Conclusions and Recommendations from the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
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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.

Pharmacovigilance (PV) Priorities for World Health Organization (WHO):

- Increasing access to essential, quality, safe and affordable medical products is a leadership priority for WHO. The ongoing WHO-reform process is to ensure that the organization is more effective, efficient, responsive, objective, transparent and accountable to its partners and stakeholders. The scope of the Safety and Vigilance (SAV) team within WHO includes: advocacy for safety and vigilance activities, establishing and consolidating partnerships for implementing and advancing the safety and safe use of medical products, strengthening infrastructure, active surveillance and training in pharmacovigilance (PV), and supporting the use of effective tools and systems for monitoring medical products of significant public health importance.
- The 2016-2017 priorities for SAV/Medicines Safety are to focus on a few countries, to build capacity and support them through the full cycle of PV activities, from collecting PV data and information, to making regulatory decisions and therapeutic choices based on the collected information. The strategy would be to assess and to improve the quantitative and qualitative aspects of PV activities and outcomes in these countries. The long-term objective is to build comprehensive, sustainable, results-driven PV systems that improve our knowledge, power our decisions and promote the safe use of medicines.
- In moving forward, WHO should consider if the current programme needs to be more 'global' and include the safety and vigilance of all health-care products including medical devices, and diagnostic tests, how the lessons learnt from the WHO Programme for International Drug Monitoring (PIDM) could be developed further, and how PV systems could be enhanced to cover emerging priorities such as monoclonal antibodies, biosimilars and products of human origin.

WHO Collaborating Centres (CCs) that support the WHO PIDM:

- The Uppsala Monitoring Centre (UMC), a WHO CC for International Drug Monitoring will continue to develop user-friendly information materials on PV and step up its support to countries in signal detection, through the refinement of UMC's training curriculum and updates of data management tools such as VigiLyze and VigiFlow. The Centre will implement automated feedback to national PV centres (NPCs) submitting Individual Case Safety Reports (ICSR).
- In improving PV in sub-Saharan Africa, the WHO CC in Accra, Ghana, will collaborate with partners for comprehensive health and epidemiological surveillance systems and platforms for long-term and sustainable drug and vaccine safety monitoring in these settings. The Centre will provide training and support PV research and other activities in countries, including cohort event monitoring (CEM) and targeted spontaneous reporting of specified products and relevant data management systems.
- The WHO CC in Rabat, Morocco, plans to provide courses on medication errors and promote the P-method2 and use of root cause analysis, to detect and understand the reasons why preventable adverse events (AEs) continue to occur. The Centre will continue its work on integrating vigilance systems and harmonizing Arabic terminologies in PV.
- The WHO CC in the Netherlands will continue to exploit its research and experience in patient reporting, for additional insights into the value of patient reports, to support NPCs in setting up and running patient adverse drug reaction reporting systems. The Centre will support WHO in integrating PV in the medical curriculum. Its experience in establishing registers on the use of medicines in pregnancy as well as a toolkit will be useful to WHO in providing technical and country support in this area of work.
- The broader scope of PV requires a regulatory framework, to include planning, assessing and taking action in addition to collecting and investigating evidence of harm. The proposal to establish a new collaborating centre for PV in India should be considered in light of these requirements.
- The use of mobile phone and smart phone technology in AEs data collection and transmission is progressing rapidly, but given the limited internet access in some settings, applications that do not need immediate internet connectivity should be considered and promoted. Both WHO and its CCs should make this a priority and provide guidance and ensure that the necessary tools are available to those in resource-limited settings.

WHO-Bill and Melinda Gates Foundation (BMGF) partnership for PV:

- According to the report of the BMGF-appointed Safety Surveillance Working Group, new drugs, vaccines and diagnostics are now being developed specifically for low- and middle-income countries (LMIC) and it is a challenge for PV activities to keep pace with this new trend. In consequence, LMIC can no longer rely on post-market safety surveillance from developed economies. LMIC would thus need to be supported with a prioritized, well-coordinated and agile PV system. The Foundation supports focusing surveillance initially on specific risks and on products with a high risk profile, for a targeted period of time, through a single system for both vaccines and medicines, with tailoring only when required, using existing standards and platforms (Council of International Organization of Medical Sciences, CIOMS; ICH, WHO and others) and ongoing initiatives (e.g. African Medicines Regulatory Harmonization, AMRH; African Vaccines Regulatory Forum, AVAREF). PV capacity varies between countries and a stepwise approach appropriate to each country is needed. Overall there is strong encouragement and support for this approach.

- BMGF notes that there are many different stakeholders conducting a mixture of PV activities which are not coordinated and have resulted in duplication of efforts. WHO is in a key position to coordinate these activities. The divide between pre and post market safety data is merging, with some newer products reaching the market earlier in the phase of development. Risk management planning will be very important for these products and the role of WHO-appointed committees such as ACSoMP and the Global Advisory Committee on Vaccines Safety (GACVS) will be important in both risk management planning and in reviewing the global safety data from such products.

Medicines in Pregnancy:

- Sodium valproate, although very effective in epilepsy, has teratogenic properties and a serious risk of neurodevelopmental disorders. A number of regulatory steps to communicate and minimize risks have been pursued by the European Union (EU) regulatory authorities. However, there is still insufficient knowledge on the safety of this and other drugs during pregnancy, more needs to be done to improve understanding as well as risk minimization practices.
- A diagnostic decision-making tool using about 200 original cases of thalidomide-associated limb deformities and 200 negative controls (cases of known hereditary problem) has been developed to sift out the more robust cases. The tool has around 95% positive predictive value and 80% negative predictive value (i.e. it could miss 20% of people eligible for compensation). This tool is the result of a technical consultation convened in WHO upon the request of the United

Kingdom (UK) Thalidomide Association. Full details of this work are available in a complete report and can be requested from WHO.

- ACSoMP suggested that the principles, ideas and logic used to form this tool should be used to develop a generic tool for similar situations with other medications taken in pregnancy. The Committee could also be requested to review information on specific risks with medicines in pregnancy and to advice on how best to signpost new information. Agencies such as the European Medicines Agency (EMA) could be approached to organize a scientific workshop on drugs in pregnancy, to help WHO develop a general guidance document on the subject.

WHO guidance on Minimum PV Requirements:

NPCs have requested revisions to the WHO Minimum PV Requirements (Core Components) document. The existing version was designed for a specific purpose: to help the Global Fund (GFATM) support and monitor the implementation of PV within countries that received financial aid from GFATM. The revised document needs to be more comprehensive, designed to present the requirements more clearly and concisely, with a detailed description of the requirements that considers special needs of smaller countries, and provides broad guidance on the implementation of the requirements together with references to any existing guidelines. The Minimum PV Requirements document needs to align with the WHO PV indicators and the WHO National Regulatory Agency (NRA) assessment tool, and the step wise approach adopted in these documents.

PV of medicines used in TB treatment:

- Multi Drug-Resistant Tuberculosis (MDR-TB) or Extensively Drug-Resistant TB (XDR-TB) patients are being treated with new medicines (e.g. bedaquiline (BDQ), delamanid), novel regimens (e.g. MDR-TB shorter regimen) and repurposed drugs (e.g. clofazimine, linezolid). Three levels of monitoring are being used: Core package, which requires monitoring for and reporting of all serious adverse events (SAEs); Intermediate package, which includes SAEs as well as AEs of special interest; and Advanced package, which includes all AEs of clinical significance. The level of monitoring is selected in accordance with the PV capacity in the country, for example a country with limited capacity may adopt the core package.
- The Drugs Controller General of India (DCGI) has approved the use of BDQ to treat MDR-TB in six TB-treatment centres across India, the country with the highest TB burden (annual incidence 2.2 million). The first patient was enrolled in June 2016. Owing to the complexity of treatment (involving as many as 16 medicines), extensive training of medical staff is needed. A national workshop on BDQ was held in July 2015 and a subsequent workshop that focuses on PV, CEM

and causality assessments will take place in August 2016. The Indian Council of Medical Research (ICMR) and Central TB Division have developed guidelines, ready-reckoners and reference manuals for patients, health workers, medical officers and specialists for prevention and management of anti-TB drugs. Two reporting forms have been developed for CEM: a treatment initiation form and a treatment review form for use at every follow-up visit or event. Paper forms will be filled on site, and then entered into the TB software, NIKSHAY. Parallel to this, routine spontaneous reporting forms will also be available. Any SAE will be reported within 24 hours through NIKSHAY (automatic Short Message Service (SMS) and email to the Data Safety Monitoring Committee (DSMC)). This data will then pass via the NIKSHAY-VigiFlow bridge to VigiFlow, the national data management system used by the PV programme in India (PvPI), ensuring seamless transfer of information between the TB programme and the PV Centre. Causality assessment will be carried out at the treatment sites and interpreted further by the expert safety committee, DSMC that includes a hepatologist, cardiologist, respiratory specialist and a general physician. The DSMC will also carry out periodic benefit harm assessment to inform the Revised National Tuberculosis Programme (RNTCP) and the DCGI on safety aspects of BDQ-containing regimen.

- Whilst it is necessary to monitor adverse effects, the effectiveness of new products such as BDQ is also very important and needs to be captured to assist in benefit-harm assessment and to provide balanced therapeutic recommendations. It is also important to have access to pre marketing safety and efficacy data. In the interest of patients and global learning, ACSoMP recommends sharing of pre marketing and post marketing safety and effectiveness data on BDQ by all concerned: EMA and US FDA who originally approved its use; countries that are rolling out BDQ; and Janssen Pharmaceuticals, the manufacturer.
- India would also request ACSoMP's review of data as these accumulate. Acknowledging the local solutions proposed by countries such as India and Indonesia, to share data between the TB programmes and the PV centres, ACSoMP recommended similar collaborations and software solutions for seamless data entry and data sharing between PV centres and other public health programmes.

Integrating PV in seasonal malaria chemoprevention (SMC) programmes:

- The SMC programme involves treatment at monthly intervals with amodiaquine and sulfadoxine-pyrimethamine for children aged between 3 and 59 months living in areas of high seasonal malaria transmission across the Sahel region. The treatment begins at the start of the malaria transmission season and continues for up to four months during the season. The treatment gives a high level of

protection for four weeks, so it has to be taken at monthly intervals. PV is very important for the success of this programme and needs strengthening throughout the region. A 3-day workshop on PV in SMC was held in Rabat, Morocco in 2015. In a second meeting held in February 2016 which focused on lessons learnt, participants requested more PV training in countries implementing SMC, with contents tailored to the different cadres of care providers. WHO has now adapted the WHO-International Society of Pharmacovigilance (ISoP) PV curriculum to SMC-specific PV training modules and will use this in subsequent PV trainings in the countries implementing SMC.

- The Committee endorsed the training material and emphasized the importance of involving PV centres in the training, to include training well before SMC-launch, and tailored-training. The Committee also reiterated its previous recommendation that all AEs (both serious and non-serious events) should be collected in SMC.
- A SMC safety review committee has been established, to review PV data from SMC in countries and to provide advice on any risk management plans.

Antimalarial cardiotoxicity :

Several WHO-recommended quinoline antimalarials (chloroquine, quinine, mefloquine and piperaquine) are associated with prolongation of the QTc interval. A lengthened QT interval is a risk factor for ventricular tachyarrhythmias, like torsades de pointes (TdP), which can cause sudden cardiac death. TdP is a significantly underestimated problem. There are often many potential confounding factors, including many concomitant medications that could provoke QT prolongation. There is a possibility that these factors are not captured adequately in spontaneous reports of TdP. WHO is reviewing all available data on cardiotoxicity of antimalarials, and will provide these to an Expert Review Group, to understand the magnitude of the problem and propose how the risk could be managed. A recommendation was made that AEs detected in clinical studies are submitted to VigiBase®, the WHO Global database of ICSR.

WHO response plan to identified safety concerns of antimalarial medicines :

No medicine is without risk. Risk assessment considers the specific risks of the medicine, together with the seriousness of the condition being treated, the expected benefit of the drug, the population being targeted, the expected use of the medicine in actual practice, the setting of care, the potential for misuse, and the available alternatives. A number of tools can be used for risk minimization, including information notes and guidelines, updating product information, and manufacturing restrictions such as restricted pack size and withdrawal of a product from the market. The WHO Global Malaria Programme (GMP) has proposed a framework for risk management plans to identified risks and safety concerns with antimalarial medicines. The framework is

intended for various stakeholders including pharmaceutical industry, private-public partnerships, for example, medicines for malaria venture (MMV) and will advance risk management plans that consider feasibility (on the ground practicalities), proportionality and burden when making decisions. The framework on the response plan will be elaborated to provide detailed guidance on avoiding risk (when possible) and early detection, empowering patients and health care providers. Planning and frequent communication will form essential elements of the plan.

Control of soil-transmitted helminthiasis (STH) (deworming activities):

- STH is endemic in 102 countries, and there are approximately 266 million preschool-age children, 600 million school-age children and 250 million women of child-bearing age at risk. They are at risk because they are in a period of intense need of micronutrients, and a high worm load is very demanding nutritionally. The WHO objective is to reduce morbidity due to STH to a level below which it would not be considered a public health problem. At-risk groups in endemic areas are given preventive chemotherapy consisting of large-scale administration of the anthelminthic drugs albendazole and mebendazole. From the veterinary field, there is evidence that helminths can develop resistance against benzimidazoles when drug pressure is intense. For this reason it is proposed to limit drug distribution to the above-mentioned at-risk groups and to maintain a background number of unexposed individuals in the population. In order to broaden drug treatment options against STH, it is now being proposed to use three different drug combinations: (1) albendazole and ivermectin (existing combination but new indication for STH); (2) pyrantel and oxantel; and (3) tribendimidine and moxidectin (innovative drugs). Retrospective data will be collected on the safety of these medicines, using literature reviews, other large-scale Neglected Tropical Diseases (NTD) campaigns, VigiBase® and EudraVigilance. New data will be collected from drug trials when existing safety and efficacy data are insufficient.
- ACSoMP will be fully informed of potential 'new' drugs/drug combinations for STH and the rationale for treatment expansion, and will be requested to provide input on sources of safety data and to provide guidance on appropriate steps for increasing drug expansion in NTD recommendations. The Committee will be updated on progress of collection of safety data.
- The Committee noted that communication before rolling out large scale deworming programmes is very important, particularly since many teachers and community workers are involved in the administration of medication. Integration of the NPC with the National NTD programme facilitates communication and reporting of adverse effects. Greater links with WHO CCs on the field would also be useful.

- Mass drug administration of the new medications will not be considered in the initial stages of use as safety data from clinical trials are insufficient. The safety profile should be gathered from use on a small scale before scaling up. If available, periodic safety update reports (PSURs) for the listed medications in the EU should be shared with the WHO NTDs. Safety reports/evidence should be reviewed by ACSoMP or a subgroup that is accessible to ACSoMP before presentation to the decision makers.

Updates on PV in EU:

- The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee at the EMA that is responsible for planning, assessing and monitoring safety issues for human medicines. In 2015, they reviewed over 650 draft risk management plans. Risk management plans are critical for early market entry of promising medicines with limited safety data.

- Approximately half of new and follow-up signals that are presented to PRAC lead directly to a label change, highlighting how a PV system can lead to regulatory change.
- Large volumes of PSURs are submitted to the EMA through one portal within the EU. High level summaries of the reports are made public.
- In January 2016, PRAC adopted a strategy for measuring the impact of PV activities. The Key Performance Indicators (KPIs) used to measure the impact of PV are being analysed within the European system and can be presented to ACSoMP at a future meeting. During the development of the KPIs, the WHO PV Indicators were noted and additional regulatory indicators were added. WHO/SAV is encouraged to consider a subset of relevant KPIs in its work. A workshop on measuring the impact of PV activities will be held at the EMA office in London, 5-6 December 2016. The workshop will focus on the methodology of measuring impact in three areas: process, health related, and patient engagement.
- There is a legal requirement to develop a new version of the EudraVigilance that delivers better health protection through simplified reporting, better quality data and better searching, analysis and tracking functionalities. The new International Organization for Standardization (ISO)-ICSR data format will be used. All reports from EudraVigilance will go directly to UMC (rather than from 31 individual EU countries). This will start in late 2017