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 17th meeting of ACSoMP is provided below.

WHO 5-year Strategic Plan to improve Global Regulatory Systems (2019-2023)

The WHO Strategy provides the framework for all activities across the entire regulatory spectrum for medicines, vaccines, diagnostics, etc. Pharmacovigilance (PV) activities span across the four priorities of the strategy. The following activities are proposed for the biennium (2020-2021):

- **Strengthen Country and Regional Regulatory Systems.**
  The goals are to strengthen safety surveillance, to support and safeguard the uptake of newly manufactured products and to support regulatory convergence through the convening power of WHO.
- **Improve regulatory preparedness for public health emergencies (PHEs) and health product shortages**
  The goal is to increase the number of countries that have adapted their regulatory preparedness for PHEs.
- **Strengthen and expand WHO's prequalification (PQ) service**
  To expand the range of products eligible for PQ.
- **Increase the scope and impact of WHO's regulatory support activities**
  To enhance monitoring of WHO's impact on regulation and access to health products.

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

Much of UMC's efforts in 2020 were devoted to Covid-19 work, and a task force was established to undertake these new activities. The top priority is signal detection and analysis related to Covid-19 treatments and vaccines as they become available. This involves providing summary reports of VigiBase data and developing syndromic detection methods to identify any emerging harm to patients. It is important to ensure that the data reaching VigiBase is timely and relevant, which means adapting the tools to accommodate the data and working with WHO to establish a flow of data from public health programmes. VigiFlow developments intend to improve support for vaccines in PV data entry and for immunization programme reporting and feedback, in order to facilitate geographical analysis and efficient global sharing of data.

The core of UMC is signal detection and capacity building. Since individual case safety reports are the absolute core, it is critically important that UMC receives the data that it needs. Structured data facilitate signal detection.

Access to Covid-19 Tools Accelerator (ACT A)

The aim of the ACT A strategy is to accelerate global access to tools that reduce the risk of severe disease, thereby ending the acute phase of the Covid-19 pandemic and restoring societal and economic health. Access to these tools, as well as their allocation, needs to be equitable otherwise they will just be used in high-income countries.

The vaccines component or pillar is led by CEPI (Coalition for Epidemic Preparedness Innovations) and GAVI (The Vaccine Alliance), whereas the therapeutic pillar is led by the Wellcome Trust and UNITAID. ACT A was launched in late April by WHO, the European Commission and France. WHO is responsible for overall coordination and ensuring that norms and standards relating to PQ policy and technical guidance remain in place.

GAVI is hosting the "Risk Pooling" mechanism in collaboration with WHO and CEPI, which should ensure that once a vaccine proves to be safe and effective there is a good chance that countries worldwide will be able to access it. Some countries will be self-financing but others will receive vaccines via the GAVI mechanism.

At the moment, there are still no strong therapeutic candidates for dealing with severe cases. There are currently 1700 ongoing therapeutic trials, which can be grouped into five categories according to treatment use: pre-exposure prophylaxis, post-exposure prophylaxis, mild cases, moderate cases and severe/critical cases. Studies with monoclonal antibodies are showing very promising results, but the ability to deliver at scale is very small.

WHO COVAX Regulatory Update on Covid-19

As part of the support to COVAX activities, WHO has been looking to see how regulatory preparedness can be improved across the product streams on all the Access to Covid-19 Tools

(ACT) pillars, for instance, by ensuring that regulators are informed and involved, initially in the research and development activities, but now more importantly in preparedness activities. Mechanisms have been set up to collaborate with regulators across the world to allow the rapid exchange of information on Covid-19 developments. The overall aim is to promote regulatory alignment in order to facilitate rapid access to quality, safe and effective products.

WHO is working closely with the International Coalition of Medicines Regulatory Authorities (ICMRA) in order to avoid duplication and to leverage developments within the ICMRA countries. It is also working with the regional regulatory groups to ensure that they are aligned on the specific PV preparedness regarding the expected adverse events following immunization. A roadmap has been produced to help align the assessment process and facilitate in-country approval. This applies to all Covid-19 vaccines, not merely those that come within the scope of the COVAX facility, but focusing on those at the most advanced stage.

One of the greatest challenges identified in the roll-out of vaccines is, given the speed of developments, making sure that there are appropriate feedback mechanisms in order to be able to monitor and identify any risks and update as necessary. By aiming to have the best possible Global Monitoring System, the challenge of how different processes are aligned can be addressed (e.g. information coming through both public health systems and regulatory authorities).

One big concern is the communication of risks to the general population and the media. The best way to counter misinformation is to direct countries to websites with correct information. There is a need for a Vaccine Adverse Event response plan functioning at three levels: on the ground, between countries and at the global level.

There is a real need for pro-active communication in the context of the roll out of vaccines. WHO has communication experts who are examining this from a pro-active perspective, taking into account the different national situations.

There is a need for a coordinated approach to making the data accessible from different data sources, e.g. aggregate AEFI data that arrive through the WHO/UNICEF joint reporting form. The WHO standard reporting form used for collecting case-based AEFI data is being incorporated into VigiFlow (a national PV data management system developed and offered to countries by WHO/UMC), which will help immunization programmes to collect data from the district level up to the national level, where data will be shared between the regulators and the EPI programme.

Review and analysis of safety data for new TB medicines and regimens

Safety data in the active TB Drug Safety Monitoring (aDSM) database was evaluated by WHO in order to better understand the benefit and risk profiles of bedaquiline, delaminid, clofazimine and linezolid in the treatment of multidrug-resistant tuberculosis (MDR-TB). The aim was to identify for these four TB drugs any new potential "signal" and to review any new emerging characteristics with known safety concerns. A review was also made of the data quality and minimum data fields that support meaningful data analysis and causality assessments.

Signal detection exercise carried out on aDSM data reconfirmed the listed safety adverse event profiles for these four TB drugs, and provided a level of reassurance that known events were being reported to the aDSM database. The committee recommended that systematic reviews such as this one should be performed on the safety of all new WHO-recommended products in public health programmes. Systems such as aDSM can be used to identify potential signals for further in-depth review and analysis. In addition, as not all adverse events are reported to traditional databases, such as VigiBase, the time needed to identify potential signals of rare adverse events could potentially be decreased by using aDSM data.

Sodium valproate

Valproate has been on the WHO Essential Medicines List for 40 years, having first been listed as an antiepileptic in 1979. It is also on the list for bipolar disorder but only for the treatment of adults. Thus, the listing of valproate on the model Essential Medicines List (EML) is in full alignment with the current recommendations in the WHO guidelines for use in epilepsy and bipolar disorder. The first WHO guidelines for epilepsy were issued in 2009/10 as part of WHO's mental health Gap Action Programme (mhGAP) guidelines. They were updated in 2015/16, and work on a further update started in 2020.

The risk of anti-epileptic medications to women of childbearing age applies during the preconception phase, pregnancy and breastfeeding. WHO's position on the use of valproate has been clearly stated in the WHO Pharmaceuticals Newsletter (2020) that:

- medicines containing valproate (e.g. sodium valproate, valproic acid, divalproex) should be avoided in pregnant women or in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects (such as spina bifida, facial, skull, limb and heart malformations) and developmental disorders in infants who are exposed to valproate in the womb.
- When alternative treatments are not available or appropriate, female patients prescribed valproate medicines should be made aware of the risk and use effective contraception methods.

WHO guidelines have made a strong recommendation, since 2009, that valproate should be avoided for women of childbearing age, both for epilepsy and bipolar disorder, the challenge is to ensure better implementation. Therefore, in addition to updating the guidelines, resource materials and tools are now available for implementing the recommendations at country level. These include mhGAP intervention guide, training manuals for trainers, as well as for health-care providers, and care has been taken to make this information accessible to both specialists and non-specialists.

Investigational drugs used for treatment of Covid-19: remdesivir (Veklury)

Marketing authorization in the European Union for remdesivir was granted in July 2020. This was a conditional approval, the indication being the treatment of adults and adolescents (aged 12 years and older and with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. There is a risk management plan (RMP) and, an expedited summary safety review. This medicine is subject to additional monitoring. The full report for remdesivir is available on the European Medicines Agency (EMA) website.

A new signal of acute renal injury was detected and validated by EMA and confirmed by its Pharmacovigilance and Risk Assessment Committee (PRAC) in September 2020. The causal relationship is yet to be determined and warrants further investigation. Although the known safety profile of remdesivir is currently limited, more than half of reported adverse events (from the compassionate use programme, the expanded access programme and spontaneous cases) belong to the unexpected adverse reactions.

Interim results from the WHO Solidarity trial published in October 2020 indicate that remdesivir, along with some other Covid-19 drugs, seems to have little or no effect on 28-day mortality or the in-hospital course of Covid-19 among hospitalized patients. The WHO prequalification listing of the drug will be reviewed following the recommendation from the WHO Guidelines Review Panel or following a review of the conditional approval by EMA.

Dolutegravir

Dolutegravir (DTG) is an antiviral medication used, together with other medications, to treat HIV/AIDS. In May 2018 a potential association between DTG use and an increased risk of neural tube defect (NTD) in infants born to women who were taking DTG at the time of conception was reported in a large observational study of birth outcomes that started in 2014 in Botswana. In August 2018, ACSoMP set up a subcommittee on DTG to review all available evidence, to confirm or refute this signal of NTD.

DTG is one of the first cases where ACSoMP has undertaken a very careful and detailed analysis of accumulating evidence. After a period of decline since the original safety signal, the prevalence of NTDs among infants born to women on DTG at preconception appears to be stabilizing at a low prevalence level of 0.19%. This is no longer significantly higher than for preconception non-DTG ART, although it remains statistically significantly higher than preconception EFV and in HIV-uninfected women.