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REGIONAL OFFICE FOR THE WESTERN PACIFIC

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MEETING REPORT

THE SEVENTH WORKSHOP FOR NATIONAL REGULATORY AUTHORITIES FOR MEDICAL PRODUCTS IN THE WESTERN PACIFIC REGION

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NOTE

The views expressed in this report are those of the participants of the workshop for Seventh Workshop for National Regulatory Authorities for Medical Products in the Western Pacific Region and do not necessarily reflect the policies of the conveners.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the Seventh Workshop for National Regulatory Authorities for Vaccines and Medicines in the Western Pacific Region in Manila, Philippines from 29 to 30 August 2018.

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Abbreviations

AEFI	adverse events following immunization
ASEAN	Association of South East Asian Nations
CARM	Centre for Adverse Reactions Monitoring
CTs	Clinical Trials
DAV	Drug Administration Viet Nam
EMT	Essential Medicines and Technologies
ECSPP	Expert Committee on Specification for Pharmaceuticals Preparations
GBT	global benchmarking tool
GCP	good clinical practice
GMP	good manufacturing practice
ICDRA	International Conference of Drug Regulatory Authorities
IDP	institutional development plan
IVI	International Vaccine Institute
MFDS	Ministry of Food and Drug Safety, the Republic of Korea
MoH	Ministry of Health
NIFDS	National Institute of Food and Drug Safety Evaluation, the Republic of Korea
NCL	national control laboratory
NRA	national regulatory authority
NPRA	National Pharmaceutical Regulatory Agency
NZPhvC	New Zealand Pharmacovigilance Center
PICs	Pacific Island Countries
PIDM	WHO Programme for International Drug Monitoring
PMDA	Pharmaceuticals and Medical Devices Agency
PMMD	Pharmaceuticals and Medical Devices, Manufacture Division, Mongolia
PMS	Post Marketing Surveillance
QMS	quality management system
PV	pharmacovigilance
RA	Regional Alliance
R & D	research and development
RRP	Regional Regulatory Partnership
RSS	regulatory systems strengthening
RS	Reference Standards
RASC	Regional Alliance Steering Committee
TGA	Therapeutic Goods Administration, Australia
TWG	Technical Working Group
UMC	Uppsala Monitoring Centre
VAEIMS	Vaccine Adverse Events Information Management System
WHA	World Health Assembly
WHO	World Health Organization
WHO CC	World Health Organization Collaborating Centers
WPR	Western Pacific Region

SUMMARY

National Regulatory Authorities (NRAs) for medical products play an essential role in safeguarding public health by assuring the product quality, safety and efficacy. They contribute to achievement of universal health coverage (UHC) and the sustainable development goals (SDGs).

The Regional Alliance of NRAs in the Western Pacific Region was initiated in 2011, initially aimed at promoting information sharing and collaboration in the area of vaccines regulation. Over the years, the Alliance has contributed to identifying priorities for collaboration and capacity building for key regulatory functions; partnership and resource mobilization to support resource-constrained NRAs; harmonization of approaches for medical products regulations and annual forum for information sharing on lessons learnt and best practices among NRAs; and joint planning for taking future actions.

The Seventh Workshop for National Regulatory Authorities for Medical Products in the Western Pacific Region was held in Manila, Philippines from 29 to 30 August 2018. Fourteen countries and areas participated in the workshop were as follows: Australia, Brunei Darussalam, Cambodia, People's Republic of China, Hong Kong SAR (China), Japan, the Lao People's Democratic Republic, Malaysia, Mongolia, New Zealand, Papua New Guinea, the Republic of Korea, Philippines and Viet Nam. As platform for information sharing and experiences between Member States, the participants were able to listen and learn from the matured regulatory systems on marketing authorization and registration, regulatory inspection, post marketing surveillance, laboratory access and pharmacovigilance. With the increasing challenges in strengthening the regulatory systems, all countries acknowledged that NRAs need to work together to strengthen regulations and that collaboration and convergence is the most cost effective approach.

The participants were also able to discuss strategies on how to support resource-constraint countries in conducting regulatory capacity gap assessment and to use benchmarking processes in strengthening the regulatory systems.

Prior to the workshop, the Regional Alliance Steering Committee was held in 28 August 2018 to discuss on the governance and operational issues of the Alliance. Following the development of the terms of reference of the Alliance in 2017, the meeting provided an opportunity to execute the arrangement stipulated in the governance and operation of the Alliance. The Steering Committee will be acting as an executive board and the technical working groups will be established based on the needs of the Member State, dealing with the scientific and technical matters. The participants discussed the selection process of the seven members of the steering committee in which prescribed ratio between mature and developing countries have been agreed on a voluntary basis. In voluntary basis, Australia, Brunei, Japan, Republic of Korea, Papua New Guinea, Philippines and New Zealand signified their interest in becoming a member and will confirm their membership upon the receipt of formal letter from WHO.

1. INTRODUCTION

1.1 Meeting organization

The two-day workshop for national regulatory authorities (NRAs) in the Western Pacific Region was held in Manila, Philippines from 29 to 30 August 2018. The participants were from fourteen countries and areas including Australia, Brunei Darussalam, Cambodia, People's Republic of China, Hong Kong SAR (China), Japan, the Lao People's Democratic Republic, Malaysia, Mongolia, New Zealand, Papua New Guinea, the Republic of Korea, Philippines and Viet Nam.

1.2 Meeting objectives

The objectives of the Seventh Workshop for NRAs for Medical Products in the Western Pacific Region were:

(1) to review the progress of recommendations from the previous workshops;

(2) to jointly plan to support resource-constrained countries in conducting regulatory capacity gap assessment and implementation of institutional development plans with interested partners; and

(3) to identify priority areas and actions for regional regulatory convergence and cooperation.

2. PROCEEDINGS

2.1 Opening session

Dr Shin Young-soo, WHO Regional Director for the Western Pacific delivered the opening remarks. He highlighted the fundamental roles of the NRAs in improving health of people in the Region particularly concerning recent episodes such as recall of blood pressure drugs and infant deaths after MMR vaccination. He also emphasized the need of both strong regulators in each country, and a strong network of regulators across the Region recognizing that as there are inequities in access to medicines and vaccines between countries, the level of regulatory capacity varies between countries and areas. Thus, it is important to focus on closing the gaps in regulatory capacity so that all countries ensure safe and good quality medical products for everyone – this is a key component of universal health coverage. With this goal in mind, in 2017 the Regional Committee for the Western Pacific endorsed the Regional Action Agenda on Regulatory Strengthening, Convergence and Cooperation for Medicines and the Health Workforce. The Action Agenda provides guidance to Members States on strengthening regulatory systems and calls for convergence and cooperation – in order to best ensure the safety, effectiveness and quality of medicines and vaccines cross-border. It also provides a framework for sharing experiences across countries, and building upon the best regulatory practices. Regulatory convergence and cooperation are desirable at both national and international levels. Our goal is for every Member State to have the capacity to take necessary, timely and effective actions to ensure safety and quality of medical products and protect public health.

He urged regulators in this region to continue to be at the forefront of improving and securing the health of the people in the Region with the continued commitment and support of this Alliance.

Following the opening remarks, Dr Geraldine Hill was nominated and agreed to serve as the chairperson for the workshop, Mr Vali Caro as the vice-chairperson and Mr Rosni Jair as rapporteur. Dr Socorro Escalante, Coordinator, Essential Medicines and Technologies, WHO Regional Office for the Western Pacific Region gave an overview of the two-day workshop.

2.2 Session 1. Why Do We Need to Work Together?

This session aimed to provide background information about the reasons why regulation exists, what challenges are faced by countries to implement their roles, and what strategies/approaches are to address the challenges.

Session 1.1 Regulation in the broader context of public health

Dr Socorro Escalante first presented a framework of the access to medicines, particularly highlighting the goals of regulatory interventions; 1) ensuring the availability of safe, effective and quality-assured medicines on supply side and 2) on demand side, ensuring that medicines are selected and procured based on evidence of safety and cost-effectiveness, rationally prescribed and used, and that the optimal benefits of financing are met by monitoring consumption and expenditure.

Key challenges and issues that a number of countries are facing include;

- Lack of capacity and resources to implement the full range of regulatory functions
- Rapid evolution of regulatory science, requiring constant adjustment and capacity
- Inadequate legal frameworks and low level of technical competence to implement

The Regional Action Agenda was developed because of the following primary reasons;

- Widely various regulatory systems in terms of the range of regulatory functions performed and the level of capacity
- Type of regulatory functions and the level of sophistication depending on the development status of the country and the pharmaceutical or activity
- No country rigorously performing all regulatory functions all the time
- The Western Pacific Region with potential of resources for training and capacity building globally for the less developed countries to utilize

As identified in the Regional Action Agenda, core regulatory functions that WHO recommends all NRAs to adopt are as following based on the lifecycle of the medicines;

- For entry: licensing of establishment, clinical trial oversight, and marketing authorization or registration
- For continuing quality assurance: quality assurance in production & good manufacturing practice inspection, quality control testing, quality assurance in storage, distribution & GSP/GDP inspection, market surveillance on quality, and pharmacovigilance
- For exit: recall and withdrawal

However, given the fact that not all NRAs may be able to implement all these functions in a short period of time, a stepwise approach is recommended. This approach takes the context and legal frameworks of countries into consideration, and more importantly the degree of sophistication of the pharmaceutical markets. For instance, most of the countries among Pacific Island Countries (PICs) cannot perform some basic regulatory functions. Some countries have expressed that they are aware and are striving to implement these regulatory functions but do not have the know-how, legal frameworks and the resources to undertake them.

A potential mechanism to address this is the establishment of a sub-regional platform for pharmaceutical regulations which is in line with the Regional Action Agenda.

She reiterated the overall outcomes of the implementation of the Regional Action Agenda from the public health perspective of medical products, and the Regional Alliance is the platform to implement the agenda.

Session 1.2 Challenges and emerging issues for medical products regulations in the Region

Dr Jinho Shin in his presentation discussed the challenges and issues regarding safety and quality of medical products. He shared the following relevant events that were faced by countries recently:

- New safety data and labelling change of dengue vaccine (Dengvaxia) was published in The New England Journal of Medicine in June 2018, suggesting increased risk of hospitalization for virologically confirmed dengue (VCD) or severe VCD in seronegative children. The Philippines is one of the country to license dengue vaccine and use in the school-based dengue vaccination in 2017 but officially suspended following the announcement of Sanofi Pasteur regarding the safety concern.
- Samoa was also put in a spotlight after reports on the deaths of two infants following vaccination with Measles Mumps and Rubella combined vaccine.
- Recall of heart and blood pressure drugs known to contain N-nitrosodimethylamine (NDMA) classified as a probable human carcinogen.
- Plagiarism on clinical efficacy/safety data of a life-saving medicine
- Recall of substandard rabies and DTaP vaccines in China
- Discrepancy in results of animal toxicity tests for a pentavalent vaccine lot release in Viet Nam between the manufacturer and the national control laboratory (NCL)

He also highlighted the areas of regulatory system contributing to universal health coverage (UHC) where the quality attributes of product (tangible) include the product safety and efficacy, quality attributes of service (intangible)consist of service safety, effectiveness, timeliness, efficiency, equity and people-centeredness. There are overlapping/common attributes between the product and the service that need close cooperation the product regulators and service delivery program workers: safety and efficacy/effectiveness.

Perception on product quality is often shaped by the locations of manufacturers and the strength of regulatory systems although the end users' confidence in product quality is largely influenced by service delivery of health care workers (HCWs). Also, considering that product regulators have limited exposure to or engagement with end users, communication priority of HCWs vs product regulators is often different, leading to conflicts often (e.g. speedity vs accuracy of sharing

information). It is important to make an effort to collect end users' responses and develop closer collaboration with national, regional and international parties and exchange best practices.

Session 1.3 The role of the Regional Alliance on NRAs

Dr Geraldine Hill summarized the discussion points from RASC meeting held on 28 August 2018. She highlighted that the Regional Alliance (RA) for NRAs was established to promote and support strategies and programs to develop and strengthen NRAs to ensure that vaccines and medicines meet required standards for quality, safety and efficacy. The RA was launched with focus on vaccines only in 2011 with four countries, Japan, China, Australia, and Korea. In 2014, discussion to expand the scope to include medicines began, and the expansion was adopted in 2017 upon the agreement of most countries. The mission of RA is to provide an effective platform for regulatory convergence and cooperation in the WPR. Participating countries commit to work together ad cooperate to strengthen regulatory systems in the Region, ensuring the quality, safety and efficacy of medical products, contributing to Universal Health Coverage. The membership of the RA is voluntary and by Member States with duly designated representative who is the head of the NRA or his/her alternate. Participating countries of the RA include Australia, Brunei Darussalam, Cambodia, China, Hong Kong SAR, Japan, Lao PDR, Malaysia, Mongolia, New Zealand, Papua New Guinea, Philippines, Republic of Korea, Singapore, and Viet Nam.

Regarding the funding source, initially the RA was supported by the WHO and then by the Republic of Korea. RA Steering Committee has been given a role to identify sustainable funding source. Overall governance structure was also described; The General Assembly, as the highest decision-making body, shall appoint/designate members of the Steering Committee. The Steering Committee shall recommend policies and strategic direction of the Alliance to the General Assembly and oversee the implementation and/or the operationalization of the RA work.

The RA Terms of Reference was discussed in details at the 6th workshop and finalized between meetings. The ToR is yet to be officially endorsed by country MOHs. One of the outcomes of RASC discussion was the prioritization of the RA scope as medicines/vaccines, other biological products, medical devices/diagnostics, and traditional medicine.

A proposed Technical Working Groups (TWGs) will need to be presented to the General Assembly. TWGs may be composed of types of products and granularities including subgroups will be determined later on. Partners may include institutions in academia, laboratory centers, etc. On the second day of this workshop, there will be a call for nomination and election for countries to become RASC next year.

2.3 Session 2. What do we need to strengthen together?

This session provided a view on how a specific regulatory function is built in ideal settings. This would set later on an area of discussion what we need to do to strengthen together.

Session 2.1 Marketing authorization and registration

Dr Yasuyuki provided an overview of market authorization and registration in Japan. The regulatory authority is split between the Pharmaceuticals and Medical Devices Agency (PMDA), and the Ministry of Health, Labour, and Welfare (MHLW). PMDA is responsible for scientific and technical functions of drug review, while MHLW gives final authorization of applications, publishes guidelines,

and supervises PMDA activities. Under PMDA, new drugs are reviewed in Offices of New Drugs and Office of Vaccines and Blood Products. Also, cellular and tissue-based products are reviewed in Office of Cellular and Tissue-based products.

A brief history of PMDA was presented; until the establishment of PMDA's forerunner organization, the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), new drug reviews were performed at the MHLW by about 2 pharmacists for each new drug. However, health scandals such as the HIV-tainted blood scandal made it clear that more specialized reviews were necessary, leading to the establishment of the PMDEC in 1997. When the PMDEC was established, there were two medical doctors involved in the review of all products, along with a review team composed of a pharmacist, toxicologist, statistician. The idea was to perform reviews from various perspectives by reviewers with different fields of expertise. This formed the basis of the review team system which continued to this day at the PMDA.

In Japan, sponsors submit an application form at the time of registration, and MHLW issues the application form as a marketing approval document at the time of approval. The contents of the marketing approval document is regarded as the "approved product information" and the marketing authorization holder must comply with this approved product information. Sponsors also need to submit a Common Technical Document (CTD) with their application forms. To avoid the need to generate and compile different registration dossiers, ICH M4 guideline describes a format for the CTD that will be acceptable in three ICH regions (the EU, Japan and U.S.). Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between regulatory authorities will be simplified.

The process of new drug approval begins from holding an expert discussion with external experts in quality and toxicology. Based on the submitted CTD and response to inquiries, the review team summarizes key review points in the first review report for expert discussion. This report consists of two folds: Summary of the submitted data and outline of the review by PMDA. Based on the report, the review team clarifies the discussion points for expert discussion before expert meeting. After expert discussion some inquiries are communicated, and finally the review team makes a conclusion in the 2nd review report. In the 2nd review report, the review team summarizes expert discussion and the applicant's plan for post-marketing risk management. The review team makes its final conclusion whether the applied drug may be approved. The reports and results are notified to Minister of MHLW. The Minister consults the application to Pharmaceutical Affairs and Food Sanitation Council (PAFSC) prior to the application approval.

He also highlighted the risk/benefit assessment in new drug evaluation process, which should be undertaken by confirming that the new drug does not fall under the "condition of approval rejection" defined in the PMD Act. The first conditions for approval rejection are matters of license; 1) the applicant does not have the marketing business license. 2) the manufacturing sites are not licensed or accredited to manufacture any pharmaceutical product. Approvals are also not granted when the drug is not shown to possess the indications, or when the drug is found to have no value as a drug because the risks outweigh the benefits in the approved indications.

To increase transparency and predictability of the review process, in 2008, PMDA finalized points to be considered by the review staff involved in the evaluation process of new drug, and has made it open to the public. However, its scope is limited to basic points generally considered (i.e. there may

be many other points on a case-by-case basis) and mainly related to clinical studies. For the standard review, the period between application and approval is about 12 months.

He iterated two important points from this presentation;
1) It is important to ensure consistency, transparency, and predictability of drug review.
2) Given that the market authorization system is uniquely tailored to the laws, national priorities, and mandate in Japan, it is important to understand the rationale behind the system and adapt the principles to each NRA's needs.

During the discussion, several issues were raised such as what is the specific role of NRAs in terms of Antimicrobial Resistance (AMR). Surveillance reveals that one of the major contributor of AMR is the proliferating substandard and falsified medicines in the market, where the coordinated efforts of post market surveillance, regulatory inspection and laboratory testing are important. Another problem is the timely access of medicines and the availability of alternate antibiotic during stock outs and shortages, in which marketing authorization and registration takes part.

Patent linkage is another issue. As NRAs are placed under pressure between supporting innovation and access, patent should be carefully taken into consideration; NRAs should focus on the scientific data and not on patent.

Session 2.2 Regulatory inspections

Ms Kristy Tomas shared the regulatory inspections practices in Therapeutic Goods Administration (TGA). She provided an overview of TGA and its role to safeguard and enhance the health of the Australian community through effective and timely regulation of therapeutic goods. TGA monitors and assesses the full life cycle of a product through a number of different activities. Specifically, TGA regulates manufacturers of medicines intended to be supplied to the Australian market. Manufacturers intending to supply product to the Australian market must meet the manufacturing principles specified in the Australian legislation which is the PIC/S (Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme) Guide to GMP, and other applicable standards.

TGA Manufacturing Quality Branch is responsible for ensuring manufacturers meet appropriate quality standard through physical inspection of manufacturing facilities in Australia and overseas or provision of GMP clearance for facilities where suitable inspection has been carried out by a comparable overseas regulator (s).

Onsite inspections are carried out only after reviewing applications to determine whether an onsite inspection is required. If an inspection is required, TGA determines scope of inspection (e.g. manufacturing steps, product type being manufactured etc.), duration of inspection, and number of inspectors and skillsets required. Inspection is assigned to suitable qualified inspector(s) through an independent process. When critical deficiencies are found during inspection, TGA can take immediate actions (i.e. revoke or suspend a licensed manufacturer, or recall a product in Australia).

GMP clearance process is a non-statutory mechanism used to verify that overseas manufacturing sites comply with the principles of GMP for the products being supplied to Australia. There are two pathways to obtain a GMP clearance depending on the location of the manufacturer and international agreement with other NRA: (1) Onsite inspection (2) desk top based assessment which can be categorised into two:

- The IVI Recognition Agreement (MRA) pathway is, if available, for manufacturers located within the borders of a country that has an MRA with the TGAand has been inspected by that country's regulatory authority.

- The Compliance Verification (CV) pathway is available for manufacturers which does not meet the criteria for the MRA pathway and has been inspected by a regulatory authority that has an agreement or arrangement with the TGA, including US FDA and MRA regulators.

The evidence requirements for GMP clearance are carefully considered based on risk and can vary depending on the location of the manufacturer, the inspection authority and the collaborative agreement in place, and the risk/complexity of the product/process.

TGA is one of the few regulators that have adopted a desk top assessment (DTA) process in lieu of an onsite inspection. PIC/S recently adopted a new guidance on GMP inspection reliance based on the draft by the International Coalition of Medicines Regulatory Authorities (ICMRA) of which Australia is the vice-chair. The level of adoption by PIC/S participating authorities remains voluntary but reflects the increasing international trend on utilizing DTA processes where appropriate. TGA accepts compliance of an overseas site with the local GMP requirements based on a current GMP certificate issued by the regulatory agency of the other party to the MRA. CV assessment is permitted wherever the TGA has an international cooperation arrangement, such as memorandum of understanding or PIC/S membership. It involves a detailed assessment by the TGA of specified documentary evidence supplied by the manufacturer/sponsor for products to be supplied in Australia.

International harmonization of standards and inspections allows for a shared workload with regulators in other countries. PIC/S is a non-binding co-operative arrangement between Regulatory Authorities in the field of GMP of medicinal products for human or veterinary use. It is open to any authority having a comparable GMP inspection system. PIC/S mission is "to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products". They achieve this mission by harmonising inspection procedures worldwide, developing common standards in the field of GMP, and providing training opportunities to inspectors facilitating co-operation and networking between competent authorities, regional and international organisations, thus increasing IVI confidence. TGA also participates in various PIC/S activities such as sub-committees on the harmonisation of GM(D)P as well as on budget, risk & audit, data integrity, and harmonization of the classification of deficiencies.

Session 2.3 Post-marketing surveillance

Ms Somiyaton Binti MOHD Dahalan shared post market surveillance (PMS) activities in Malaysia. She introduced the organization of National Pharmaceutical Regulatory Agency (NPRA), under which pharmacovigilance section, surveillance & product compliant section, and cosmetic section. The surveillance & product complaint section consists of product complaint unit, routine surveillance unit, and special surveillance unit. Regulatory components include registration, pharmacovigilance, surveillance, analysis, licensing, and education.

PMS activities are carried out to continuously monitor quality, safety and efficacy of medicines in the market (after registration). The goals of PMS are as follows:

- Ensure that products are of quality, efficacious, and safe and continue to meet required standards whilst in the market
- Ensure necessary actions are taken for products found not in compliance with the Drug Control Authority (DCA) requirements
- Ensure follow up of corrective and preventive measures implemented to improve product quality
- Remove unsafe products from the market in a timely manner

PMS involves active and reactive PMS; active PMS refers to sampling and testing products in the market, while reactive PMS refers to follow up on complaints received. PMS activities are mainly four-fold; surveillance activities, investigation of product complaints, and handling of alerts as well as out of specification (OOS) reports from manufacturers.

PMS activities are further categorized into three; routine surveillance, risk-based surveillance, and special surveillance. Under routine surveillance, products will be sampled at least once in its registration period. Samples are collected from product registration holders, manufactures, importers, wholesalers, and distributors. The surveillance is conducted in collaboration with NPRA, pharmaceutical enforcement division, and product registration holder. Risk-based surveillance is for the products with complaints, ADR reports, history of laboratory testing failure, and products known to have formulation problems. Under special surveillance, products from market are tested base on complaints and advertisements.

She also briefly explained the surveillance work process. For label monitoring, NPRA ensures no deviation in the formula in terms of ingredients and contents. NPRA also checked records and shelf-life to ensure that products are manufactured by the approved manufacturer in adherence to approved limit.

Product complaint is an effective tool to conduct surveillance. System to monitor product quality should be in place by regulators, hospitals, clinics and industry. Any problem of deficiencies or defects encountered with a registered product can be forwarded to NPRA using a standard form. The product registration holder should notify the NPRA of any product quality related problems (with registered products) that the holder is aware of. It is also the responsibility of the prescribers, pharmacists, as well as all other health professionals who come into contact with the drug to report to NPRA by using the NPRA complaint form, which is available at the website of NPRA. All complaints received will be investigated by the NPRA as well as product registration holder/manufacturer. It is the responsibility of the company to determine the appropriate corrective and preventive action. Upon receipt of a product complaint, registration status is verified. Based on the outcome of all findings, NPRA decides an action to be taken; recall, warning, intensifying surveillance of manufacturer/other products, GMP inspection of premises, or no action because the problem is not due to the product per se.

For information sharing mechanism, PICs Rapid Alert/ASEAN Alerts is a rapid mechanism for alerting member countries to minimize the adverse impacts of the distribution and use of medicinal products with quality defects, including counterfeit medicine. In 2017, a total of 121 alerts were received (1418 products were involved) from the ASEAN countries with Malaysia contributing a total of 37 (30.59%) reports. Through the RAS information sharing network, a total of 124 reports were received in 2017 and one of them has led to a voluntary recall by the registration holder of the product.

Panel discussion

The aim of the session is to facilitate discussion between less mature countries and share their reflections from the presentations of the more mature countries. It was facilitated by Dr. Lucky Slamet with panellists, composed of representatives from Lao PDR, Mongolia, Philippines and Cambodia

Mongolia shared that support is needed on post market surveillance.

Philippines identified that the gap is a number of manpower compared to the number of applications for registration, GMP inspection, etc.

Lao PDR develops yearly plan of actions, which are not always implemented due to financial limitations. Capacity building of personnel and enhancement of systems including quality control system are challenges. Lao PDR occasionally relies on other NRAs for inspection to protect consumers from substandard products.

Cambodia shared challenges on implementing post-marketing surveillance and GMP inspection.

Session 2.4 Laboratory Management and NRA Support of National Institute of Food and Drug Safety Evaluation (NIFDS)

Dr. Kwangmoon Lee presented the overall structure of MFDS and NIDFS and the responsibilities of the different Offices. NIFDS is responsible for the product review, market authorization, scientific research, development of testing and evaluation methods, and risk assessment.

Laboratory activities are mainly three folds; 1) laboratory quality management, 2) national lot release, and 3) reference standards.

On laboratory quality management NIFDS is accredited by ISO 17025 demonstrating its competence for testing and calibration laboratories for 12 testings (9 biological and 3 pharmaceutical testings). NIFDS is adheres to quality management by maintaining up to date quality documentation such as quality procedures, quality instructions, and standard operating procedures (SOPs). Also, MFDS conducts validation/calibration of facilities and equipment, annual quality system management review and internal audit, provides staff trainings, and manages national reference standards.

National lot release is a process of NRA/NCL evaluation of an individual lot of a licensed biologics before its release onto the market. According to WHO TRS 978, the guidelines for independent lot release of vaccines by regulatory authorities, a careful independent review of manufacturing and QC data on every lot is necessary before it is marketed. National lot release is required considering that biologics usually have a large and complex structure; as biologics are unstable, it must be processed under carefully defined conditions, and should be stored in proper condition with monitoring. Also, given that biologics cannot be heat-sterilized, aseptic manufacturing is essential to preclude contamination. Safety issues may have a drastic impact because vaccines are used in healthy populations, especially infants and children. The impact of substandard lots may not be detected for a long time. Thus, large numbers of healthy individuals receive vaccines before problems are recognized. Regarding national lot release system in Korea, each lot of biologics such as vaccines and plasma-derived products is carefully monitored by reviewing manufacturing documents such as summary protocol and national lot release testing by MFDS before being release for sale in Korea.

According to WHO TRS 978, summary protocol (SP) is a document summarizing information from all manufacturing steps and test results for a vaccine lot, which is certified and signed by the responsible person of the manufacturing company. For quality control testing, since biologics are manufactured from materials derived from living organisms, their quality management is much more difficult than chemical drugs, and their safety and efficacy are immeasurable by physicochemical testing. Biologics require rigorous review and testing.

MFDS launched a new lot release system in 2016, testing various factors affecting quality of a product, such as history and results of national lot release as well as GMP inspection, domestic and overseas safety information, and license change. Products are classified into levels 1-3; level 1 products (e.g. new products) require all test items. For level 2 products, general test items (e.g. pH, volume, dose uniformity, sterility, etc.) are waived. Level 1 product are waived for all tests except summary protocol review only.

Reference standards (RS) are used for identity test and impurity test and potency assays. The first national RS was a chemical and made by MFDS in 1991, followed by biopharmaceutical RS, herbal RS, in vitro diagnostics RS, and quasi-drug RS. Currently there are 489 NIFDS RSs. A process of establishing and managing of RS was explained. Once it is registered as a NIFDS RS, it can be distributed externally although a periodic stability test should be performed. Storage conditions for RS should be maintained using thermos-hygrostat, temperature monitoring system, and alarm system.

NIFDS is highly engaged in international cooperation, an MOU was established with National Institute of Biologic Standards and Control (NIBSC) to establish and improve quality control of measurement standards for biologicals and in-vitro diagnostic devices, and facilitate information sharing and joint studies in October 2016. In addition, an MOU was established with National Institute of Infectious Diseases (NIID), Japan to strengthen collaboration, facilitate staff exchange and joint studies on new infectious diseases in February 2017. NIFDS, as a WHO CC since 2011, has been providing trainings on use of equipment for vaccine quality control, support for laboratory set-ups, GMP education, and lot release testing.

Session 2.5 Pharmacovigilance

Dr. Michael Tatley presented the pharmacovigilance system in New Zealand. He started by sharing why ADRs are a cause for concern in New Zealand. A study reveals that medicines are the 3rd leading cause of adverse event and has considerable impact on prolonged hospitalization, disability and death, it also contribute to increasing cost. The study also shows that almost a half of adverse events (AE) are preventable. He also shared that compensation program is in place in New Zealand to cover drug injuries.

The national monitoring center for medicines and vaccines was established in 1965 and one of the founding member of WHO Program on International Drug Monitoring in 1968.

In line with the regulatory framework he presented the pharmacovigilance systems in New Zealand according to the six general evaluation framework:

1. Vigilance regulatory framework – legal provisions, regulations & guidelines are in place stipulating the duties of importer/manufacturer to report untoward effects of medicines and monitor safety of medicines. The ADR/AEFI monitoring system in New Zealand is unique in a sense that it is independent from the regulator, pharmacovigilance services are provided by

University of Otago to Medsafe under contract with MoH. The PV center provides support in clinical decision making and research.

2. Arrangements for effective organization and good governance- He shared the organizational structure consisting of the different players of PV from Medsafe the regulatory body and responsible for clinical risk management, Medicines Adverse Reactions Committee (MARC) considers medicine and vaccine safety issues without executive or regulatory activities, and Medicines Assessment Advisory Committee (MAAC). It interfaces with other relevant groups such as vaccine safety expert advisory group and vaccine sub-committee of PTAC (Pharmacology and Therapeutics Committee).

3. Human resources to perform vigilance activities- each of the monitoring programs and technical committees has their respective experts, mangers, administrative support and tools to perform their duties in supporting the safety of medicines and related products through voluntary reporting of ADRs/AEFIs..

4. Procedures established to implement and perform vigilance activities- although healthcare professional have traditionally submitted the majority of reports, anyone can report suspected ADRs directly to the Centre for Adverse Reactions Monitoring (CARM) within the NZPhvC using online reporting forms, the electronic adverse reaction tool in practice management software programmes, and phone applications. CARM is also available to discuss ADRs by telephone and accepts reports by email or fax. One third of the reports are related to vaccines, and 60% of ADR/AEFI reports are from healthcare professionals (i.e. nurses, doctors, and pharmacists). Each event or reaction is coded according to the WHO criteria using WHO-ART (Adverse Reaction Terminology). For all spontaneous reports, tailored response is sent to every reporter with causality, relevant additional information at risk groups, and follow-up information if required. Spontaneous monitoring is important to detect patterns of AEFIs/Reactions, signal new AEFIs/Reactions, and contribute to individual patient safety. NZPhvC records drugs/vaccine-specific ADR/AEFI alerts as warning (precaution) and danger (contraindication/life threatening). A pilot project, Medication Error Reporting and Prevention (MERP), operated by the NZPhvC was implemented in accordance with the importance of identifying medication errors highlighted by the WHO. The MERP, an online, national reporting system, collects reports of errors to supplement, contribute to and improve the safe use of medicines.

5. Mechanism exists to promote transparency, accountability and communication- cultivating "vigilance culture" is important. NZPhvC provides various communication mechanisms and support, including online/telephone on-demand access by clinicians for ADR/AEFI discussion, supporting clinical decision-making through ADR/AEFI data, and promotional activities and presentations. Other efforts to promote transparency and accountability is to make reporting easy to suit all, provide feedback on each report and follow up for clarity or outcome(s). NZphvC also closely works with Medsafe and immunization programs by conducting weekly teleconference, issuing weekly or adhoc summary report on specific vaccines or medicines as well as quarterly reports to the Medicines Adverse Reactions Committee (MARC). There is also publically accessible database of adverse events, called "suspected medicine adverse reaction search (SMARS)".

6. Mechanism in place to monitor regulatory performance and output are in place, committee meetings are organized by MARC and published meeting minutes. NZPhvC submit annual report to the MoH, prescribers updates to facilitates awareness and Official Information Act enquiries to which responses are posted on MoH webpage.

He concluded by highlighting the key success factors in sustainability of the pharmacovigilance system in New Zealand, such as research support, patient-centered focus, communication, and informing national policy.

Panel Discussion

Dr. Yeowon Sohn facilitated discussion between countries on laboratory and pharmacovigilance with panellists from Viet Nam, New Zealand, China, and Hong Kong SAR.

Panellists introduced a brief overview of laboratory access and pharmacovigilance systems in their countries. Vietnam shared its efforts in the preparation for WHO assessment this 2018, on laboratory support, Vietnam requested guidance in implementing risk management, and training support for laboratory testing, for pharmacovigilance lot of work in needed to increase public awareness and media management.

Medsafe New Zealand contracts with Environmental and Scientific Research (ESR) to conduct laboratory testing. On pharmacovigilance, investigating the increasing compliant on brand medicines is becoming challenge.

China particularly concerning a potential impact of any information to the public (e.g. a recent recall of Valsartan), the mechanism of sharing information in a timely manner should be in place. On Laboratory, the National Institute for Food and Drug Control (NIFDC) seeks more collaboration with other countries especially on development of regional standards.

In Hong Kong, laboratory testing is undertaken by a central laboratory that supports all testing including forensic and activities of enforcement agencies but currently limited capacity to conduct biologicals testing including vaccines. For pharmacovigilance, reporting mechanism for all health products are in place, the Pharmacy and Poisons Board of Hong Kong coordinates with the public hospitals who management and analyse ADRs. A dedicated person is assigned for web based monitoring.

Overall, one of the challenge identified is to regulate imported products particularly in a country where standard laboratory is not in place hence implies the importance of collaboration. Facilitating expedited process of importation is also an important area for consideration.

2.4 Session 3. How Do We Work Together

This session provided an opportunity to identifying approaches and strategies to strengthen regulatory systems.

Session 3.1 Roles of Norms and Standards in strengthening regulatory systems

Dr. François-xavier Lery, shared how WHO works on development of norms and standards in strengthening regulatory systems. There are 85 Technical Report Series (TRS) on medicines quality assurance guidelines and 93 TRS for vaccines and bio therapeutic products guidelines or recommendations. International pharmacopeia is also published and updated every year with more than 540 specifications. These guidelines were adopted by the expert committee at the end of 2017. The guidelines published in 2018 entail;

- Procedures and data requirements for changes to be approved for biotherapeutic products
- HIV rapid diagnostic tests for professional use and/or self-testing, and establishing stability of in-vitro diagnostic medical devices for in vitro diagnostics
- Quality, safety, and efficacy of Ebola vaccines for vaccines
- Good herbal processing practices and good manufacturing practices for herbal medicines
- WHO guidance on testing of "suspect" falsified medicines
- Monographs on herbal medicines and for compounded preparations for good pharmacopoeial practices
- Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

One of the activities in regulatory system strengthening (RSS) is Global Benchmarking Tool (GBT) is to monitor the level of implementation of WHO and other international guidelines for NRAs to be functional. WHO is also working in promoting reliance moving towards WHO Listed Authorities, however, there would be still need of further work on fine-tuning of definition and implementation using WHO GBT.

He discussed upcoming guidelines and recommendations, the following new standards to be adopted by the Expert Committee for Biological Standardization (ECBS) by the end of October or early November:

- Quality, safety and efficacy of hepatitis E vaccines
- Biosafety risk assessment and guidelines for the production and QC of novel human influenza candidate vaccine viruses and pandemic vaccines
- Safe production of polio vaccines
- Q & A on WHO Guidelines for similar bio therapeutic products

Projects for ECBS 2019 include guidelines for RSV vaccines, which are under consultation in September 2018, and a new project on nucleic acid based vaccines of importance for public health emergencies (i.e. revision of guidelines for DNA-based vaccines, and generation of points to consider on RNA-based vaccines).

The pipeline for ECSPP includes WHO Biowaiver Project, which is a proposal to waive in vivo bioequivalence requirements for medicines included in the WHO Essential Medicines List (EML). This project is designed to facilitate the registration of generic medicines by reducing regulatory requirements, particularly medicines on EML and thus promote access to essential medicines. It is based on the Biopharmaceutics Classification System (BCS), classifying active substances based on aqueous solubility and intestinal permeability. This is a mechanism for waiving in vivo bioavailability and bioequivalence studies. A brief timeline of the pilot project was also shared; from October 2017 for start of the pilot to October 2018 for presentation of test results and methodological evaluation for pilot expansion. Collaborating laboratories for the pilot project are located in the U.S., Spain, and China.

Implementation of these guidelines is aligned with the 13th general programme of work (GPW) 2019-2023. Regulatory burden is decreased through implementation of WHO quality standards. For instance, the External Quality Assurance Assessment Program (EQAAS) aims participating QC labs to measure its performance and allows QC labs to monitor quality of medicines. Another approach to promote implementation of guidelines is to hold implementation workshop. For instance, there were 2 HPV workshops in Thailand and China in 2016, and GMP for biological and typhoid conjugated vaccine workshops in Thailand and Republic of Korea, respectively, in 2017. Other workshops regarding biotherapeutics including biosimilars, GMP and typhoid conjugated vaccines are scheduled in 2018.

He concluded his presentation by highlighting the importance of promoting access to safe, quality-ensured, and efficient medicines.

Session 3.2 Convergence and cooperation and Global Benchmarking Tool (GBT): their roles in strengthening national regulatory systems

Dr. Samvel Azatyan provided a brief overview of global challenges in terms of access to medicines, especially for low and middle-income countries, persistently, insufficient regulatory capacity and lack of harmonized technical requirements for medicines regulation still a major challenge. Gap between regulatory capacities in different countries persist particularly in human and financial resources, regulatory functions effectively performed, expertise availability, proper systematic training for regulators and applying quality management principles.

NRAs are the forefront of changing paradigm and realities including globalization of regulatory science, introduction of new complex products and sophisticated health systems and quality use. Moreover, health systems and health providers are varying in strength between countries. WHO has been taking an active role in helping countries to strengthen its systems, including facilitation of good decision making processes, including promoting and facilitating building up national regulatory systems as part of overall health systems strengthening, supporting regulatory workforce development.

Multiple approaches are proposed to address these challenges including promotion of regulatory cooperation, convergence and harmonization. There are many ways of collaboration, very common are bilateral agreement that can be entered between geographical neighbours or non-neighbour and multilateral collaboration either regional or international.

Potential areas of convergence and harmonization were presented including:

- Legislation & regulations – harmonization, where possible;
- Clinical trials:
  - harmonization of requirements for applications to conduct clinical trials;
  - recognition of clinical trial audits;
  - clinical trial registries;
- Medical product registration:
  - harmonization of technical guidelines & registration requirements;
  - reliance of GMP audits & dossier assessments;
  - work-sharing of dossier assessments;
- Post-market surveillance activities:
  - information-/work-sharing of ADR/safety assessments;

- work-sharing/reliance on product testing results;
- Information-sharing on counterfeit medical products, product defects and GMP non-compliance of manufacturers.

He highlighted that engaging in regulatory cooperation doesn't mean a loss of national sovereignty / autonomy, in all cases the regulatory decision itself remains firmly in the hands of sovereign nations.

The success factors for convergence and harmonization initiatives are:

- Well elaborated and clearly understood vision, mission, roles and responsibilities;
- Political will and continuous support;
- Effective management and administration;
- Active participation of all potential stakeholders (NRAs, industry, development partners);
- Ownership by the NRAs.
- To be based on the modern science and reaching the consensus
- Engagement by all parties to implement the documents developed and to follow them
- Well defined decision making mechanism and procedures
- Adequate human and financial resources
- Transparency and effective communication.

The role of benchmarking tool in framing strategies for regulatory strengthening

Benchmarking of national regulatory authorities means evaluation of systems through a comprehensive and systematic benchmarking process. It is a part of WHO five steps capacity building.

The benchmarking methodology is a sophisticated process that starts from pre visit, self-benchmarking, then finally to benchmarking and to continuous follow up and monitoring. The GBT is built upon the Good Regulatory Practices and has adopted the maturity level concept, this way, gaps are easily figured out (inter and intra regulatory functions) and hence capacity building priorities are defined.

The GBT will also be used in establishing a system for recognizing and listing WHO Listed Authorities (WLA) after rigorous consultation process with all stakeholders. The GBT aims to provide a robust framework to promote trust, confidence and reliance and thereby enable efficient use of regulatory resources; it also encourages continuous improvement of regulatory systems.

More importantly from the perspective of public health, it helps in procurement decisions on medical products by UN and other agencies, as well as countries; and finally, it expands the pool of regulatory authorities contributing to efficiency of WHO Prequalification Programme.

The development GBT is a continuous process and will remain open for further developments, because this has to be aligned with the dynamic regulatory environment. NRA's are advised to visit WHO website for the latest version of GBT fact sheets.

Session 3.3. Regional adaptation of WHO GBT

Dr. Jinho Shin provided an update on the implementation of the GBT at the regional level. The Regional Alliance for NRAs during the 3rd and 5th Workshop played an important role to disseminate

the developments of the tool including the transition from self-assessment focusing on vaccines until the current state.

The regional strategy composed of series of steps starting from guiding the countries to conduct self-assessment, followed by inviting experts to validate the assessment or map out the evidences. The experts together with WHO will support in the development of an institutional development plan and assist in the implementation.

WHO conducted rapid benchmarking with the key focus on maturity level 1 to 3 indicators in Mongilia (2016), Papua New Guinea (2016), Cambodia (2017), Lao PDR (2017). WHO conducted GBT briefing to Malaysia (2017), Republic of Korea (2017), Viet Nam (2017), and Philippines (2018).

In the region the new features of WHO GBT (harmonized vaccine and medicine tool) found valuable by many the countries because if offers:

- comprehensive system-based benchmarking
- flexible options for country to choose areas of product regulation across different medical product streams
- enhanced ability for customization of the tool based on functional streams and maturity level depending on country's way of sourcing vaccines and/or medicines and extent of regulatory functions established (full vs. rapid benchmarking)
- comprehensive guidance for benchmarking
- maintenance of functionality concept as part of eligibility criteria for WHO prequalification

However he also shared points for further improvement including: clear and concrete instruction for "minimum ML" and "scoring" and publication of algorithm of how maturity level is calculated, what are assessors qualification criteria and how to ensure inter-assessor reliability.

Session 3.4. Sub-regional regulatory platform

Dr Socorro Escalante, explained the objective of setting up a sub-regional regulatory platform, this is in line with the overarching goal that supports the access to medicines of assured and safety and efficacy for all peoples in the Pacific by strengthening regulations and legal frameworks for pharmaceutical systems.

She explained the situation in PICs in which they are facing perennial issues on shortage of medicines over the years, strengthening procurement as single approach can no longer save the issue. In addition it will be more difficult with entry of new products and increasing health demands. Regulations are not in place in all the countries, in general, all countries need to strengthen regulatory However, countries will not be able to undertake all these regulatory functions effectively, largely because of human, financial, and knowledge constraints

Therefore, WPRO developed the stepwise approach to establishing/strengthening essential regulatory functions. These approach takes into consideration the context and legal frameworks of countries, and more importantly the degree of sophistication of the pharmaceutical markets. For PICs, all of the countries are importing medicines. Therefore the core regulatory functions for PICs need to cover: licensing of establishments (importers, wholesalers, distributors, and retailers); registration of

products; market surveillance and pharmacovigilance and recall/withdrawal of products that do not meet specifications. However, most of the countries cannot perform even these basic regulatory functions.

During the meeting, it was raised that most of PICs are aware of these gaps and are working to put these regulatory functions in place but do not have the know-how, the legal frameworks and the resources to undertake them.

A potential mechanism to address this is the establishment of a sub-regional platform for pharmaceutical regulations. This will provide mechanism for cooperation in pharmaceutical regulations: reliance mechanisms and/or joint or collaborative regulations, where needed and mechanism for capacity development: mobilize support from more stringent regulatory authorities for learning and coaching of regulatory authorities in PICs.

It is envisaged, that when feasible and approved by the Organization as well as accepted by countries, a unit may be established that will be operated by a technical officer and assistant. Tools and online platforms will be developed as functional tools for regulatory activities and systems building.

Session 3.5 Strengthening Pharmacovigilance and Medicines Support Systems in the Pacific

Dr Michael Tatley from the University of Otago presented a proposal on pharmacovigilance strengthening that can be a potential area of consideration as part of the sub regulatory platform for PICs. He highlighted the importance of efficient and timely pharmacovigilance systems in safeguarding public access and use of medicines and vaccines. Despite being an important area in public health the low and middle income countries continue to face many challenges including resources pressure and limitations, suboptimal systems and system infrastructure, unattended and unrecognised needs and limited access to support.

If these inadequacies will not be addressed in timely manner this will lead to compromised capacity to monitor safety of medicines and vaccines to identify and respond emerging safety concerns; inaccurate information or rumors will spread fast in social media, inadequacies will also change perceptions about the products and immunization, other disease control programs and finally countries will miss the opportunity to be part of Global Pharmacovigilance Safety Network.

In addition, there are also issues in translation gap, such as perception on inability to match mature pharmacovigilance systems and perception on mature systems is the standard for all. Pharmacovigilance training translation also had become challenge, despite many trainings attended by countries they stumble on implementation and momentum. Considering these underlying issues, the challenge now is that what could be the appropriate approach or strengthening model for the low and middle income countries especially for the PICs.

Dr Tatley proposal highlights three underlying principles: first is to build on existing training and support not necessarily reinventing the wheel, second is assistance in translating and embedding and third is ongoing support. He provided emphasis on assistance in translating and embedding, to help the countries in transitioning after the training, to identify obstacles in implementing the acquired training, to provide close contact until the level of local self-sufficiency and confidence is increased.

The elements of the proposal are:

- System enhancements: to review existing systems on the medical products itself such as available tools and infrastructure to manage data and reporting system, causality evaluation, mechanism to investigate, metrics etc. In parallel, Medication error is also another important area to consider (e.g the patterns, practice issues and learning opportunities) as well as medicines regulatory support. For system enhancement there are academic opportunities for under and post graduate training to grow PV resource skills/capacity and developing local research capacity.
- Integration with public health programmes: strengthening needs to illustrate the relevance of PV to PHPs that counters misinformation and improves adherence to the PHP and must sustain the confidence, it is important the integration needs to be sympathetic and seamless, it not should burden the program.
- Networking and stakeholder involvement
- Project implementation

2.5 Session 4. Partnerships and collaboration

Session 4.1 DFAT Programme on Regulatory Strengthening and Regional Partnerships

Alex Stephens from DFAT Australia shared the program on Regional Regulatory Partnership (RRP) for malaria elimination. The RRP was established in 2014 with the aim of strengthening NRA capacity and regional collaboration on regulatory practice to improve the region's malaria response, it was established by Asian Pacific Leaders Malaria Alliance Secretariat (APLMA), WHO, Asian Development Bank, Center of Regulatory Excellence and TGA.

The RRP brought together the NRAs and national malaria control programs from the ASEAN region, India and Papua New Guinea, along with the technical and development partners.

Mr Stephens also shared the newly established Indo-Pacific Regulatory Strengthening program that aims to strengthen the capability of NRAs to increase the availability of safe and effective medicines and medical devices through improved regulatory practice and regional collaboration. Currently, the program includes six countries: Cambodia, Indonesia, Myanmar, Lao PDR, Papua New Guinea and Viet Nam.

The programme has been set up in partnership with Australian Therapeutic Goods and Administration (TGA) to implement a regulatory strengthening program. Several in-country missions were conducted in Lao PDR, Indonesia, Myanmar and Papua New Guinea initially to understand the current operating environment and capacity, and to discuss the design of the program.

Session 4.3 USP Programme on medicine and quality assurance

Mr Ng Cheng Tiang provided an introduction about USP, which is a non-profit organization found in 1820 that has a goal align with the US FDA, that is to improve the health of the people around the world through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods., USP sets standards for quality, purity, strengthen and consistency of these products-critical to public health.

USP roles in medicines quality includes helping resource-strapped countries build capacity in QA systems to better monitor, test and regulate quality medicines and offers education, training, resources and guidance to help regulators, QC Labs and manufacturers to build strong quality capability.

Mr Tiang shared USP initiatives to drive medicines quality:

- Education: USP has organized more than 50,000 trainings since 2000 covering all spectrums of medical products and practices.
- Networks of Official Medicines Control Laboratories (NOMCoL): This network was established by Official Medicines Control Laboratories, in the region there is a NOMCoL - Asia/Pacific that aims to strengthen the technical and procedural capacity of its members towards achieving and maintaining international medicines control laboratory standards.
- Medicines We Can Trust campaign: The campaign aims to raise awareness about poor-quality and counterfeit medicines to make sure everyone has access to safe, quality medicines which is accessible at this webpage (https://medswecantrust.org/)
- Promoting the Quality of Medicines Program: primary tool for United States Agency for International Development (ASAID) to help Asia Pacific countries to strengthen quality assurance and quality control systems increased the supply of quality assured medicines, combat against substandard and counterfeit medicines and provide technical leadership and global advocacy.
- Policy Positions: contributes in antimicrobial resistance, substandard and falsified medicines, compounding, dietary Supplements

Session 4.4 IVI vaccine research and development of AEFI tool

Ms Deok Ryun Kim shared IVI Institute activities as part of the global vaccine safety initiatives. IVI is an independent, nonprofit, international organization initially created as an initiative of the UN Development Programme (UNDP).

As a partner and collaborator IVI aims to provide support in strengthening vaccine pharmacovigilance. IVI developed a Vaccine Adverse Events Information Monitoring System (VAEIMS) which is computerized software that processes data reported from local level of the health care systems into the central database then analyze data into useful information.

This is part of the effort to address the gaps identified in many low and middle income countries such as unclear systems how data are collected and analyzed; non-existent mechanism of AEFI reporting and no harmonized format available within countries; no/ minimal national repository to store and extract information (non E2B), countries not able to identify vaccine safety issues, signals and provide feedback at local/national and international level.

VAEIMS has been developed for countries to rapidly adapt to their local context with minimum alternations/modifications; a customized VAEIMS has been deployed in several countries.

Development of VAEIMS is continuously evolving; it expanded not only within National AEFI program but also includes manufacturers. Currently IVI is working with United States National Institute of Health on dengue vaccine safety data monitoring, to develop a centralized database for clinical trials of evaluating dengue vaccine candidates, TV003 and TV005.

The new feature of the VAEIMs includes the following:

- Epidemiology dashboard presents bar chart, pie chart, and map of AEFI data by person, time, seriousness, outcomes

- Visualization function as generating descriptive epidemiology presenting bar chart and pie chart and map
- Incidence Rate Calculation by Vaccine
- Signal Detection
- Coding of AE term with international medical terminology
- Multiple language Support
- Auto-generated AEFI Epidemiology Bulletin
- E2B (R2) converter

IVI also is organizing training on the use of the tool either in-country or the first regional training will be organized in September 2018.

2.6 Session 5. General Assembly

Session 5.1 Report on the output of the RASC meeting

Following the development of the terms of reference of the Alliance in 2017, the meeting provided an opportunity to execute the arrangement stipulated in the governance and operation of the Alliance.

The Steering Committee will be acting as an executive board and the technical working groups will be established based on the needs of the Member State, dealing with the scientific and technical matters. The participants discussed the selection process of the seven members of the steering committee in which prescribed ratio between mature and developing countries have been agreed on a voluntary basis.

Recognizing that the region has the most advanced national regulatory systems for medical products in the world, this provides an opportunity for less-mature regulatory systems with resources for training and capacity building. On this purpose, the participants pre-identified potential experts and institutions to support the work of the Alliance.

The meeting has finalized the scope of the Alliance based on four products streams (Medicines, vaccines and other biological products, medical devices and traditional medicines.

Session 5.2 Election for RASC Members

As stipulated in the concept paper the terms of seven countries Australia, China, Japan, Republic of Korea, Philippines, Malaysia, and Vietnam as steering committee for four years has ended this year. It's time for election of new membership. As agreed by Steering committee during the first day meeting, the proportion for representation is composed of three members from developed (more mature) NRAs and four members from developing (less mature) NRAs, was presented to General Assembly. With 11 votes and three abstains out of 14 countries, this representation is adopted.

According to the Terms of Reference (TOR), the Steering Committee shall: recommend policies and strategic directions of the Alliance to the General Assembly; oversee the implementation and or/operationalization of the work of the Alliance, propose technical working groups to be approved by

the General Assembly; and advise the General Assembly on any other matters pertaining to its conduct of business, operations and strategic directions.

Four from the more mature NRAs voluntarily signified interest for RASC membership compose of Australia, Rep of Korea, Japan and New Zealand and three countries voluntarily signified interest for RASC membership from less mature NRAs: Papua New Guinea, Philippines, and Brunei.

The secretariat will follow up with an official letter to each country directed to the head of NRAs for the confirmation of the RASC membership, and then RASC will be formally constituted. Once the RASC is formally constituted, the financial sustainability will be discussed and determined.

Session 5.3 Election of the Chair and Vice Chair of RASC

Currently, the leadership of the SC meeting and workshop is rotating alphabetically between member countries, but there is a proposal to change following the change of membership to the SC. As there are still lot of issues to manage including the governance of the RA, the election of the Chair and Vice Chair was not thoroughly discussed this workshop but the participants agreed to manage during the mid-year meeting of the Steering Committee.

Session 5.4 Presentation of the proposed technical working groups

Technical working groups are proposed to provide expert advice to the alliance on specific areas of work across the domains of regulatory functions and product-specific issues.

After debate on the composition of the working groups whether according to product streams or regulatory function, the participants agreed on regulatory functions because the availability and capacity of individuals to support the Alliance is based on expertise that cuts across all regulatory functions and that vertical strategy (product stream) will bring duplication of work.

The participants also agreed that among the many regulatory functions, there is a need to prioritize an area of work starting from (1) marketing authorization and registration (2) good manufacturing practice (3) quality assurance (4) pharmacovigilance, and later on include other functions as it progress.

The members of the technical working groups will be identified later after the Secretariat will consolidate the list of experts and institutions as starting point and will circulate to all participants.

Session 5.5 Venue and dates of the 8th workshop

A call on interest to host the 8th workshop was presented to the Steering Committee, Japan has signified its interest and sates and venue of the 8th workshop will be identified in December 2018 after the confirmation from the government of Japan

2.7 Session 6. Closing session

The workshop ended with reflections from each participant and a strong message on the need to continue collaboration with other countries.

3. CONCLUSION AND RECOMMENDATIONS

3.1 Conclusions

Regional Alliance Steering Committee Meeting

Following the development of the terms of reference of the Alliance in 2017, the meeting provided an opportunity to execute the arrangement stipulated in the governance and operation of the Alliance. The Steering Committee will be acting as an executive board and the technical working groups will be established based on the needs of the Member State, dealing with the scientific and technical matters. The participants discussed the selection process of the seven members of the steering committee in which prescribed ratio between mature and developing countries have been agreed on a voluntary basis.

Recognizing that the region has the most advanced national regulatory systems for medical products in the world, this provides an opportunity for less-mature regulatory systems with resources for training and capacity building. On this purpose, the participants pre-identified potential experts and institutions to support the work of the Alliance.
The meeting has finalized the scope of the Alliance based on four products streams (medicines, vaccines and other biological products, medical devices and traditional medicines.

At the end of the general assembly the participants were updated on the outcome of the steering committee and presented the mechanism for selection of steering committee members. In voluntary basis, Australia, Brunei, Japan, Republic of Korea, Papua New Guinea, Philippines and New Zealand signified their interest in becoming a member and will confirm their membership upon the receipt of formal letter from WHO.

Dates and venue of the 8th workshop will be identified in December 2018 after the confirmation from the government of Japan.

Workshop

Progress of recommendations from the previous workshops

As platform for information sharing and experiences between Member States, the participants were able to listen and learn from the matured regulatory systems on marketing authorization and registration, regulatory inspection, post marketing surveillance, laboratory access and pharmacovigilance.

With the increasing challenges in strengthening the regulatory systems, all countries acknowledged that NRAs need to work together to strengthen regulations and that collaboration and convergence is the most cost efficient approach. Even the highly developed countries like Australia for example are also considering GMP inspection reliance pathways.

Support to resource-constrained countries in conducting regulatory capacity gap assessment and implementation of institutional development plans with interested partners

- Benchmarking of NRAs is now better understood by the participants from many countries. There is an increasing request from the countries to guide them on the use of global benchmarking tool which will provide guidance for NRAs in analyzing current status and potential gaps of performance maturity level. Several visits relating to applying and promoting GBT were already conducted in many countries in the region. For instance, WHO conducted rapid benchmarking with the key focus on maturity level 1 to 3 indicators in Mongilia (2016), Papua New Guinea (2016), Cambodia (2017), Lao PDR (2017). WHO conducted GBT briefing to Malaysia (2017), Republic of Korea (2017), Viet Nam (2017), and Philippines (2018).
- In response to the persistent challenge on the scarce availability of experts, the Regional Alliance aims establish a pool of experts and institutions to support strengthening of NRAs with focused support to lesser-resourced countries, a partial list of experts were identified and will be refined by the secretariat prior to circulation.
- A sub regulatory platform was proposed as mechanism for cooperation in the PICs for pharmaceutical regulations, it will be built upon the concept of reliance mechanisms and/or joint or collaborative regulations, where needed and mechanism for capacity development: mobilize support from more stringent regulatory authorities for learning and coaching.
- A framework on strengthening pharmacovigilance and medicines support systems in the PICs was proposed in collaboration with the relevant stakeholders including the University of Otago in New Zealand. This will be a priority area as part of the sub regulatory platform.
- The workshop also provided an opportunity to discuss regulatory systems strengthening activities with the following development partners:

    - The Australian Department of Foreign Affairs and Trade (DFAT) introduced its program, the Indo-Pacific Regulatory Strengthening Program (RSP) in partnership with Therapeutic Good of Australia which aims to strengthen NRA capacity and enhance regional collaboration on regulatory practice.
    - International Vaccine Institute (IVI) has developed a tool called Vaccine Adverse Event Management Information System to collect and analyze AEFIs. The tool was piloted in Cambodia, Lao PDR, Mongolia and Viet Nam
    - United States Pharmacopeia (USP) Promoting the Quality of Medicines had been a long partner in helping resource-strapped countries builds capacity in QA systems to better monitor, test & regulate quality of medicines.

Priority areas and actions for regional regulatory convergence and cooperation.

The participants has identified potential working groups based on regulatory functions which is cross cutting in all products streams starting from (1) marketing authorization and registration (2) good manufacturing practice (3) quality assurance (4) pharmacovigilance.

3.2 Recommendations for Member States

Member States are encouraged to do the following:

(1) to continue collaborating and working with each other by utilizing the Regional Alliance for NRAs in the Western Pacific Region as a platform for information sharing and developing regional strategies.

(2) to continuously conduct self-benchmarking and use GBT as guide to develop institutional development plan and implement stepwise approach in implementing strengthening activities.

(3) to undertake measures in ensuring the timely availability of vaccines and medicines in public health by applying the concept of reliance and convergence starting from clinical trials (recognizing GCP audits from other NRAs), registration of medicines (reliance of GMP audits and works sharing of dossier assessments) and post marketing surveillance (information-/work-sharing of ADR/safety assessments; work-sharing/reliance on product testing results; information-sharing on counterfeit medical products, product defects and GMP non-compliance of manufacturers)

(4) to facilitate expedited procedures and reduce regulatory burden for products needed to cross borders in case of emergency situation (e.g. laboratory testing)

(5) to strengthen efforts in timely information sharing of medical products that are recalled due to quality and safety issue to other NRAs and especially to the public.

(6) to strengthen pharmacovigilance and monitoring systems for adverse events to improve patient safety and quality of care at all levels.

(7) to ensure monitoring of quality and safety of antimicrobials and regulating their distribution and use- to help prevent antimicrobial resistance

3.3 Recommendations for the Steering Committee

(1) to follow-up with formal letter for government to affirm members who voluntarily signified interest to be part of the steering committee

(2) to organize follow-up meeting of the steering committee at midyear to elect Chair and Vice-chair and determine ways of working and finalize the logo.

3.4 Recommendations for the Regional Alliance

(1) follow-up with formal letter for government to affirm members who voluntarily signified interest to be part of the steering committee

(2) organize follow-up meeting of the steering committee at mid-year to elect Chair and Vice-chair and determine ways of working and finalize the logo

(3) consolidate the needs of each country based on the workshop as well as the pool of experts and institutions and match the needs of countries to resources available within the Region

(4) establish web-page for the Regional Alliance to include donors and partners

(5) build information –sharing platform/mechanism amongst the members

3.5 Recommendations for WHO

WHO is requested to do the following:

(1) to continue supporting the Regional Alliance in closing the gaps in regulatory capacity and the implementation of its work while complementing with the other existing initiatives in the region

(2) to keep Members States updated on regulatory reforms and activities

(3) to support Member States in their activities towards convergence and cooperation by facilitating bilateral or multilateral agreement.