The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it, to the Member States of WHO, on safety issues relating to medicinal products. A summary of discussions and key recommendations from the 16th meeting of ACSoMP is provided below.

WHO Programme for International Drug Monitoring: A milestone
In November 2018, the WHO Safety & Vigilance (SAV) Team organized a celebration to mark the 50th anniversary of the WHO Programme for International Drug Monitoring (PIDM). The celebratory event was followed by the usual annual (technical) meeting of WHO PIDM members, attended by representatives of national pharmacovigilance centres.

Collaborations in WHO on Safety & Vigilance
ACSoMP noted that relations continue to get stronger between the WHO SAV team and WHO disease control and treatment programmes. When requested, SAV extracts and reviews data from the WHO global database of Individual Case Safety Reports, Vigibase, on medicines used within these programmes. And through ACSoMP, SAV has been supporting the programmes with timely advice on the safety of these medicines.

ACSoMP members commented that the potential value of greater collaboration with the immunization and vaccines safety programmes would be worth exploring.

The Council for International Organizations of Medical Sciences (CIOMS) has the status of a non-State Actor (NSA) in official relations with WHO. SAV team collaborates with CIOMS in preparing the workplan on projects of mutual interest. The workplan for the years 2019-2021 was approved by the Executive Board at its 144th Session in January 2019, with a decision to maintain the CIOMS official relations with WHO. The Executive Board will review the status of the implementation of the workplan in 2022, according to its triennial schedule for reviews.

A WHO policy brief, drafted by the WHO Technology, Standards and Norms (TSN) Team aims to guide regulators in traceability standards and ensure appropriate governance. Many traceability standards already exist, and WHO does not aim to develop new standards, but to explain the opportunities of track & trace technologies (and their risks), to ensure greater accountability, and to enhance information-sharing. Pharmacovigilance is in scope of the project and the goal for the policy guidance would be to enable local and global pharmacovigilance.

The Identification of Medicinal Product (IDMP) standards were developed by the International Organisation for Standardisation (ISO) to facilitate the reliable and consistent exchange of medicinal
product information by providing a common product “language”. In terms of pharmacovigilance, IDMP standards would enable adverse event reports to be based on a harmonized set of product definitions, improving the quality of data used for signal management, and speeding up communication, decision-making and actions.

WHO SAV and the WHO Regulatory System Strengthening (RSS) teams are organizing a workshop to discuss the IDMP use-cases as well as the maintenance of the Pharmaceutical Product Identifiers (PhPIDs) within the IDMP. ACSoMP welcomed the idea of a global system of identification of medicinal products as this would facilitate pharmacovigilance. A WHO-led joint maintenance strategy for IDMP pharmaceutical product identifiers would be ideal.

ICH E19 Working Group: WHO SAV also participates, as an observer in this working group, for the elaboration of the ICH guideline on Optimisation of Safety Data Collection. The draft guideline is currently undergoing public consultation, for review and comments.

WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC)

The Uppsala Monitoring Centre (UMC) has been responsible for the technical and operational aspects of the WHO Programme for International Drug Monitoring since 1978. UMC submitted its current workplan to ACSoMP, listing strategic objectives and activities for 2019. Strategic objectives included: (1) building capacity for pharmacovigilance with a focus on analysis (through in-depth analysis and research, and a range of training methods); (2) identifying who is at risk, why and when (through identifying plausible risks and enabling therapeutic decision-making); (3) focusing on patient perspectives; (4) safeguarding and promoting the clinical value and relevance of information in VigiBase (through new data fields that aid analysis, and by promoting the value of global pharmacovigilance data); and (5) providing a high-quality WHO drug portfolio to support safety management throughout a product’s life cycle.

ACSoMP noted that sound methods and tools are needed for risk–benefit assessment and better decision-support. A proposal was made to establish a partner strategy to encourage active and productive collaboration between WHO/UMC and regulators. There was a call for a serious look at how the knowledge that has been accumulated by UMC can be used in training young doctors. Members described UMC as a rich resource for reviewing signals.

It was agreed that the next meeting of ACSoMP should include a discussion on operational aspects related to signals. A future discussion was also requested on crisis prevention and management.

Smart Safety Surveillance

The WHO pilot project on Smart Safety Surveillance, funded by the Bill & Melinda Gates Foundation (BMGF), will end in 2019. It was noted that the principles of Smart Safety Surveillance are aligned with the principles of ‘Smart’ regulation of medicinal products; getting ‘Pharmacovigilance-ready’ for new products ahead of their launch, sharing resources through collaboration, reliance, and recognition of mutual expertise between countries would be the hallmark of this ‘Smart’ approach. While six countries are being supported through the BMGF grants, funds and resources from other partners (UNITAID, UMC in particular) have been used to integrate the 3S principles in a second set of countries. Members agreed that the principles of 3S should continue to inform the work of the SAV programme. An additional set of countries will be supported in 3S-principles with Global Fund grants in the next phase.
Country support

SAV Medicines Group has also stepped-up its collaboration with the WHO RSS team in its **Global Benchmarking** activities, to assess the PV systems and functions of the National Regulatory Agency in different Member States. The Institutional Development Plans (IDP) resulting from these assessments will inform the SAV efforts and strategic activities, to allow a systematic, needs-driven technical assistance and support to countries.

Between 2017 and 2018, WHO SAV supported the launch of smart-phone based adverse drug reaction (ADR) reporting tools in Burkina Faso and in Zambia. The objective is to support countries with a smart, integrated application that would not only help ADR reporting, but would also be an effective interface for health-care professionals to access key information on the medicinal products of their interest. In the scale-up phase, WHO is introducing the tool to an additional 8 countries, from different geographic regions. Both MHRA and the UMC are assisting WHO with the relevant technical support.

A number of workshops in **pharmacovigilance inspections** have already been conducted and a practical manual is being developed to support further trainings in this area. The ACSoMP members advised that the EMA has pharmacovigilance training material and there could be discussions with WHO on how the EMA’s resources could be shared with a global audience.

Prequalification of medicines

Prequalification (PQ) of medicines began in 2001, and PQ of active pharmaceutical ingredients (API) started in 2010. The scope of PQ is now limited to nine therapeutic areas. Since 2018 WHO is piloting biotherapeutic products in its prequalification service.

Two pathways are used in the assessment of products submitted for prequalification: a full assessment pathway or an abridged pathway. In the full assessment pathway, WHO’s PQ team fully reviews the quality, safety and efficacy data submitted in the application, inspects finished pharmaceutical products (FPP) and API manufacturing sites to verify compliance with WHO Good Manufacturing Practices, and inspects clinical testing sites in relation to the product in order to verify compliance with WHO Good Clinical Practices and WHO Good Laboratory Practices.

An abridged assessment pathway is used when WHO recognizes the evaluation of products by Regulatory Agencies that apply standards equivalent to those recommended by WHO. Additional information is required for biotherapeutic products and for biosimilar products. A WHO-prequalified product will be due for requalification at least every 5 years and will need to meet the corresponding requalification requirements to continue to be prequalified.

The SAV Medicines Group is currently collaborating with the PQ team on a proposed structure for the WHO PQ-specific addendum to the Risk Management Plans for Similar Biotherapeutic products (SBPs)/biosimilars.

The PQ process is responsible for undertaking a scientific assessment, but does not put the product on the market, nor does it issue a marketing authorization. Some of the procurement agencies supply markets that have no pharmacovigilance facilities. ACSoMP members noted that pharmacovigilance responsibilities would need to be clearly discussed and agreed with sponsors and should be part of the PQ arrangement.

In some countries the manufacturer has no legal obligation to conduct post marketing surveillance.
ACSoMP recommended that it would be useful to learn what the standards/requirements are and who is responsible for surveillance of a particular product in a specific country; WHO should map the requirements and responsibilities for post-marketing surveillance in countries.

**WHO benchmarking and health systems strengthening**

Universal healthcare cannot be achieved fully unless people have access to quality-assured health products that are affordable, effective and safe. Universal access therefore depends on effective and efficient regulatory systems. The work that WHO carries out to support Member States in effective and efficient regulation includes the use of the Global Benchmarking Tool (GBT), to identify strengths and gaps, and develop an Institutional Development Plan (IDP) to address the gaps.

WHO uses a five-step capacity-building model, to help National Regulatory Agencies (NRAs) reach a minimum capacity commensurate to a stable, well-functioning and integrated regulatory system.

The GBT has four maturity levels based on ISO 9004. Only 50 countries currently operate at maturity levels 3 (‘Stable, well-functioning and integrated regulatory system’) and 4 (‘Regulatory system operating at advanced level of performance and continuous improvement’). More than half (100) of WHO Member States are still at maturity level 1 (‘Some elements of a regulatory system exist’), while 44 countries are at Maturity level 2 (‘Evolving national regulatory system that partially performs essential regulatory functions’). Training and support are provided to regulatory experts from low- and middle-income countries, based on needs identified through the IDPs.

SAV has stepped-up its collaboration with the WHO RSS team in its benchmarking activities, to assess the PV systems and functions of the National Regulatory Agency in different Member States. Future benchmarking activities will also include UMC staff on the roster of assessors for PV; the IDPs resulting from these assessments will inform both SAV and UMC efforts in countries.

Members were assured that although the term “benchmarking” implies assessment, the main objective is the IDP where the findings from the assessment are used to move countries forward. In this regard, it would be useful to have alliances or partnerships between mature pharmacovigilance systems and younger ones, once again underscoring the 3S principles, of sharing resources, for cost-effective pharmacovigilance.

The [Coalition of Interested Parties (CIP)](https://www.who.int/rss/cotip) has been established by WHO to coordinate support from development agencies and their funders in its [Regulatory system strengthening](https://www.who.int/rss) work. CIP is a WHO-led partnership in which participation is voluntary and is open to both state and non-state actors. The aim is to bring together all partners that are supporting regulatory systems, to avoid overlap. At the same time, WHO is working with mature NRAs to host placements and hands-on training of regulatory experts from NRAs in low- and middle-income countries (LMICs). The CIP is not a regulatory network but takes account of, and can lend support to, networks of regulatory authorities.

**A global competency and curriculum framework for regulators**

WHO and partners have developed a comprehensive global competency framework and curriculum covering key regulatory functions, including pharmacovigilance. Such a framework would benefit NRAs, for example, when recruiting new staff, provide on-the job training and evaluate performance more effectively, and it would benefit individuals who would be able to see a clear skills-development and professional growth in their regulatory work.
The draft global competency framework is aligned with the global benchmarking tool (GBT), and is flexible to allow NRAs at different maturity levels to adapt the framework to fit their context and needs. The framework includes mandatory competencies that form the foundation for success in the world of work, core competencies that are cross-cutting for NRAs corresponding to the regulatory system activities as defined by the GBT, and lastly, role/occupation specific competencies, including vigilance. Further, each competency is classified at three levels according to progression in skill acquisition from (1) advanced beginner, (2) skilled / competent and (3) proficient/expert level.

The draft global competency framework is currently being piloted, with a few NRAs and training providers. The framework will be published for comments before it is finalized.

ACSoMP encouraged further study of the use of the competency model, together with a certification of training.

**Product specific issues**

**Artesunate-pyronaridine (Pyramax)**

This is the first artemisinin-based combination therapy (ACT), to be specifically indicated for the blood-stage treatment of malaria due to *P. falciparum* and *P. vivax*. It was granted a positive scientific opinion under the European Medicines Agency (EMA)'s Article 58 procedure in 2012, but to be used only ‘in the treatment of acute, uncomplicated malaria infection caused by *P. falciparum* or by *P. vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance, to be used only as a single treatment course in any given patient” . The labelling required systematic liver-enzyme testing before and after treatment because of concerns over hepatotoxicity of the pyronaridine component, and the lack of real-life data on safety following repeat dosing.

In 2015, an EMA Scientific Advisory Group concluded that cumulative safety data on hepatic events yielded sufficient evidence to use artesunate-pyronaridine (Pyramax) for treatment and retreatment of uncomplicated malaria in patients without signs of hepatic injury (including children from 5 kg). This conclusion led EMA to remove all restrictions from the product’s label on repeat dosing, on use only in areas of high resistance and low transmission, and on requirements for liver function monitoring. In addition, a positive scientific opinion was granted for artesunate-pyronaridine (Pyramax) granules for the treatment of children of 5-20 kg body weight.

The WHO malaria treatment guidelines (2015) still reflect the previous EMA position. According to the WHO guidelines (2015), in areas with multiple drug resistance where there are few alternatives, the use of artesunate-pyronaridine may be considered. However, it is not recommended for general use; additional data are required on efficacy in children <5 years and safety, especially with repeated doing.

In the period between May and December 2018, a sub-committee of ACSoMP, together with two expert hepatologists, reviewed all available data on artesunate-pyronaridine (Pyramax), including accumulating data from an ongoing study by the Central Africa Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM) and concluded as follows:

- The role of ACSoMP is not to advise the development of WHO treatment guidelines. Separate WHO procedures and expert committees exist for this purpose. However, the
ACSoMP would make recommendations based on safety review of specific products for the consideration of WHO disease programmes and through them, to the relevant guideline development committees.

- Taking into account all the available and accumulating evidence, ACSoMP recommends that the current safety restrictions in the WHO malaria treatment guidelines (2015), on the use of artemesunate-pyronaridine (Pyramax) in the treatment of uncomplicated malaria, are no longer justified.
- In view of the limited clinical use of the product, the lack of safety data from clinical use is notable, particularly in vulnerable patients with comorbidities.
- The absence of evidence in subgroups strongly supports the need for active, robust surveillance of the product once used in a wider setting. This could be through enhanced spontaneous reporting or observational cohort studies. Specific advice on the design of such surveillance could be sought from the ACSoMP.
- The benefit-risk balance of a medicinal product depends very much on the clinical context of its use, and the ability of the environment in which it is being used to recognize risks and manage them effectively. This requires a stable and well-performing safety surveillance system embedded in a regulatory infrastructure that allows prompt, risk-minimizing actions when needed. These aspects need to be taken into consideration in the roll out of artemesunate-pyronaridine (Pyramax).
- In general, WHO should ensure that medicinal products that it endorses for use are actively monitored. This would likely involve WHO collaboration with other organizations and could ensure that relevant information about the benefits and risks of the product is collated and assessed, to advise WHO policy.

**Bedaquiline**

Active TB drug-safety monitoring and management (abbreviated as aDSM) describes a WHO TB programme component to provide for the active and systematic clinical and laboratory assessment of patients on treatment for XDR-TB, or with new TB drugs or novel MDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

The aDSM ‘database’ aims to

(1) facilitate the collection, harmonization and pooling of data from different sources for the surveillance of TB drug safety,

(2) enable early detection of potential safety signals, and

(3) use the information, in addition to information collected in the WHO Global ICSR database, Vigibase and/or collected through other channels, to inform treatment guidelines for specific populations.

The contributing country is the owner of the data in aDSM database; WHO collects the data for analysis but does not give data-access to third parties; standard channels of communication need to be maintained between national pharmacovigilance programmes and the national aDSM database. The objective of the WHO analysis of the data is to generate evidence to support TB patient treatment guidelines.

Sixteen countries have so far reported data, from 889 patients, to the aDSM database, with 891 adverse events reported from 14 countries. A 2018 analysis of 418 SAEs, that reviewed a treatment
regimen (containing BDQ or not) and different associations, did not identify any safety concerns /signals.

ACSoMP commended the WHO Global TB programme, GTB, for developing structured pharmacovigilance around a very important product used to treat a serious disease. The Committee advised integrating the aDSM data in Vigibase, to allow broader analysis, and recommended a more rigorous evaluation of the data in the aDSM database by a group of pharmacovigilance experts.

**Dolutegravir**

In April 2018, an update on WHO ARV toxicity monitoring work was presented at the 15th meeting of ACSoMP where it was highlighted that with dolutegravir (DTG), there were remaining gaps in safety data in pregnancy and breastfeeding. In May 2018 new data were published from a large observational study of birth outcomes since 2014 in Botswana (the Tsepamo study), showing a potential association between DTG use at the time of conception and an increased risk in neural tube defect (NTD) in infants born of women who were taking DTG at the time of conception. In August 2018, a subcommittee of ACSoMP was set up, to review all available data on DTG, to refute or confirm the safety signal.

The DTG subcommittee’s latest meeting had been on 6 May 2019 just prior to the 16th meeting of ACSoMP. The report and recommendations of the DTG sub-committee were presented by the chair to ACSoMP members.

The prevalence of NTD with periconception DTG in the Tsepamo surveillance study has significantly declined from 0.94% (95% CI 0.38, 2.4%) in May 2018 to 0.30% (95% CI 0.13, 0.69%) in March 2019. However, the NTD prevalence difference between periconception DTG and each of the other exposure groups, including non-DTG ART or EFV ART from conception (0.10% and 0.03%, respectively), or DTG or non-DTG started in pregnancy (0.03% and 0.05%, respectively), and HIV-uninfected women (0.08%) (all of which have remained stable over time), remains statistically significantly elevated.

From an extensive review of the literature, only one other NTD has been reported with periconception DTG in 247 prospective exposures (0.35%) from the U.S. However, outside of the Tsepamo study, the majority of data come from countries with food folate fortification, and hence, a lower background NTD prevalence and higher numbers of exposures are required to refute an association.

The sub-committee noted that, in the Tsepamo study the adverse pregnancy outcomes (miscarriage, stillbirth, preterm birth, low birth weight, small for gestational age, neonatal mortality) other than neural tube defects do not appear to be increased with periconception DTG use compared to periconception non-DTG ART or ART started during pregnancy.

Continued surveillance is needed to more definitively confirm or refute the NTD signal, and a number of studies are ongoing to address this. If the NTD signal currently observed in Tsepamo is confirmed, although it is three-times higher than other populations, the absolute risk is very low, 0.30% - a risk difference of 2 excess NTD per 1000 periconception exposures.

While there are some suggestive findings, there is no definitive pathogenic mechanism for NTD with periconception DTG exposure. Evaluation of the available basic science studies by experts in the field would be very useful.
The ACSoMP subcommittee strongly supports continuation of the Tsepamo birth surveillance study, not only to provide a definitive answer to the question of a NTD signal, but also as a general model for studying the safety of drugs in pregnancy. The collaborative effort of the subcommittee members from a range of institutions was considered an excellent model of bringing a relevant and up-to-date critical appraisal of drug safety from ACSoMP to the WHO’s Guideline Development Group.

**Fexinidazole**

ACSoMP received a proposal for a post-authorization safety study of fexinidazole for human African trypanosomiasis (HAT) based on the secondary use of data prospectively collected by WHO in selected sub-Saharan African countries. The EMA gave a positive opinion for fexinidazole (Winthrop) on 15 November 2018 in accordance with its Article 58, which does not authorize the product for use in the EU but provides a scientific expert opinion on the safety and efficacy of the product for use.

An alternative name for HAT is sleeping sickness which, if untreated, is almost always lethal over time. WHO began to target the disease for elimination in 2012. Five medicines can be used, are effective but are logistically difficult to administer, especially in second stage HAT with a regime of intravenous administration twice a day for 7 days combined with an oral drug. Fexinidazole is taken in a 10-day oral course which has advantages over injectable administration but also leads to potential problems of compliance. Additionally, there are some new disadvantages in that fexinidazole must be taken with food (solid not liquid) in the stomach, otherwise the absorption is 3-fold lower. There are also problems of vomiting (42%, and up to 69% in children), nausea (35%) and psychiatric events such as insomnia, psychotic symptoms, depression and anxiety (32%), which may further affect compliance.

EMA has asked Sanofi, the manufacturer, to conduct a phase 3 post-authorization safety study of fexinidazole. Additionally, WHO wishes to monitor real-life effectiveness. Training of staff is mandatory for administering fexinidazole, and pharmacovigilance can be included in the same training. A protocol for the 16-country study has been drafted by Sanofi, to study safety in real-life conditions plus effectiveness at 12 and 24 months of follow-up.

It was agreed to set up a small group of experts from ACSoMP, together with an independent disease specialist, to review and provide input to the study protocol.

The protocol would be reviewed by PRAC and the study will begin in the third quarter of 2019. Fexinidazole has also been submitted for inclusion in WHO’s Essential Medicines List.

**Tafenoquine**

More than one-third of the world’s population is at risk of *Plasmodium vivax* (*P. vivax*) malaria, the second most common species of malaria. For the treatment of *P. vivax* malaria, WHO recommends standard antimalarial medicines followed by a 14-day regimen of primaquine to prevent relapses of the disease. Though primaquine is highly effective, patients are required to take daily doses of the medicine for a full 2-week period. As such, treatment compliance is a challenge.

A new medicine, tafenoquine, offers fresh hope in global efforts to combat *P. vivax* malaria. Due to its long half-life, tafenoquine has the distinct advantage of being a single-dose treatment, thereby
increasing the likelihood of treatment compliance. It was recently approved by 2 regulatory agencies, the US FDA and the Australian Therapeutic Goods Administration (TGA), for adults 16 years of age and older.

There is, however, a key safety challenge associated with both tafenoquine and primaquine. Among patients who have a deficiency of the enzyme G6PD (glucose-6 phosphate dehydrogenase) – a genetic condition with a prevalence of up to 35% in some countries affected by *P. vivax* malaria – the drugs can trigger a severe blood disorder known as acute haemolytic anaemia. Primaquine, which is eliminated in a matter of hours, can be stopped if symptoms and signs of haemolysis occur. But tafenoquine remains in the blood for several days, and haemolysis could continue for days in patients with G6PD deficiency if given tafenoquine. A precise measurement of G6PD status (quantitative) is required before initiating treatment with tafenoquine. At present, quantitative G6PD tests are only accessible in well-resourced laboratory settings; such tests are not readily available in resource limited countries affected by *P. vivax* malaria. In these settings the introduction of tafenoquine should be accompanied by a WHO prequalified point-of-care quantitative G6PD test.

Several point-of-care quantitative G6PD tests are either under development or have recently entered the market; some are expected to be submitted by manufacturers for review by WHO’s prequalification team in late 2019. WHO guidance around the use of tafenoquine for the treatment of *P. vivax* malaria will be developed in parallel, with a review of G6PD point-of-care quantitative tests. The guidance will be developed in an independent, comprehensive and efficient manner through a collaborative process that involves the three levels of the Organization and multiple departments.

The Advisory Committee was briefed on the above developments. Members noted that the complexities of this process made for an extremely challenging situation.