Conclusions and Recommendations from the Fifteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
24 - 25 April 2018

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 Fourteenth meeting of ACSoMP are presented below.

1. WHO reports

1.1. Safety and Vigilance (SAV): Medicines

WHO's programme of work for 2019–2023: While the standardized approach to pharmacovigilance will continue, there will be more focus on strengthening capacity to promote the safety of medicines, especially in low- and middle-income countries (LMICs). There is to be a focus on country ownership, but with better quality data, faster detection of signals, reduced costs and reduced mortality and morbidity.

Normative work will be boosted in countries by encouraging more consistent engagement in the work of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as well as continuing close collaboration with the Council for International Organizations of Medical Sciences (CIOMS). The pharmacovigilance toolkit is being updated and expanded. Indicators are being prepared to assess how ready countries are to use new pharmacovigilance products, and the WHO-ISoP pharmacovigilance curriculum is being adapted to a more competency-based model. WHO's training will include a module on ICH approaches for countries that are interested in this.

Technical assistance: The short-term (1–2 years) aim is to gather intelligence on a small number of products and build minimum capacity for surveillance support to 4–6 countries that will use the products. A further short-term project is to pilot a WHO undergraduate curriculum on pharmacovigilance in selected countries, while general support to countries will aim to link pharmacovigilance activities to the regulatory function. In the longer term (5 years) the goal is to scale up the number of countries supported for preparedness and ensure alignment with the Global Benchmarking Tool priority countries, supporting pharmacovigilance goals and strengthening work. Particular aims will be to support countries to link pharmacovigilance to

regulation, and to strengthen the use of new technical developments – such as the Web-RADR (Recognising Adverse Drug Reactions) application and electronic health records.

Significant dates: The 41st annual meeting of national pharmacovigilance centres which will take place in Geneva on 5-9 November 2018 will mark the 50th anniversary of the WHO Programme for International Drug Monitoring (PIDM) and the 40th anniversary of the Uppsala Monitoring Centre (UMC) which has provided technical support for the programme since 1978. The year 2018 also marks the 70th anniversary of the creation of WHO.

Summary of Discussions/Recommendations

- A future meeting of the Advisory Committee should include a session on capacity-building. The Advisory Committee called for more emphasis on building competency in pharmacovigilance for medical products.
- In planning and implementing training curricula, WHO should consider the work of ICH, universities, and of professional societies.
- While there is to be a focus on national ownership, a regional approach to pharmacovigilance could be supported where relevant.
- Because of all the data in assessment reports on various products, sharing these reports amongst various stakeholders would greatly increase knowledge to help guide future safety and vigilance efforts. The Advisory Committee agreed to propose protocols to further encourage access to the data that already exist.
- WHO should help direct people to pharmacovigilance data that are publicly available.

1.2. WHO Collaborating Centre for International Drug Monitoring

Milestones: The Uppsala Monitoring Centre (UMC) reported on research milestones, including:

- Investigating variations in risk between the sexes and between different subgroups of patients;
- A pilot study on detecting systematic medication errors in VigiBase, identifying 10 potential safety issues;
- A project in collaboration with Australia's Therapeutic Goods Administration (TGA) and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) to develop and refine methods for de-identifying case narratives through the use of deep neural networks;
- Completion of the Innovative Medicines Initiative's Web-RADR project;
- Complementing the BLIS methodology for predicting indications in electronic medical records with cluster analysis that grouped related medical events, followed by a pilot study;
- Finalization of four modules on signal detection and causality assessment for the UMC distance learning course.

UMC collaboration: It was reported that collaboration is expanding with a number of partner agencies. UMC now has joint user group meetings and training sessions with the MSSO, the

maintenance organization for the Medical Dictionary for Regulatory Activities (MedDRA). Most reports to UMC still come from the United States Food and Drug Administration (FDA), but in 2017 about 10% of reports came from China with large and increasing numbers also from India and the Republic of Korea. Many countries are requesting help in developing skills for data analysis and not just data collection. UMC is therefore increasingly focusing its training in this area.

Summary of Discussions/Recommendations

- Now that database system differences, which caused difficulties in the past, are no longer the main problem, UMC should focus more on encouraging countries to work together.
- More work is needed to help countries understand what actions to take when a signal is announced.
- Since UMC functions as the lead WHO technical partner for the PIDM, it is important that ACSoMP plays a role in guiding the work of UMC by reviewing UMC workplans and submitting comments to the UMC board. UMC will continue to share the workplans with WHO, and through WHO, with ACSoMP for input and advice.
- As the situation in many countries is changing fast, there is a need for a long-term strategic view of pharmacovigilance in order to guide investment for change in 10 years' time. In that regard, ACSoMP should consider having a bigger role in reviewing the workplan of WHO's SAV team (and its collaborating centres).
- Institutions responsible for carrying out pharmacovigilance around the world should be helped to have the capacity to do data analysis and make decisions as to what their data show.
- Efforts should be strengthened to help countries obtain tools to make safety reporting easy. The United Arab Emirates used its own resources to launch the generic version of the WEB-RADR app, Zimbabwe also launched an ADR reporting app.
- As other actors develop apps for data reporting, UMC, a WEB-RADR partner, was urged to complete its development of an interface platform so that data from all sources can be gathered.
- Although there are considerable safeguards on data use, commercial enterprises are able to use online search data to build user profiles. Advice should be developed on data privacy, proposing how and when pharmacovigilance data may be used.

2. The Smart Safety Surveillance (3S) project

Background: WHO and the Bill and Melinda Gates Foundation (BMGF) have introduced "Smart Safety Surveillance" (or 3S), which is a risk-based approach to pharmacovigilance (PV) for new products that have not been introduced into reference regulatory markets and therefore no longer possible to draw on the experience of those markets. The 3S project, which was described at the fourteenth meeting of the Advisory Committee, will include piloting a set of key pharmacovigilance principles using selected new products in selected countries.

Aim of the 3S project: The aim is to establish the proof of concept for strategies for building or strengthening pharmacovigilance systems in LMICs. The strategies are to assess product launches over the coming 10 years, the time frame for product launches, anticipated/potential risks with the products, and capacity for pharmacovigilance in launch countries. Key objectives are to strengthen the functionality of pharmacovigilance systems, to build capacity to analyse safety data, to improve regulatory decisions, and to support collaboration between public health and pharmacovigilance programmes. Key principles of 3S are to leverage product introduction, to focus surveillance initially on areas identified during development and on products with a high-risk profile, to undertake active surveillance to a targeted period of time, to use current standards for safety, and to leverage and build on current harmonization platforms.

Products: Three products have so far been selected for the pilot project – the tuberculosis medicine bedaquiline (BDQ), the malaria medicine tafenoquine (TFQ), and the rotavirus vaccine Rotavac. A shortlist of priority countries has been drawn up and assessments of these are under way in order to select the final set of countries for the pilot. Discussions have been held with WHO's programmes on tuberculosis, malaria and HIV both to fine-tune details of the pilots and to define criteria for selecting countries. A Project Advisory Group has been set up and includes the chairpersons of ACSoMP and the Global Advisory Committee on Vaccine Safety. In addition, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) has received a grant from the BMGF to provide technical support to 3S.

Summary of Discussions/Recommendations

- Experience gained during 3S could be used to address other issues in resource limited settings (such as substandard products). Although the project is geared to individual countries, there may be implications at a regional level.
- Committee members expressed overall support for 3S and for its pilots. Although the activities are centred around specific medicinal products, the purpose of the project would be to build sustainable systems and capacity for pharmacovigilance.
- Although different countries are expected to have different approaches to pharmacovigilance, and with a different focus and priority, the underlying principles must be the same.
- 3S must ensure that patients' privacy is protected when data are gathered.
- Cultural sensitivities will be important, as will the readiness of industry to become involved and the extent of collaboration with WHO and national disease programmes.
- As the 3S project evolves, thought should be given to the future role of UMC and what more it could do.

2.1. Bedaquiline (BDQ)

One of the pilot projects of 3S will focus on the introduction of the new tuberculosis (TB) medicine bedaquiline (BDQ).

Background: Bedaquiline (BDQ) is the first representative of a new class of medicines expected to address the high unmet medical need for new treatment options for pulmonary multidrug-resistant tuberculosis (MDR-TB). FDA has granted accelerated approval to Sirturo (bedaquiline)

tablets in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) as part of combination therapy in adults in 2012. Bedaquiline (BDQ) was authorized in the European Union (EU) in 2013 with a conditional marketing authorization under the trade name Sirturo with the marketing authorization holder (MAH) Janssen-Cilag International. The European Medicines Agency (EMA) recommended granting conditional marketing authorization because, although the data supplied by the applicant showed that the medicine's benefits outweighed its risks, the data are not yet comprehensive. Therefore, additional studies on the use of BDQ should be conducted by the MAH with the final analysis of the data in November 2021. The authorized indication (EMA, FDA) of BDQ is for the treatment of adults with MDR-TB of the lungs, to be always used in combination with other anti-TB medicines.

Conditions of use: WHO issued an interim guidance which provides advice on the inclusion of bedaquiline in the combination therapy of MDR-TB in accordance with the existing WHO Guidelines for the Programmatic Management of Drug-resistant TB (2011 Update).

BDQ as a 3S Project 'candidate': The decision to include BDQ in the 3S pilot project is based on the selection criteria that were developed by WHO (Safety & Vigilance and WHO Global TB Programme (GTB), and under the advice of the WHO ACSoMP. In brief:

- BDQ is being introduced conditionally, as a pilot phase, in some low and middle income countries (LMICs) at the same time as its introduction in high income countries (HICs) with an orphan status. Since MDR-TB incidence is low in HICs, the medicine has been licensed under the orphan-drug approval process; thus LMICs do not have much data on BDQ from HIC to lean on. Monitoring BDQ, within the 3S project in LMICs, will provide the much needed data on BDQ for LMIC-specific use, about the QT prolongation impact of the medicine in the treatment , all other hitherto unknown adverse events and the implementation of patient inclusion and monitoring in every day practice.
- Nearly 60% of all MDR-TB patients live in LMICs in Asia and Africa. It is critical that robust data on BDQ are available quickly in these settings through 3S and other projects, to support the scale up of BDQ, from pilot to full-access programmes in LMICs.
- Phase II and Phase III trials are unlikely to provide an exhaustive understanding of the safety profile of a medicine, particularly for harms and drug-drug interactions (DDI) that are uncommon, and therefore surveillance of the kind proposed by this initiative will add to current knowledge.

Summary of Discussions/Recommendations

- In many countries data on new medicines are not shared and ways need to be found to encourage sharing.
- National TB programmes should be urged/supported by WHO to collect data and to share these with national regulators, other countries and ultimately with the WHO global database, for mutual learning.

2.2. Tafenoquine (TFQ)

Background: *P. vivax* malaria has a significant public health and economic impact, with millions of clinical infections, primarily in South and South East Asia, Latin America and the horn of Africa. At present primaquine (PRQ) is the only treatment approved for the radical cure (prevention of

relapse) of vivax malaria. PRQ is administered as a once-a-day oral dose for 14 days and it is widely accepted that the long dosing leads to reduced compliance and hence reduced clinical efficacy. Alternative treatments with less frequent dosing regimens are needed.

Tafenoquine (TFQ) is an 8-aminoquinoline derivative with activity against the *P. vivax* lifecycle, including hypnozoites. It has the potential to provide alternative treatment in *P. vivax* infections which can be administered as a single dose. Co-administration with another blood schizonticide (chloroquine) will be required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection.

GlaxoSmithKline (GSK) has applied to the Australian Therapeutics Good Administration (TGA) seeking approval of single-dose tafenoquine treatment for the radical cure (prevention of relapse) of *P. vivax* malaria. GSK also plans to progress regulatory filings in other countries in 2018. Approval of TFQ by TGA will likely facilitate registrations in other malaria-endemic countries in the region. However, as there is no prior experience with TFQ in any country for preventing relapse of *P. vivax* malaria, LMICs will not have sufficient post-marketing safety data when TFQ is introduced in their settings and will need to collect and analyse their own data on TFQ for this indication.

Summary of Discussions/Recommendations

- LMICs within the 3S project must be prepared and supported to monitor TFQ to provide the much-needed post-marketing data on TFQ.

2.3. Pharmacovigilance readiness of 3S pilot countries

Indicators: To carry out a baseline assessment of preparedness, a list of indicators was drawn up and approved by ACSoMP in May 2017. The 21 structural indicators aim to show the presence of key pharmacovigilance structures, systems and mechanisms; 15 process indicators aim to show the extent of pharmacovigilance activities; and a set of outcome and impact indicators is used to identify results of interventions and changes as a measure of impact (such as new legislation or restructuring). The status of public health programmes is also considered. Each set of indicators (structural, process, outcome) covers five areas, namely: 1) Policy, law and regulation, 2) System structure and stakeholder coordination, 3) Signal generation and data management, 4) Risk assessment and evaluation, and 5) Risk management, plus communication and commensurate resources needed for the pharmacovigilance system.

Summary of Discussions/Recommendations

- The systematic approach to organizing the project was welcomed.
- On BDQ, there are four issues that need resolution – data need to be collected, data must be shared with the national authorities, national authorities need to share data with VigiBase, and clarification is needed on who is responsible for analysis.
- Ideally all safety data should be chanelled through the national PV system to the global database. If an non-governmental organization (NGO) collects data, on behalf of a marketing authorization holder (MAH), a first step could be to urge the NGO to share its data promptly with the government and arrange for the government to share with WHO/UMC.

- It is important for each country to receive all data on products available in that country. As capacity increases and the country is able to analyse its data, it will also benefit from the data that are in VigiBase. The national regulator and pharmacovigilance centre are accountable for the safety of the patients in their country.
- The 3S project anticipates several levels of pharmacovigilance: with only minimal resources, reporting can be strengthened and encouraged, but in countries with more resources, more advanced pharmacovigilance functions could be implemented.
- Since India has some ongoing studies on Rotavac as well as spontaneous reporting, the aim of the Rotavac pilot is to verify safety and build reassurance.
- The core principle for using key products is to strengthen country pharmacovigilance systems and not only to acquire more data.
- The WHO TB programme's active TB drug safety monitoring and management (aDSM) database collates data from settings with poor or nonexistent pharmacovigilance systems. The data in aDSM are in a format that can be easily transferred to other databases.
- WHO should work on proposals to support data sharing between National TB treatment programmes and the Regulator/National PV Centres.

3. Data access

3.1. Proposed access policy for VigiBase

Background: The WHO Collaborating Centre in Uppsala, (UMC) in Sweden manages the global ICSR database, Vigibase, on behalf of WHO and its Member States participating in the WHO Programme for International Drug Monitoring (PIDM). The original agreement between WHO and the Swedish government only mentioned WHO PIDM use of the data, but subsequent WHA and ICDRA recommendations have requested greater openness. As a result, in 2012 ACSoMP had discussed a proposal about making VigiBase data available to the general public. This led to VigiAccess, for broad, high-level public access to summary information from Vigibase. More recently, academic and industry groups, as well as some training organizations who work with WHO, have requested various levels of access. UMC has prepared a proposal on data access policies. The proposal was presented to the committee for review and advice.

The draft data access policy drew attention to the fact that VigiBase information was collected "for the sole purpose of carrying out the pharmacovigilance activities agreed on within the WHO Programme for International Drug Monitoring (PIDM)" and was intended to strengthen capacity for pharmacovigilance and promote the safe use of medicines. The draft policy identified six groups of stakeholders for Vigibase pharmacovigilance data, namely:

- UMC itself and its Signal Review Panel;
- Approved national authorities of WHO Member States who are members of the PIDM;
- academia;
- marketing authorization holders;
- the general public;

- participants in training activities organized by UMC or other WHO collaborating centres within the PIDM.

In addition, the policy proposed five general principles for data use, namely:

- VigiBase contains anonymized information transferred from Member States. Confidential patient and reporter details should be removed before transfer to VigiBase.
- No onward transfer of the ICSRs in VigiBase is allowed.
- Only anonymized information may be made public.
- All attempts to re-identify data subjects from VigiBase data are prohibited.
- Access to VigiBase data requires signature of a valid user licence agreement, including acceptance of a statement on the nature, confidentiality and limitation of use of the data.

Three levels of access (public, intermediate and extensive) were proposed, to balance transparency and patient confidentiality, access to information, academic interest and towards pharmacovigilance obligations of various stakeholders. ACSoMP members were requested to comment on the scope and content of the proposed policy and the proposed levels of access.

Summary of Discussions/Recommendations

- ACSoMP members were generally positive about the proposed policy which would facilitate data access and give clear guidelines.
- Each country supplying data has to comply with its own national laws on data protection as well as the terms of the policy.
- Access to some data fields will need to be blocked. In the EU, to strengthen anonymity, if there are fewer than three reports on an issue, they are described as EU or non-EU with no indication of country.
- The EMA reported that it does not give access to academic enquirers unless they give evidence of ethics approval. All academic requests should go through some kind of process to ensure that the request is serious and the project is worthwhile.
- Enquirers who want to have data from a specific country should be directed to ask the relevant authority in that country as UMC is concerned only with global data and not country-specific data.
- ACSoMP gave their overall approval to the proposed access policy. The proposal will be formally presented to Member States in the upcoming WHO Annual Meeting of Representatives of National Pharmacovigilance Centres for comments and consideration.

3.2. Regional data platforms

Background: Some groups of countries have expressed interest in operating their own regional pharmacovigilance databases with more comprehensive data on regional issues. One argument is that regional databases could encourage countries to contribute data to the global database. In addition, some regional groupings have asked to have access to the full data held by each country in the group including the case narratives. However, such an arrangement would

require all countries of a region to have contractual agreements with each other. For instance, not only would sufficient case details for efficient analysis need to be provided, but collaboration agreements between countries would be required for data-sharing to take place, a data access policy would need to be agreed by all, and there would need to be agreement on the process for granting controlled access.

If this were to go ahead, each country in a region would continue to have its own data in its own VigiFlow/other national database, and submit the data to VigiBase. Instead of seeing only a certain limited level of data from other countries via the VigiLyze interface, as today, the proposal is that each country in a defined regional group could in future access a more detailed set of data from countries in the group.

Additionally, some countries with limited capacity for data management have requested all reports from all companies on all medicines. The concern is that countries that have done little data collection and use so far may be overstretched if they receive all global MAH reports.

Summary of Discussions/Recommendations

- The sharing of data as requested by regions is technically feasible. Countries would be able to join their own regional consortium and submit data in order to use regional data. The EMA's Eudravigilance database was described as a model for this. Another example is VigiFlow, originally developed for Swissmedic, to cater for reporting and data sharing between regional centres in the country.
- Any such request by regional groupings for VigiBase data would need to be made at the highest level. This issue should be taken forward by UMC in consultation with WHO.
- There are different views in countries in some regions, so WHO is attempting to obtain ministerial approval from each country before going ahead with this.
- It would be important to know if a country's laws permit the requester to hold the data being requested, in a regional database.
- Since generics manufacturers are the predominant suppliers of medicines to many resource limited countries, safety data from such companies would be particularly relevant in some regional databases.
- It was agreed that a subgroup of ACSoMP members should draw up a short policy statement setting out the issues of collection and management of global MAH data and making some draft proposals that ACSoMP members could then review and contribute to. This topic could be discussed at the WHO meeting of national pharmacovigilance centres.

4. Pharmacovigilance of HIV medicines during pregnancy

4.1. Update on toxicity monitoring of dolutegravir

Members of ACSoMP received a presentation on "Enhancing toxicity monitoring and active safety surveillance during pregnancy for new antiretroviral (ARV) medicines". As the world is moving towards 30 million people receiving antiretroviral treatment (ART) in 2020, there is a need to transition to optimized ART regimen. With dolutegravir, there are remaining gaps: in efficacy data with regard to use with TB drugs, and in safety data in pregnancy and

breastfeeding, and in children. It is necessary to look at population-level data over long term use and review any unexpected complications that may arise.

The HIV programme is learning from past experience with some other ARV medicines which resulted in serious adverse complications that led to policy changes in the use of ARVs (WHO 2010 introduction of tenofovir to replace stavudine, and of efavirenz in 2013 to replace nevirapine in preferred 1st line). As a result, in July 2017 WHO issued new technical guidance on transitioning to new ARVs, with programmatic considerations including a section on monitoring of toxicity. The guidance presents approaches for routine HIV patient monitoring, active ARV toxicity monitoring (CNS, IRIS, long-term toxicities), surveillance through ARV pregnancy registry and surveillance for congenital anomalies as well as monitoring of mother–infant pairs during breastfeeding.

Among countries that have started transitioning to dolutegravir, Brazil has implemented a pharmacovigilance programme. As of August 2017, approximatively 52 000 patients were receiving DTG (with an average of 8000 new patients per month) and, of these, some 36 000 had started ART with DTG. The active toxicity monitoring programme included 45 000 patients and found that 3% referred to experiencing an adverse event, although only 79 patients interrupted DTG because of such an event. Regarding safety during pregnancy, very few countries use DTG in 1st line treatment during pregnancy (example, Botswana), while other countries substitute DTG to another ARV, or use DTG ONLY in exceptional clinical situations. The WHO Guidelines released in 2016 cautioned that there were insufficient data for using DTG during pregnancy or breastfeeding and recommended efavirenz (EFV) in combination with tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) as the preferred option in pregnancy. The main sources of data during pregnancy are the Antiretroviral Pregnancy Registry in the USA, the European Pregnancy and Pediatric HIV cohort collaboration, and an active birth outcomes surveillance study - TSEPAMO study, conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana where DTG is used in first-line regimen.

WHO statement and Q&A on potential safety issue related with DTG

It is important to note that since the ACSoMP meeting took place on 24-25 April, WHO was informed by the investigators from the Botswana Tsepamo study in May of a potential safety signal related to neural tube defects in infants born to women taking dolutegravir at the time of conception.

WHO released a statement on 18 May 2018, available at link:

http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1.

WHO is proactively engaging with countries and partners in addressing policy and programmatic implications of these findings for national HIV programmes. To inform the discussions and to guide decision-making, WHO has also released a "questions and answers" (Q&A) document, available at link:

http://www.who.int/hiv/mediacentre/news/dtg-statement/en/

See other resources below.

WHO and the Tropical Disease Research (TDR) Programme have established a WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy AND a central repository for safety evaluation of dolutegravir (general population) to pool data from programmes and studies to get bigger samples more rapidly and be able to analyze toxicity data. A data entry interface for supporting countries to enter their data into the WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy was presented to ACSoMP as well as the list of tools available. It includes: a list of standard variables, data dictionary, data entry programme, user guide, newborn surface examination video. WHO has issued important surveillance recommendations –

- to invest in standard and active monitoring of toxicity to generate data and inform future treatment policies, and
- to share data between studies and types of sites into WHO/TDR platforms with a multi country approach to learn quickly and globally.

List of resources that underscore the above text include:

1. WHO 2017 Transition to new antiretrovirals in HIV programmes: http://www.who.int/hiv/pub/toolkits/transition-to-new-arv/en/
2. TDR Central registry for epidemiological surveillance of drug safety in pregnancy: http://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en/
3. EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1
4. FDA: https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm
5. PEPFAR: https://www.pepfar.gov/press/releases/282221.htm
6. USG: US Guidelines notice: https://aidsinfo.nih.gov/news/2094/statement-on-potential-safety-signal-in-infants-born-to-women-taking-dolutegravir