Eleventh Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

Geneva, Switzerland, 14-16 May 2014

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. A summary of the discussions from the 11th meeting of ACSoMP is included below.

Safety and Vigilance (SAV) at WHO, Geneva

Safety and vigilance activities related to all medical products fall under the purview of the Safety and Vigilance (SAV) Team in the Department of Essential Medicines and Health Products (EMP). The SAV team is also responsible for the programme on monitoring and surveillance of substandard/spurious/falsely-labelled/falsified/counterfeit medical products (SSFFCs). The overall goal of SAV team is to provide evidence-based support to countries, to ensure the safe use of health technologies (devices, medicines, vaccines, procedures and systems) in patients. The SAV team works in close collaboration with the three other teams of medical products unit (Norms and Standards, Prequalification and Regulatory Systems Strengthening teams), with WHO public health programmes, with the National Regulatory Authorities, the national pharmacovigilance centres, the Uppsala Monitoring Centre (UMC) and other relevant WHO Collaborating Centres (in Oslo, Ghana, Morocco, the Netherlands), UN procurement agencies, WHO Advisory Committees, professional associations such as the International Society of Pharmacovigilance

(ISoP), groups representing industry (International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Council for International Organizations of Medical Sciences (CIOMS), control laboratories, manufacturers as well as other internal and external stakeholders. Supporting the development of national vigilance systems and guiding them with relevant norms and standards, advancing the principles and exploitation of a global adverse events database, providing independent safety review and advice on priority products (vaccines and medicines) through committees of experts, strengthening the regulatory oversight for these, and developing effective monitoring tools and systems for SSFFC medical products are some of the key priorities for SAV.

Collaborating centres as core support to the WHO safety and vigilance programmes

There are 5 collaborating centres (CCs) that support SAV in its pharmacovigilance (PV) programme goals and objectives: WHO CC in Uppsala (the UMC), Norway , Ghana, Morocco, and the Netherlands. WHO SAV is responsible for the PV programme policies, framework, guidelines and a strategy for their implementation. The technical support for implementing WHO PV policies and guidelines is provided by the WHO CCs with a focus on building capacity in the countries for collecting, assessing and acting on pharmacovigilance data within the countries. Each Centre works with a set of core responsibilities, some of which are unique to the Centre in question while some overlap with the activities of other Centres. The UMC is the only Centre responsible for managing and maintaining the WHO global individual case safety reports (ICSR) database, data analysis and signal detection. A side event in future annual meetings of national pharmacovigilance centres will discuss joint strategies and work plans of the WHO CCs and WHO SAV, to allow better coherence and efficiency in their work.

WHO guidance on reporting forms

Public health programmes (PHPs) often request a standard Adverse Drug Reaction (ADR) reporting form from SAV, to collect and report the adverse events associated with treatment within these programmes. While the CIOMS form is useful for ADR reporting by manufacturers, it is not sufficient to catch all the details that are of importance to PHP, for example, details that would allow identification of programmatic errors. Besides, and in view of the

widening scope of PV worldwide, the ADR reporting form needs to support the detection of irrational use, medication errors, include features for recording information on specific products such as herbals and traditional medicines, etc. Some countries are also of the opinion that a WHO endorsed reporting form would be better accepted and promote ADR reporting in some settings. A WHO guidance document on the core information to be captured with the above objectives in view, together with a prototype reporting form would help PHPs and countries. The principles for a proposed model reporting form should define the data requirements, data structure, and the recording media (paper, electronic or both) and should support data transfer to a database or a computerized repository.

'APPS' for ADR reporting and the value of Electronic Health Records (EHR) in PV

WEB-RADR (Recognizing Adverse Drug Reactions) is a project funded through the private public partnership, the Innovative Medicines Initiative (IMI). The project aims to set policy & guidance and deliver robust information technology tools to address the potential for the reporting of adverse drug reactions (ADRs) through mobile applications and the recognition of drug safety signals from user comments in social media and the internet.

In the USA, RAPID (Real-time Application for Portable Interactive Devices) grew out of the experience with Adverse Events (AE) collection for the experimental drug peramivir during the 2009 H1N1 influenza pandemic. PV departments are encouraged to work with IT departments to optimise the use of such technologies. Smartphones and 'apps' may hold the key for improving ADR and Adverse Events Following Immunization (AEFI) reporting.

EHR is used in countries like the USA and its use makes the tracking of ADR submission convenient. EHR support the smarter management of information and reduce the inconvenience of paper files. EHR can serve as a nation's public health data, and EHR that includes PV data support patient management and assist signal detection. A working group should investigate the usefulness of EHR in patient care and for collecting PV data in low and middle income countries (LMICs).

Medication errors and risk minimization actions

A Risk Minimization Plan (RMP) defines the steps to minimize the probability and occurrence of harm to patients following the use of medicines. This responsibility (to develop an RMP) lies with the Market Authorization Holder (MAH). The traditional tools applied in routine risk minimization are product leaflets, labelling, Summary and Product Characteristics (SPC), pack-size and design, prescription status of the product, and in some cases, educational programmes. But in addition, the public health system should build risk minimization plans that complement the RMP from the MAH and through proactive PV activities to minimize harm. Actual risk minimization in practice is the result of good coordination between various stakeholders. A document that provides a step by step guidance on the roles and responsibilities of various stakeholders in managing Medication Errors (ME) through appropriate risk minimization plans and activities should be developed.

Minimal Information Model (MIM) for reporting safety incidents in health care

MIM is an inter-department initiative within WHO. The aim is to understand common information needed to capture patient safety incidents with various health-care interventions: blood transfusion, herbal medicines, injections, in-vitro diagnostics, medical devices, radiation, medicines, vaccines, etc. There are failures in learning from a patient safety incident. The MIM goal is to capture minimal concepts and relationship from a report to elicit learning. The current draft of MIM data elements are: incident identification (patient, age, time and location), incident type, outcomes, resulting actions and the reporter. Next steps include an in-depth inventory of reporting systems and how they operate at a country level and understanding how the reporting systems lead to learning.

Initiatives for harmonizing PV practice

The African Medicines Registration Harmonization (AMRH) aims to improve medicines regulation, through harmonization agreements on various aspects, including pharmacovigilance, and capacity building. Data sharing would improve regulatory decision-making in the region. There is some interest in setting up an African PV database, however, more clarity is needed on the objectives of setting up such a database, and to see if the WHO global PV database could address those objectives. Regional networks do fulfil a specific

regional need because of common interests, but guidance is needed to explain the concept of good collaboration and how the existing global system could support the regional needs without investing in a parallel system.

The Asia-Pacific Economic Cooperation (APEC) comprises of 21 economies, and, primarily exists for trade facilitation to promote economic growth. Regulatory convergence is one of the end goals. At the November 2013 APEC activity in Korea for PV convergence, the WHO Programme was acknowledged as an important part of global PV. The role of WHO in defining the PV curriculum and the need for compliance with the E2B standards were raised as important issues. There is opportunity for PV to be an economic driver with public health influence. The APEC process helped move up China as a manufacturer of a prequalified vaccine for WHO. One of the major challenges is the variation in languages in the region. The International Conference of Drug Regulatory Authorities (ICDRA) is another platform where the issue of regional harmonization can be raised and resolved among regulators, reinforcing the role of WHO as a coordinator of the process.

CIOMS activity report

The Council for International Organizations of Medical Sciences (CIOMS) acts as a forum to bring regulators and industry together to complement WHO's work. CIOMS' facilitation of communication between the global stakeholders has increased the spread of scientific knowledge and access to new PV data of public concern, and increased preparedness when launching vaccines in new regions or countries. Within the new European Union (EU) PV legislation, the definition of the term Adverse Reaction includes Medication Error. The CIOMS work includes grouping system organ classification with events that lead to medication errors.

Signal detection

Over the years, the UMC has actively revised the signal detection process, refining it to detect duplicate reports, drug-drug interactions and signals that are specifc to paediatric population. The main goal has been to detect and understand the variety of conditions on the ground, to enable the safer use of medicines as well as to minimize and prevent problems with medicines. In cases where avoidable (preventable) ADRs keep recurring (and surfacing as reports), this may actually be a relevant signal and indicator of medicine misuse,

or lack of knowledge of correct medicine utilization. The UMC has now started investigating for "evergreens", that is, known, preventable ADRs that continue to occur and get reported. In other words, a UMC research wing is focusing on "signals of preventable adverse drug reactions". It is important to follow up known signals because the disproportionate statistics may relate to use, storage, handling, product quality etc.

Reporting ADRs in preventive chemotherapy

The WHO Neglected Tropical Disease (NTD) programme is concerned with the quality and safety of medicines for the prevention of lymphatic filariasis (LF), onchocerciasis, trachoma, and schistosomiasis. Currently, seasonal malaria chemoprophylaxis is also being added to the program. A WHO handbook on ADR management in preventive chemotherapy was published in 2011, but the implementation remains a challenge. A majority of products within the NTD campaigns are donated by industry and are administered by non-medical personnel in a non-medical setting. As a result, ADR reports are not collected or managed systematically or by qualified medical professionals within the national NTD programmes. A more systematic and comprehensive NTD treatment plan is clearly needed. The vaccine safety blueprint for introducing AEFI reporting within Immunization programmes is a good model to introduce and build capacity for PV of medicines within NTD programmes.

Training courses database

A global mapping of available training courses was carried out by WHO through a web-based survey to create a database of available training courses. The database includes information on objectives, key subjects, target audience, venue and duration. Quality assurance of courses through standard setting exists and the evaluation of courses and their impact is the next step in this initiative.

ATC DDD Toolkit

The ATC DDD Toolkit is intended to pool together various reference documents on the Anatomical Therapeutic and Chemical (ATC) classification system and the Defined Daily Dose (DDD) for medicinal products and to support drug utilization research. When completed it will serve as a one-stop data source for all reference and guidance material that can support drug utilization research in countries with a view to improving quality of drug use. Results of surveys in EU and Pan-American countries show wide variation in

the knowledge and use of ATC DDD protocols. The creation of the ATC DDD toolkit was recommended at the 34th meeting of the International Working Group for Drug Statistics Methodology in Oslo, Oct 2013. Once developed it will be hosted as part of the PV Toolkit managed by the WHO CC in Ghana. ATC DDD can support pharmacoepidemiology and strengthen PV work.

EudraVigilance (EV)

EV is the European database of suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA). It is managed by the European Medicines Agency (EMA) on behalf of the EU medicines regulatory network. EMA provides data services, makes aggregated data public, sends available cases to the company marketing the medicines, provides monitoring services to identify signals of new or changing safety issues. In line with the new EU legislation on pharmacovigilance the EMA is currently working on the addition of the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre as a new stakeholder group, to be provided with individual case safety reports (ICSRs) originating from within the EEA in electronic format on a weekly basis. The benefits of these arrangements are that all EU case reports are delivered weekly to WHO according to the letter of the law. There are legal and technical conditions underpinning this exchange. Until those legal and technical requirements are met, EU national centres will continue to report directly to UMC.

Integrating PV within TB treatment programmes

The introduction of new drugs like bedaquiline into a regimen for adult patient with pulmonary multi drug resistant (MDR)-TB is subject to certain conditions. These are: close monitoring, appropriate patient selection and informed consent, use according to set of clinical recommendations and having an active pharmacovigilance in place. Ensuring proper monitoring of effectiveness and safety is particularly important for new drugs, novel regimens and when drugs are used off-label, to prevent avoidable harms. A policy on delamanid use is forthcoming. There are projects which have started in Belarus on Cohort Event Monitoring (CEM) of Antiretroviral/Anti-TB drugs and of linezolid in MDR-TB patients. WHO will assess the drug-safety profile of shorter regimens for MDR-TB in three countries in 2014-2015. PV for TB features prominently in a number of key TB publications, including the Global TB Report 2013, the forthcoming companion handbook to the WHO guidelines

on the programmatic management of drug-resistant TB, the bedaquiline guidance, the post-2015 WHO Global strategy for TB control and the International Standards for TB care.

A new AEFI causality assessment method

Application of the 6-category classification (very likely/certain; probable; possible; unlikely; unrelated; unclassifiable) that is currently used in the assessment of ADRs poses difficulties when applied to AEFI. According to the revised cause-specific categorization of AEFI by the Council for International Organizations of Medical Sciences (CIOMS) and WHO in 2012, there are 5 types of AEFI;

a. Vaccine product related reaction

b. Vaccine quality defect related reaction

c. Immunization error related reaction

d. Immunization anxiety related reaction

e. Coincidental event

In 2013, the WHO Global Advisory Committee on Vaccine Safety (GACVS) revised the AEFI causality assessment methodology and developed a new tool that has a four step process; (i) Eligibility: to determine if the AEFI case satisfies the minimum criteria for causality assessment, (ii) Checklist: to systematically review the relevant and available information to address possible causal aspects of the AEFI, (iii) Algorithm: to obtain a trend to the causality with the information gathered in the checklist and (iv) Classification: to categorize the AEFI's association to the vaccine/vaccination on the basis of the trend determined in the algorithm. At the end of the AEFI causality assessment, the event will be classified into 3 major categories viz.

-Consistent to immunization: this includes (vaccine product, vaccine quality defect, and Immunization error and immunization anxiety related-reactions)

-Inconsistent to immunization (coincidental events) and

-Indeterminate.

AEFI cases with inadequate information are deemed as unclassifiable.

The AEFI assessment method is not meant to replace the WHO causality assessment method currently used by countries to assess adverse reactions reported with drugs. A communique explaining the need for and use of the AEFI assessment method and worksheet should be sent from WHO to all countries.

Widening scope of PV

UMC has developed an algorithm for the detection of suspected SSFFC products through the analysis of clusters of suspected product inadequacies in Vigibase. The algorithm has been tested on existing datasets, as a retrospective validation of the method. During 2013-2014, a pilot study has been set up with six national centres to evaluate the algorithm in a more realistic setting. UMC will now perform a 'needs analysis', to determine the prerequisites that need to be in place for a country to be able to effectively detect SSFFC products through its pharmacovigilance system. The ultimate aim is to determine the role of pharmacovigilance networks as additional data sources to detect SSFFC products.

The WHO Expert Committee on Drug Dependence (ECDD) undertakes medical and scientific assessment of dependence producing medicines and their abuse liability. The ECDD meets every 4 years and provides recommendations on the level of control of substances. The UMC is exploring the potential use of PV data to inform scheduling decisions. In 2014, upon request, the UMC provided the ECDD committee with pharmacovigilance data on tramadol and ketamine, for the committee to consider in its deliberations. WHO SAV will continue to explore additional ways to support the functions of other WHO Expert Committees with PV data.

Use of hydroxy-ethyl starch (HES) solutions

The EMA has recommended that HES may continue to be used in severe haemorrhage at the discretion of the treating physician, while its continued use in peri-operative setting be put to further research. HES is a polymer of the polysaccharide amylopectin, used in hypovolemic conditions. Current information on usage show that 45% of resuscitation cases used HES. In 2008 to 2012, concerns on HES related adverse effects such as renal function in sepsis patients surfaced, prompting a risk-benefit assessment by EMA.

Based on available evidence, the EMA allowed the use of HES in severe haemorrhage at the discretion of the treating physician but contraindicated its use in sepsis and in critically ill patients. Furthermore, risk minimization measures such as limit on dose, limit on duration of use, monitoring renal function within 90 days of use, and asking industry to submit risk management plans to regulators were recommended. A call for more studies on use in peri-operative and trauma settings was made.

The evidence on HES is still evolving. However, in the meantime, and given its use outside Europe, WHO/SAV will develop an Information Note to Member States, to reinforce the conditions of use and safety measures to adopt when using HES. The Information Note will be communicated though the usual WHO communication means such as Drug Alerts, the WHO Pharmaceuticals Newsletter and the WHO Drug Information.

Thalidomide Embryopathy (TE)

A report from a consensus meeting organized by the UK Thalidomide Trust for establishing the criteria and decision tree for diagnosing Thalidomide Embryopathy (TE), and current theories of causative mechanisms in TE formation was discussed. Knowledge about thalidomide has informed certain restrictions on its use to avoid harm in fetus. However, given the wide re-use of this medicine, current controls may not be comprehensive enough to cover the vulnerabilities within the entire supply / use chain. The mechanism for teratogenicity is not fully elucidated.

Although the Consensus meeting was an initiative to develop criteria for TE diagnosis, ACSoMP endorsed the TE meeting report and acknowledged that the methods could be used for a wider capture of pregnancy-drug exposure data. WHO wishes to develop the principles for diagnosing embryopathies due to any medicine and to elucidate the mechanisms. This will complement the WHO work on setting up pregnancy registers to follow effects on children born to mothers who were exposed to medicines during pregnancy.