Annual Report
WHO Headquarters
Safety and Vigilance/Medicines 2015/2016

World Health Organization
Activities from October 2015 to October 2016
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About Safety and Vigilance at WHO Headquarters

The World Health Organization (WHO) is the United Nation’s specialist agency for health. Amongst a range of health issues, it covers safety and vigilance of medicinal products via the WHO Programme for International Drug Monitoring (PIDM), which was set up in 1968 following the thalidomide tragedy. WHO pharmacovigilance (PV) activities are coordinated by the Safety and Vigilance (SAV) team which forms a sub-unit of the Essential Medicines and Health Products Department at WHO Headquarters in Geneva.

WHO SAV’s overall goal is to provide evidence-based support to countries to guide the safe use of health technologies (devices, medicines, vaccines, procedures and systems) in patients, although at present the focus is primarily on medicines and vaccines. Future developments will address safety issues of other technologies and how these could be effectively managed through the SAV team.

SAV works in close collaboration with the WHO Medical Products unit (Norms and Standards team, Prequalification team, and Regulatory Systems Strengthening team), with WHO public health programmes, with National Regulatory Authorities, the National Vigilance Centres, with various WHO Collaborating Centres, UN procurement agencies, 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, and manufacturers as well as other internal and external stakeholders.

The WHO overall vision is that health is a fundamental human right, and everyone has the right to the highest possible level of health. The primary role of WHO is to direct and co-ordinate international health. The detection, assessment and prevention of adverse drug reactions (ADR), through PV, ultimately improve patient care and safety. WHO aims to define norms and standards of PV internationally, provide leadership and strategic guidance to PV centres, monitor trends and articulate policy options. The WHO PIDM is the platform that allows SAV to pursue its PV objectives for medicines. The platform is coordinated by SAV/Medicines with technical support from four Collaborating Centres to advance PV in countries. These are, in the order of establishment, the WHO Collaborating Centre (WHO CC) for: International Drug Monitoring, Uppsala, Sweden; Advocacy and Training in PV, Accra, Ghana; Strengthening PV Practices, Rabat, Morocco, and PV in Education and Patient Reporting, Lareb, the Netherlands. These four WHOCCs are responsible for research and scientific development, capacity building and technical support to countries. The WHO CC in Sweden also maintains and manages the global database of individual case safety reports, Vigibase on behalf of WHO and its Member States. A fifth Collaborating Centre, the WHO CC for Drug Statistics Methodology, located in the Norwegian Institute of Public Health in Oslo, Norway, supports WHO/SAV by developing and training countries in the use of the Anatomical Therapeutic and Chemical Classification system for medicinal products and their Defined Daily Doses (ATC/DDD).
## Abbreviations

ACSoMP: Advisory Committee on Safety of Medicinal Products
AMRH: African Medicines Regulation and Harmonization
APEC: Asia-Pacific Economic Cooperation
ATC/DDD: Anatomical Therapeutic Chemical classification and Defined Daily Doses
BMFG: Bill & Melinda Gates Foundation
BDQ: Bedaquiline
CC: Collaborating Centres
CEM: Cohort Even Monitoring
CHAI: Clinton Health Access Initiative
DFID: UK Department for International Development
EAC: East African Community
EMP: Essential Medicines and Pharmaceutical Policies
EMRO: WHO Eastern Mediterranean Regional Office
EFPIA: European Federation of Pharmaceutical Industries and Associations
EWG: Expert Working Group
GAB: General Advisory
GA-DDD: Guyana Government Analyst Food and Drug Department’s
HQ: Headquarters
ICDRA: International Conference of the Drug Regulatory Authorities
ICH: International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA: International Coalition of Medicines Regulatory Authorities
ICSR: Individual Case Safety Report
ISOP: International Society of Pharmacovigilance
LMIC: Low and Middle Income Countries
MDR-TB: Multi Drug Resistant Tuberculosis
MedDRA: Medical Dictionary for Regulatory Activities
MoU: Memorandum of Understanding
MRH: Medicines Regulatory Harmonization
MSH: Management Sciences for Health
NC: National Centre
NEPAD: New Partnership for Africa’s Development
NMRA: National Medicines Regulatory Authorities
NPVC: National PV Centres participating in the WHO Programme for International Drug Monitoring
PAP: Pan African Parliament
PHP: Public Health Programmes
PIDM: Programme for International Drug Monitoring
PV: PV
PVSF: Pharmacovigilance Sans Frontiers
REC: Regional Economic Communities
RCOREs: Regional Centres of Regulatory Excellence
RSS: Regulatory System Strengthening
SIAPs: Systems for Improved Access to Pharmaceuticals
SMC: Seasonal Malaria Chemoprevention
SSFFCs: Substandard Spurious Falsely Labelled Falsified Counterfeit
TB: Tuberculosis
TBS: Technical Briefing Seminar
UMC: Uppsala Monitoring Centre
UNAIDS: Joint United Nations Programme on HIV/AIDS
USAID: United States Agency for International Development
WAHO: West African Health organization
WEB-RADR: Recognizing Adverse Drug Reactions
WHO: World Health Organization
WHO CC: WHO Collaborating Centre
WHO/SAV/Medicines: Medicines group in WHO Safety and Vigilance team
WPRO: Western Pacific Regional Office (of WHO)
Advisory Committee on Safety of Medicinal Products

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003 to provide advice to WHO and its Collaborating Centres, and Member States of WHO (through WHO), on safety issues relating to medicinal products. ACSoMP guides WHO on general and specific issues related to PV (PV). The Committee is composed of 12 members drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management, and where appropriate, in consultation with other relevant WHO clusters and expert advisory panels. ACSoMP meets once a year to discuss ongoing and new PV topics, with focus on issues related to public health programmes.

Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products Geneva, Switzerland

The Thirteenth meeting of the WHO ACSoMP took place in Geneva, Switzerland from 21 to 22 June 2016.

The Thirteenth ACSoMP meeting discussed:

- Strategy for PV in low and middle income countries
- Medicines in pregnancy: thalidomide, valproate
- WHO guidance on minimum requirements for PV
- PV of medicines used in TB treatment
- Integrating PV in Seasonal Malaria Chemoprevention
- PV of antimalarials
- EU initiatives that might be of benefit to other WHO countries
- PV of neglected tropical medicines

Recommendations from the meeting are available in Annex 1.
Drug Statistics Methodology

The International Working Group for Drug Statistics Methodology supports the WHO Collaborating Centre in Oslo in developing and maintaining the Anatomical Therapeutic Chemical classification of medicinal products and their Defined Daily Doses (ATC/DDD). The Working Group meetings are twice a year (one face to face and one virtual meeting) for approving/reviewing ATC codes and DDDs. Drug utilization studies are also a focus of these meetings. WHO SAV/Medicines appoints the Working Group members and, together with the WHO CC, convenes the Working Group meetings.

The 39th (virtual) and 40th (face to face, in Geneva) meetings of the WHO International Working Group for Drug Statistics were held on 17th of March 2016 and 27th-28th October 2016 respectively. The Centre assigned 72 new ATC 5th level codes and 47 new DDDs in 2015.

The first WHO workshop on drug utilization research and tools was held from 5 to 7 October 2016 in Rabat, Morocco. Please see page 22 for more details.
## Summary of Publications

### WHO Pharmaceuticals Newsletter

Six issues of the WHO Pharmaceuticals Newsletters. The WHO Pharmaceuticals Newsletters shared:

- Information on regulatory decisions and safety of medicines worldwide
- Recommendations from the 2016 ACSoMP meeting
- Signals published by UMC
- Feature articles on training courses

### Guidelines, manuals and recommendations

- Recommendations from the thirteenth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), see Annex 1.
- French translation of WHO PV indicators: A practical manual for the assessment of PV systems.

### Research publications co-authored by WHO/SAV/Medicines Safety (2015-2016)

PV proposal within the initiative for African Medicines Regulatory Harmonization (AMRH)

In 2008, at the 13th International Conference of the Drug Regulatory Authorities (ICDRA), members (100 WHO Member States) made a request for WHO to support harmonization approaches. This would enable national medicines regulatory authorities (NMRAs) to use their resources more effectively. In response to this request, WHO initiated discussions with global partners. This led to the formation of a consortium consisting of eight main members: the New Partnership for Africa’s Development (NEPAD), the Pan African Parliament (PAP), the Bill & Melinda Gates Foundation (BMFG), the UK Department for International Development (DFID), the Clinton Health Access Initiative (CHAI), the Joint United Nations Programme on HIV/AIDS (UNAIDS), World bank, and the World Health Organization (WHO). In February 2009, NEPAD and PAP organized a conference in Birchwood, Johannesburg, South Africa. A wide range of stakeholders, over 40 NMRAs, and nine Regional Economic Communities (REC) attended. A consensus was reached and the African Medicines Regulatory Harmonization (AMRH) was established.\(^1\) The AMRH initiative aims to improve the access of safe and effective medicines in Africa through regulatory harmonization in the continent. The AMRH programme supports African RECs and countries. In 2012 WHO and NEPAD Agency entered into a Memorandum of Understanding (MoU) with WHO to collaborate on the implementation of the AMRH Programme.

Initially the programme focused on harmonizing requirements for medicines registration. However due to demand by RECs and countries there was a drive to promote harmonization of PV and clinical trials. In May 2014, NEPAD agency designated Regional Centres of Regulatory Excellence (RCOREs) to specific regulatory functions. RCOREs are institutions or partnership of institutions with specific expertise and strength in training. The aim of the RCORE initiative is to increase capacity development in Africa in the expert areas of regulatory function. The designated RCOREs for PV are: WHO Collaborating Centre for Advocacy and Training in PV, Accra, Ghana; and the Pharmacy and Poisons Board in Kenya.

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\(^1\) WHO support for medicines regulatory harmonization in Africa: focus on East African Community. WHO Drug Information,. 2014;28(1)
East African Community Medicines Regulatory Harmonization (EAC-MRH) Programme

The East African Community (EAC) is a Regional Economic Community (REC) consisting of five Member States: Burundi, Kenya, Rwanda, Uganda and United Republic of Tanzania. EAC was the first REC to secure funding from AMRH to support the implementation of the AMRH initiative (see page 9). This led to the formation of the Medicines Regulatory Harmonization (EAC-MRH) project which was formally launched during a meeting in March 2012 in Arusha, United Republic of Tanzania. The main purpose of the EAC-MRH project is to improve access to safe, efficacious and good quality medicines by harmonizing medicines regulation systems and procedures in accordance with national and international policies and standards.

The EAC-MRH project is guided by the steering committee which provides oversight to the project objectives and implementation. WHO is a member of the steering committee. EAC had prepared a proposal on strengthening PV and post marketing surveillance systems for medical products in the region. The proposal was discussed at the sixth meeting of the Steering Committee on 5 March 2015 in Kigali, Rwanda. The Steering Committee recommended the following:

a) The draft project proposal on PV be reviewed by WHO by May 2015.

b) The EAC Secretariat to convene a meeting of the Expert Working Group (EWG) and supporting partners and submit the final project proposal to the 7th Steering Committee meeting for consideration.

WHO, under the advice of ACSoMP, reviewed the draft proposal in 2015, to guide the alignment of the proposal with the WHO minimum PV requirements and good vigilance practices. In July 2016, EAC convened a meeting to develop an implementation plan on the PV proposal; the meeting was held in Entebbe, Uganda. As a technical partner, WHO contributed to the process and guided the work-plan.

International Council on Harmonisation of Technical Requirements for Pharmaceuticals for human use

International Council on Harmonisation of Technical Requirements for Pharmaceuticals for human use (ICH) is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety quality and efficacy of medicines. ICH makes recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration on an international level. Hence, it aims to reduce unnecessary duplication of clinical trials in humans and minimize the use of animal testing during the research and development of new medicines. This is more economical and can eliminate unnecessary delay in the global
development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

WHO follows the activities of ICH over regulatory harmonization and supports countries outside ICH to implement good practices. WHO has been an observer of the committee since ICH was created in 1990. WHO/SAV/Medicines has attended two ICH meetings from October 2015 to October 2016, in particular the sessions on MedDRA Management Board and expert working group on electronic transmission of ICSRs and multi-regional clinical trials.

Seasonal Malaria Chemoprevention

Severe malaria is a life-threatening disease that occurs mostly among children living in Africa, where it is estimated that a child dies every minute from malaria. Natural immunity to malaria is usually acquired in children living in malaria endemic areas by the ages of seven to ten years. However younger children living in these areas have inadequate immunity and are at greater risk of developing severe malaria.

In 2012, WHO made a recommendation for the implementation of Seasonal Malaria Chemoprevention (SMC) in areas of high seasonal malaria transmission across the Sahel sub-regions. This consists of a combination of amodiaquine and sulfadoxine-pyrimethamine (AQ + SP) which will be administered to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season, provided both drugs retain sufficient antimalarial activity.

ACCESS-SMC is a UNITAID-funded project, led by the malaria Consortium in partnership with Catholic Relief Services, which is scaling up access to SMC across the malaria endemic sub-Saharan countries. The project will last three years and is supported by London School of Hygiene and Tropical Medicine, Centre de Support de Santé International, Management Sciences for Health, Medicines for Malaria Venture, and Speak Up Africa. It will provide 30 million SMC treatments annually to 7.5 million children less than five years of age in Burkina Faso, Chad, Gambia Guinea, Mali, Niger and Nigeria, potentially averting 49,000 deaths due to malaria.

The countries providing SMC vary in PV capacity. Some have an established PV system, and others have no formal National Centres for PV and are not part of the WHO PIDM. In order to ensure effective safety monitoring, the 2012 WHO policy for the Global Malaria Programme recommends that existing PV systems require strengthening and where PV does not exist, it should be instituted.
The WHO SAV/Medicines Group is working with other WHO departments, WHO CCs and access-SMC to build PV capacity in countries that will deploy SMC. In February 2016, a workshop was organized to share lessons learnt after the first year of SMC deployment. Following this workshop WHO developed PV training modules based on WHO-ISOP\(^2\) curriculum to address training needs (see page 19). The modules were developed and a three-day workshop was organized in Ouagadougou, Burkina Faso in September 2016 (see page 22).

**Bill & Melinda Gates (BMGF) Foundation Project**

Access to medicines and medical products in low and middle income countries (LMIC) has improved in the last few years. But development in PV systems have been slow and inadequate to effectively monitor the safety of these products. This is a concern given the number of novel products that are likely to be introduced exclusively in LMIC, with limited or no experience from resource-rich settings to guide their introduction in LMICs. In September 2016, SAV signed a grant agreement with the Bill & Melinda Gates Foundation for a project on “Optimizing post-marketing surveillance of priority medicines and vaccines in low and middle income countries”. The Project will run for 36 months (three years) and proposes strengthening of PV systems and practices in selected countries in Africa, to support the introduction of new health products through identification, assessment, and management of any risks associated with them. The activities will include piloting a set of key pharmacovigilance (PV) principles using selected new products, in selected countries, to establish the proof of concept for strategies aimed at building or strengthening PV systems in low- and middle-income settings. Project activities will include close liaison with the WHO Regulatory System Strengthening (RSS) team.

**UNITAID-funded projects**

UNITAID is a global health initiative financed by a levy on airline tickets. Established in 2006 by the governments of Brazil, Chile, France, Norway and the United Kingdom, it provides sustainable funding to tackle inefficiencies in markets for medicines, diagnostics and prevention for HIV/AIDS, Tuberculosis and Malaria in developing countries.

Since 2013 SAV/Medicines supports UNITAID efforts in improving access to medicines through a comprehensive four step strategy:

\(^2\) WHO-ISOP curriculum was developed by WHO in close collaboration with the International Society of PV (ISOP)
1. Determine the UNITAID supported products that are expected to be introduced in low and middle income countries (LMICs) over the next five years and the countries where these products will be introduced.

2. Review known and incompletely characterized post-market safety risks of those drugs.

3. Assess current capacity of the launch country to undertake post-market safety surveillance of high-risk products.

4. Develop methods to better characterize the safety profile of UNITAID supported products; build capacity in launch-countries to undertake post marketing surveillance of UNITAID products.

In 2015, a paper on targeted spontaneous reporting (TSR) in patients on ARV therapy in Uganda was published in Drug Safety, as was a paper on implementation of cohort event monitoring (CEM) in four African countries. In addition, experience with CEM of malaria treatment in Tanzania was described in a research article that was sponsored by WHO.

In 2016 the PV team in WHO is analyzing large individual patient data series for well-documented reports of sudden cardiac death following drug exposure. The analysis includes possible exposure to concomitant medicines which prolong the QTc interval. The overall aim of this project is to investigate the risk of cardiotoxicity in quinolone antimalarials, as background work for the WHO Malaria Expert Review Group, and for advice on updates to malaria treatment guidelines.

SAV is adapting its WHO ISoP PV curriculum to develop a training course for health-care professionals involved in SMC. A training course was provided to clinicians, nurses and pharmacists at district level and to support countries in forming district investigation teams to manage adverse events (particularly serious adverse events) during SMC, other public health programmes and adverse drug reactions in general (see previous section on SMC page 11 and page 22).

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Web recognition of adverse drug reactions (WEB-RADR): General Advisory Board

The WEB-RADR (Recognizing Adverse Drug Reactions) project is a consortium of leading experts in pharmacovigilance from regulatory agencies, research and academia. Together with European Federation of Pharmaceutical Industries and Associations (EFPIA) partners 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. The policies, guidance and tools delivered through WEB-RADR will be underpinned by extensive academic research and user testing to ensure the project meets the needs of all stakeholders.

The project is managed by the Vigilance and Risk Management of Medicines Division at the UK Medicines and Health Products Regulatory Agency (MHRA) (the project Coordinator).

WHO SAV is represented by Dr S Pal on the General Advisory Board (GAB) that has been established to provide general guidance and recommendations to the Steering Committee of the WEB RADR project on scientific, technical and ethical aspects of the WEB RADR work program, to support the successful delivery of the project. The GAB consists of the project Coordinator (MHRA), seven Work Package Leaders or Work Package co-Leaders (one member from each Work Package), and seven members collectively chosen by the participants for their expertise.

The face to face GAB meeting in April 2016 reviewed the issue of alternative data sources in view of planned new access policies to data sources such as Facebook. A paper on alternative data sources and sustainability plan has been developed as part of the project risk register and will guide the consortium in mitigating this risk. A smart-phone based adverse events (AE) reporting ‘App’ has been developed as part of the WEB RADR project. WHO SAV is in discussions with MHRA and other WEB RADR partners to pilot the ‘App’ in selected non-EU, low and middle income countries.

International Coalition of Medicines Regulatory Authorities (ICMRA) pharmacovigilance project

International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities. Pharmacovigilance is one of the strategic initiatives and the ICMRA pharmacovigilance project team is chaired by Australia and currently comprises 14 countries/ international groups, as follows: TGA Australia (also as secretariat), ANVISA Brazil, Health Canada, EMA, CFDA China, COFEPRIS Mexico, MHLW and PMDA Japan, HPRA Ireland, HSA Singapore, MHRA UK, MPA Sweden, Swissmedic Switzerland, WHO and US FDA.
Each regulator in ICMRA has established processes and international pharmacovigilance systems under WHO. The collaboration identifies areas for sharing of learnings to assist policy discussions at the agency head level with the potential for developing collaboration on information sharing in selected areas in the longer term. There are three priorities that the ICMRA PV project will focus on: 1) how best to utilize “big data” for pharmacovigilance purposes; 2) what policy approaches are most successful in increasing the rates of adverse reporting, in particular from health care professionals; 3) are there workable approaches by which the existing pharmacovigilance systems can be linked? It was agreed to have three subgroups, each focusing on one policy issue. Several members volunteered to take part in a small working group to develop a discussion paper on each policy issue. WHO is a member of each project group. Each of the three groups has developed a reflection paper which summarizes a number of the key issues and current programs operating in participating regulators and internationally around each of the three topics. The papers were made available to the ICMRA management (MC) committee end of June 2016 together with work priorities for the period to the end of 2016 for endorsement.

A few specific issues were raised by the MC on sub-projects, however the planned focus and work areas for each of the PV sub-projects were endorsed. The project team was asked to make sure that the PV projects didn’t duplicate any other activities that were underway. Other specific comments were made:

**Big data:**
- The ICMRA MC meeting agreed that it would be good, if possible, to reach out to other ICMRA regulators for lessons learned because we are all still learning about how to acquire and use such datasets.
- Some prioritization of activities was discussed including how we can draw on the experience of other ICMRA members.
- Some discussion about where big data work might go in a couple of years’ time (eg ICH, international pharmaceutical regulators forum, etc) but that there was still work to do under the ICMRA banner over the intervening period.

**Adverse events reporting:**
- The proposed immediate priorities were agreed.
- It was particularly noted that some of the approaches to increasing adverse event reporting, especially by health professionals, were important but would involve additional cost and effort. Discussion included that it was important to consider the cost versus the additional benefits for stimulated adverse event reporting. In particular, MC members expressed interest in learning more about the experience of different regulators with stimulated adverse event reporting.
- There was also interest in the patients’ perspective and the work being done by the UK and in the EU SCOPE initiative and others, including on registries.
Linking existing PV systems:
- It was agreed (and EMA had also made this point with Ireland), that this project is important, but had limited scope and duration.
- Discussions included how to make existing systems work better and interact better with each other.

**Training, meetings and Capacity Building**

**November 2015**

38th annual meeting of National PV Centres participating in the WHO Programme for International Drug Monitoring (PVC), New Delhi, India

The 38th annual meeting of representatives of National PV Centres participating in the WHO Programme for International Drug Monitoring (NPVC) was organized by WHO/SAV/Medicines, the WHO country office in India and the Pharmacovigilance Programme of India (PvPI).

The meeting was hosted in New Delhi, India. The Minister of Health and Public Welfare in India attended the inauguration ceremony and made a speech. Over 100 representatives from over 40 countries attended the meeting.
During the meeting, countries had the opportunity to interact with the four WHO CCs that support WHO PIDM. They learnt of the type of support available and were able to inform WHO and WHO CCs of their centres work and development plans.

The meeting sessions consisted of plenaries, updates, working groups and problems of current interest. Each plenary was chaired by a panel, and delegates participated in discussions following presentations. Topics covered in the plenary sessions included, the importance of storytelling in PV, success stories in Oman and Chile, building a global safety culture, PV in a small country (strategies, challenges, opportunities and inspirations), signal detection, the PV programme in India: current status, integration with public health programmes, and the role of adverse drug reaction (ADR) monitoring centres. During the update sessions, presentations were made on: adverse events reporting during mass drug administration, patient reporting, using PV indicators in routine PV practice, and the WHO-UMC algorithm to detect Substandard/spurious/falsely-labelled/falsified/counterfeit medical products (SSFFCs). Eight working groups took place over the first two days of the meeting. Delegates had the opportunity to select and attend two. During the working groups participants took part in discussions and worked together to formulate recommendations for NPCs, WHO and WHO CCs. The recommendations were presented to all participants on day 3 of the meeting. The recommendations from the meeting were published in the WHO Pharmaceuticals Newsletter No1, 2016⁶ (see extract from Newsletter in Annex 2, on page 26).

December 2015

Workshop on PV Inspections, China

The WHO HQ (SAV and RSS) and the Country Office organized a workshop on PV inspection upon request from the State Food and Drug Authority (SFDA) SFDA, in China from 14 to 18 December 2016. PV inspectors from the Agency for Medicinal Products and Medical Devices of Croatia, Halmed were appointed chief facilitators at the course. The course integrated technical information using interactive and participatory methods of teaching. The workshop consisted of three days of classroom learning and mock inspections at two pharmaceutical sites, one for vaccines and one for medicines.

African Pharmacovigilance experts- Pharmacovigilance Sans Frontiers (PVSF)

The seventh meeting of Pharmacovigilance Sans Frontiers (PVSF) took place in Accra, Ghana from 26 to 27 November 2015. PVSF is a group of African consultants with interest in pharmacovigilance whose focus is on drug safety issues in the African setting and has helped

strengthen the establishment of PV in Africa. Communication of safety messages and strengthening communication skills for the effective engagement with policy makers and other stakeholders were discussed.

**African Society of Pharmacovigilance (ASOP)**

The African Society of Pharmacovigilance (ASoP) is an international non-profit scientific organisation, which aims to foster pharmacovigilance both scientifically and educationally, and enhance all aspects of the safe and proper use of medicines, in all countries in Africa. ASOP was formed during the 32nd Annual Meeting of National Centres participating in the World Health Organisation Programme on International Drug Monitoring in Rabat, Morocco, in November 2009. The second Annual ASOP meeting was held in Accra, Ghana from 25 to 27 November 2015. The theme for the conference was: Pharmacovigilance in Africa; New Methods, New Challenges, New opportunities. Participants from both public and private sectors attended the meeting. Discussions included upcoming deployment of innovative health products in the next few years and the need to organize continental human resources to ensure that PV is strengthened to meet the emerging challenges of the continent.
February 2016

Seasonal Malaria Chemoprevention and PV workshop, Rabat, Morocco

Seasonal malaria chemoprevention (SMC, previously known as intermittent treatment), is defined as the intermittent administration of full treatment courses of antimalarial medicines during the malaria season to prevent malaria illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk (see page 11).

Following on from a workshop in May 2015 which aimed to strengthen PV or support countries to build a PV system (if non-existent), representatives from the National Malarial Programmes and National PV Centres in countries that deploy SMC medicines met again to discuss challenges, success and lessons learnt after the first year of SMC.

The workshop was hosted by the WHO Collaborating Centre for Strengthening PV Practices, in Rabat and organized in collaboration with WHO and London School Hygiene and Tropical Medicines. Representatives from Ghana and Senegal also joined.

The workshop lasted three days and started with a presentation of safety activities implemented by each of the countries. Countries presented their key achievements and challenges associated with integrating PV. Discussions on the reporting flow, referral systems and capacity for
performing laboratory investigations when needed were held. Feedback on PV training during the SMC campaign was provided. In addition, examples of different reporting tools, e.g. e-reporting, phone-reporting and SMS-reporting were presented. Finally, a plan to form a regional safety committee was consolidated. Moving forward, it was agreed that more time needs to be allocated to PV training in future campaigns, and that training should extend to doctors/nurses/pharmacists in district hospitals. Technology was identified as a key tool to assist with reporting, for example the use of e-reporting. WHO agreed to use the WHO ISOP PV curriculum to update existing PV modules to assist with PV training in SMC. In addition, e-reporting is available to VigiFlow® users with no additional costs.

April 2016

East African Advanced Course on Pharmacovigilance and Risk Management

WHO supported a conference/workshop that was organized by the Government of Eritrea, Ministry of Health, National Medicines and Food administration Agency, in Asmara, Eritrea from 11 to 15 April 2016. Theme of the workshop was: Safer drugs and vaccines to market by analyzing latest developments in PV, drug safety and risk management. The course covered a wide spectrum of topics, building an effective PV system, preparing for PV audit/inspection and signal detection.

May 2016

Francophone Technical Briefing Seminar, Geneva, Switzerland

Since 1998, the WHO Department of Essential Medicines and Pharmaceutical Policies organizes a number of Technical Briefing Seminars (TBS) every year. These seminars are aimed at people working on medicines issues in pharmaceutical and health sector programmes in developing and transitional countries. Each seminar aims to provide a technical update on a range of issues and programmatic approaches, with opportunities for discussions between participants and other experts around topics related to quality, access and use of medical products. The Francophone seminar was conducted, and attendees included staff from governments and non-governmental organizations, technical advisers, medicines experts working in the public sector institutions, field staff at WHO and staff from other UN bilateral agencies. A session on PV and the WHO PIDM was provided in by the WHO CC, Rabat on behalf of WHO/SAV/Medicines.

Tenth Annual training course for PV in Francophone countries

WHO supported the annual PV training course for Francophone countries, which was organized by the WHO CC for strengthening PV systems, and took place in the Centre Anti poison et Pharmacovigilance du Maroc, in Rabat Morocco from 9 to 20 May 2016. The course included key
concepts of PV with practical activities to integrate pharmacovigilance within public health programmes.

**September 2016**

**In-country training on basic PV**

To support the Guyana Government Analyst Food and Drug Department’s (GA-DDD) plan to create a PV centre, WHO organized a workshop in Georgetown, Guyana from 13 to 17 September 2016. The workshop was delivered in two phases. The first phase was a two day sensitization workshop designed for health-care professionals. The second phase lasted three days and was delivered to GA-FDD staff members and focused on establishing and running a PV centre. The workshop built awareness about overall public health and patient safety concerns in relation to medicines use. Basic concepts, methods, and terminologies used in PV were introduced. Staff members of the GA-FDD learnt about coding, data-management, causality assessments, signal detection, benefit-harm assessment, evidence based regulation and treatment policies.

**PV education in undergraduate curricula**

WHO and the WHO CC for PV and Patient Reporting held a meeting to discuss the development of PV global core curriculum for undergraduate medical, pharmacy and health-care professional students, in the Lareb PV Centre in ‘s-Hertogenbosch, the Netherlands, from 29 to 30 September 2016. During the meeting, subjects to be included in the core curriculum were defined, recommendations on when subjects should be taught, which other subjects can be combined to PV subjects, and the best methods of teaching PV were made. Participants included academics from India, Italy, Oman, Sierra Leone and the Netherlands.

**Asia-Pacific Economic Cooperation Harmonization Center PV Workshop and Training, Seoul, Republic of Korea**

Asia-Pacific Economic Cooperation (APEC) is a regional economic forum established in 1989 and currently consists of 21 members (Australia, Brunei, Darussalam, Canada, Chile, People’s Republic of China, Hong Kong China, Indonesia, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, Philippines, Russia, Singapore, Chinese Taipei, Thailand, United States of America, Viet Nam).

An APEC PV workshop was held in Seoul, South Korea. Approximately 180 participants joined the workshop (1 day) on 5 September 2016, from National PV Centres, regulatory authorities, industry and academia from APEC economies. The workshop included PV activities of EU, Asia-Pacific, and Industry (regulatory perspective). A representative from WHO took part as a panelist in one of the sessions.
Following the APEC PV workshop, a training programme was organized by the Korea Institute of Drug Safety and Risk Management in collaboration with APEC Harmonization Centre and Ministry of Food and Drug Safety, from 6 to 8 September 2016. The programme lasted three days and included presentations and hands on training on ICH E2B guidelines, PV methods, causality assessment, risk-benefit assessment and communication.

**October 2016**

**Workshop on integrating ATC DDD system in PV and drug utilization research: promoting the quality of use of medicine**

WHO and, the WHO CC for Strengthening PV Practices (Rabat, Morocco) and the WHO CC for Drug Statistics and Methodology (Oslo, Norway) organized the workshop, which took place in Rabat, Morocco from 5 to 7 October 2016. The objectives of the workshop were to: introduce the principles of drug utilization research data sources and methods for collecting on drug use; to introduce the principles of investigating quality use of medicines and to share country experiences on medicines-use surveillance for selected products such as amoxicillin and levonorgestrel; to demonstrate the use of tools and resources to detect and analyze medication errors and preventable adverse drug events. Participants included health-care professionals from Kenya, Niger, Oman, Tunisia, Uganda, United Republic of Tanzania and Zanzibar.

**Workshop on integrating PV in Seasonal Malaria Chemoprevention in Burkina Faso**

A three day workshop was organized by WHO in Ouagadougou, Burkina Faso. The workshop was designed for participants from district hospitals. Participants included doctors, nurses and pharmacists from different districts in Burkina Faso. In addition, the focal persons for the national malaria programme and national PV programme in Burkina Faso and other Francophone countries that deploy SMC (Chad, Guinea, Mali, and Niger) also attended. The programme consisted of presentations on basic PV concepts and techniques, with a focus on adverse drug reactions in children and the pharmacology of medications used in SMC. Group exercises included causality assessments. The concept of district investigational team, was introduced and roles and responsibilities of stakeholders were discussed. Participants expressed that they appreciated having the workshop in country and at district level and proposed that the workshop is repeated in other countries that deploy SMC medications.
Countries joining the WHO Programme for International Drug Monitoring from November 2015 to November 2016

At present, there are 153 National PV Centres who have joined the WHO Programme for International Drug Monitoring (PIDM). The newest members are Haiti, and Malawi, who joined as associate members. In addition two countries (Afghanistan and Panama) made the transition from associate members to full reporting members of the programme.

International Society of Pharmacovigilance meeting in Agra

International Society of Pharmacovigilance (ISOP) is a professional, independent, non-profit society open to anyone with an interest in the safe and effective use of medicinal products. The annual ISOP meeting took place in Agra, India from 16 to 19 October 2016. The theme of the meeting was: Pharmacovigilance for safer tomorrow. WHO was involved in shaping the agenda and was part of the scientific committee. A representative from WHO chaired the session on Global PV perspectives and was Chair of the poster prize committee. In addition, a WHO abstract for a systematic review of the economic costs of adverse reactions to drugs in low and middle-income countries was presented as an oral presentation. The abstract has been published in the journal Drug Safety (2016, Vol 39, No.10).

Anatomical Therapeutic Chemical (ATC) classification and Defined Daily Dose (DDD) Toolkit

WHO has developed a toolkit for the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) methodology. The toolkit is a comprehensive online resource for drug utilization studies. The toolkit will be available for use by the end of 2016, early 2017.
### Summary of training events and meetings supported by WHO/SAV

<table>
<thead>
<tr>
<th>Event/meeting</th>
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<tr>
<td>Annual conference of the Society of PV</td>
<td>31 October-2</td>
<td>Kolkata, India</td>
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<td>November 2015</td>
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<td>38th annual meeting of representatives of National PV Centres participating in</td>
<td>4-6 November</td>
<td>New Delhi, India</td>
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<td>WHO Programme for International Drug Monitoring</td>
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<td>Meeting of African PV experts- PV Sans Frontiers (PVSF)</td>
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<td>(PVSF)</td>
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<td>African Society of Pharmacovigilance (ASOP)</td>
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<td>International Council on Harmonisation of Technical Requirements for</td>
<td>5-10 December</td>
<td>Jacksonville, USA</td>
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<td>Pharmaceuticals for Human Use (ICH) meeting (MedDRA management board,</td>
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<td>PV inspection course</td>
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<td>Joint training course between the Uppsala Monitoring Centre and –JSS</td>
<td>18-29 January</td>
<td>Mysore, India</td>
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<td>Monitoring Centre and –JSS University India</td>
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<td>Seasonal Malaria Chemoprevention and PV Workshop</td>
<td>10-12 February</td>
<td>Rabat, Morocco</td>
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<td>39th meeting (Virtual) of the WHO International Working Group for Drug</td>
<td>17 March 2016</td>
<td>Conference call</td>
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<td>Francophone Technical Briefing Seminar by WHO Department of Essential</td>
<td>9-13 May 2016</td>
<td>Geneva, Switzerland</td>
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<td>Medicines and Pharmaceutical Policies</td>
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<td>International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) meeting (MedDRA management board, working groups for: electronic transmission of ICSRs, multi-regional clinical trial)</td>
<td>11-16 June 2016</td>
<td>Lisbon, Portugal</td>
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<td><strong>July</strong></td>
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<td>The second WHO working group meeting on interaction of herbal medicines with other medicines</td>
<td>11-16 July 2016</td>
<td>Oxford, Mississippi, USA</td>
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<td>Asia-Pacific Economic Cooperation(APEC) Harmonization Center PV Workshop and APEC PV CoE pilot program</td>
<td>5-8 September 2016</td>
<td>Republic of Korea</td>
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<td>PV training course in Guyana</td>
<td>13-17 September 2016</td>
<td>Georgetown, Guyana</td>
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<td><strong>September</strong></td>
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<td>Meeting to review the Erice PV declaration</td>
<td>25-28 September 2016</td>
<td>Erice, Italy</td>
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<tr>
<td>Workshop on Integrating PV into Seasonal Malaria Chemoprevention</td>
<td>27-29 September 2016</td>
<td>Ouagadougou, Burkina Faso</td>
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<td>Meeting on PV education in undergraduate curricula</td>
<td>28-30 September 2016</td>
<td>‘s-Hertogenbosch, the Netherlands</td>
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<td><strong>October</strong></td>
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<td>WHO workshop on drug utilization research and tools</td>
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<td>Technical Briefing Seminar by WHO Department of Essential Medicines and Pharmaceutical Policies</td>
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Annex 1 Recommendations from thirteenth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

Conclusions and Recommendations from the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
21 - 22 June 2016

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 PV (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:**

National Pharmacovigilance Centres (NPVCs) 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, ACoSMP 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 ACoSMP’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, ACoSMP 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 PV (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 PV 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.
Annex 2 Recommendations from the Thirty-eighth Annual Meeting of National PV Centres, 2015, New Delhi, India

The thirty eighth annual meeting of representatives of National PV Centres participating in the WHO Programme for International Drug Monitoring was held from 4 to 6 November 2015, at New Delhi, India. The meeting included eight working groups that discussed various issues in PV.

WG1. Practicalities of establishing and running a pregnancy register to follow outcomes of drug exposure

For WHO CCs and WHO:
- Lareb (the WHO Collaborating Centre for PV in Education and Patient Reporting) to provide technical support, with WHO as lead, in the development of tools (which would include specific guidelines, communication and training materials) that would be used by other countries. The developed tools should take into account the differences between countries.
- WHO to support model National PV Centres in the process of developing tools.

For National PV Centres:
- To support the integration of ‘pregnancy PV activities’ into their public health programmes.
- Countries that would like to develop registries should start on a small scale and expand

WG2. Reporting and learning systems for medication errors, the role of national centres, WHO collaborating Centres and WHO

For National PV Centres:
- To increase capacity and competence of the National PV Centres to identify and analyze Medication Errors (ME).
  - Identify obstacles to reporting ME and learning
  - Document procedures
  - Investigate if funds from public health programmes may be used to support MEs Reporting and Learning Systems
  - Invest in research on ME, to find out the burden of MEs in public health programmes.
- To optimize the Individual Case Safety Reporting Forms to capture MEs.
- To focus on reporting and publishing.
- To adapt definitions of adverse drug reaction and medication errors for the local legal situation (e.g. in the EU, medication errors are included in the definition of ADR).
- To improve individual record-keeping in medical facilities.
- To pursue regional collaboration between centres for competence-sharing and training on ME analysis.
• To make ADR/ME reporting one of the criteria in the private health care sector for accreditation.
• To follow the US model of getting hands-on training for pharmacists joining the PV centre, to get 6 months training in the FDA and six months in the Institute for Safe Medication Practices (ISMP).
• To conduct a study with volunteer countries to validate the ‘P method’ for detecting preventable ADRs.

For WHO and WHO CCs:

• To propose a Council for International Organizations of Medical Sciences (CIOMS) working group, to clarify discrepancies in definitions between patient safety and PV networks

WG3. Data mining/signal detection at national centres: when, how, why

For WHO and WHO CCs:

• To help with capacity building in NPCs for data-mining and signal detection.
• To facilitate training through e-training and e-fora.
• To develop standardized tools for data-mining and signal generation (incorporating VigiLyzeTM).
• To help develop a template/generic SOP for signal detection to be adopted by interested countries. To help build data-mining and signal detection into public health programmes at the point of inception, and to advise on/provide software to assist this process.
• To continue to develop and increase awareness of software, in particular VigiLyzeTM, for data-mining and signal detection and make these freely available to the countries (downloadable on the internet) to help compare national data with that of other countries.
• To support NPCs with a strategy for raising funds for this area of work

WG4. How can PV centres work with any relevant associations that can provide data and/or insights, including patient organizations and public health programmes

National PV Centres should consider the following in their collaborations with:

1. Public health programmes (PHPs)

   • Collaborations should be beneficial for both parties
   • Make best use of the available resources
      - PHP infrastructure to promote reporting
PV centre knowledge for designing reporting form for PHPs (which might need modification from the spontaneous reporting form) and signal detection

- Schedule regular meetings where information is exchanged, so that all information can be used both by PHP and PV centres in their decision making
- Define roles and responsibilities clearly
- Keep scientific independence
- Document agreements (memorandum of understanding)
- Consider that different PHP programmes in one country may require a different approach.

2. Patient organizations

- Collaboration should be beneficial for both parties
- Listen to what patient organizations want
- Clarify what can and cannot be done
- Use patient organizations as ambassadors for National PV Centres
- Also involve other organizations, for example women’s associations or consumer organizations
- For contacting patient organizations:
  - Raise the awareness about PV centres and what is being done in media directed to the public (this will encourage patient organizations to contact or invite National PV Centres to collaborate)
  - Choose either an umbrella organization or the biggest/most active organizations and approach these actively.

**WHO and WHO CCs are recommended to:**

- Create a platform where experiences (success stories but also initiatives that failed) can be shared. The stories should be practical, so that readers can try and adopt them in their own setting
- Modify existing platforms such as VigiMed and Uppsala Reports instead of creating new ones
- Include these subjects (PHPs, patient organizations) in training, using experienced organizations as trainers.

**WG5. Where is PV heading/ the future of PV**

**For all:**

- Develop and promote education and training for health-care professionals and PV staff
- Support and streamline existing curriculum initiatives (including WHO-ISoP and Lareb curricula) to meet the needs of basic medical and PV education

- Explore innovative methods for raising public awareness of PV.

- Facilitate the collection of best practice examples for sharing among member countries (including the dissemination of ‘Take&Tell’)

- Implement the WHO PV indicators in member countries using a standard protocol

- Assess impact of PV activities

- Explore new sources and new methods for collection of patient safety data

- Explore the benefits of engaging professionals from other disciplines such as psychologists, health economists, social scientists, implementation scientists, communications experts, eco-pharmacologists, and others

- For WHO CC UMC:
  - Find a technical solution for reporting adverse drug reactions in situations without internet access
  - Develop Vigimed as a user-friendly collaboration portal and encourage its use
  - Familiarize all member countries with the use of database tools such as VigiLyzeTM, VigiGrade, etc.

The working group recognizes and commends the Sierra Leone PV Centre for its courage and persistence they displayed in the Ebola epidemic in their country; the working group proposes that such vivid examples of the robust effectiveness of PV should be collected and used at the highest levels for the purposes of advocacy and fund-raising.

**WG6. The need for quantitative benefit-risk assessment in PV**

**For WHO and WHO CCs**

- Provide training (capacity building)
- Provide technical guidance
- Include benefit-risk information in newsletters
- For National PV Centres
- Regulators such as FDA and EMA should share how they reach benefit-risk conclusion
WG7. Revisiting the WHO Minimum PV Requirements

For WHO:

- WHO should develop the new set of minimum requirements for PV and detailed guidelines to accompany the minimum PV requirements, and submit these to the 2016 National Centres meeting for approval.
- Proposed Minimum Requirements for National PV Centres
- A National PV Centre collaborating with the WHO Programme for International Drug Monitoring and implementing at least a spontaneous reporting system
- National spontaneous reporting system with form(s) for capturing and reporting adverse events to medical products including medicines, vaccines, medical devices etc.
- A national database or system for collating, managing and sharing PV data
- A functional national advisory body for PV
- A communication plan for stakeholders in PV (to include over-the counter, internet purchases and non-medicinal drugs)
- Legislation on PV
- Formal link to National Regulatory Authority
- Established procedures for measuring impact of the national PV system
- Designated full-time staff to fulfil the minimum requirements of national PV centre
- Dedicated financial and technical resources to fulfil the minimum requirements of national PV centre

WG8. How to capture adverse events due to over-the counter (OTC), internet purchased (IP) and non-medical drugs (NMD)

- Set up a website of agents/groups that are accredited for online sale of medicines.
- Develop a tool that can help NPCs to detect adverse events online e.g. stories shared on social media
- Make Vigimed more user-friendly
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