

Roadmap to Promote Regulatory Convergence for PV (ver3)

Slogan:

- **Protecting and promoting the health of the public by pharmacovigilance**

Goals :

- To facilitate convergent evolution of pharmacovigilance (PV) activities among APEC economies that will support harmonized and pragmatic regulatory requirements in pharmacovigilance by 2020;
- To identify opportunities for strengthening PV standards to better protect public health in the APEC economies;
- To promote public health protection by coordinating evolution of PV standards that support sustainable risk-benefit assessment and management for medical products in the context of capacity-building constraints across the APEC economies; and
- To accelerate mutual recognition through enhancing trust among and between APEC member economies.

Backgrounds and Challenges :

- Pharmacovigilance (PV), defined by the World Health Organization (WHO) as ‘science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems,’ plays a key role in ensuring that appropriate patients receive medical products that are safe in the context of the benefits these products provide. Recently, definition of PV boundaries by the WHO has been widened to include: herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. We should pay attention to monitoring safety not only the medicinal products but also the all of the approved medical products.
- Adverse effects of pharmacologically active substances have been recognized for many centuries, although the importance of PV has increased dramatically since the risks of congenital anomalies associated with thalidomide emerged in the 1960s. Recent events such as the withdrawal of rosiglitazone and sibutramine highlight the continuing importance of drug safety under conditions of actual use. Moreover, there have been safety concerns regarding traditional medicines, suspected counterfeit products, co-morbidities, severity of disease and suspected interactions arising from simultaneous use of multiple medicinal products, etc. These latter conditions are confounders and are often excluded from clinical trials. Further, the numbers of subjects in clinical trials are rather small, so rare adverse reactions may not be detected in a pre-marketing development program. Therefore, post-marketing surveillance is essential to ensure the safety of medication in real world settings.

- According to the Erice Declaration (International Conference on Developing Effective Communication in Pharmacovigilance, 1997), every country should have a system with independent experts to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and the associated implications are made accessible to all.

- A suspected Adverse Drug Reaction (ADR) is defined (WHO, 1975) as ‘Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.’ The concept of an ADR has evolved (Heads of Medicines Agencies and the European Medicines Agency, consolidated definitions in 2012) to include any administration of any dose and a reasonable possibility of a causal relationship, as follows: ‘A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include overdose, misuse, abuse and medication errors.’ It is possible that genetic or ethnic factors play a role in certain ADRs, however, such differences in either efficacy or safety or both are often difficult to detect. Additionally, racial differences in response to drug treatments may exist. This underscores the importance of post-authorization safety monitoring activities, including standardization of scientific and regulatory requirements, in each country/region.

- Since the PV systems of each APEC country have been developed and run locally, they reflect differences in the PV needs and constraints of individual countries. These differences in systems and policies on PV can be grouped into several categories, including:
 - Pharmacovigilance monitoring system, including tools for risk-benefit assessment and management;
 - Single case safety reporting requirements and safety data repositories;
 - Aggregate safety data analysis, interpretation, and reporting (e.g., signal detection, observational studies, active surveillance, etc.); and
 - Oversight of the pharmacovigilance system by the responsible regulatory authority.

- Public awareness and expectations for timely and efficient safety signal detection for drugs, therapeutic biologics, and vaccines have been increasing. In the borderless drug market, more and more medical products have been developed through multi-regional trials and been launched worldwide.

- Therefore it is important for APEC to harmonize regulatory requirements that would facilitate convergence of PV standards through active communication among the countries, which would handle overall needs of drug safety within the APEC. The APEC, as an eco-geographical community in the same pharmaceutical environment, needs a coordinated system to ensure that safety information on all available drugs is adequately collected, impartially evaluated in the context of benefits, and

- For the convergence of the PV process, consensus on the definition and criteria of PV is required at first and at the same time standardized terminology and PV processes should be shared. However, eventual PV requirements and process should add value to protecting the public health and not be overly burdensome. International guidelines such as International Conference on Harmonization (ICH) E2, M1, M2, M5, European Medicines Agency (EMA) Good Vigilance Practice (GVP) guidelines, Council for International Organizations of Medical Sciences (CIOMS) expert reports, WHO guidelines, and guidelines of certain countries should be considered when building comprehensive infrastructure to embrace all APEC economies; there are different items and contents in each guideline that must be considered in developing a harmonized approach that facilitates access to and optimal use of needed therapies across the APEC economies. It is important to note that APEC participates in the ICH consensus process via the ICH Global Cooperation Group and the ICH Regulators' Forum. The implementation of relevant international PV standards in the context of local settings will not only promote the convergence of PV regulatory requirements, but will also facilitate realization of APEC RHSC objectives.
- Until now, several PV training programs have been developed by the WHO, the International Society of Pharmacovigilance (ISoP), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the International Society for Pharmacoepidemiology (ISPE), the Drug Information Association (DIA), and others. However, collaborative education and training programs specific to the APEC countries will be needed as harmonized standards evolve. A model of PV standards and system in developed countries should be shared and the challenges for their implementation in developing countries should be discussed.
- A roadmap to promote the convergence of PV standards in the APEC region is proposed herein to encourage the collaboration and transparency of PV processes in the APEC region. This approach is recommended in the LSIF strategic plan.
- The plan suggests “considering the development of roadmaps to achieve desired objectives” for the purpose to promote a strategic, effective and sustainable approach to training and capacity building activities within the APEC region.
- Another key issue for promoting pragmatic PV standards is how to establish mechanisms for facilitating prompt detection and communication of emerging safety concerns among countries, as well as steps being taken to resolve the concern. A network or other confederation may be needed to accomplish this. Because collaboration, common guidelines or other criteria are needed to proceed with development of a more robust roadmap without unnecessary delay, related organizational activities should be conducted in parallel with activities to promote collaboration.
- Proactive risk-benefit management planning and improved PV tools, as well as metrics for measuring effectiveness of these tools, will provide additional opportunities to regulators and industry to protect

the public health. Concurrently, safety surveillance systems are anticipated with the object of indentifying and confirming adverse drug reactions, including the creation of large PV databases and collaboration with pharmacoepidemiological experts. The development of new methodologies and access to large, distributed databases that contain longitudinal data on large numbers of lives, as is envisaged for the Sentinel System in the US and MIHARI in Japan, will support rapid queries and protocol-based assessments of drug-event pairs. In some circumstances, output from such queries may be applicable in APEC jurisdictions.

- Sustainable global PV needs regional collaboration and public-private partnership. The term ‘public-private partnership’ describes a range of possible relationships among public and private entities in the context of infrastructure and other services. These relationships can be established nationally, regionally or even globally with funds or in-kind contributions from international donors, including foundations and medical companies, as well as non-governmental organisations that can also contribute technical support. Despite emphasis on the relationship, transparency must be assured.

Overview of Roadmap for Regulatory Convergence

- The roadmap is organized into Steps 1-4 and may include any of the following activities. Any portion of the proposed activities and timing can be modified by the RHSC as indicated by progress and intermediate results.
 - Evaluate current PV status and related infrastructures of each APEC economy
 - Review international best practices (ICH E2, M1, M2, M5, and EMA GVP guidelines, and CIOMS expert reports, etc.)
 - Develop necessary items for training/workshop to promote PV and good practices
 - Develop pragmatic ways of collecting, analyzing and communicating information about the safety of medical products
 - Implement APEC-centric training/workshops for those involved in PV
 - Issue recommendations on the regulatory convergence of PV standards for APEC that are consistent with global guidelines issued by consensus bodies (e.g., ICH, CIOMS, etc.), as relevant to the APEC eco-system
 - Develop and implement sustainable pan-APEC PV standards, which incorporate transparency and, as appropriate, public-private partnerships
- Establish common understanding regarding key issues including the following within the APEC region under the auspices of LSIF. PV Workshops will be organized to facilitate awareness of the following
 - Definition collection, validation, and management of data on suspected ADRs and analysis of aggregate data;
 - Definition, detection, characterization, reporting, management, and resolution of a safety signal from any source;
 - Design, conduct, interpretation, and reporting of pharmacoepidemiologic study
 - Structured assessment of risk-benefit;

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- Determination of important identified risks, important potential risks, and important missing information as well as risk minimization (mitigation) plans and actions; and
- Practical method for risk communication across the APEC region should be developed.
- This roadmap applies to all pharmaceuticals including biologics(including vaccines), blood derivatives, biotherapeutic products, traditional medicine (herbal products).
- RHSC will support the activities and the development of recommendations for the proposed next steps of the PV subteam of the RHSC.

Activities

Step 1: Assessment (2013-2015)

Through the APEC PV workshop and other meetings/seminars, the current status of PV activities in each APEC country will be evaluated. From the workshops, strategic plans for improving PV in the APEC region should be derived. In this workshop, a survey for understanding the status of current PV requirements and systems can be performed. The strategic plan will take into consideration information on the gap between the current status and developmental goals. The strategic plan will identify a path forward for development of relevant points-to-consider documents or suggestions for the convergence initiatives. Review of international and local guidelines regarding PV and their significance and feasibility will be discussed in symposia and workshops under APEC sponsorship.

Assessment should be made on the following aspects:

- Current status of PV requirements, related infrastructures, and regulatory capacity of each APEC economy
- Gaps between the current status in the regulatory systems of each APEC economy
- Prioritize list of needs (essential and desired) and activities required for convergence
- Find administrative barriers for the standardization of PV – e.g., various levels of PV infrastructure and regulations
- Appropriate areas where standard development and regulatory convergence are needed, as well as areas where barriers to regulatory convergence currently exist
- Global and regional venues for collaboration and supervision for implementation of the roadmap

RHSC will facilitate this process. An assessment will include recommendations for Step 2.

Step 2 : Training/workshop (2014-2017)

Based on the recommendations from the Step 1 assessment, an economy/economies will develop a training/workshop curriculum and conduct training/workshop in cooperation with other APEC economies and/or RHSC, depending on the situation of the economy/economies. PV workshop may consider making

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curricula for training various workers from regulatory authorities, academia, the medical industry, or research institutes.

The training should address basic principles of PV and may contain the following:

- Gaps in the PV system between international standards (ICH, CIOMS, EMA, etc) and APEC region
- Spontaneous adverse event reporting system
- Standard international reporting form for individual case reports
- Current causality assessment algorithm of each APEC economy
- How to raise the level of awareness in the healthcare community of reporting spontaneous adverse drug events
- How to establish a signal detection and management system
- Standardization of terminology and disease classification, i.e., use of international consensus standards
- Active surveillance, e.g., rapid queries or protocol-based assessments of electronic medical records or prescription event monitoring, etc.
- Pharmacovigilance of traditional medicines (herbal preparations), suspected manufacturing defects, suspected, counterfeit products, etc.
- Pharmacoepidemiologic study for risk assessment: examples of cohort and case-control studies
- Pharmacoepidemiologic study for risk assessment: examples of retrospective study using a large-scale claims database
- Possible use of large longitudinal databases for PV in each APEC economy, including discussion of common potential confounders
- Find the opportunities to leverage large, disease-specific clinical registries for monitoring drug safety
- Risk management and prevention or minimization of adverse drug reactions
- Risk-benefit analysis methods and models
- Best practices and guidelines about PV education programs
- Standardization of the regulatory PV process
- Establishment of a collaborative surveillance system of PV
- Communication of safety information among APEC economies
- Development of plans to build public-private partnerships and transparency in PV systems

The curricula established in the economies and PV workshops will be part of coordinated programs to “train the trainers” so that APEC economies will have the ability to conduct additional training and to share practices. Training curriculum and materials will be developed based on the strategic plan. Also, depending on recommendations made at the end of Step 1, other actions should be taken. They may include drafting templates to list characteristics of each population from the viewpoints of medical practice, demographics, environmental factors, etc.

It is expected that by the end of Step 2, highly applicable insights regarding PV as well as practical visions will be developed.

Step 3 : Assessment for training/workshop (2017-2018)

The outcomes of Step 2 training/workshop that include the status of implementing international guidance as well as those of other challenges in conducting PV will be reviewed in symposia and workshops under APEC. Recommendations to improve the efficiency of PV in APEC economies will be formulated.

- Understanding of supporting effectiveness and efficiency of regional PV activities
- Activation of regional educational workshop/program for PV
- Necessity of training modules and instructors for PV standards
- The concept of convergence toward international standards

Step 4 : Training/workshop to reach the goals and recommendations for regulatory convergence (2019-2020)

Based on the process preceding, international best practice would be documented during the Step 4 and PV network in the APEC would be discussed and established for the collaborative surveillance system for the drug safety. Series of initiatives should be developed and run to implement desired changes that can improve efficiency and effectiveness of regulatory convergence.

- Based on the recommendations from Step 3 assessment, an economy/economies may develop a rationale to revise the training/workshop curriculum and conduct training/workshop with assistance from other APEC economies and/or RHSC, depending on the situation.
- All of the economies have in the goal of developing a regulatory system that converges with international best practices.
- The use of case studies based on actual safety issues in the APEC region should be developed along with consensus expectations for appropriate action scenarios in responding to drug safety concerns. The planning of a collaborative surveillance system of PV should also be considered.

Finally, the PV subteam of the RHSC should draft recommendations for regulatory convergence to be authorized by RHSC based on the experiences and activities during the annual roadmap intervals.

Action Plans

Step	Goal	Content	Method	Schedule
Step1 Assessment ('13~'15)	Assessment of the current status of PV activities of	<ul style="list-style-type: none"> • Assess current status of PV activities of APEC RHSC Members(11 countries) 	<ul style="list-style-type: none"> • survey 	~2013.10 (Finish)

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	APEC countries	<ul style="list-style-type: none"> • Share results from the current status assessment for PV of each APEC economy • Discuss training module for PV development and regulatory convergence 	<ul style="list-style-type: none"> • AHC PV workshop 	2013.11 (Finish)
		<ul style="list-style-type: none"> • PV status quo research on nonparticipating APEC economies 	<ul style="list-style-type: none"> • survey 	2014~2015
Step 2 Training/Workshop (‘14-‘17)	Develop training program	<ul style="list-style-type: none"> • Establish working group* to develop training program - Collaborate with WHO for developing training module 	<ul style="list-style-type: none"> • e-mail 	2014.2~5 (Finish)
		<ul style="list-style-type: none"> • Circulate training module draft for comments and revise draft * working group always active 	<ul style="list-style-type: none"> • e-mail, teleconference 	2014.3~10
		<ul style="list-style-type: none"> • Develop training program • Develop common essential items for WHO ADR reporting 	<ul style="list-style-type: none"> • research • research e-mail, teleconference 	2014.3~10
	Hold training/workshop	<ul style="list-style-type: none"> • Annual training with PV training center 		Every Sept (from 2015).
		<ul style="list-style-type: none"> • Hold regular PV workshop 		Every May (from 2015)
Step 3 Assessment for training/workshop (‘17-‘18)	Assess training outcome	<ul style="list-style-type: none"> • Share assessment results of PV training outcomes (basic) 	<ul style="list-style-type: none"> • annual meeting & workshop 	2017
		<ul style="list-style-type: none"> • Share assessment results of PV training outcomes (advanced) 	<ul style="list-style-type: none"> • annual meeting & workshop 	2018
	Revise PV training program	<ul style="list-style-type: none"> • Revise and update training program/workshop content 	<ul style="list-style-type: none"> • e-mail, teleconference workshop 	2017~2018 (If needed)

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	Find best practices	<ul style="list-style-type: none"> • Share best practices on PV development 	<ul style="list-style-type: none"> • annual meeting & workshop 	2017~2018
Step 4 Recommendations (‘19-’20)	Provide recommendations	<ul style="list-style-type: none"> • Establish plan for collaborative surveillance system of PV 	<ul style="list-style-type: none"> • annual meeting & workshop 	2019~2020
		<ul style="list-style-type: none"> • Provide recommendations on PV regulatory convergence 		
		<ul style="list-style-type: none"> • All APEC economies establish regulatory system in convergence with international best practices 		2020

Proposed Performance Indicators:

Reports to be provided by the PV sub-team at each RHSC meeting against milestones described in step activities proposed above

- Training program (development, design, delivery, effectiveness metrics)
- Development of draft, pragmatic, consensus guidelines for APEC PV harmonization
- Annual Assessment Reports according to the goals of PV roadmap
- Final summary Assessment Report

Relevant Guidelines:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), multiple guidelines
- The Council for International Organizations of Medical Sciences (CIOMS), multiple expert reports
- Global Harmonization Task Force (GHTF)
- Pharmaceutical Inspection Cooperation Scheme (PIC/S)
- World Health Organization (WHO)
- World Trade Organization (WTO)
- European Medicines Agency (EMA), good pharmacovigilance practices (GVA)

Partnerships

- World Health Organization (WHO)