives:

- To discuss the current activities that are ongoing in PV centres related to drug exposure during pregnancy
- To discuss and come up with minimum requirements (material and tools) for collecting and managing prospective and retrospective data
- To identify the stakeholders of PV
- To list the resources needed by national PV centres for the management of drug-risk during pregnancy

Expected outcomes:

- Short list a few 'feasible' methods to collect data of drug exposure during pregnancy and impact (on fetus, mother, child /neonates)
- Provide recommendations on
  - How PV centres could engage in these methods and with groups collecting data
  - How WHO should support these efforts (develop guidelines; coordinate efforts; establish international platforms?)

- How WHO CCs could support the process (develop tools, provide training?).

Discussions: Some centres receive reports on adverse pregnancy outcome through the yellow card (ADR reporting form). But the yellow card is not designed to collect information on pregnancy. Most health-care professionals (HCPs) do not report pregnancy status. Some PV Centres collect additional information on drug exposure retrospectively, when there are cases of congenital anomalies, but this works only when there is a good system for keeping health and treatment records. Some centres collaborate with academic researchers to generate information on possible drug exposure and adverse pregnancy outcome.

The group made the following general recommendations:

- Additional fields (example, yes/no check boxes should be added to ADR reporting forms to record pregnancy; and to record date of last menstruation.
- Medicine use data can be approximated for exposure data in a community; use of other health records as additional source of pregnancy outcome and drug exposure could also be considered if available;
- A national centre should design a specific form for prospective data collection on exposure to specific medicines during pregnancy; Use electronic patient management tool to generate data on exposure and outcome
- The PV Centre should advocate expedited reporting of congenital anomalies in fetus/neonates; reports of late fetal death; reports of spontaneous abortion; and reports of ADRs in a newborn/neonate that is fatal, life-threatening, resulting in persistent or significant disability/incapacity or resulting in or prolonging hospitalization
- The PV centre should design an investigation form and a protocol to support relationship assessment between drug exposure and adverse pregnancy outcomes
- PV centres should educate public and health professionals on the appropriate use of medicines and raise awareness to the risk of abortions and fetal abnormalities with some medicines

The group made the following specific recommendations:

WHO to:

- Support the efforts of national centres in developing specific guidelines, methods and algorithms for assessment; coordinate PV efforts; establish international platforms and expert committees

WHO CCs to:

- Support the process by developing tools, providing training, updating pregnancy data in VigiFlow, and harmonising inter-country data for exchange of information

WG5. Providing information: helping consumers understand benefits versus risks with medicines

Objectives:

- To highlight the importance of providing benefit / risk information to consumers
- To underscore the fact that communicating with consumers is quite different from communicating with health professionals and authorities
- Understand the challenges in providing Benefit /Risk information to consumers: balancing the information (not sensationalising / fear-mongering), balancing right to information, and confidentiality issues; etc.
- Discuss various methods, tools and information products for communicating with consumers
- Understand what countries are doing in this area (legal framework? NGOs? Methods?).

Expected outcomes:

- Key points on what, when and how to communicate Benefit /Risk to consumers
- A mapping of what or if countries are doing to communicate Benefit /Risk to consumers
- Any specific action required of WHO (e.g. Guidelines)
- Any specific recommendations to WHO CC (e.g. develop communication tools; provide communication platforms)
- Any specific recommendations to countries (e.g. to publish experiences, share know-how through WHO PV Toolkit, VigiMed etc.).

Discussions: The group discussed specific aspects of communication in PV: proactive communications approach; planning and message content using appropriate materials for patients; the various channels to use to publicise the materials; the need for a dedicated person/toll-free number for patients and their care givers to contact for information; cultivating good relations between media and the centres; conveying a balanced information to patients.

The group made the following recommendations:

WHO/WHO CCs to:

- Develop a tool kit for communicating with patients that national centres can adapt (a 'pick and choose' menu).
- Provide more in-depth training for PV professionals on how to communicate with patients and care-givers (outside of the PV training)
- Provide a platform for sharing PV information with patients and caregivers

PV Centres to:

- Have an in-house communication professional
- Provide general training to all centre staff in communicating safety information and interacting with the public
- Organize national/regional training in public relations and PV communications

WG6. Signal detection in low and middle income countries (LMIC): relevance and approach

Objectives:

- To explore the WHO definition of 'Signal' and the type(s) of Signals implied in this definition
- To understand various PV issues in countries that need 'signalling': ADRs, interactions, misuse, off-label use, quality issues, lack of awareness, programmatic errors, process related issues (e.g. labelling deficiencies) etc.
- To discuss the role and collaboration of various groups in determining such Signals
- To discuss the current Signal detection process at the UMC and how this could be developed in view of the expanding scope of PV to meet country needs.

Expected outcomes:

- To identify priority safety issues related to product, process, use-related and programmatic issues in countries
- To recommend a process for the development of the Signal detection method, to identify the priority issues
- To propose roles and responsibilities for various stakeholders (PV centres, WHO CCs, WHO, health professionals, others) in implementing the full scope of PV and Signal detection.

Discussions: The group discussed the existing definition of Signal and to what extent it applies to the needs of LMIC. In general, in the 1990s, there were many more developed countries with functional PV systems; LMIC on the other hand had little or no engagement in PV.

The products in the developed country market were then 'relatively' new, with the potential for new ADRs and Signals. But now, as the LMIC are catching up, the PV activities in these countries are unlikely to pick up any new Signals for the products available since the 1990s. However, it is timely to focus on Signals of products that are being used only in these settings, for example, some of the antimalarial medicines. It is now possible to think of Signal detection in the specific context of LMIC needs because ADR reports are now becoming available from these countries.
But on the other hand, there are use-related issues that can be signalled and picked up through PV activities in both LMIC and HIC. Problems of misuse/overuse of antibiotics and injectable products, ignorance or lack of adherence with known contraindications, off-label use, irrational combinations and problems related to quality issues such as decreased or lack of effect, and self-medication can be signalled through an alert PV system.
In other words the concept of Signal detection needs to evolve in a manner that is both relevant for the present times and also useful for all Member States (WHO PIDM).

A country should first define and prioritize the medicine-related problems that it wishes to 'Signal' and address: ADRs with medicines (and indications) that are specific to their setting, irrational use, quality issues, and preventable adverse events etc. Some methods may be used in specific situations, for example, the Pmethod, developed by the WHO CC Rabat, to Signal/ Flag issues of preventable 'ADRs' from a national PV database, and VigiLyze could be used to search the WHO Global database, to validate / strengthen the Signal. VigiMed, the electronic information exchange platform managed by UMC, could also be used by countries to flag and query Signals and information of mutual interest.

The Group made the following recommendations:

National PV Centres to:

- In order to identify issues that are relevant to the country in question, LMIC should utilize their own data instead of fully relying on the UMC and/or big regulatory agencies
- LMIC should NOT only try to detect previously unknown ADRs, but they should also pay attention to Signals of public health concerns and drug related problems in their respective countries.
- The Regulators in LMIC should take regulatory measures according to the identified Signals and alert HCPs as well as public to minimize risks. But,
  - Before following the decisions from other countries, regulators in LMIC should carry out their own benefit-harm assessment and validation of the decision for local relevance and decide accordingly.
  - Countries should share the decision, together with the basis for the decision, with other Member States and WHO.

WHO-CC (UMC) to:

- Develop the use of disproportionality ratios for Signal detection within national or regional datasets

WHO to:

- Promote the full scope of PV and Signal detection to support also the detection of Signals of all problems associated with medicines, not only new ADRs

WG7. Patient reporting and involvement of civil society in PV: what is the added value?

Objectives:

- Identify additional groups we should engage with
- Learn how (if) countries engage such groups in PV
- Value added, roles and responsibilities
- Framework, rules of engagement, supportive processes and technical solutions to engage these stakeholders.

Expected outcomes:

- A shortlist of groups and ongoing country efforts in this area
- Recommendations to countries, WHO CCs and WHO for relevant action in this area.

Discussions: The group addressed the usual concerns and objections to patient reporting:

- The volume of reports: experience from other countries suggests it is a manageable workload
- Fake reports: this can be a problem but should not stop us accepting reports from patients

On the other hand patients are more likely to report “embarrassing” ADRs that they would not usually share with the HCPs. Patients might be taking herbal or other self-medication that they may not want their doctor to know. Patients provide more information about the impact of ADRs on the quality of life, an aspect only they can report, adding to our understanding of the full significance of an ADR. On the question of whether reports from patients should be stored in a separate database, the group agreed that, to support a comprehensive understanding of the issues, it might be better to store all reports in the same database, but flag the source of the reports (from patients, hospitals, pharmacies etc.).

How to stimulate patient reporting? This is best done through campaigns by patient organizations/ communities. The campaigns need to be regular and sustainable. It should be easy to report, asking least but most essential information from the patient, using a reporting device and format with simple terminologies and adapted to the target group (paper forms, telephone, apps, reporting via a pharmacy or pharmacist). Feedback is essential to sustain the interest in patients, both to acknowledge the contribution and to provide useful advice on the treatment and the ADRs.

The Group made the following recommendations:

- WHO should issue a statement to encourage patient reporting in countries.
- UMC and MedDRA MSSO to collaborate on the development of patient friendly reporting terminologies.
- WHO should develop an easy to use medication guide for patients.

WG8. Signal detection in vaccines: What can be learnt from Signal detection of drugs and what needs to be specifically developed for vaccines?

Objectives:

- Discuss the definition of Signal
- Define Signals in the context of drugs and vaccines
- Understand current practice in Signal detection:
  - How it is done for medicines (with examples); what have we learnt through this process; how do we communicate Signals
  - How it is done for vaccines (examples); what have we learnt through this process.

Expected outcomes:

- To have a better understanding of Signal detection issues for vaccines and medicines
- To map areas of collaboration and mutual learning for Signal detection (between vaccines and medicines networks)
- To propose recommendations to countries, WHO CCs and / or WHO for improving Signal detection for medicines and vaccines.
- How do we communicate Signals

Discussions: The group compared the CIOMS and WHO definitions of a Signal and noted that the CIOMS definition is more detailed and includes the concept of beneficial as well as adverse effects. Most countries do not consider beneficial effects when characterising a Signal. The group also considered definitions of ADR (WHO), AE (FDA) and AEFI. Some countries still use the term ADR, while some countries are replacing this with AE, as used by the US FDA for medicines, and which is also similar to the AEFI definition. Some countries (e.g. Canada, USA) have separate reporting systems and databases for vaccines and medicines. Some countries have the same reporting system but analyse data separately: of the countries in the working group, Sweden, New Zealand, Australia and Italy use the same data mining tool but compare vaccines with vaccines only; Korea is considering a similar approach. In Malaysia, the PV centre analyses AEFI data together with the immunisation program. Korea collects both medicines and vaccines in the same database but AEFI data are also collected by the public health institute, this has resulted in duplicates; Korea is now considering a project to integrate the two. Many countries have access to vaccine expertise through expert advisory committees while many countries assess AEFI with the help of the Immunisation Programmes.

Exposure or denominator data (=number of individuals given a vaccine or a medicine) are needed when analysing Signals. For medicines this information can be obtained from dispensing databases, and for vaccines information can be obtained from vaccination registers. Italy has a vaccination register which also collects safety data.

Communication strategies/views on publishing information on Signals are different for the Immunization Programmes and for the National PV Centre. The CIOMS Taskforce on Vaccine Safety is working on a guideline on crisis management for vaccines. There are different thresholds for communicating Signals for vaccines and medicines, possibly higher for vaccines so as not to raise unnecessary concerns.

The group concluded that there are many similarities between drugs and vaccines in Signal detection and analysis; however, specific issues that are relevant to vaccines have to be considered. One common database (for medicines and vaccines adverse events) at the national centres is helpful and efficient although it should be possible to share data between PV centre and Immunization programmes. Similarly, analysis and Signal detection and investigations could be managed through a common advisory group that includes vaccines and medicines specialists and experts from the Immunization Programme and PV Centre. Different approaches would be needed for communicating and acting on Signals, for vaccines and medicines.

The group made the following recommendations:

Countries to:

- Establish a separate procedure (even if maintained in the same database) for data analyses of drugs and vaccines

WHO to:

- Promote stronger integration between drug monitoring and immunization programmes at all levels
- Provide more guidance on communication strategies for vaccines

UMC to:

- Improve VigiLyze for vaccines e.g. disproportionality analysis only within vaccines