About this newsletter
Providing updates on GVSI activities

The GVS Bulletin\(^1\) newsletter provides updates on the implementation of the Global Vaccine Safety Initiative (GVSI)\(^2\), a forum aiming to synergize the knowledge and expertise of its stakeholders to help ensure the safety of vaccinations through the implementation of the three strategic goals of the Global Vaccine Safety Blueprint\(^3\) which are summarized in a products portfolio.

To optimize collaborative activities, the GVSI Bulletin aims to provide all stakeholders of the Initiative with a practical overview of activities identified. Components of the portfolio and activities of GVSI stakeholders that match the eight objectives of the Global Vaccine Safety Blueprint and profiles of stakeholders are presented to increase visibility of actions and support synergies.

The Global Advisory Committee on Vaccine Safety (GACVS) celebrates 15 years of existence.
Geneva 11 June 2014

Patrick Zuber

On the occasion of its 30th meeting on 11-12 June 2014, GACVS also

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celebrated its 15th anniversary. WHO’s vaccine safety advisory committee first met on 14-15 September 1999. Since then, the Committee has met regularly twice a year and has also been convened by telephone conference more frequently when needed.

The Committee’s regular reports are published soon after each meeting in the WHO’s Weekly Epidemiologic Record, while urgent reports are posted separately online, and a compendium is available on the GACVS website maintained by WHO\(^1\). Since the committee was established in 1999, it has produced over 100 reports related to vaccine safety issues. GACVS role is primarily to assess risks related to vaccine use in order to assist policy-makers in establishing benefits and risks as part of evidence-based vaccination policies. With respect to WHO advisory bodies, GACVS risk assessments are regularly used by the Strategic Advisory Group of Experts (SAGE), the Expert Committee on Biological Standards (ECBS) as well as regional technical advisory groups related to immunization.

A total of 39 experts have served on GACVS to date, the current committee being composed of 15 members. Current and past members represent all WHO regions, although a majority (26) do originate from industrialized countries in Europe, North America or Australia. They provide expertise in multiple fields related to vaccine safety including epidemiology, statistics, clinical medicine, pharmacology and toxicology, infectious diseases, public health, immunology, vaccinology, pathology, ethics and health product regulation. GACVS members, in addition to participating in bi-annual in-person meetings also contribute to the work of the committee through various sub-groups that develop statements on selected topics between regular meetings.

Former GACVS members joined the current committee to discuss a review of its work over the years and provide perspectives from immunization programs, regulatory agencies, work of clinicians, WHO collaborating centres and technical advisory committees on immunization. The evolving global immunization landscape, vaccine supply and regulation provide new opportunities and challenges. In particular, a larger and more diverse set of vaccine products, some of which are specifically designed for parts of the world with limited vaccine safety monitoring. A discussion paper is in preparation that will address future approaches for GACVS, that will take into consideration areas where its contributions are the most needed. It will also consider how to take into account new standards of scientific review in order to maintain the highest level of scientific excellence.

**NRA Assessment**

Assessing the national regulatory system for vaccine pharmacovigilance in China 14 to 18 April 2014 the quality of the national regulatory system for vaccines in China

Zuo Shuyan, Christine Maure and Patrick Zuber

In order to ensure that health products are of assured quality, the World Health Organization (WHO) established a programme to strengthen national regulatory authorities through periodic assessment of their regulatory functions. These

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\(^1\) See http://www.who.int/vaccine_safety/committee/topics/en/
assessments are aimed to guide the countries through a gap analysis using an indicator-based assessment tool. China has been first assessed in December 2010 and declared officially functional for the vaccines area in March 2011. Currently one vaccine has been prequalified (JE vaccine) from Chengdu Institute of Biological Products (CDIBP) for the period 2014-2016 and it is expected that more vaccines will be prequalified in the coming years.

To ensure that the Chinese vaccine regulatory system still meets the standard, a WHO assessment team consisted of 17 experts and one observer assessed the regulatory system of China and its six functions including oversight of clinical trials, marketing authorization, manufacturing and distribution inspection, laboratory access, lot release, and vaccine pharmacovigilance (PV) from 14 to 18 April 2014. Four experts focused on the vaccine pharmacovigilance system at central and provincial level, by visiting Chongqing and Hubei Provinces.

The WHO indicator-based National Regulatory Authorities (NRA) assessment tool was used for the assessment. This tool defines the following seven key components for an effective vaccine pharmacovigilance system and provides main indicators to measure their status:

- Institutional regulations and guidelines for the monitoring and management of AEFIs;
- Quality Management System for pharmacovigilance activities;
- Human resource management;
- Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action;
- Capacity to detect and investigate significant vaccine safety issues;
- Regulatory action regarding vaccine performance;
- Communication system in place to periodically inform stakeholders about AEFIs.

For each main indicator, a series of twenty-six sub-indicators, reflecting the required structure, process and outcome, are used. These indicators were assessed by in depth interviews, document reviews and observation at the relevant level of the health system at central level and in the provinces of Chongqing and Hubei (Ministry of Health, National Regulatory Authorities, Expanded Programme on Immunization).
The review identified that the pharmacovigilance system is supported by adequate regulation and standard guidelines, sufficient and adequately trained staff in the areas visited, advanced use of information technologies, good traceability of activities, regular compilation of reports and adequate feedback to health system and communities. In addition, experts committees are meeting regularly, as required by AEFI surveillance, and there is good communication on AEFI between national regulatory authority and EPI programme, the health authority.

AEFI reporting keeps increasing and, above 95% of counties has reported 137,414 AEFI in 2013 compared with 1,932 cases reported by 5% of counties in 2005 when the system initiated; the performance indicators, e.g., reporting/investigation within 48 hours increased from 76% to 99%, from 2005 to 2013. In December 2013, National authorities thoroughly investigated a series of serious AEFI related to one particular brand of China domestically produced hepatitis B vaccine. A precautionary suspension could be lifted within one month, following clinical and epidemiological review of cases, laboratory testing of suspected products, as well as re-inspection of the production procedures. Communication around the event was also timely and comprehensive. Also, periodic safety update report is now prepared by local manufacturers, following two training conducted with WHO support.

![Graph showing number of AEFI cases reported & percentage of counties reporting AEFI, 2005-2013, China](image)

It was concluded that in general, all indicators are well covered ensuring the functionality of the system. Aiming for a continuous improvement, specific recommendations were made to further develop the system.
GVSI Planning Group Retreat
An update on the strategic approaches to further position the Initiative discussed at Sciez-sur-Léman, France, 28-29 May 2014.

Isabelle Sahinovic

The GVSI steering committee, the Planning Group (PG), met for the 5th time since the launch of the Initiative. The committee role is to give direction to the Initiative by guiding the implementation of the Blueprint, the work of the Initiative, and providing input on the Initiative’s strategic and financing plans. It also oversees the review of the main strategic products, the Initiative’s work plan and budget, activity reports and other Initiative’s outputs. Further, it reviews applications for participation in the GVSI and advises WHO accordingly.

The retreat gathered six of seven PG members and representatives from four WHO Regional offices. For the first time, Secretariat members from the Essential Drugs and Medicines (EDM) group participated.

Among topics discussed during the first day of the retreat were the new structure for pharmacovigilance in WHO, its vision, mission, and strategy, the WHA Resolution on National Regulatory Authorities and its implications for national pharmacovigilance systems, the PIP framework and the use of Partnership Contributions on national regulatory capacity building, opportunities and challenges regarding malaria and IPV vaccines introduction.

The GVSI portfolio of activities was reviewed and newly submitted projects prioritized. Challenges and constraints in implementation and funding were discussed for planned and ongoing activities. A particular focus was given to completed activities and the first GVSI products available. The opportunity was taken to talk about lessons learnt, how the GVSI products are being taken forward by countries and their impact on national pharmacovigilance systems.

To access the portfolio: http://www.who.int/vaccine_safety/news/highlight_3/en/

The second day of the retreat was mainly dedicated to discuss the pertinence of using the WHO NRA assessment tool to measure progress in countries following implementation of GVSI products and activities. Is the Initiative making a difference in building effective PV systems? The PG agreed to establish a working group tasked with the development of an evaluation framework to measure the Initiative’s impact. The working group will include a PG member and the Secretariat supported by a
monitoring and evaluation expert. The draft framework would include a description of evaluation indicators, a proposed tracking tool, and an internal and external monitoring process. The draft will be reviewed by a “sounding board”, including all stakeholders, and then shared with the GVSI Planning group and ultimately to the GVSI forum by the October meeting.

The Planning Group also discussed what should be the way forward to reach out to stakeholders, and suggests to prepare a communication and advocacy strategy targeting funding and technical agencies, prepare a report on the GVSI, its achievements and future steps and invite stakeholders to present, during the GVSI General Meeting, their contribution to the Global Vaccine Safety Blueprint. The need to promote GVSI and its products was stressed.

The main retreat’s conclusions included a revised portfolio, an agreement on using the portfolio process as data source for ongoing progress monitoring and evaluation and the identification for cross-cutting activities between vaccines and other health products pharmacovigilance work. The planning for the annual GVSI General Meeting will start immediately. It will precede the annual Pharmacovigilance Centers meeting on 13-14 October in Tianjin, China.

Third Global Vaccine Safety Initiative Meeting, 13-14 October 2014, Tianjin, China.

Christine Maure

The Third Global Vaccine Safety Initiative Meeting will be held in Tianjin city, China, from 13 to 14 October 2014. This meeting is an important forum for country representatives and major stakeholders in vaccine safety to discuss progress on implementation of national and global vaccine pharmacovigilance activities and define plans for further development.

For the first time, the GVSI meeting is being organised back to back with the 37th Annual meeting of National Pharmacovigilance Centres, attended by around 150 delegates from over 50 countries last year. Fruitful interaction between key players in the field of pharmacovigilance is expected during a joint session between participants of the two meetings planned on the 14 October.

Focus on Africa
Building vaccine safety and pharmacovigilance capacity in Africa

Akanmori Dicky, Balakrishnan Madhava Ram, Mumba Mutale, Sahinovic Isabelle & Zuber Patrick

Vaccine safety and pharmacovigilance has assumed even greater significance in Africa in the context of the planned introduction of pneumococcal conjugate, conjugate meningococcal A meningitis, HPV, IPV, rotavirus and rubella vaccines in several countries. It is also possible that a new vaccine against malaria will become available in the near future.
In response, WHO has enhanced its support for capacity building to WHO African Region to meet the critical need for pharmacovigilance. The Global Vaccine Safety Blueprint is the strategic framework for strengthening the safety monitoring and response to Adverse Events Following Immunization (AEFIs). It proposes three main strategic objectives:

1. Assisting low and middle income countries to have at least minimal capacity for vaccine safety activities.

2. Enhancing capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics or that both manufacture and use prequalified vaccines and

3. Establishing a global vaccine safety support structure.

Pharmacovigilance of vaccines is one of the six regulatory functions of National Regulatory Authorities (NRAs). In this context, WHO has developed an assessment tool to support institutional capacity building of NRAs. Assessment is done through achievement of targets outlined in seven indicators and 28 sub-indicators. This allows countries to prepare development plans that guide institutional capacity building efforts and to identify technical support needs for all areas of regulation of medicines, including vaccines.

To support selected countries to build national vaccine safety and pharmacovigilance capacity, the Vaccine Regulation and Essential Drugs and Medicines areas of work of AFRO conducted workshops for selected English-speaking and French-speaking countries.

**Objectives**

The plan was to support selected countries to build national vaccine safety and pharmacovigilance capacity and to achieve the following objectives:

- Ensure countries are familiar with vaccine safety and the Global Vaccine Safety Blueprint (GVSB),
- Establish an inventory of resources available for vaccine safety and pharmacovigilance and make the WHO existing resources available to countries,
- Support countries to develop country roadmaps for vaccine safety and pharmacovigilance for 2014 – 2015, based on the Global Vaccine Safety Blueprint and the Institutional Development Plans and in line with their National Health Strategic Plans
- Develop a framework for monitoring the implementation of the Roadmaps.
Method of work

Two workshops were conducted. One took place in Grand Bassam, Cote d’Ivoire from 23 - 25 April 2014 for seven French-speaking countries, namely Burundi, Cameroon, Côte d’Ivoire, Democratic Republic of the Congo, Madagascar, Guinea and Togo. Eight English-speaking countries participated in a similar workshop in Accra, Ghana from 28-30 April 2014. Ethiopia, Ghana, Kenya, Malawi, Nigeria, Tanzania, Uganda and Zimbabwe were countries that participated to the workshop.

These workshops uniquely brought together participants from national EPI, National Regulatory Authority, Pharmacovigilance centres, and WHO national focal persons for EPI and Essential Medicines and Health Products. The workshops were facilitated by experts from HQ, the RO and ISTs as well as the WHO Collaborating centre for pharmacovigilance.

Prior to the workshops, the national participants discussed with their stakeholders and mapped existing resources and identified the needs for vaccine pharmacovigilance in 2014 – 2015. A draft plan of activities, priorities and the support that was required were identified.

During the workshops, the countries shared information on the status of their vaccine pharmacovigilance systems, needs and priorities. The key facilitators provided an update on the GVSI and an online demonstration of the resources available on the WHO vaccine safety website (http://www.who.int/vaccine_safety/en/) and the Pharmacovigilance toolkit (http://vaccinepvtoolkit.org/pv-toolkit/). The presentations, demonstrations and discussions that followed formed the basis for the development of an action plan for 2014-2015. A Gantt chart was also developed by each country specifically identifying the activities planned and prioritised.

Outcomes and next steps

On the final day of both workshops, the countries presented three key activities they prioritised identifying deadlines and focal persons. The next steps include:

- Obtaining endorsement and operationalizing the workplans in the African context using the framework of the Vaccine Safety Blueprint.
- Follow up discussions through face-to-face meetings and teleconferences to closely monitor implementation, provide supportive supervision and deal with bottlenecks.
- Training AEFI review committees of two countries on use of the new WHO causality assessment tool, combined with training of trainers for the rest of the countries .

It is expected that there will be improvement in monitoring, reporting and causality assessment of adverse events following immunization and vaccine safety in general in the region.

The success of the implementation of the work plans will depend upon teamwork between national programs, WHO and partners.
Capacity Building on AEFI Causality Assessment in EMRO
Strengthening capacity of national programmes in determining causality after AEFI
Langar Houda & Balakrishnan Madhava Ram

Nine countries from the Eastern Mediterranean Region of the WHO (Egypt, Iran, Jordan, Morocco, Oman, Pakistan, Saudi Arabia, Sudan and Tunisia) participated in the Regional Training Workshop on Revised WHO Methodology for Assessment of causality for Adverse Events Following Immunization (AEFI), held in Muscat from 23 to 26 June 2014. The 27 participants included national regulatory officials, pharmacovigilance center’s representatives, Expanded Programme on Immunization (EPI) managers, pediatricians and epidemiologists. The workshop was coordinated by the WHO Eastern Mediterranean Region (EMR) and facilitated by experts from WHO and the Medical University of Iran.

As part of the Global Vaccine Safety Initiative, the main objective of this workshop was to build country capacity in post-marketing surveillance of vaccines. The workshop focused on the new WHO methodology for causality assessment of adverse events following immunization that was recently revised and endorsed by the Global Advisory Committee on Vaccine Safety (GACVS). The workshop was also an opportunity for the participating countries to develop their national plans for 2014-2017 to strengthen the vaccine safety systems. The workshop addressed the needs expressed by EMR member states where pharmacovigilance systems are established and national AEFI causality committees are operational or being implemented.
All sessions of this workshop were interactive, with group exercises on selected serious AEFI cases that occurred in EMR countries, which gave participants the opportunity to practice the revised methodology and apply the systematic scientific approach to assess causality of serious adverse event and reach a logic conclusion based on available evidence.

Each of the nine participating countries devoted the last day and half to develop draft country action plans for strengthening the pharmacovigilance systems for 2014-2017, based on discussions country representatives had before they come to this meeting, with various stakeholders in their respective countries on this matter. During the workshop, countries selected priority activities and suggested having regular teleconferences (coordinated by WHO) as a sort of mechanism to monitor and evaluate country progress in implementing these plans.

Most important upcoming plans of the participating countries include updating their AEFI reporting forms to include the 22 core variables, updating AEFI investigation forms and revising their national AEFI guidelines. Some countries plan to establish (if pending) their AEFI causality assessment committees to systematically assess causality using the revised WHO causality assessment methodology. All countries prioritised ongoing training of health professionals on AEFI surveillance and monitoring as well as establishing efficient coordination mechanisms between EPI and NRAs for ensuring an effective AEFI surveillance system.