



**Asia-Pacific
Economic Cooperation**



APEC Harmonization Center Annual Report 2013



APEC Harmonization Center
Ministry of Food and Drug Safety

Director's Message



The APEC Harmonization Center (AHC) was founded under the National Institute of Food and Drug Safety Evaluation (NIFDS) in the Ministry of Food and Drug Safety in June 2009. AHC works to achieve global harmonization in quality and safety management system, production and supply of medical products in the APEC region.

Since its establishment, AHC has successfully hosted workshops which have played a significant role in facilitating regulatory harmonization among APEC members. At the workshops, international experts and regulators gathered together in order to share information on the current regulations and have discussions on regulatory harmonization. At the same time, AHC has contributed to strengthen the network among regulators and related experts in the APEC region and beyond.

The APEC Harmonization Center Annual Report 2013 is to give an overview of AHC's activities, thereby further promoting communication and cooperation in APEC.

AHC will continue to broaden its scope of work in regulatory harmonization for better health care which will lead to prosperity in the APEC region.

December 2013

Wang Jin-Ho
Director of APEC Harmonization Center
Director General, National Institute of Food and Drug Evaluation, Ministry
of Food and Drug Safety

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INTRODUCTION OF AHC

- 1. History
- 2. Objectives
- 3. Logo
- 4. Organization
- 5. Works and Activities

I . INTRODUCTION OF AHC

1 History

The establishment of the APEC Harmonization Center (AHC) was proposed at the APEC Life Science Innovation Forum (LSIF)¹⁾ as an organization to promote regulatory harmonization in medical products among the APEC member economies²⁾. After the endorsements from meetings of APEC Leaders and Ministers in Peru in November 2008, AHC was launched in Seoul, Korea in June 2009 under the National Institution of Food and Drug Safety Evaluation (NIFDS) in the Ministry of Food and Drug Administration (MFDS).

Since its founding, AHC has organized a number of training programs and workshops on various aspects of regulations on medical products and devices that have brought together hundreds of regulators, experts and industry representatives. In the meantime, AHC has invited trainees from travel eligible economies³⁾ to provide opportunity for capacity building which, in turn, will contribute to the development of the health industry.

AHC work is complemented by support from the Korean government and collaboration with the Regulatory Harmonization Steering Committee (RHSC)⁴⁾. The Korean government has been offering financial support and AHC closely cooperate with RHSC from workshop topic discussion to training activities.

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- 1) **Life Science Innovation Forum (LSIF)**: Since the establishment by APEC Leaders in 2002, the LSIF has grown to become APEC's leading initiative on health and health sciences innovation. It engages representatives from the highest levels of government, industry and academia to create the right policy environment for life sciences innovation.
 - 2) **APEC members (21 economies)**: Australia, Brunei Darussalam, Canada, Chile, People's Republic of China, Hong Kong, Indonesia, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Papua New Guinea, Peru, Philippines, Russia, Singapore, Chinese Taipei, Thailand, United States, Viet Nam
 - 3) **APEC Travel Eligible Economies (11)**: People's Republic of China, Chile, Indonesia, Malaysia, Mexico, Papua New Guinea, Peru, Philippines, Russia, Thailand, Viet Nam
 - 4) **APEC Regulatory Harmonization Steering Committee(RHSC)**: Established in 2009 under the authority of LSIF in order to promote a strategic and coordinated approach to regulatory harmonization and capacity building efforts within the APEC region. RHSC implements projects and supports the development of policies focused on the adoption and implementation of harmonization guidance and regulatory best practices.

To create synergy effects, AHC also works with key regulatory policy-making and international organizations, such as the International Conference on Harmonization (ICH), the International Medical Device Regulators Forum (IMDRF), the Asian Harmonization Working Party (AHWP), the World Health Organization (WHO), the European Medicines Agency (EMA) and others.

AHC is now considered as a good example of how APEC's inclusive and nonbinding format can be leveraged to create effective, long-term public-private partnerships that build capacity and help economies achieve ambitious region-wide objective.

2 Objectives

The APEC Harmonization Center's mission is to facilitate international cooperation for regulatory harmonization and trade facilitation of medical products.

In recognition of benefits and importance of harmonization, AHC focuses on:

- Supporting access to guidelines for regulatory harmonization in life science and best practices
- Promoting collaborative efforts and a wide range of information sharing among member economies
- Promoting clinical trials that meet international standards
- Enhancing quality, safety and efficacy of medical products to improve health outcomes in APEC and facilitate international trade of medical products

3 Logo

The logo of AHC symbolizes the *Taegeuk*⁵⁾, which represents the harmony of *yin* and *yang*, as the origin of things in the universe. *Yin* and *yang* can be thought of as complementary forces that interact to form a dynamic system in which the whole is greater than the assembled parts.



〈AHC Logo〉

On the basis of the principle idea of *yin* and *yang*, the logo is designed to indicate harmony of the East and the West parts of Asia Pacific.

The red and blue arms of *Taegeuk* are joined together at the center and extend outward representing continuation of successful progress of international regulatory harmonization initiative across APEC through coordinated, collaborative approach.

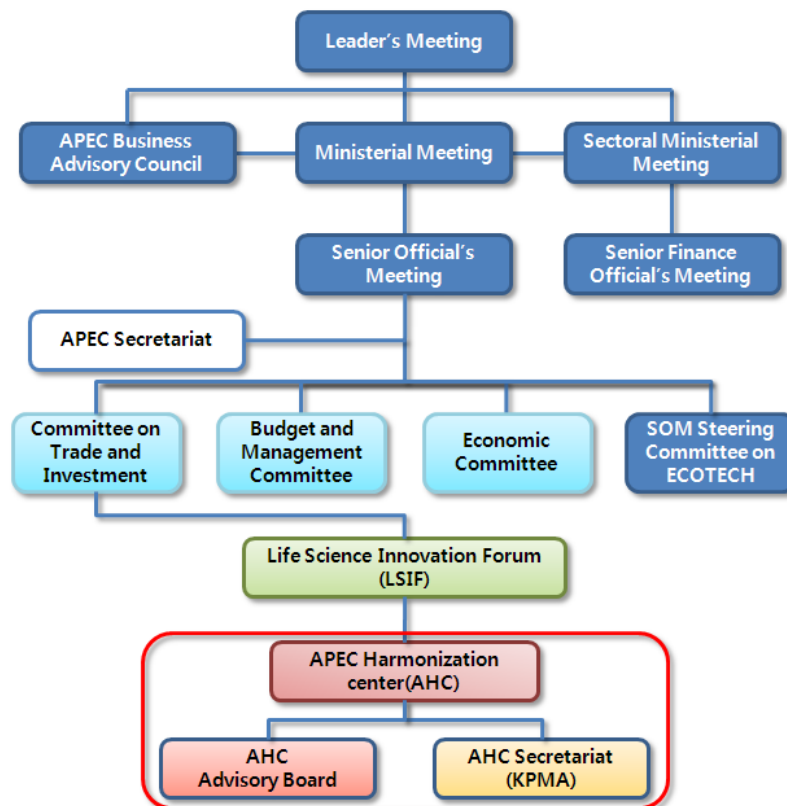
Under the overarching theme of the East meets the West, the APEC Harmonization Center aims to enhance communication among APEC member economies by providing venues to exchange high-standard international harmonization guidelines and to advance effective trade facilitation and regional economic integration agenda, towards sustainable economic growth and prosperity.

4 Organization

AHC operates under the authority of LSIF which provides, through RHSC, strategic direction to AHC in accordance with established regulatory priorities and programs. The Drug Review Management Division in Drug Evaluation Department of the NIFDS is responsible for works of AHC. The main roles are to establish strategies and plans and organize all activities taking place under the name of AHC.

5) *Taegeuk* is the symbol that makes up the center of the Korean Flag and the source for its name, *Taegeukgi*.

Structure of APEC and AHC



APEC Harmonization Center consists of

- **AHC Director:** the director general of the NIFDS serves as the Director of AHC. Director's duties include coordinating works among LSIF, RHSC, AHC secretariat and AHC advisory board and leading all activities and events taking place in AHC.
- **AHC Secretariat:** the secretariat is responsible for administrative tasks and plays a role as a point of contact. Since 2013, the Korea Pharmaceutical Manufacturers Association (KPMA) serves as the secretariat for AHC.
- **Advisory Board(AB):** the AHC director acts as a chair of the Advisory Board. Chairs of LSIF Planning Group and RHSC are official members of the Board. AB members are appointed on the basis of their ability to provide technical inputs and professional expertise on the specific curriculum and projects, to develop training modules and to secure appropriate trainers across the range of topics.

AHC Advisory Board Members (24 members, December 2013)

Name	Affiliation	Position
Jin-Ho Wang	National Institute of Food and Drug Safety Evaluation, MFDS	Director General
Hiroshi Ishikawa	Toshiba Medical Systems Co.	Assistant to President
Kian Ming Lam	Health Sciences Authority	Division Director, Strategic
Willam Wang	Merck & Co, Inc	Head of Asia Pacific Operations
Herng-Der Chern	Center for Drug Evaluation	Executive Director
Rae Yuan	Roache Pharma	Asia Pacific Head of Pharma Development
Heng Siew Christine Ngin	Celgene Co.	Director, Regulatory Affairs, SE Asia
Toshiyoshi Tominaga	PMDA ⁶⁾	Office of International Programs
Yves Juillet	LEEM ⁷⁾ / IFPMA ⁸⁾	Senior Advisor (LEEM)/Chair of Regulatory Policy & Technical Steering Committee (IFPMA)
Stuart Walker	Center for Innovation in Regulatory Science	Founder
Lembit Rago	WHO	Coordinator, Quality Assurance and Safety of Medicines (QSM)
Odette Morin	IFPMA / ICH	Director, Regulatory and Sciences Affairs (IFPMA)/ Director, ICH Secretariat & ICH SC and GCG Member (ICH)
Andre W. Broekmans	MSD	Vice President, Most of World Regulatory Policy & Regulatory Affairs
Tomas Salmonson	CHMP, Medical Products Agency, Sweden	Vice-Chair CHMP
Michael B. Gropp	Medtronic Co.	Vice President, Global Regulatory Strategy
Mark Paxton	Food and Drug Administration	Technical Advisor
Nancy Travis	AdvaMed	Vice President, Global Strategy and Analysis
Florence Houn	Celgene Co.	Vice President, Regulatory Policy and Strategy
Marie Vodicka	(Former) PhRMA	(Former) Assistant Vice President, International Regulatory Affairs
Romi Singh	Amgen Inc.	Executive Director, Global Regulatory Affairs & Safety
Chiwan Chen	Pfizer Inc.	Executive Director, Global CMC
Jeffrey Gren	U.S. Department of Commerce	Director, Office of Health and Consumer Goods
Patricia Pineda	COFEPRIS ⁹⁾	Manager, International Affairs of Chemicals
Hans Vasquez Solpopuco	DIGEMID ¹⁰⁾	Specialist Reviewer in Clinical and Pharmacology

5 Works and Activities

To provide a platform to address and solve priority concerns of APEC member economies on regulatory harmonization, AHC has engaged in various activities.

1) Scope of Work

AHC's works for harmonization of regulations among members are:

- Providing training programs such as workshops, symposiums, seminars, and fellowship programs (especially for APEC travel eligible economies)
- Research on policies and identification of best practices and challenges
- e-publication and management of AHC website for information sharing and raising awareness
- Development and dissemination of regulatory harmonization models
- Promoting international cooperation by helping to build networks for information sharing among members

2) RHSC Priority Work Areas and Roadmaps

RHSC, working to advance greater alignment of regulatory approaches and standards in the areas of medical products, developed the Strategic Framework "Vision 2020". The Strategic Framework, endorsed by APEC Ministers in November 2011, outlines strategic multi-year approach to achieve greater regulatory convergence by 2020. The overall goals, guiding principles and multi-year approach for greater regulatory value were also developed.

6) Pharmaceuticals and Medical Devices Agency (PMDA)

7) The Pharmaceutical Industry Association in France (LEEM)

8) International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

9) Sitio Oficial de la Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)

10) Dirección General de Medicamentos, Insumos y Drogas (DIGEMID)

To meet the goals in the most effective and efficient way, roadmaps were developed for eight Priority Work Areas, led by each champion economy.

Priority Work Areas (PWAs) within the Strategic Framework are:

- Pharmacovigilance (championed by Korea)
- Biotherapeutic Products (championed by Korea)
- Multi-regional Clinical Trials (championed by Japan)
- Good Review Practice (championed by Chinese Taipei)
- Combination Products (championed by Chinese Taipei)
- Good Clinical Practice Inspection (championed by Thailand)
- Advanced Cell and Tissue Therapy (championed by Singapore)
- Integrity of Supply Chain (championed by the U.S.)

3) AHC Workshops

Since its inception in June 2009, 18 workshops have been hosted 18 workshops. With the endorsement of detailed RHSC's roadmaps, efforts have been made to promote eight PWAs through workshops, in partnership with RHSC and roadmap champion economies.

AHC workshops have been the venue for national regulatory authorities, industries and academia to share information and identify challenges. Workshops have also played a role as a training opportunity, especially for those from APEC travel eligible economies. Trainees from travel eligible economies are invited to workshops to build capability and network.

In addition, workshops had been recorded to be posted on the AHC website along with workshop materials so that anyone who is interested in the topics can have access to them.

List of AHC Workshops

	Date	Workshop topics	Venue	Participants
1	June 2009	Multi-Regional Clinical Trial	Seoul, Korea	562 (16 economies)
2	Sept. 2009	Biotherapeutics: Biosimilars	Seoul, Korea	434 (13 economies)
3	Nov. 2009	Pharmaceutical GMP Validation	Seoul, Korea	458 (domestic)
4	May 2010	Globalization of the Pharmaceutical Supply Chain	Seoul, Korea	287 (10 economies)
5	Sept. 2010	Multi-Regional Clinical Trial	Seoul, Korea	415 (15 economies)
6	Nov. 2010	Clinical Evidence on Medical Devices	Seoul, Korea	186 (8 economies)
7	Apr. 2011	AHC-DIA-IFPMA Asia Regulatory Conference	Seoul, Korea	729 (24 economies)
8	July 2011	AHC Workshop on Medical Devices: Implementation of GHTF Documents	Seoul, Korea	281 (13 economies)
9	Oct. 2011	AHC-ICH Official Integrated Implementation Training Workshop for ICH Q8 & Q10	Seoul, Korea	513 (18 economies)
10	Nov. 2011	MRCT Workshop highlighting Korea, China and Japan Tripartite Symposium	Tokyo, Japan	400 (9 economies)
11	Apr. 2012	Biotherapeutics: Biosimilars	Seoul, Korea	438 (17 economies)
12	Aug. 2012	AHC and RHSC Awareness	Singapore	115 (17 economies)
13	Oct. 2012	Pharmacovigilance	Seoul, Korea	209 (4 economies)
14	Nov. 2012	APEC-AHWP Joint Workshop on Medical Device Combination Products	Taipei, Chinese Taipei	290 (20 economies)
15	May 2013	Medical Products Safety and Public Awareness and Establishing SPOCS	Seoul, Korea	120 (21 economies)
16	Sep. 2013	Biotherapeutics	Seoul, Korea	368 (15 economies)
17	Nov. 2013	Pharmacovigilance	Seoul, Korea	283 (15 economies)
18	Dec. 2013	AHC & RHSC Awareness	Seoul, Korea	57 (domestic)

II

REVIEW OF 2013

1. AHC Workshops
2. Website Renewal
3. APEC International Meetings

II. REVIEW OF 2013

1 AHC Workshops

In 2013, AHC organized workshops on supply chain, biotherapeutics and pharmacovigilance after the endorsement of them at the RHSC meeting. The workshops were held on the basis of the RHSC's Vision 2020.

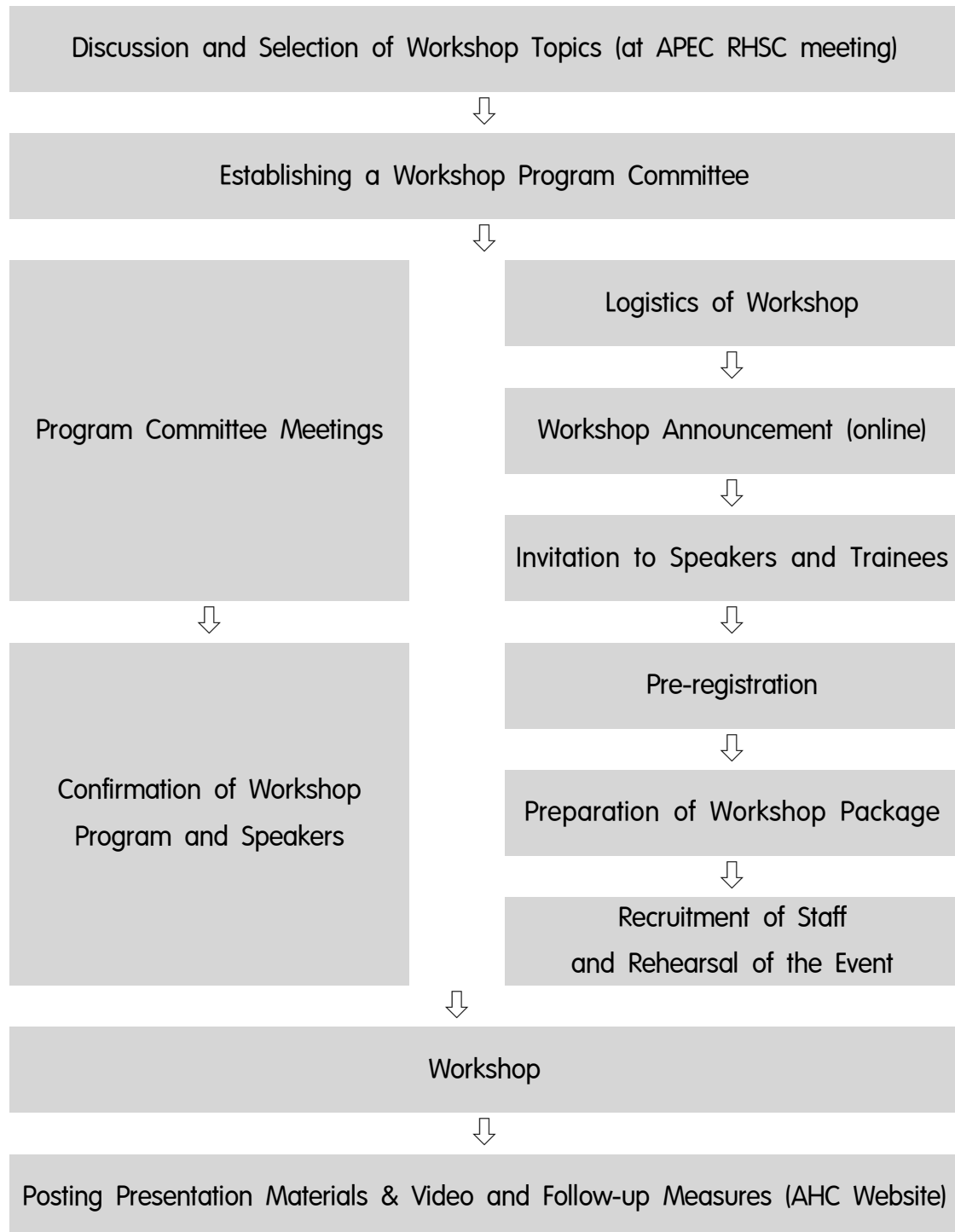
For every workshop, surveys were conducted to evaluate results from the participants which, in turn, reflected into plans of future workshops to meet demands of participants.

The MRCT workshop was planned to be held in the latter half of 2013. However it was forced to be replaced with the AHC and RHSC Awareness Workshop which not enough time to prepare. The workshop was held in Korea for only the Korean pharmaceutical industry to promote the activities of AHC and discuss the future direction of AHC.

2013 AHC Workshops

	Date	Workshop Topics	Venue	Participants
1	May 2013	Medical Products Safety and Public Awareness and Establishing SPOCS	Seoul, Korea	120 (21 economies)
2	Sep. 2013	Biotherapeutics	Seoul, Korea	368 (15 economies)
3	Nov. 2013	Pharmacovigilance	Seoul, Korea	283 (15 economies)
4	Dec. 2013	AHC and RHSC Awareness	Seoul, Korea	57 (domestic)

Workshop Work Flow



1) The 15th AHC Workshop (Supply Chain)

1-1) Overview

- Topic: Medical Products Safety and Public Awareness and Establishing "Single Point of Contact System (SPOCS)"
- Date: 22 - 23 May 2013 (2 days)
- Venue: Renaissance Seoul Hotel, Seoul, Korea
- Host: AHC, APEC LSIF and USAID
- Participants: 120 guests (20 economies), 19 invited foreign trainees(8 economies)

1-2) Main Topics

The current situation and methods to raise public awareness on counterfeit medical products:

- Critical situation on sales of counterfeit medical products in APEC economies and countermeasures for them
- Promotion of anti-counterfeit campaign through various media channels
- Case studies and measures to fight against counterfeit medical product sales on the Internet

Public awareness toolkit for counterfeit medical products in APEC:

- Development of the common definition of "unsafe" medical products, broad definition of general medical products and toolkits

Development of SPOCS among APEC economies:

- Introduction of the current contact systems in APEC and importance of SPOCS
- Introduction of active SPOCS within each APEC economy

APEC SPOCS Toolkit:

- Need for definition of "counterfeit" medical products and international cooperation to combat counterfeiting

- Development of domestic information sharing system and international cooperation system

1-3) Workshop Results and Discussion Topics

Participants suggested to add "Be Aware"(published by the World Health Professions Alliance, WHPA) to APEC's public awareness toolkit for counterfeit medical products.

Participants agreed that public awareness and SPOCS toolkits should be translated into as many languages as possible to facilitate prompt use of them.

Participants also agreed to form SPOCS in APEC and to appoint a representative among senior regulators as a single contact point and suggested an annual face-to-face meeting or conference for networking and information sharing.

Discussions were made whether to include "substandard" in the definition of counterfeit and health supplementary foods and traditional therapies in the definition of medical products.

1-4) Workshop Survey Results

Workshop Program

Participants found the workshop program was very much instructive as it consisted of both presentations and group discussions. Active panel discussions for each country's case study as well as Q&A sessions were also favorably received.

Facilities and organization of the workshop were highly acclaimed such as clear images on the big screens, audio system, interpretation and hospitality of staff.

How to Improve Workshop

Suggestions made for the better workshops are:

- Report of the results of the workshop and the follow-up actions
- Extended time for workshop (in general) and discussion

- Reception for all participants for networking in prior to the beginning of a workshop
- More participants from legal areas, government agencies and businesses especially Korean participants
- Presentation on practical results of workshop

Topics recommended for the future workshops are:

- Case studies and study results
- Regulations for online sales of counterfeit medical products and investigation of offenses including online crimes
- Supply management and tracking technology for online medical products
- How to eradicate counterfeit products (case study)
- Development of effective communication channels
- Domestic and international practice in combating counterfeit medical products

Recommended action plans are:

- Development and promotion of networking mechanism such as Webex's
- Follow-up action through online and face-to-face meetings
- Development of plans at a national level
- Evaluation of 6-month and 1-year progress after development of standard
- Information sharing on SPOCS activities and current situations in APEC
- Sharing contact information for follow-up and information related to actual cases in each economy

The 15th Workshop Program

22 May 2013	
8:00 – 8:30	Registration
8:30 – 9:00	Opening Ceremony Welcoming remarks: Jin-Ho Wang (AHC) Congratulatory remarks: Byung-Won Jang (MFDS) Opening remarks: Mark Paxton (US FDA)
09:00 – 09:15	Summary of APEC LSIF Activities to Combat Counterfeit/Falsified Medicines: Jeffrey Gren (U.S. Department of Commerce)
09:15 – 09:30	Medical Product Quality, Supply Chain Integrity and Gap Analysis: Mark Paxton (US FDA)
09:30 – 10:40	Panel Discussion- Importance of Public Awareness on Medical Product Safety: Chair: Mark Paxton (US FDA) Panelists: Shaba Mohammed (NAFDAC ¹¹), Nigeria A. Retno Tyas Utami (NADFC ¹²), Indonesia Libby Baney (ASOP ¹³)
10:40 – 10:55	Coffee Break
10:55 – 12:05	Panel Discussion- Public Awareness on Medical Products in APEC Economies Moderator: Jeffrey Gren (U.S. Department of Commerce) Panelists: Manzatul Azrul Azrie Bin Sulaiman (Ministry of Health, Malaysia) Eugene Goh (HSA ¹⁴), Singapore)(Video Presentation) Yuwadee Patanawong (TFDA, Thailand) Hsueh Yung (Mary) Tai (FDA, Chinese Taipei)
12:05 – 13:05	Lunch
13:05 – 14:10	Panel Discussion- Patient Organization and Industry Activities Related to Public Drug Safety Public Awareness Moderator: Jeannie Salo (Eli Lilly and Company) Panelists: Bejon Misra (Partnership for Safe Medicines) Abul Hashem (Project HOPE)(Video Presentation) Simon Collier (Eisai)
14:10 – 14:30	Overview of Draft APEC Public Awareness Toolkit: Simon Collier (Eisai)
14:30 – 15:00	Coffee Break
15:00 – 16:00	Panel Discussion- Proposal for APEC Public Awareness Toolkit Moderator: Mark Paxton (US FDA) Panelists: Jeannie Salo (Eli Lilly and Company) Hsueh Yung (Mary) Tai (FDA, Chinese Taipei) Anita Derks (Roche)

	Manzatul Azrul Azrie Bin Sulaiman (Ministry of Health, Malaysia) Simon Collier (Eisai) Libby Baney (ASOP)
16:00 – 17:15	Review of Panel Discussions and Group Discussion
17:15 – 17:30	Summary of Day 1
18:00 – 19:30	Reception
23 May 2013	
8:30 – 9:15	Public Awareness in the Age of the Internet-The Threat of Illegal Online Drug Sellers: Libby Baney (ASOP)
9:15 – 10:00	Panel Discussion- Importance of Single Point of Contact System (SPOCS) for Medical Products (Part 1) Moderator: Anita Derk (Roche) Panelists: Aline Plancon (Interpol) Samson Chiu (PSI) Matthias Stacchetti (Swissmedic) A. Retno Tyas Utami (NADFC, Indonesia) Stephen Hawgood (Eli Lilly and Company)
10:00 – 10:20	Coffee Break
10:20 – 11:45	Panel Discussion- Importance of Single Point of Contact System (SPOCS) for Medical Products (Part 2)
11:45 – 12:15	Proposal for APEC Single Point of Contact System Toolkit-Overview of Proposal: Matthias Stacchetti (Swissmedic)
12:15 – 13:15	Lunch
13:15 – 14:30	Panel Discussion- Proposal for APEC Single Point of Contact System Toolkit: Moderator and Panelists: Anita Derks, Matthias Stacchetti, Aline Plancon, Samson Chiu, Jeffrey Gren
14:30 – 15:30	Review of Discussions
15:30 – 15:45	Coffee Break
15:45 – 16:45	Final Discussion- Future APEC Regulatory Harmonization Steering Committee Roadmap on Product Quality and Supply Chain Integrity Activities
16:45 – 17:00	Closing remarks
17:00	End of Workshop

11) National Agency for Food and Drug Administration and Control (NAFDAC)

12) National Agency for Drug and Food Control (NADFC)

2) The 16th AHC Workshop (Biotherapeutics)

2-1) Overview

- Topic: 2013 APEC Harmonization Center Biotherapeutic Workshop
- Date: 25 - 27 September 2013 (3 days)
- Venue: The Ritz Carlton, Seoul, Korea
- Host: AHC and MFDS (Biopharmaceuticals and Herbal Medicine Bureau)
- Participants: 368 guests (15 economies), 5 invited foreign trainees (9 economies)

2-2) Main Topics

Introduction of biotherapeutics and APEC's biotherapeutics roadmap

- Characteristics and development strategy of biotherapeutics including biosimilar
- Roles and efforts of WHO and ICH for biotherapeutics
- The current status of implementation and the needs for regulatory harmonization for international guidelines in APEC economies

Review of guideline and case studies for biotherapeutics

- Evaluation of guidelines for non-clinical and clinical trials for biotherapeutics, case studies and immunogenicity evaluation
- Guidelines and case studies for quality of biotherapeutics
- Forecasts for development of next generation biotherapeutics and necessity for regulatory harmonization

2-3) Workshop Results and Discussion Topics

Participants agreed to use guidelines of international organizations for biotherapeutics including ICH and WHO to realize regulatory harmonization in APEC.

13) Alliance for Safe Online Pharmacies (ASOP)

14) Health Science Authority (HSA)

Participants shared a view on the importance of gap analysis in APEC and necessity of implementation of guidelines from international organizations.

From Regulators' Meeting

Regulators suggested to reflect not only APEC's biotherapeutics roadmap but also RHSC's roadmap into the 2014 MFDS and WHO joint workshop.

With the recognition of importance of effective communication among APEC economies, regulators suggested to develop online platform for regular communication.

Regulators agreed to conduct surveys to identify the current level of harmonization of biotherapeutics in APEC. Proposals were made for some economies to develop draft survey questionnaire and circulate them.

2-4) Workshop Survey Results

Workshop Program

Responses in general from participants of the workshop was satisfactory, especially for appropriate topics for sessions and keynote speeches, active participation of general guests, discussions among international organizations on newly developed issues and constructive and free panel discussion. Unfortunately, some respondents pointed out that allocated time for presentations and networking was relatively short.

The workshop was considered to be organized well. Preparations for speakers and trainees were particularly praised. The prompt communication and other efforts from AHC were favorably received.

How to Improve Workshop

Suggestions made for the better workshops are:

- Extended time for each session
- Covering more case studies
- More specific and targeted topics for harmonization
- Promotion of workshops for more participants from overseas research centers

- Surveys after each session

Topics recommended for the future workshops are:

- Biosimilar
- Quality by Design (QbD)
- GMP Guideline
- Chemistry, Manufacturing and Control (CMC)
- Vaccine (preventive vs therapeutic vaccine)
- Each country's requirements for Global Marketing Authorization Application (MAA)
- Immunogenicity
- Gap analysis in APEC
- Risk management

Recommended action plans are:

- Review of the results of the workshop for better understanding of action plans and roadmap
- To upload workshop video and presentation materials on the AHC website
- Development of training programs including specific case studies
- Sharing WHO survey results and suggestions for training programs
- Surveys on the current situation regarding regulations

Suggestions made for further regulatory harmonization are:

- Case study related information sharing
- Development of online platform for communication for all
- Sharing follow-up action results about the implementation of regulatory harmonization
- To invite more participants from South America
- Analyses on ICH guidelines

The 16th Workshop Program

25 September 2013	
8:00 – 9:00	Registration
9:00 – 9:20	Opening Ceremony Welcoming remarks: Byung-Guk Kim (MFDS) Opening remarks: Jin-Ho Wang (AHC) Congratulatory remarks : Byung-Won Jang (MFDS) Congratulatory remarks: Won-Bae Kim (KPMA)
9:20 – 9:35	Congratulatory remarks and Introduction of 2013 AHC Biotherapeutics Workshop : Romi Singh (Amgen)
9:35 – 9:50	Keynote Speech: Soon-Wook Hong (MFDS)
9:50 – 10:05	Group Photo and Coffee Break
Session 1: Overview of Biotherapeutics and a Roadmap Towards Convergence • Session Leader: Jerry Stewart (Pfizer) • Chair: Yeo-Won Sohn (MFDS) • Co-chair: Jerry Stewart (Pfizer)	
10:05 – 10:30	Biologics vs Small Molecule Pharmaceuticals: Kum Cheun Wong (Novartis)
10:30 – 10:55	Current Development/Regulatory Strategies of Biotherapeutics Products - Key Points to Consider vs Small Molecules: Jane Bai (Bayer)
10:55 – 11:10	Progress and Updates on Biosimilars Development in Korea: Hyuk-Jae Lee (Celltrion)
11:10 – 11:30	Overview of Biotherapeutics Roadmap: Byung-Guk Kim (MFDS)
11:30 – 11:50	2012 AHC Biosimilar Workshop Report: Jerry Stewart (Pfizer)
11:50 – 12:10	What is required to do further for Biosimilar Regulatory Harmonization?: Judith Macdonald (Pfizer)
12:10 – 12:40	Q&A and Discussion Review of Session 1 and Closing
12:40 – 14:00	Lunch
Session 2: Role of ICH and WHO in Setting Standards for Biotherapeutics • Session Leader: Romi Singh (Amgen) • Chair: Ivana Knezevic (WHO) • Co-chair: Jee-Won Joung (MFDS)	
14:00 – 14:35	Development and Implementation of WHO Guidelines for Biotherapeutics Evaluation: Ivana Knezevic (WHO)
14:35 – 14:55	Key Issues of Clinical Trial Review for Regulators: Jian Wang (Health Canada)
14:55 – 15:10	Panel Discussion

15:10 – 15:45	ICH Current Status and APEC Regional Harmonization Efforts: Mike Ward (Health Canada)
15:45 – 16:00	Coffee Break
16:00 – 17:20	Panel Discussion- Opportunities of Regulatory Harmonization
	<p>Biologics Evaluation in Malaysia (Case Study): Yvonne Khoo (NPCB¹⁵), Malaysia)</p> <p>Biologics Evaluation in Japan (Case Study): Yasuhiro Kishioka (PMDA, Japan)</p>
16:00 – 17:20	Implementations of WHO and ICH Guidelines (Case Studies) What are the opportunities for Regulatory Harmonization?
	<p>Panelists: Fia Ya-Ting Chen (Ministry of Health and Welfare, Chinese Taipei)</p> <p>Yasuhiro Kishioka (PMDA, Japan)</p> <p>Jee-Won Joung (MFDS)</p> <p>Yvonne Khoo (NPCB, Malaysia)</p> <p>Prapassorn Thanaphollert (Ministry of Public Health, Thailand)</p> <p>Romi Singh (Amgen)</p>
17:20 – 17:50	Review of Session 2 and Day 1: Ivana Knezevic(WHO)
18:00 –	Reception

26 September 2013

Session 3: Clinical/Non-Clinical (Case Study)

- Session Leader: Lila Feisee (BIO)
- Chair: Jian Wang (Health Canada)
- Co-Chair: Ziqun Han (AbbVie)

9:00 – 9:45	Introduction of Non-Clinical ICH S6 Guideline: Mr. David Hutto (Eisai)
9:45 – 10:15	Importance of Immunogenicity Assessment of Therapeutic Proteins: Steven Swanson (Amgen)
10:15 – 10:30	Coffee Break
10:30 – 11:00	Clinical Data Requirements for Biotherapeutics Registration: Freddy Faccin (AbbVie)
11:00 – 11:35	Panel Discussion and Q&A Review of Session 3 and Closing

Session 4: CMC Considerations - Manufacturing and Quality

- Session Leader: Wassim Nashabeh (Genentech)
- Chair: Chung-Keel Lee (MFDS)
- Co-Chair: Wassim Nashabeh (Genentech)

11:35 – 12:15	ICH Quality Guidelines for Biologics (Q5 Series and Q6B Guideline): Kowid Ho (Roche)
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12:15 - 13:15	Lunch
13:15 - 13:45	Review of Recent ICH Quality Guideline (Process/Product Understanding, ICH Q8-11): Mats Welin (Medical Products Agency)
13:45 - 14:05	Feasibility of Application of ICH Q8-11 to Biotherapeutic Products (Case Studies from the Industry): Lynne Krummen (Genentech)
14:05 - 14:25	Life Cycle Management for Biotherapeutics: The Complex World of Post-approval Changes (Case Studies from the Industry): Rick Lit (Amgen)
14:25 - 14:45	Key Points from the Biotherapeutics GMP: Chung-Keel Lee (MFDS)
14:45 - 15:15	Q&A and Discussion Review of Session 4 and Closing
15:15 - 15:30	Coffee Break
Keynote Speeches - Emerging Biotherapeutics Technology	
15:30 - 16:15	High-level Overview of new Innovative Technologies in Biotherapeutics: Therapeutic Vaccine Antibody Drug Conjugates (ADC) James Merson (Pfizer)
16:15 - 16:45	Q&A and Discussion Review of Day 2 and Closing
16:45 - 17:15	Summary and Conclusion: Wassim Nashabeh (Genentech)
17:15 - 17:20	Closing remarks: Sun-Hee Lee (MFDS)
18:00 -	Farewell Dinner
27 September 2013	
9:00 - 10:00	Wrap-up meeting for reports
10:00 - 11:00	Discussion on Results of WHO Survey and Harmonization Efforts among DRAs: Chair: Ivana Knezevic (WHO) Co-char: Yeo-Won Sohn (MFDS)
11:00 -	Local Biotherapeutics Plant Tour (Hanmi Pharmaceutical Co., Ltd.)

3) The 17th AHC Workshop (Pharmacovigilance)

3-1) Overview

- Topic: How to Harmonize the Pharmacovigilance in the APEC Region
- Date : 20 - 21 November 2013 (2 days)
- Venue: Grand Hilton Seoul Hotel, Seoul, Korea
- Host: AHC
- Participants: 283 guests (15 economies), 21 foreign speakers and invited foreign trainees

3-2) Main topics

Presented and discussed topics at this workshop are:

- Introduction of harmonization activities of APEC, WHO, ICH and academia for Pharmacovigilance
- Results of the survey on the current status for regulatory harmonization in pharmacovigilance from nine APEC economies
- Issues and challenges of pharmacovigilance among governments, industry and academia
- Information sharing and discussions on pharmacovigilance status in the APEC region
- Introduction and the current status of risk communication

3-3) Workshop Results and Discussion Topics

The representatives of WHO-UMC (Uppsala Monitoring Center), governments, industry and academia shared information on pharmacovigilance activities. Participants acknowledged importance of cooperation for pharmacovigilance in APEC.

The current status of pharmacovigilance regulations in APEC was identified by surveys and panel discussions.

From Regulators' Meeting

Regulators proposed to add vaccines as part of factors to consider in the pharmacovigilance roadmap.

Given the importance of development of training programs in the APEC region, regulators discussed how to organize and operate working group for training. Representatives from WHO notified that the organization intends to support development of training program.

Regulators pointed to "medical product risk evaluation" as the top priority for training program.

3-4) Workshop Survey Results

Workshop Program

Participants found this workshop very informative as a unique opportunity to learn about economies such as Indonesia, Thailand, Peru, Chile and Brunei. Enough time and opportunities for Q&A after each session were also highly acclaimed. Unfortunately, simultaneous interpretation was not provided for Chinese and Spanish producing time delay and other issues.

How to Improve Workshop

Suggestions made for the better workshops are:

- Fluent interpretation for languages other than English
- More information sharing on case studies
- Extended time for presentation and discussion
- More participants from the industry and academia
- More specific and targeted topics
- Better access to a workshop venue and providing meals for all participants

Topics recommended for the future workshops are:

- Identification of signal related cases
- Periodic benefit risk evaluation report
- Risk management
- Re-evaluation management
- Practical training for Individual Case Safety Report (ICSR) and aggregate report by EMA and US FDA
- Causality assessment
- Potential changes of regulation with promotion of roadmap

Recommended Action Plans are:

- Report of the results of the workshop for better understanding of action plans and roadmap
- Development of platform for continuous networking among participants
- Tailored training for experts
- Publication of newsletters on pharmaceutical regulations
- Creation of a regulatory working group for the roadmap
- Posting presentation videos and materials on the AHC website

Suggestion made for further regulatory harmonization are:

- Training programs including case studies
- Detailed explanation on pharmacovigilance and time schedule for each goal, area and process for harmonization
- Development of timeline of post-marketing adverse event report

The 17th Workshop Program

20 November 2013	
8:00 – 9:00	Registration
9:00 – 9:15	Opening Ceremony Opening and Welcoming Remarks: Jin-Ho Wang (AHC) Congratulatory Remarks: Byung-Won Jang (MFDS) Congratulatory Remarks: Kyeong-Ho Lee (KPMA)
9:15 – 9:35	Keynote Speech: Moo-Young Yoo (MFDS)
9:35 – 10:00	Group Photo and Coffee Break
Session 1: Harmonization Efforts on Pharmacovigilance Co-chair: Byung-Joo Park (KIDS) Wimon Suwankewasong (TFDA)	
10:00 – 10:20	APEC Efforts on Pharmacovigilance and Overview of Pharmacovigilance Roadmap: Jong-Pill Park (MFDS)
10:20 – 10:50	WHO's Activities on Pharmacovigilance: Shanthi Narayan Pa I(WHO)
10:50 – 11:10	ICH Activities on Pharmacovigilance Gerald Dal Pan (US FDA)
11:10 – 11:30	Academia's Activities on Pharmacovigilance: Ian Chi Kei Wong (University of Hong Kong/ISoP ¹⁶)
11:30 – 12:00	Q&A and Discussion
12:00 – 13:30	Lunch
Session 2: Issues and Challenges towards Pharmacovigilance Harmonization Co-chair: Sun-Hee Lee (MFDS) Antonio Mastroianni (UMC)	
13:30 – 13:40	Global Leadership for the Safer Use of Medicines: Antonio Mastroianni (UMC)
13:40 – 14:00	Results from Pharmacovigilance Questionnaire of APEC RHSC: Young-Jin Ahn (MFDS)
14:00 – 14:30	1) Issues and Challenges from Regulators' Perspective Indonesia: Siti Asfijah Abdoellah (NADFC) Thailand: Wimon Suwankesawong (TFDA) China: Li Zhang (CFDA)
14:30 – 14:40	2) Issues and Challenges from Industry's Perspective: Jean-Christophe Delumeau (Bayer HealthCare)
14:40 – 14:50	3) Issues and Challenges from Academia's Perspective: Nam-Kyong Choi (SNU ¹⁷)
14:50 – 15:10	Coffee Break

Session 3: Current Status and Gaps of Pharmacovigilance System in APEC Economies

Co-chair: Gerald Dal Pan (U.S. FDA)

Siti Abdoellah (NADFC)

15:10 – 16:40	<p>Panel Discussion- What are the Current Status of and Gaps in Pharmacovigilance?</p> <p>Panels: Rokiah Isahak (Ministry of Health, Malaysia) Li Zhang (CFDA, China) Maria Aldunate (Institute of Public Health, Chile) Wimon Suwankesawong (TFDA, Thailand) Cecilia Beltran Noblega (DIGEMID, Peru) Don-Woong Choi (MFDS, Korea) Ola Strandberg (WHO-UMC)</p>
16:40 – 17:00	Coffee Break
	<p>Keynote Speech- Risk Communication</p> <p>Co-chair: Jin-Ho Lee (KoPERM¹⁸) Jean-Christophe Delumeau (Bayer Health Care)</p>
17:00 – 17:35	<p>Risk Communication Introduction and Current Practices:</p> <p>Gerald Dal Pan (US FDA)</p>
17:35 – 17:45	Q&A and Discussion
17:45 – 17:55	Review of Day 1
17:55 – 18:00	Closing Remarks: Sun-Hee Lee (MFDS)
18:30 –	Reception

21 November 2013**Regulators only Session**

9:00 – 12:00	<p>Co-chair: Gerald Dal Pan (US FDA) Don-Woong Choi (MFDS)</p>
12:00 – 13:00	Lunch
13:30 – 16:30	<p>Pharmacovigilance related Organizations Tour (only foreign participants)</p> <p>1) Korea Institute of Drug Safety and Risk Management (KIDS) 2) Seoul National University Hospital Pharmacovigilance Center</p>

16) International Society of Pharmacovigilance (ISoP)

17) Seoul National University (SNU)

18) Korean Society for Pharmacoepidemiology and Risk Management (KoPERM)

4) The 18th AHC Workshop (AHC & RHSC Awareness)

4-1) Overview

- Topic: Raising Awareness and Setting Operational Plans for AHC
- Date: 11 December 2013 (1 Day)
- Venue: AW Convention Center, Seoul, Korea
- Participants: 57 guests (from MFDS, Korean pharmaceuticals and associations)

4-2) Workshop Program

Introduction of AHC and RHSC

- Introduction and achievements of AHC
- Overview and activities of RHSC
- APEC RHSC roadmaps (Biotherapeutics and pharmacovigilance) led by Korea

Mid and long term plan for AHC

- 2014 AHC Plans
- Panel discussion on developing mid and long-term AHC plans

4-3) Workshop Results

Recognizing the current of approval and authorization system is important to set up a mid and long-term plans. Researches are recommended for future development plans. Given the importance of international information sharing on development of innovative new drugs, forums for discussion among industry experts should be offered. To encourage participants from multinational pharmaceutical companies, more workshops are recommended to be held overseas.

One of the key obstacles to foreign market entry is lack of regulatory information. To lower the barrier, data for each economy should be collected and analyzed before categorizing economies according to the results.

More active and longer term (at least six months) promotion is required. Press release and PR materials for international workshops should be distributed in advance by both MFDS and AHC. Associations are required to encourage participation of the industry.

Having contact points of associations will reduce miscommunications and enhance efficiency of publicity of events.

Potential participants will have greater access to workshop information, if workshop agenda, venue and other related information is posted on the AHC website in advance, together with distribution of workshop package through associations and pharmaceuticals.

Each business may have different priorities over regulations. It is not only unrealistic but also inefficient to cover all regulations at one workshop. Therefore, in-depth discussion is required to find out pressing issues and most wanted topics for workshops.

AHC and KPMA will continue to actively publicize APEC Harmonization Center and its works to related committees and personnel.

The 18th Workshop Program

11 December 2013	
13:00 – 14:00	Registration
14:00 – 14:05	Opening Ceremony Opening remarks: Jin-Ho Wang(AHC Director)
Session 1: Introduction of AHC and RHSC	
14:05 – 14:25	Introduction of AHC
14:25 – 14:45	Achievements of AHC
14:45 – 15:00	Introduction and Activities of RHSC
15:00 – 15:10	APEC RHSC Roadmap (Biotherapeutics)
15:10 – 15:20	APEC RHSC Roadmap (Pharmacovigilance)
15:20 – 15:50	Q&A and Discussion
15:50 – 16:20	Coffee Break
Session 2: Mid and long-term Plans for AHC	
16:20 – 16:30	2014 AHC Work plans
16:30 – 17:50	Mid and long-term plans for AHC Panel Presentations Panel Discussion
17:50 – 18:00	Closing Remarks
18:00 –	Dinner

2 AHC Website Renewal (www.apec-ahc.org)

For the better user navigation and management, AHC renewed its website. The site was re-designed according to web standards with new layout and admin system.

As a result, timely announcements for upcoming workshops can be made and presentation materials, video recordings and speaker profiles can also be posted without delay. Website content was re-organized to improve user experience.

The renewal was made in compliance with guidelines for personal information protection and web security to strengthen access security. With web standard compliance which supports numerous browsers (cross-browser), greater user accessibility and prevention of malicious cyber attacks will be secured. Web Accessibility Certificate Mark is planned to be issued by April 2014.

New Site Map

Sitemap			
About AHC	Event	Training Program	Archive
<ul style="list-style-type: none"> About Us Welcome message Organization Advisory Board Members Contact Us 	<ul style="list-style-type: none"> Calendar of Events 	<ul style="list-style-type: none"> Upcoming Workshop <ul style="list-style-type: none"> Workshop Overview Workshop Agenda Speakers Previous Workshops <ul style="list-style-type: none"> 2013 2012 2011 2010 2009 	<ul style="list-style-type: none"> AHC <ul style="list-style-type: none"> Public RHSC APEC LSIF Others
Bulletin			
<ul style="list-style-type: none"> Notice Press Release FAQ Discussion (Members Only) Free Board 			

Renewed AHC Website (<http://www.apec-ahc.org>)

The screenshot displays the homepage of the APEC Harmonization Center (AHC) website. At the top, there is a navigation bar with links for Home, Contact Us, and Sitemap. Below this, the AHC logo and name are prominently displayed, along with a brief description of its mission: "The APEC Harmonization Center (AHC) provides a platform to address and solve priority concerns of APEC member economies on regulatory harmonization".

The main content area features a large banner with the text "APEC Harmonization Center" and a sub-header "APEC Harmonization Center provides a platform to address and solve priority concerns of APEC member economies on regulatory harmonization". Below the banner, there are two main sections: "Notice" and "Event / Meeting". The "Notice" section lists several announcements, including "2013 AHC Pharmac...", "Re-Construction Announcement", "Online Registration 2013 AHC Biot...", "2013 AHC Biothera...", and "SAVE THE DATE 2013 APEC Harmon...". The "Event / Meeting" section includes a small image of a meeting.

On the right side of the page, there is a "Partners" section listing various organizations such as APEC Life-Sciences Innovation Forum, International Conference on Harmonization, International Medical Device Regulators Forum (IMDRF), Drug Information Association, International Federation of Pharmaceutical Manufacturers & Association, Asian Harmonization Working Party, Pharmaceutical Research and Manufacturers of America (PhRMA), and Advanced Medical Technology Association (AdvaMed).

Below the "Partners" section, there is a "Family Sites" section listing websites like Asia-Pacific Economic Cooperation (APEC), Ministry of Food and Drug Safety, National Institute of Food and Drug Safety Evaluation, and Korea Pharmaceutical Manufacturers Association.

At the bottom of the page, there is a footer section with the AHC logo and contact information for the APEC Harmonization Center Secretariat, including the address, phone number, fax number, and email address.

3 APEC International Meetings

AHC participated in 2013 APEC Senior Officials' Meetings (SOM) and presented AHC's current status, since it is under the authority of LSIF. The director of AHC was presented at the SOM I and SOM III, in which APEC RHSC regular meetings are generally held, and shared results of AHC's activities and discussed on cooperation between AHC and RHSC.

In 2013, AHC took part in and attended the following meetings.

The first Senior Official's Meeting (RHSC meeting), 1 - 2 February 2013

The results and accomplishments of AHC 2012 workshops were presented and the plan of 2013 workshops was endorsed. Also, information was updated regarding a new AHC secretariat.

In addition, AHC introduced the EBI Project - a strategic training plan for regulatory harmonization.

EBI Project focuses on

- Activity **Evaluation**: evaluation of activities for travel eligible economies and analysis of trainee survey for further programs
- **Broader** Participation: expansion of participation by holding more workshops overseas, inviting trainees from different background and providing supports for online training programs (AHC website)
- Quality **Improvement**: higher quality of training by having four workshops per year, developing workshop programs that meet needs of participants and posting higher quality of training materials on the AHC website for greater understanding of participants

The third Senior Official's Meeting (RHSC meeting), 1 to 4 July 2013

AHC participated in both the LSIF special session and the RHSC regular meeting where it introduced structural change of MFDS, new managing division of AHC and a new secretariat. With the AHC's work plan in the first half of the 2013, long-term direction of AHC was presented.

Pharmacovigilance roadmap, which is one of the PWAs led by Korea, was approved in principle. RHSC members endorsed biotherapeutics and pharmaceutical workshops to be held in the second half of the 2013 in Korea.

RHSC meeting



III

ANNEXES

1. 2013 Workshop Summaries
2. 2013 Workshop Photos
3. References

1 2013 Workshop Summaries

The 15th AHC Workshop (Supply Chain)

» Opening Ceremony

▣ Welcoming Remarks

- **Jin-Ho Wang**, Director of AHC welcomed experts, speakers and participants. He said that the workshop would be a place to discuss safety issues of counterfeit medical products, ways to enhance public awareness, and cooperative measures, sharing safety information at a single contact point. He hoped that the workshop would become a venue to seek ways for international collaboration in regulatory harmonization.

▣ Congratulatory Remarks

- **Byung-Won Jang**, Vice Minister, MFDS also welcomed participants to the workshop. He introduced the new roles and goals of MFDS which recently restructured. He believed that discussion of global cooperation for sharing safety information on illicit and counterfeit medical products would help further develop of safety management system.

▣ Opening Remarks

- **Mark Paxton** of the US FDA gave an opening remarks at the workshop. He noted the five-year effort of Korea Health Industry Development Institute (KHIDI) laid the foundation for AHC. Also, he noted the activities regarding the APEC RHSC roadmap supported by the Korean government and AHC. He expressed gratitude to USAID and Jeffrey Gren for supporting this conference.

» Summary of APEC LSIF Activities to Combat Counterfeit and Falsified Medicines

- Jeffrey Gren, U.S. Department of Commerce



- He briefed on history of the APEC LSIF under the theme of falsified anti-counterfeit medical products initiative which led to the development of different action plans.
- LSIF organized a series of 3 medical product seminars and many of the people in this audience were involved in those 2008 and 2009 seminars.
- LSIF developed the anti-counterfeit medicines action plan and revised action plan based on constructive comments, APEC LSIF Planning Group endorsed the plan.
- APEC LSIF Workshop on Medical Product Safety and Detection Technologies was held in Beijing in September 2011.
- Korea hosted APEC LSIF Workshop on Medical Product Safety Public Awareness & Establishing of SPOCS in May 2013.
- It's important to reflect all aspects of each APEC economy in the plan, APEC economies should work together to collect data on counterfeit medicines.
- Many counterfeit medicines enter APEC economies through the Internet sales. Detection technologies became more and more important because we need methods to detect unsafe medicines, including the ones crossing borders or within the drug supply chain.
- After the workshop in Beijing in September 2011, we are looking at the possibility of conducting follow-up measures to this workshop and continuing the work in cooperation with APEC economies. Actions beyond a mere development and use of the detection technologies are expected.
- There are a number of initiatives or agencies which have plans for ensuring safety of medical products.
- APEC LSIF has become a leader in global efforts to promote safe medical products and regulatory harmonization roadmap.

» Medical Product Quality and Supply Chain Integrity and Gap Analysis

- Mark Paxton, U.S. Food and Drug Administration,
APEC Regulation Harmonization Steering Committee



- With increasing imports of raw materials, drugs or medical devices, all regulatory authorities have to deal with the phenomenal norm of outsourcing of manufacturing that is leading to just a complex web of supply chains. Also, the global market is becoming filled with different types of adulterated, substandard products.
- For example, Avastin is an approved vial made by Genentech which is a US company that is wholly owned by Roche. Genentech is the only company approved to market that product in the United States. The falsified products with secondary packaging in Arabic has no active ingredient. There is ongoing investigation on this product.
- The brand name drug of Altuzan marketed in Turkey is Avastin from Roche. If you take a look at the package, you will see the packaging is in English.
- Gap analyses are the linchpin of our five-year project. Based on the evaluation result, we are going to develop training tool kits which was put in the strategic plan. In addition, creating a subcommittee under the authority of RHSC is critical as well.

» Panel Discussion 1: Presentation on the Importance of Medical Product Safety Public Awareness

(Moderator: Mark Paxton, US FDA, APEC RHSC)

1. Shaba Mohammed,

National Agency for Food and Drug Administration and Control, Nigeria



- Protecting public health is the first priority of any sovereign government by collaborating and communicating with government agencies and NAFDAC is one of them.

- Counterfeit medical products are defined as a product that is deliberately and fraudulently mislabeled with respect to sources. It can apply to both branded and generic products and may include products with the correct ingredients, wrong ingredients, without any active ingredients, insufficient active ingredients with fake packaging. Therefore, counterfeit medicines are one of the most serious problems faced with regulators.
- The preventive efforts against trade of narcotic products which led by the US and Mexico, have actually resulted in encouraging drug smuggling groups to do their businesses in safer and more lucrative manners. Hence counterfeit medicine markets going more global and sophisticated.
- Nigeria is one of the targeted countries of smuggling of counterfeit drugs as it has a large population of around 167 million. In other words, Nigeria has huge markets and purchasing power, with lack of supply for locally produced products. The major counterfeit medicines circulating in Nigeria are anti-malarias, antibiotics and anti-hypertensives.
- Nigerian government supports to improve capacity of domestic manufacturers by cooperating with national pharmaceutical committee, state department, and other government agencies.
- Nigeria protects consumers from counterfeit medical products by detecting counterfeit drugs and medical devices and introducing state-of-the-art technologies such as Truscan, RFID, GPHF Minilab Test Kits and Black Eye MAS.
- NAFDAC has adopted a holistic, multi-faceted, diverse and well-coordinated anti-counterfeiting strategy.
- Medical products detection technologies and global electronic single window platform are key to ensure secured global supply chains and quality safe medicines to be provided to the public.
- All those interested parties need to support and collaborate together to expand existing anti-counterfeit medicines systems and improve information sharing system relating to anti-counterfeit medicines systems to protect public health.

2. A. Rento Tyas Utami,

National Agency for Drug and Food Control, Indonesia



- Indonesia is a unique country located in between South East Asia and Australia, and composed of many islands, making it very difficult to identify and regulate supply chains of counterfeit medicines.
- To regulate supply chains, it is necessary to make inspections on wholesalers, pharmacies, hospitals, clinics and drug stores to ensure good distribution practices. The country also has a surveillance system for the early detection of illegal and counterfeit pharmaceutical products and investigation to track illegal product suppliers.
- Counterfeiting medical products, in Indonesia, are on the rise because of low purchasing power due to economic slowdown, the medical product shortages in local clinics and lack of public awareness in counterfeiting medicines.
- Indonesia has strengthened its operating system through regular inspection, monitored to break down supply chain of illegal medical products and enhanced private investigative capabilities with consistent legal cooperation.
- To combat the counterfeit medicines, Indonesia has provided easier access to medical information to consumers and improved public awareness through training and information sharing. Hence, protecting consumers from counterfeit products.
- To promote public awareness, the Health Minister launched a campaign called GNWOMI (the national campaign to combat the illegal products) on 8 February 2013. Both public and private sectors and communities are participating in GNWOMI to build capacity and optimize operation.
- Counterfeit drugs are not only responsibility of NADFC but also other stakeholder such as pharmaceutical associations and manufactures. Also related associations are encouraged to take part in efforts such as introduction of security system, using security tags to secure their own stocks of medicines, packaging materials, and regular surveys.

- economies should have effective regulatory system to control supply chain of products especially in combating counterfeit medicines.
- Effective strategies to combat counterfeit medicines should take into account breaking the supply and demand chain of the products.
- Consumer empowerment and matured public awareness can reduce demand of counterfeit products.

3. Libby Baney,

Alliance for Safe Online Pharmacies



- I understand the importance of the Internet pharmacies' safety issues and what it means to the public.
- About 97% of online pharmacies are illegitimate.

» Panel Discussion 1 Q&A

Q: Does the survey result of 6.4% cover both counterfeits and sub-standards?
(Shaba Mohammed)

A: Yes, the number covers both of them. It is difficult to divide the two because Truscan gives a pass mark to samples that surpass 60% of lama spectrum.(Simon Collier)

Q: Are there institutes in Nigeria that can conduct research on samples which are not able to be detected by machine. If so, how many are they?(Shaba Mohammed)

A: There are several licensed institutions under NAFDAC.(Simon Collier)

Q: What are the laboratory capacities in Indonesia?

A: There are few institutes that are able to test samples. Therefore, Indonesia work with HSA research center or inquires collaboration with independent pharmaceutical research centers.

Q: How do you follow up public reaction toward public awareness campaigns or projects?

A: We track information coming through call centers. With the start of campaigns, more and more calls come in proving effectiveness of such programs. Most calls came from educated people and housewives. It has not been available to see the reaction from uneducated people.

» Panel Discussion 2: Medical Product Public Awareness in APEC Economies – Case Studies and Best Practices

(Moderator: Jeffrey Gren, U.S. Department of Commerce)

1. Manzatul Azrul Azrie Bin Sulaiman, Ministry of Health, Malaysia



- Malaysia Ministry of Health (MoH) has three different arms: pharmacy enforcement, pharmacy practice and development division. It also has the regulatory section which is the national pharmaceutical control bureau. For enforcement, MoH has 440 officers all over the country. The private sector has license and is regularly inspected at least once or twice a year. However, in case of traditional or over the counter products, we give license to wholesalers. Retailers are not licensed and are vulnerable to this type of substandard, spurious, falsely-labelled or counterfeit medicines.
- From 1985, MoH started controlling medicinal products before expanding its scope of control and surveillance to non-prescription and OTC products in 1988, traditional medicines in 1992 and cosmetics in 2002. There are 6 different categories.
- There are chances to misuse registration numbers. We have found out that some products carrying fake registration number while some registration numbers are mixed up. To deal with the problem, Malaysia introduced a new technique called the Meditag hologram sticker. It can be applied to all pharmaceutical products on the market in Malaysia.

- The hologram helps us to strengthen control and to restore consumers' confidence. Also it facilitates consumers, retailers and enforcement officers to identify whether pharmaceutical products on the market carry right registration numbers.
- The sticker facilitates enforcement particularly with respect to product authentication with easier identification of fake drugs. As technologies advance, holograms are accordingly upgraded.
- In order to improve public awareness, we had live talks on television or created videos. We train pharmacists, wholesalers and retailers on how to use hologram and Meditag decoder to find genuine products.
- The MoH conducts various awareness activities. We distribute posters, postcards, leaflets, special bands and calendars with information about counterfeit medicines. We also make media announcements on medical information.
- With the introduction of cutting edge detection system, more counterfeits were detected from 2008 to 2012. Between 2004 and 2012, the number of consumer awareness activities increased as well.
- The MoH works together with other national agencies including the Malaysia Customs Department, Malaysia police, and the pharmaceutical industry. Malaysia also works with international organizations such as WHO, PIC/S, ASEAN and Interpol.
- The implementation of the security hologram has proven to be an effective and practical tool to facilitate enforcement work with respect to product authentication.
- MoH has to keep on improving itself and coming up with new strategies to educate and empower the public. Moreover, it needs to be aware any changes in the ways of making counterfeit medical products.

2. Yuwadee Patanawong,

Thai Food and Drug Administration, Thailand



- Adulterated products according to the definition of Thai FDA include: first, both wholly or partly imitated drugs. second, products with false names or expiration dates, third, those with false manufacturer or location of a manufacturer, fourth, with unauthentic registration number. fifth, products with substance which are lower or higher than 20% of the minimum and maximum standards.
- According to the definition of counterfeit medical products above, Thai FDA takes control of exporting and importing products. Those dealing with counterfeits will be sentenced to up to three year imprisonment or be fined.
- Since October 2009, Thai FDA has operated an ad-hoc task force called the Center for Prevention and Suppression of the Act in Violation of the Law on Health Products. We established the center of the surveillance and complaint center which has encouraged the public report any issues caused by health products.
- Thai FDA created a consumer working group in 2007. We would like to have representatives from every province to monitor counterfeiting cases occurring at boarder lines. Another important task is collaboration with police, customs department, medical research centers, legal institutions, schools and media to provide education and enhance public awareness.
- Thai FDA has been running a campaign called "Do not easily believe" since July 2004. Thai FDA hosted several exhibitions and community festivals so that it could enhance public's perception on medical products. According to the result of research reported that 88.9% respondents communicate with Thai FDA.
- The HPVC safety news program was established to report adverse events, share information, and provide HPVC safety news, allowing medical personnel and related agencies to utilize the information. HPVC also cooperates with ASEAN, AHWP and GHTF to name a few.
- For a smoother investigation and policing, seminars and workshops have been held. Training and education programs will let people know counterfeit medical products. We give consumers access to guidelines at schools and hospitals.

3. Hsueh Yung(Mary) Tai,

Food and Drug Administration, Chinese Taipei



- Majority counterfeit drugs in Taiwan are for: weight control, sexual enhancement, analgesic and anesthetic. Most of the illegal drugs are distributed through the Internet, night markets and pharmacies. Also they are promoted on television, newspaper, magazine, radio, and the Internet.
- For more efficient combat, we established an inter-department task force.
- According to statistics from 2010 to 2012, there were more than 1,500 inspections per month by the government and the number of illegal drug detection declined accordingly. Also advertisements for illicit drugs were started to go down at the same period from 13.93% to 4.08%.
- The inter-department cooperation has been pursued by the department of health, NCC national commission of communication and a fair trade commission to monitor various types of media.
- In 2006, Pharmaceutical Affairs Act was amended to strengthen penalties for offenders. In 2007, another round of revision was made to be able to revoke licenses.
- The Department of Health is under the process of amending related laws to increase the fines for illicit advertisement. Companies aired advertisement for incorrect information should correct any inaccurate or misleading messages with the same exposure as the illicit ones with apologies to the public.
- The government also launched a lot of campaigns to promote public awareness regarding seriousness of counterfeit drugs to student, the elderly, community, pharmacies, and general public.

» Panel Discussion 3: Patient Organization and Industry Activities Related to Drug Safety Public Awareness

(Moderator: Jeannie Salo, Eli Lilly and Company)

1. Bejon Misra, Partnership for Safe Medicines (PSM)



- PSM's objective is to have a globally adjusted definition on counterfeit or spurious medical products and protect people from those medicines. And we also want to enhance our understanding on how we can bring in technologies to empower the consumer. The last objective is to ensure that all of us focus on patient safety more than commerce or profit.
- PSM India was founded based on the eight mottos: standard, choice, accessibility, non-discrimination, transparency, information and quality.
- PSM uses a simple language which enables patients to easily detect authenticity of products. We make sure that people are empowered and can have access to medical products that they want.
- India is well aware that the country makes and distributes largest number of counterfeit and illicit drugs and its investigative capability and technologies are lacking, making difficult to catch violators. In other words, India can be a leader in activities combating counterfeiting medical products and increasing public awareness.
- To lead global efforts to fight against counterfeiting medical products and protect consumers from them, PSM India has had regular meetings with stakeholder who is socially influential and has been working on ensuring transparency within the agency.
- PSM India helped the public build ownership within their own communities to take the lead in combating counterfeiting products.

- The result of a sample test showed that merely 0.04% was found to be counterfeit or falsified or as spurious as to define. Also 6-8% products were found to be sub-standard. However, we are still making all our efforts to reduce the number further.
- PSM India is trying to make drug regulators involve in our works to stronger surveillance and control on illegal medical products and to collect more science-based and reliable data which is supported by formal president of India, Dr. APJ Abdul Kalam.
- We believe that the pharmaceutical industry should take a look at multifaceted threats of counterfeiting medical products and establish a technical road map for the sake of patients' safety.
- Furthermore, we hope that PSM India Initiative will seek ways to ensure safe medical products and safe sources, educate consumers and encourage more active communication.

2. Simon Collier, Eisai Co. Ltd.



- IFPMA has long been involved in the work since the 1980's, supporting WHO and the technical work of IMPACT. Then in 2010 the IFPMA released its ten principles on counterfeit medicines which is to contribute to enhancing public awareness in cooperation with other interested parties including PSI.
- The pharmaceutical industry's first priority should be protecting patients. Patents on medical products is not related with counterfeiting products which are threatening not only legitimate medical products but also illegitimate ones. That is why showing leadership by WHO is critical.
- IFPMA is globally supported by universities and pharmaceutical associations, making a number of plans to combat counterfeiting medical products, and providing various activities to enhance public awareness.

- The goal of IFPMA's projects is to build leadership movement that can organize patient protection groups. Such movement will be evolved into collaborative activities by using existing resources and data.
- For successful movement, it is necessary to share consumer experiences and provide training and educational programs.
- We are going to start campaigns and online platforms that help improve transparency, create local groups, and support policy makers.
- We think communication, media and events will facilitate anti-counterfeit medicines campaigns, information sharing and education.

» Panel Discussion 3 Q&A

Q: Everyone agrees that cooperation with various groups and communities are important. Then what are the proper steps if an individual or a group wants to join a global effort?

A: I don't think a movement has yet to be properly established. I think the industry can get in touch with IFPMA or me to get information. Of course, answers may differ depending on entities. However, for the industry, the IFPMA has a role to play.

Q: I want to point to Bejon's use of data. I haven't seen the protocol but you are looking at 0.04% of counterfeits in two different studies in India and I believe the first one was done by WHO office in South East Asia region, but I don't know if Bejon can clarify who did the second study in 2009 and also what are you going to focus on?

A: In fact, the second study was done by the regulators who are in the drug controller's office in India. What PSM India is trying to do now is to bring out data which is acceptable to anyone because these two studies handle all different issues in terms of its methodology, implementation. Therefore it is important to conduct research by regulators both from health organizations and government.

Q: Approaching customers with good anecdotes that are easily understood is a good idea. Still, having a certain protocol or methodology could be another good way.

A: PSM India is definitely looking at how we can build that kind of a methodology which enable transaction for everybody. People actually get off the track through misleading information. Therefore, I definitely agree with you that we must focus on that.

A: Anecdotes get your attention, but you don't make decision only upon anecdotes. Once you are engaged in a study, then you make policies and I think that's a proper step. However, I believe that anecdotal campaigns for consumers could be more effective

» Overview of Draft APEC Public Awareness Tool Kit

- Simon Collier, Eisai Co. Ltd.



- The World Health Professions Alliance(WHPA) brings together different global associations and different health care professionals (physicians, pharmacists, nurses, physiotherapist, dentists). On the strategies, it provides those health care professionals with the tools needed to advocate for appropriate investments in the education and capacity building of health care, of health professionals so that they can better detect counterfeits and also inform colleagues and patients.
- WHPA came up with health care professional point of view and it aims to help educate and improve the capacity of health professionals for detection, reporting and prevention of counterfeit medical products. Also, it cooperates with health professionals around the world.
- "Be Aware - Take Action" was begun in May 2010 to hold regional workshops by inviting medical professionals, patient groups, legal and regulatory authorities and other relevant parties for sharing information and experience and training. It was to create action plan within 12 months after the workshop.

- A number of fact sheets were created. And the fact sheets have opened up for different targeted audiences. Depending on audiences different fact sheets were created especially one for health care professionals, patients and public health advocates.
- WHPA also created campaign postcards. I think this was about not only how you detect, but also how you inform the public. They created the sample reporting form for health care professionals which is a great idea to spread the information in different languages. And then they provide information for patients too.
- WHPA also created posters for waiting rooms in clinics and pharmacies.
- It is important how you communicate with patients in a non-threatening manner for health care professionals. You don't want to put your patients off taking the medicines all together. So this is a big challenge for the professionals. There are several steps that block health care professionals to give patient information. So it promotes public awareness while teaching best timing to deliver certain messages and ask certain questions.
- WHPA agrees the framework for coordination and action on a global level which disseminates information through regional workshops.
- The lessons from the WHPA tool kit can be applicable to the APEC members as well. This is about working together among different organizations and economies.
- The role of policy makers is mainly to adopt laws and provide resources. And then the regulatory agencies can be a possible single point of contact. Health care professionals are at the forefront to protect their patients. Therefore, we need cooperation among many different interested parties in raising awareness for the public.

» Discussion of Proposal for APEC Public Awareness Tool Kit

(Moderators for each discussion: Mark Paxton, Jeannie Salo, Manzatul Azrul Azie Bin Sulaiman, Simon Collier, Libby Baney, Bejon Misra, Anita Derks, Retno Tyas Utami)

- Health care providers(nurses, doctors, dentists, pharmacists) are directly involved in purchasing products. Those who own their pharmacies or clinics make purchasing decisions. In other words, they are confronted with the bottom line. While doctors or physicians work in the large hospital, making them to have very different perspective on purchasing. Therefore, they guarantee the quality of medicines because they do not have a direct responsibility of the quality of medicines.
- There should be individual tools for health care professionals based on communicating with health care professionals, regulators, patients, the public, the media.
- Fact sheets should include counterfeiting medical devices.
- Since many people may not be able to understand all the questions in fact sheets we need to simplify and make clear questions for information collection. A good example is a Korea's smartphone application with simple questions, allowing to take pictures of the related product and filling out all the information that will load on to the regulatory website.
- It is good to have such systems in clinics and hospitals. Such fact sheets can help protect patients and ordinary people purchase medicines through accurate information. People can get access to medicinal information through pamphlets, posters in the market or on the Internet. The materials should be translated into different languages.
- Unfortunately, it takes long time to get information from all health care providers. Such process is unrealistic and time-consuming. An alternative way could be encouraging patients to report any issues to drug regulatory authorities when they are unavailable to discuss any problems or opinions on medicines with doctors in exam rooms.
- Another option would be airing animation in different languages globally. Also local contests can be held and recorded or used as educational materials. Hence engaging students in programs or campaigns.

- Reward systems would be a good way to combat counterfeit drugs such as rewarding tip-offs of any suspicious sales of medical products.
- Having both general statement which suits for everybody and specialized ones for different groups of people would be helpful.
- As we are concerned about the definitions of the uncertain medicinal products, it would be useful to adopt the WHO definition of words that refer to substandard, spurious, false labeled, falsified, counterfeit medical products. The WHO definition may well cover situations in different countries in general.
- In principle, WHPA tool kit was good and should be used as the APEC tool kit. But our main point is that there is a need to adopt flexibly.
- Training both law enforcement and policy makers are very important.

» Public Awareness in the Age of the Internet

– The Threat of Illegal Online Drug Sellers

- Libby Baney, Alliance for Safe On-line Pharmacies



- Many online drug sellers are operating outside the normal chain of distribution as illegal and unlicensed entities. We will talk about the risk to public health a lot of facts and data and some examples of rogue internet drug selling websites. There are challenges of going outside the regulated market and buying counterfeit goods on the Internet. The risks are especially severe because you may be getting unregulated or unapproved prescriptions.
- Patients can experience disadvantage when they purchase medical products directly online without advices from medical professionals because they may get the wrong dose of medicine. Drugs distributed online may not have appropriate monitoring or they could be used prescription drugs in a way that could harm health.
- There are 40,000 to 50,000 websites targeting consumers pedaling medicines. WHO estimates 50% of those sellers who hide their physical address sell counterfeits. The largest illegal online drug sellers can generate 1 to 2,5 million dollars each month. As we saw in other statistics Operation Pangea and the work that has been done

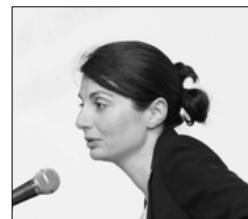
by INTERPOL and collective communities many of your economies involved in that important operation had very wide success. In 2012, 18,000 illegal online drug seller websites were taken down from around 100 countries amounting to about 4 million illicit pills.

- 97% of online drug sellers do not comply with US laws and pharmacy licensed practice standards.
- In Europe, a fake, illegal drug website was designed to try to see how many consumers would go to the website. The fake website generated 350,000 hits in just nine weeks. European counterfeiting of medicine sale is expected to continue to grow over the next 10 to 15 years getting up to be a 10 billion dollars or 10 billion euro industry.
- In China, 500 to 1000 websites are directly targeting Chinese citizens. However, they may not be operating in China and also targeting those citizens from outside of China selling medicines into the country. In the same vein, in Korea 800 to 1500 websites that are selling medicines in the Korean language. Japan which is known as a leading pharmaceutical country has also a similar problem with the two neighbour economies with 2000 to 4000 websites.
- To enhance public awareness on counterfeiting pills, education and training for health care providers and other stakeholders are necessary and supervising role of government is also important.
- We talked about model voluntary protocols that the US government supports strongly getting the online companies to voluntarily take action on themselves.
- You can run a public education contest or you can make an alliance or utilize existing ones for safe online pharmacies' existing materials. Then you can meet with the internet commerce companies to have conversations to know what they are doing to protect patients.

» Panel Discussion 4: Importance of a 'Single Point of Contacts (SPOCs)' for Medical Products

(Moderator: Anita Derks, Roche)

1. Aline Plancon, INTERPOL



- Four to five years ago, the international committee of the police would not recognize the importance of pharmaceutical crime. The Interpol did not see counterfeiters of medical products, smuggling fake medicines, or diverting or stealing as a big problem. Today, INTERPOL community recognizes the fight against pharma quait as a top priority.
- When I am talking about pharmaceutical crime, it really gathers all the counterfeiting diversion, the illicit fraud, the illicit online sales, the thefts of medicine. Therefore, we were not really prepared to see but definitely that everybody is addressing. These are linked to all the other criminal activities such as money laundering, online gambling, narcotics, and child pornographies. We see that they enlarge the capacity of counterfeiting or copying medicines.
- We had pretty white comprehension of counterfeiting medical products. There's a number of illicit websites. It is very easy for them to set them up, remove them from the Internet and then to establish them again.
- We are providing tools and services to the enforcement community and to the regulators and to the customers from our 190 members in terms of exchanging criminal data. Sensitive information can lead to better identify organized crime groups involved in pharma crimes.
- So Interpol got a secured data system called the I-247 system. It is a critical tool to be able to safely exchange data and the SPOCS needs that. This exchange led to have more and more information on transnational network trafficking fake medicines.

- In the organization, we are developing the pharmacy crime area. We see some fake medicines that are branded or generic on the market. We see some intervention of medicines, so this program is trying to reflect the reality of what enforcement and health are seeing into their investigation. The Pangea operation now covers the widest region in this area and the Storm Operation is more into Asia as we are in the spot of the world.
- The storm network is a result of work started in 2007 based on full support and input from the WPRO¹⁹⁾. The WHO opened up its doors to regulators and INTERPOL, literally to the enforcement world. The operation allowed us to build upon a trustful network of people that could meet up regularly to exchange their expertise and knowledge. Through those opportunities people they also exchange their frustration and challenges while suggesting safe platform to build on activities that would be very practical and help them achieve some tangible results.
- A number of economies have got multi-agency's committees critical chart. Enlarging this scope of the target is practical between the SPOCs and the enforcement health authorities in the region for the storm network.
- Police agencies and regulators must understand each other's position and needs. To do that, they plan ways to complement each other.
- Interpol supports international investigations, information sharing and implementation of operations to fight against counterfeit drugs and also, cooperates with various organizations for improving public awareness.

2. Samson Chui, Pharmaceutical Security Institute(PSI)

- The counterfeit medicine problem is just so serious and the crime we face is no longer domestic crime. It is actually a transnational crime related to many country. It is all organized crimes and cyber-crimes. No single agency and no individual economy are able to tackle the problem alone without international cooperations.



19) Western Pacific Original Office

- For pharmaceutical industry, when we detect pharmaceutical counterfeit or pharmaceutical products in the market, we would probably assist the concerned-authority to take action. But it has been often difficult to coordinate among different agencies, customs, police, FDA. Therefore this SPOC system will facilitate the private public partnership against counterfeit medicine problem.
- The point of contacts for police, the Ministry of Health and the pharmaceutical industry will be the first thing we need. However, legal or political issues stand in the way of further progress.
- PSI recognized the importance of the SPOC system. PSI is a non-profit organization founded in 2002 as a single point of contact.
- By that time the major pharmaceutical companies saw necessity to set up an organization to coordinate to represent all these pharmaceutical companies to deal with the pharmaceutical problem globally. And to assist agencies in different places combat the medicine crimes in that country. So the setup of PSI is actually based on a single point of contact concept.
- PSI acts as a SPOC at both the national and international levels.
- We have 27 members of major international pharmaceutical manufacturers. With cooperation, the industry can get a lot of assistance in getting of the counterfeit medicine problems in their own economies.
- As a single point of contact, PSI assesses medical product-related trends, promotes capabilities of finding counterfeiting medicines, and actively coordinates in international investigation on illicit drugs.

3. Matthias Stacchetti, Swissmedic, Switzerland

- The intentional manufacturing and distribution outside the regulatory system means deceive customers and trade fake products as genuine. Illegal medicine manufacturers and traders have no authorization or license meaning no check-up for quality effectiveness and security from any authorities. Hence high potential risk for the patients.



- The recent experiences show that the only way to solve such cases is to improve cooperation among the competent national authorities within the nation and across the border. There is also Europol and Eurojust working in the same field. In this case the collaboration between police and health authorities led to the identification of the head of the network which was an EU national. The most important lessons learned is that involving counterfeiting medical products needs cooperation among health authorities, police, customs, and justice.
- SPOC model and effective cooperation between stakeholders are important to prosecute criminal activities. The networking among SPOC is based on both domestic and international levels.
- The council of Europe is an international organization founded in 1949, with the headquarter in Strasbourg France. It is supported by 47 European countries and observers (Canada, Holy See, Japan, Mexico, and US). Within the council of Europe, the European directorate for the quality of medicines and health care EDQM is responsible for elaboration of European pharmacopoeia. The council of Europe offers specific platform for cooperation against counterfeit falsified medical products in order to minimize the risks to public health. The EDQM supports these goals with experts at a policy making level.
- The MEDICRIME convention is the first international treaty criminalizing intentional manufacturing of counterfeit medical products, supplying, offering to supply trafficking in counterfeit medical products, falsification of documents, unauthorized manufacture of supply, or supply of medicinal products or marketing of medical devices.
- APEC authorities should benefit from the network of SPOCs within their states and across borders. An effective networking across borders has to be based on common concepts, understanding, working methods, trustful platform. The council of Europe MEDICRIME convention supports measures, legal concepts in criminal law and administrative cooperation enhancing impact of other international criminal law conventions and cost efficient.

4. A. Rento Tyas Utami,

National Agency for Drug and Food Control, Indonesia



- In 2006, WHO initiated the Rome declaration and IMPACT as the organization for combating counterfeit. Indonesia participated in the enforcement working group within activities of the IMPACT. With the inception of the SPOCS in 2007, the first Asian China conference on combating counterfeit medicinal product was held to establish a networking system.
- Workshop was held on the counterfeiting medicines and we the secretariat was established for a single point of contact in Indonesia. During the two years until 2010, we had not seen much progress, so we proposed to establish a task force on combating illegal drug and food to strengthen coordination among the relevant parties.
- The task force has an objective to increase coordination and create synergy effects between NADFC BADAN POM and relevant government agencies Also it is desirable to reduce supply and demand of illegal drug and food for protection of the public health through the community organizations. The scope of this task force is tackling the illegal drugs and foods. Medicinal products include therapeutic products, traditional medicine, cosmetic as well as all those counterfeit.
- The national network is divided into two sub-groups. The deterrence and prevention activities are carried out by NADFC, Ministry of Trade and Industry, Ministry of Welfare, professional association and manufacturer association. For the national network for the law enforcement, we have national police at the general ministry of finance. This is because custom is under the ministry of finance and also the ministry of communication and informatics.
- For the international network, we are engaged with the NCB INTERPOL Indonesia, INTERPOL Lyon France, the ministry of communication and informatics and with international research centers for training regarding counterfeit medicines. Also we have work with the HAS Singapore for activities in laboratories. Collaboration projects with Interpol include Pangea and Operation Storm.

- All the data and information related to the task force are properties of NADFC and the finding of all activities can be found in our website. Also regular reports are submitted to the parliament to update the progress toward the annual target of performance. Sharing information among the task force members should be under confidentiality agreement.
- All activities are organized through a structured system to cover deterrence and prevention. The task force also aims to build a network encompassing related stakeholders for operation, training and consumer empowerment. We are still working for more efficient network and communication.

5. Stephen Hawgood, Eli Lilly

- Point of contact is usually not a person rather a department or a bureau. Without that kind of data, it is hard to develop strategies and be effective.
- If you want to know why pharmacies are selling counterfeits, you need to go and talk to them. They are the point of contact in the illegal business. They can give us data we need. We can cooperate with them as undercovering investigators.
- What is important is law enforcement. The big scale of operations is important creating huge public awareness. However, the work of small teams on a daily basis can undermine the confidence of people selling counterfeit.



»» Proposal for APEC Single Point of Contact System Tool Kit – Overview of Proposal

- Matthias Stacchetti, Swissmedic, Switzerland

- Criminals related to illegal and counterfeit drugs include manufacturers, middlemen, orderers, traffickers because they commit crimes with international network while exchanging information.



- Combatting counterfeit and falsified medical products and protecting public health require international cooperation among all competent authorities.
- Proposed SPOC system supports APEC economies to establish a SPOCS network at national level among police, customs, judicial and health authorities. Also the system strengthens existing(national) networks and supports international cooperation through "National SPOCs" of individual APEC economy.
- Information is disseminated to National SPOCs of APEC economies for international cooperation to protect public health and combat falsified medical products.
- It is important to collaborate within your competent authorities to build trust and ownership. No agency has all the resources and no single focus will work. Promoting concept of mutual reliance will benefit all of us. National focus should be on joining forces, not controlling. Increasing your authorities' resource potential and improving public health protection are critical.

» Panel Discussion 4 Q&A

Q: Interpol successfully finished its global project with as many as 193 people. How often do different subgroups meet? What sort of tools do you use?

A: Regarding the Pangea SPOCS, we are providing them with a secure email address so that they can correspond to each other and Interpol can use its service to offer the secure exchange of information. So what they exchange nonetheless is secure, but also can be used as judicial procedures afterwards. We are working on the platform that is going to be a secure exchange platform.

Q: How many times did Interpol convene meetings and what methods did Interpol use?

A: So far, we haven't been able to have them meet in the frame of Pangea, but through regional meetings and along the opportunities we have been identifying along the years. Regarding this tool enforcement networks, we make sure that we have our SPOCs meeting at least once a year. And during the operational phases and training we can maintain and stimulate contacts. So it is a minimum of once a year and according to capacity we can propose.

Q: The sense of urgency seems to be important in dealing with complaints that may have illicit nature such as being falsifying or counterfeit. What do you make of change from the historical point of view of managing complaints?

A: From my experience, it is very important to set up the right person as contacts. In Hong Kong customs, we have set up a contact list of each individual at pharmaceutical companies who is responsible to take action. At first, it is not easy because building a well-organized contact points is a step-wise work taking some time.

Q: The qualification is that some regulatory authorities like US FDA actually have offices of criminal investigations. There are a couple of agencies do that, but does US FDA actually have criminal investigation units handling pharmaceutical crimes?

A: Definitely yes, we are. What we are actually trying to do is identification of economies that are dealing with pharmaceutical crime and agencies with the highest potential and the lead role in terms of enforcement action. So, it is not about Interpol asking them to impose anything but each country decides specific role of agencies. It will be the regulatory authorities taking the lead and developing their enforcement but in some cases it will be the enforcement developing their regulatory capacities.

» Final Discussion: Future APEC Regulatory Harmonization Steering Committee Roadmap on Product Quality and Supply Integrity Activities

- WHO is piloting a surveillance programs. But these work groups have not been launched yet. Only the SPOC conference or workgroup were launched. Good distribution practices have been launched unofficially. We need to provide certain information about, whether or not we are on our target for meeting objectives, how we spent the money. So we have to develop within FDA a set of documents. We call resource kits that were deploying the each of these work groups.
- There's a couple of good import and export practices which I think honestly is one of the hot button issues with the respect to a movement of products, especially ESSFC products. We are worried about imports, not worrying about exports. However, unfortunately your import is my export and vice versa.

- We need to deal with it, even though it is a pilot programs. We do need some more participation. So I'm really reaching out to the regulatory authorities here for further engagement. The industry has been pretty robust in their participation, so I would like to have little bit more balance with the regulators. Industry has played an exceptionally important role, because they can tell us about how things actually work in the international commerce. But we as regulators need to take account of that and negotiate and discuss among ourselves what are proper solution may look like and that's what we are really trying to do with all these work groups.
- The APEC RHSC itself is putting together a regulatory network. I am going to propose that we do it on a work group by work group area level. We have a broad base of regulatory networks of regulators or broad network of regulators in APEC and in fact across the globe that we can reach out to those.
- EMA and EDQA from Europe participate in this process which is one of the key requirements for getting five year funding from APEC secretariat. In the APEC region, I believe there is no better area than the pharmaceuticals and medical devices where we can have global scales of cooperation and direct local impacts.

» Discussion on Illegal Internet Sales on Medicines

- The problem of counterfeit medicines being distributed through the Internet includes a broad category of unsafe medicines. With the rise of the internet use, increasing number of criminal will be detected on the internet. Therefore, it is required to talk about this issue at the future LSIF meeting.
- Protecting patients and giving them safe medicines should be the top priority. To that end, as much information as possible should be shared among us to figure out best solution together.
- Online pharmacies are not yet regulated. It would be beneficial to encourage APEC members to concern more about online trading related to medical products.
- As young people are more familiar with using the Internet, education for them is important to protect them from harmful medicines.
- Monitoring money flow is one of the best ways to understand the current situation regarding trading in counterfeiting and illegal medical products.

» Discussion: Future APEC Regulatory Harmonization Steering Committee Roadmap on Product Quality and Supply Chain Integrity Activities

- APEC was founded to eliminate unnecessary procedures in terms of trade and exchanges in diverse areas and to build new guidelines covering all APEC regions.
- APEC RHSC has conducted research on regulatory activities from multi-faceted aspects. APEC approved RHSC's project for medical integrity and supply chain and provides financial support for 5 years.
- The RHSC road map covers almost all process of supply chain from raw materials to finished products and the whole process is in responsible of RHSC.
- RHSC is going to broaden its scope of work by cooperating with many industries and regulatory committees through information sharing and joint projects.

The 16th AHC Workshop(Biotherapeutics)

■ Day 1

» Opening Ceremony

▣ Welcoming Remarks

- **Byoung-Guk Kim** of MFDS welcomed distinguished guests and expressed gratitude to AHC, MFDS and speakers. He applauded the work of the program committee for successful preparation of the workshop despite limited time and highlighted implication of this workshop as a first opportunity to deal with biotherapeutics roadmap in APEC. Also high expectation on this workshop to achieve goal for harmonization by 2020 was noted. He closed remarks by wishing a successful and constructive event.

▣ Opening Remarks

- **Jin-Ho Wang**, Director of AHC, also welcomed distinguished guests on behalf of AHC. He also thanked program committee members and staff of AHC for organizing the event. Special thanks also went to speakers from overseas and all participants. The director briefed on history and achievements of AHC since its inception in 2009. He expressed high hope for success of the workshop for further regulatory harmonization. Lastly, he requested for continuous interest in and support for AHC.

▣ Congratulatory Remarks

- **Byung-Won Jang**, Vice Minister of the MFDS, delivered congratulatory remarks. First of all, he welcomed honorable guests to the workshop and thanked for efforts to organize the event. Vice minister underlined the rising biotherapeutic market and vision of MFDS to become one of top 7 biotherapeutic powerhouses by 2017. Implications of the workshop for sharing current status and clinical cases of biotherapeutics were emphasized as well.

Congratulatory Remarks

- **Won-Bae Kim**, chairman of KPMA also gave congratulatory remarks. He started by welcoming and thanking all before introducing KPMA as a secretariat of AHC. Special meaning of the second workshop on biotherapeutics was noted. Efforts of AHC for harmonization were praised with high hopes for the future.

Special Remarks

- **Romi Singh** of Amgen made special remarks first to thank the program committee and AHC for their tremendous efforts for the workshop. Next, the object of the workshop bringing all related people for regulatory convergence by 2020 was noted. True meaning of harmonization (convergence) and what has been done to find out that were explored.
- By using WHO guidelines, it was found that there are three groups of economies in APEC; economies with guidelines, those in the process of developing them and others who do not even considering to develop them. After deciding to use WHO guidelines as the baseline of harmonization, favorable feedback was made. Later on, the new biotherapeutic roadmap which includes biosimilar was approved by the RHSC.
- Of five sessions, Day1 consists of two sessions: first, differences between small molecules and biotherapeutics, second, WHO guidelines including each country's implementation status.
- Panel discussion will follow after each session, allowing all inquiries answered. Activities of Day 1 will be reviewed during closing session.
- Second day will cover clinical and non-clinical areas, differences between small and big molecules, immunogenicity clinical data requirements for registration, CMC and quality issues, recombinant DNA product.
- Day 3 is for closed sessions. Regulators complete reports for RHSC and find ways to achieve a goal by 2020.

Keynote Speech

- **Soon-Wook Hong** of MFDS delivered keynote speech. Wishes were made for constructive time. General ideas on regulatory harmonization for biotherapeutics were elaborated.
- As APEC aims to promote trade among member economies, it is required to streamline regulations and procedures for medical products. AHC supports training and implementation of guidelines for harmonization with active exchanges of information and cooperation while enhancing public health through higher quality and safety of medical products in APEC. There have been various achievements of AHC including facilitation of harmonization and competition among pharmaceuticals especially for export.
- Topics of workshop are very proper and timely. One of articles from a medical magazine was borrowed to highlight rapid growth of the biotherapeutic market in the world.
- With strong political supports, the US, EU and Japan spend large amount of money for biotherapeutics.
- In Korea, public R&D investment has been made and five year plans for biotherapeutics were developed. At the same time, Korea is striving to promote biotherapeutics by strengthening international cooperation. International and regional activities for harmonization conducted by organizations like APEC, WHO and ICH are on the rise. Also in Korea, the private sector has been engaging in collaborative works such as workshops, seminars and exhibitions.
- Korea has made various efforts since the establishment of AHC in 2009, by organizing regular meetings for globally renowned experts and discussing agenda. Signing MOUs, inviting foreign regulators and operating the WHO collaborative center are among other works.
- Finally, promises were made for further opportunities to learn(e.g. EBI project) before asking supports for or interest in harmonization going forward.

» Session 1: Overview of Biotherapeutics and Roadmap Towards Convergence

(Coordinator: Jerry Stewart(Pfizer), Chair: Yeo-Won Sohn(MFDS),
Co-Chair: Jerry Stewart)

1. Biologics vs Small Molecule Pharmaceuticals

- Kum Cheun Wong,
Novartis Asia Pacific Pharmaceuticals Pte. Ltd.



- The presentation focused on differences between biotherapeutics and small molecules as a building block for the rest of the workshop with clear explanation on characteristics of biologics.
- Biological medicines provide new hope for complex diseases and opportunities for target treatment with benefits of many. The journey of biopharmaceuticals has just begun with enormous potential going forward.
- Structures of biological medicines are much more complex, sizes are bigger and their stabilities are lower when compared with small molecules. Biotherapeutics are heterogeneous, requiring unique skills and special attention for manufacturing. Also they come along with higher potential for immunogenicity. In fact, high similarity with human proteins and low toxicity reduce possibility of side effects. But special care is needed for transport, storage(in a refrigerator) and administration devices (usually injected by specialists for severe and chronic diseases).
- Since biotherapeutics deal with living organisms, manufacturing process is long with critical implications of each step. There are four levels of structures in biologics. Impurities and contaminations have important implications as well.
- Biotherapeutics may have different immunogenicity reactions to different groups of patients, requiring immunogenicity profiling. For now, due to insufficient analysis methods, there are limited standardized assays. Robust post-marketing surveillance can be the only answer.
- Another sector to be considered is regulatory aspects of any change in manufacturing process because it can pose threats to patient safety. ICH Q5E, in this regard, aims to make sure comparability in terms of quality, safety and efficacy. Changes in manufacturing process call for additional studies.

2. Current Development, Regulatory Strategies of Biotherapeutic Products: Key Points to Consider vs Small Molecules

- Jane Bai, Bayer Healthcare, IFPMA



- The presentation was mainly about definition, distinctive characteristics and challenges of related products. Also close communication should be sought to go through approval process for commercialization. Work flow for scientific advice and protocols in the EU were also briefly addressed.
- Bio-products are derived from living sources by using bio-technology. Therefore, manufacturing process is very complex and sensitive to contamination. Any change will be critical.
- Host cells can be selected from micro-organism of various species. Cell bank is source of all production matches and there is a master cell bank and a working cell bank. As safety is a big concern, careful selection of raw materials, control of manufacturing process, comparability and stability studies are important. Qualification test is to make sure free of detectable and infectious agents in all stages. Biotherapeutics demand more complicated and longer manufacturing process.
- Regulatory strategy should be able to demonstrate consistent quality and appropriate validation of products. In-process control and impurities are critical as well.
- From the early stage of development, comparability of characteristics of active substance should be ensured through clinical and non-clinical trials. Variants also need to be identified, controlled and characterized. Product-related impurities and understanding functionality are critical. As for process-related impurities, all the leftovers from the fermentation purification process should be filtered.
- To mitigate risks, strategy is important to monitor binding and neutralizing antibodies in clinical trials.
- Comparability(in this case with ICHQ5E) is critical in terms of changes because it ensures safety, purity, potency and effectiveness of products. Standpoints of regulators differ on a case by case. For demonstration of comparability, discussion among regulators is required. Comparability exercise can be conducted throughout all stages but the final goal is to secure safety of patients.

3. Progress and Update on Biosimilars Development in Korea

- Hyuk-Jae Lee, Celltrion Inc.



- Celltrion was established in 2002 and now eight biosimilars are in the pipeline. The company has Asia's largest cell culture manufacturing facilities(Top three in the world).
- Biosimilar is a new biological medicines claimed to be "similar" with medical products in the market in terms of quality, safety and efficacy, according to WHO guidelines and EU Directives. There are three categories; copy biologics, biosimilars and bio-better. Biosimilars are tightly regulated in many economies.
- Existing knowledge must be referred to minimize redundancy of new clinical trials. Many businesses and scientists are working on bio-better but none has fully succeeded yet.
- The industry and the government are focusing on biosimilars, a new growth engine in Korea. The EU, India, the US and Japan are major players in the area. Remsima is the first product of Celltrion approved by EMA and now it is distributed to markets in almost 100 countries and approved in about 40 countries.
- The Korean industry has strengths in retention of recombinant protein drug commercialization and resources with experience in production as well as world class technology. The Korean government has been providing various supports including development of guidelines, reducing review time. However there are also challenges such as lack of key patents and experience in the global market and investment issues.
- Opportunities lie in Korea with a stable antibody drug market and growing demand for cheaper products. But competition in the market is very high.
- Remsima was approved in Korea and the EU. Clinical trial phase I and III were conducted and results are available on the website of the EULAR.
- Application requirements especially bio-similarities demonstration is challenging. Celltrion went through about 100 comparability studies, analysis and others to answer questions from authorities. Specification of original drugs can only be referred. Therefore, own specification must be built. The same goes for manufacturing process.

- Only limited numbers of patients went through clinical phase I and III. Additional consideration must be given to safety.

4. Overview of Biotherapeutic Roadmap

- Byoung-Guk Kim, Ministry of Food and Drug Safety



- Korea is the champion nation for establishing the Biotherapeutic roadmap which later on expanded its scope to include biosimilars.
- The long term goal of biotherapeutic roadmap is to develop safe, innovative biotherapeutic products. There have been efforts to identify regulatory measures and implementation level of APEC economies for further understanding of each other.
- With changes in pharmaceutical environment and trends of development and production of biotherapeutic products, regulations have been developed and implemented differently and separately by APEC economies, creating regulatory gaps and differences.
- Under these circumstances, building a roadmap in the APEC region has emerged as a major issue for consistent communication between the industry and regulatory authorities, and mutual cooperation with different regulatory authorities to establish regulatory convergence and harmonization for enhanced joint efforts and transparency on biotechnology products.
- Therefore it is critical for the APEC to devise ways for regulatory convergence that would facilitate harmonization among member nations.
- Among biological products, the roadmap will only cover the area of recombinant DNA products, monoclonal antibody, and therapeutic vaccines. Vaccines, blood products and cell or gene therapy products are not within the scope of the roadmap, though they are classified as biotherapeutic products by the definition.

5. AHC 2012 Biosimilars Workshop Output

- Jerry Stewart, Pfizer



- Conclusion from last year's panel discussion was that biosimilars are not generics. Biosimilars are not totally identical to original products. Therefore, manufacturing process should meet all scientific principals, abiding by each phase's requirements. For every step, consultation with authorities must be made. Now, emerging(India, China) markets are two to three years lagging behind in terms of market application than advanced(Europe, the U.S.) markets.
- Also last year, safe management and pharmacovigilance were highlighted as the most important factors to develop biotherapeutics. All risks must be assessed in advance with plans to minimize them.
- For effective development of biosimilar product regulation, WHO guidelines can be referred. The most up-to-date regulations and guidelines from WHO and EMA were explored.
- The current challenges for biosimilar development are related to quality, safety, and approval of new products. Frameworks and guidelines of WHO and EMA can be referred to facilitate harmonization.

6. Biosimila Convergence, What is more needed?

- Judith Macdonald, Pfizer



- One of the most important factors to consider in biosimilar regulation policy is patients. Today, more and more patients want to participate in decision-making process for medical products regulation.
- Balance should be sought when proposing and developing regulations. As characteristics of biotherapeutics are different from general drugs, comparability has to be scientifically demonstrated. Ability to detect errors should be equipped. Biosimilars are neither generic nor novel products, calling for actions in between.
- Biosimilars will only be approved when they pass all processes including quality test, non-clinical and clinical assessment. Unlike chemical drugs, quality is more important than results of clinical trials when it comes to biotherapeutics.

- Some economies adopted a third pathway. A third abbreviated route toward biosimilars is often with loosely defined criteria, which allows developers to submit what they think is necessary from the public domain. So, this approach seems redundant when considering all biological products should either fall into the category of a novel biologic or a biosimilar.
- Efforts have been made for a single pivotal global study for a single reference product. In some of the emerging markets, due to lack of clarity on the analytical test, the extent of the analytical test on a locally sourced, registered reference products are required. Another issue that has been mentioned is the consistency on naming.
- As for biosimilar products, global harmonization efforts are required. Centering around the EU, attempts have been made and development of international standards is in the pipeline. Whereas complete harmonization may not be able to achieve, there are high hopes for scientific and rationale standards.

» Panel Discussion 1: Conclusion and Q&A, Roundtable Discussion

1. Q: If the original bio is chimeric, is it possible to make biosimilars a full, humanized form, while keeping the biosimilarity?

A: Quite difficult. A humanized version will be less immunogenic as a more improved product. (Judith Macdonald)

2. Q: Why did Celltrion conduct clinical trial phase I with unhealthy volunteers?

A: Usually clinical trials with healthy subjects reduce time. But Celltrion simultaneously conducted trial phase I and III after pilot studies, to reduce time as well. RA and RS were selected as the most sensitive Remicade is recommended to be used. By reviewing previous clinical data, the most sensitive indicator can be determined based on gaps, using and not using drugs. (Hyuk-Jae Lee)

3. Q: What is the type of post-approval commitments for Remsima and the trends in that area?(Judith Macdonald)(RMP)

A: The RMP focuses on immunogenicity and safety profiles measuring due to data from the limited number of people(800). Now, Celltrion has a plan to go with 13,000, responding to requests from the Korean authority for approval.(Hyuk-Jae Lee)

4. Q: Is there any case study for biosimilar against orphan biotherapeutics?

A: In Europe, there are regulations for both biosimilars and orphan drugs. However, considering or treating them together is very convoluted issues.(Judith Macdonald)

A: Some economies do not have regulatory framework for orphan drugs, let alone biosimilar. As Ms. Macdonald noted it has not been explored much. Now, regulatory pathways for orphan drugs are quicker than that of biosimilar.(Jerry Stewart)

5. Q: What is the current strategy of Korea in the post pharmacovigilance system for the biosimilar, to ensure the proper tracking of the safety signal for patient safety?

A: In general, Korea complies with INN system according to WHO's recommendation. Yet, there is no INN system for biosimilar from WHO.

Q: What is the current strategy in Korea to ensure appropriate tracking of safety signals for the biosimilars.(Yeowon Sohn)

A: Every product must demonstrate definition of the WHO INN. As for trace of biosimilar product safety after PMS period, products are prescribed by brand name. Korea is giving consideration to how to cope with policies of WHO and INN.(Ju-Won Jung)

A: There is on-going discussion on INN policy of WHO. But the question is more about traceability which is clearly stated in the guidelines for biosimilar, biotherapeutics. Brand name, name of manufacturer, lot number and INN, if possible, are used for post-marketing surveillance.(Ivana Knezevic)

6. Q: What is the situation in Korea with regards to the updates of the biosimilar guidelines since 2009?

A: Since 2009, new approaches and more specific views for regulations of biosimilars have been noticed. There are plans to update new guidelines and this year guidelines containing some part of new information and regulation were published.(MFDS)

» Session 2: ICH and WHO role in Setting Standards for Biotherapeutic products

(Coordinator: Romi Singh(Amgen), Chair: Ivana Knezevic(WHO),
Co-Chair: Jee-Won Joung(MFDS))

1. Development and Implementation of WHO Guidelines for Regulatory Evaluation of Biotherapeutic Products

- Ivana Knezevic, World Health Organization



- WHO is a specialized agency of the United Nations and serves the duty as the public health agency basically coordinating international health issues of its members. Principle objective is the highest possible level of health for all. WHO is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.
- WHO has played a key role for over 60 years in establishing the WHO Biological Reference Materials, necessary to standardize biological materials as well as developing WHO guidelines and recommendations to assure the quality, safety, and efficacy of biological products.
- WHO has the expert committee on biological standardization and this committee members are selected from the expert advisors. Technical report series has been published in the printed version, but these days many of guidelines and recommendations are published on the website.(www.who.int and www.nibsc.org)

- BTP made by rDNA technology is about all biologically active protein products prepared by rDNA technology and used for treatment of human diseases. Regulations are required for clinical trials, licensing and changes in products that are already on the market. However, only brief ideas are described in the guideline thus requiring professional knowledge and experience.
- Collaboration between clinical reviewers and statisticians in reviewing the various aspects of clinical trials is strongly encouraged. During phase III, it is important to carefully select patients and also to confirm efficacy at the chosen dose and dosing regimens to evaluate safety and monitor side effect.
- ICDRA is basically one of the big regulatory networks for all medicinal products and all health care products. Conferences take place biannually. At the regular gathering in 2010, there were talks on biosimilars.
- In some economies, standards for biotherapeutic products are insufficient, posing risks on safety of medical products. There are heated debates on whether to require additional information or revise object of products.
- Challenges related biotherapeutics are incomplete regulations and lack of professional personnel, understanding on biotherapeutics and biosimilar and labeling, materials for prescription.
- WHO is surveying on biotherapeutics development and regulation and clinical data for approved biotherapeutic products to define original and copy product.
- Information sharing of clinical trial data for already incensed products and regulations should be encouraged among different economies.

2. Key Issues the regulators should consider while reviewing CT Data

- Jian Wang, Health Canada



- Regulators' decision whether to authorize a new drug for marketing is fundamentally based on two questions: first, whether the results of well-designed studies provide substantial evidence of efficacy and effectiveness; second, whether the results show the product is safe under the conditions of use in the proposed labeling.
- Guidelines are prepared by individual regulatory authorities, such as FDA, EMA, Health Canada and others. Guidelines prepared by the International Conference on Harmonization(ICH) are abided by regulatory agencies in many developed countries.
- E3, E5, E6, E9, E10 are general guidelines prepared for pharmaceuticals, although the principle of these guidelines are still applicable to biotherapeutic products. WHO has taken the initiative in updating the WHO Guidelines on the Quality, Safety and Efficacy of biotherapeutics. This guideline is a good example for developing guidance documents based on the existing guidelines, which may lead to the regulatory convergence.
- Sufficient data and information enable regulatory authorities to assess the quality, safety and efficacy of new drugs, generally based on one or two pivotal phase III trials. The overall design should be appropriate to support the claimed indications in the targeted population(s). Randomization and blinding are essential in phase III clinical trials. Non-inferiority trials have been conducted to assess similarity instead of placebo trials that assess differences. Clinical trials are increasingly being required to show clinical end-points are beneficial than surrogate end-points. The study endpoint or outcome variable that is being used and evaluation methods are also critical.
- There are doubts on efficacy of biotherapeutics: lack of long term efficacy in some biologics; lack of efficacy due to immunogenicity; less effective when used alone; small fraction of the treated population respond to treatment; requirements of appropriate biomarkers for prediction of response.

- Common safety issues with biologics are shortage of standard pre-clinical models for safety testing, effects on immune system and mode of administration.
- As for immunogenicity issues, most biologics induce human anti-drug antibodies. Biologics should be based on studies subject to a sufficient number of patients during sufficient time. Current analytical methods cannot fully detect all changes and predict biological properties. Immunogenicity of biologics may have serious clinical consequences, which may not be predictable or foreseeable during clinical trials. Therefore, Post-marketing Risk Management Plan(RMP) is required.
- To minimize risks, use of drugs can be restricted. Identifying risks and adverse reactions in the product labeling and monitoring measures during treatment are possible as well. NATRECOR permits use of drugs only after thorough review.
- Common reasons for submission rejection are related to regulatory, study design, outcome and safety issues. Biologics can be marketed only if the manufacturers can demonstrate their products are safe and effective and the regulatory authorities are satisfied. rDNA guidelines of WHO and ICH should be considered as the principle guidance.

» Panel Discussion 2: Conclusion and Q&A, Roundtable Discussion

1. Q: Is there discussion in WHO for its growing role in biotherapeutics?

A: There are discussions in WHO to respond to demands from member states. In fact, WHO's supports for biotherapeutics have been weaker than that of vaccines. Finding agency for funding would be helpful for progress because now resources are very limited.

2. Q: Updates on survey for member states and approaches towards industries and patients groups.

A: WHO is planning to continuously carry out surveys to understand level of biotherapeutics regulatory requirements. Survey is first step to reach goal by 2020 for biotherapeutics. Clarifying annual target is another reason for survey while redefining objectives overtime.

» Summary of ICH Current Status and APEC Regional Harmonization Efforts

- Mike Ward, Health Canada



- As biotherapeutics are innovative, more guidelines are required. Differences in guidelines depending on companies and economies must be considered. In other words, new methods and issues must be reflected into guidelines. Also thoughts should be given to PMR, decision-making on orphan drugs and biotherapeutics and longer review period for biotherapeutics as well. Regulatory cooperation must focus on sharing regulatory information and having cooperative activities such as workshops.
- The ICH was established in 1990 by regulators and research-based pharmaceutical industries of EU, Japan and the US to produce harmonized guidelines and standards that define international regulatory requirements for pharmaceuticals. ICH updates common forms and tools. There are more than 75 harmonized guidelines on technical requirements for safety, efficacy and quality. Achievements of ICH include MedDRA, CTD, eCTD and ICH product scope extension. Success of ICH is owing to involvement of both regulators and the industry, relatively large role of the secretariat and strong will of regulatory authorities.
- ICH aims to link ICH member and non-member parties while encouraging information sharing for Global Cooperation Group. Also ICH is striving to contribute to global network and rigorous information sharing while exploring strategic training programs and topics.
- APEC facilitates economic cooperation which can promote further cooperation in policy and technology. Leadership of APEC comes with enormous responsibility in terms of technology, products and service.
- Life Sciences Innovation Forum(LSIF) was created in 2002 following endorsement by APEC leaders who recognized importance of life sciences innovation in promoting public and economic health. It is to harmonize regulations and faster innovation.

» Panel Discussion: Opportunities for Regulatory Convergence

» Summary of Evaluation of Biologics in Malaysia

- Yvonne Khoo, National Pharmaceutical Control Bureau, Malaysia



- The NPCB was established in 1984 for regulations of medical and cosmetic products, as the secretariat of the DCA. Guidelines of WHO, EMA and ICH are referred for medical products evaluation.
- Biologics are regulated as new products with 'high risk'. It must comply with PIC/S GMP Quality Assurance requirements. It takes usually less than 245 working days for evaluation and maximum 90 working days for priority review.
- Product dossier submission must adhere to requirements of the ASEAN Common Technical Dossier (CTD) format. (Part 1: format, Part 2: quality, Part 3: non-clinical safety test, Part 4: clinical and efficacy test)
- Biotherapeutics developed in Malaysia include vaccines blood products, monoclonal antibodies and recombinant proteins.
- The current review standard for biosimilar was established in 2008. Biosimilar guidelines were developed based on ICH Q5A, Q5B, Q5C, Q5D and Q6B (quality), ICH S6 (non-clinical) and EMA (clinical).
- As of September 2013, four biosimilars were registered in Malaysia (G-CSF 2, Somatropin 1, Erythropoietin-alfa 1).
- Opportunities for regulatory convergence lie in selection of reference products, conduct of clinical trials, extrapolation of indication, product interchangeability and automatic substitution.

» Summary of Evaluation of Biologics in Japan

- Yasuhiro Kishioka,
Pharmaceuticals and Medical Devices Agency, Japan



- Bio technological products can be categorized into recombinant products, animal or plant products, gene therapy and cell therapy products. About 100 recombinant products are registered in Japan. There are guidelines and regulations for biotherapeutics. In 2009 the minister of Health Labor and Welfare published guidances for the first time which have been revised, most recently in 2013. Consultation on biosimilar is on the rise year after year.
- Quality of biotherapeutics is secured through ICH guidelines and regulations developed in Japan. PMDA is working to enhance international cooperation through seminars and training programs by APEC LSIF, RHSC, ICH, Medical Devices and WHO.

» Panel Discussion

Panelists: Ivana Knezevic(WHO)
Yvonne Khoo(Malaysia)
Yasuhiro Kishioka(Japan)
Fia Ya-Ting Chen(Chinese Taipei)
Prapassorn Thanaphollert(Thailand)
Jee-Won Joung(MFDS)
Romi Singh(Amgen)

- Discussion on submission of MRCT data
 - Chair: Clinical trial data are required in Japan, China and Korea. Rather than separating submission of data, multi-regional clinical test should be pursued. Chemical drug trials proved that clinical trials of different races can also be reflected. However, with no trial results for biotherapeutics, more researches are required for ethnic factors in biotherapeutics.
- Number of Subjects and Use of Foreign Clinical Trials
 - Japan: 30 to 60 subjects(case by case), no acceptance of foreign clinical data
 - Korea: Number of subjects depends on cases, domestic clinical data is required

- Thailand: Foreign clinical data are acceptable (depending on products, clinical trials can be ordered)
- Malaysia: Foreign clinical data are acceptable (if GCP principals are met).
- China: At least 800 subjects

● **Feasibility and Criteria of Foreign Clinical Data Acceptance**

- Thailand: Foreign clinical data when domestically approved as reference drugs
- Korea: Only Korean reference drugs, with demonstrated comparability
- Japan: Only Japanese reference drugs, with demonstrated comparability
- Malaysia: Only Malaysian reference drugs
- Chinese Taipei: Only Chinese Taipei reference drugs, with demonstrated comparability

● **Time Required for Approval of Biotherapeutic Clinical Trial Plan**

- Chair: Supply of necessary medical products will delay if clinical trial plans are not approved quickly enough. Average time for approval is 23 months in China, 1 month in Korea and Japan.
- Audience: Process for faster approval has to be proposed. For business competitiveness, in Russia domestic law was amended to reduce approval time.
- Audience: Foreign clinical trial data cannot be referred for products with fixed-dose (not weight-based dosing) because fixed-dose can only have efficacy for Europeans not Asians. Therefore, clinical data for different races must be required.
- Korea: For cancer drugs, dose levels from MRCTs can be higher than the level that Koreans actually need.

● **Guidelines for Each Product**

- Chair: Product-specific guidelines will increase work effectiveness of reviewers. Of course, product-specific guidelines can create risks of duplication, but it will do more good than harm for facilitating regulatory harmonization.
- Malaysia: EMA already developed guidelines for each product and Malaysia is planning to refer to them. As guidelines for monoclonal antibody are being developed by several organizations, convergence can be created among regulatory authorities.

- Audience: It would be better to develop product-specific guidelines after having more experience in the field.

● Training

- Chair: Gaps exist in training programs provided by different economies. This workshop aims to have discussion for training for regulatory harmonization.
- Audience: After workshops, lectures and on-site training have to be provided simultaneously. Middle level managers can learn lessons from those activities. Outreach education can also be provided.
- Chair: Work sharing is important through bilateral cooperation.

» Session 2 Conclusion

- Ivana Knezevic, World Health Organization



- Guidelines, developed by WHO, ICH and others have been implemented in many economies. However, there are global demands for more guidelines despite several existing guidelines for biosimilars.
- Different decisions have been made for the same clinical trials. It is a good example that perfect recognition is not possible. Decisions, of course, will be made based on scientific principles by each reviewer. However, differences in each country must be acknowledged. Harmonization must be continuously pursued by using data from different economies. Discussion should be made for possible use of foreign biosimilars reference.
- Discussion agenda included using same definition for biotherapeutics, differences on CTD format, opportunities in harmonization and priorities in comparability as well as training.

■ Day 2

» Session 3: Clinical / Non-Clinical(Case Study)

(Coordinator: Lila Feisee(Bio), Chair: Jian Wang(Health Canada),
Co-Chair: David Hutto(Eisai)

1. Non-clinical ICH-S6(Non-clinical evaluation of biotechnology product)

- David Hutto, Eisai



- Non-clinical safety assessment for new therapeutics is to evaluate and identify potential human safety issues through non-human testing in vitro/ex vivo systems(cell and molecular based) or in vivo animal toxicology and pharmacology studies. In vivo animal studies predominate and non-clinical studies precede human studies. One month human study is preceded by one month animal toxicity studies. Animal testing is performed in rodents and non-rodents. Like every drug with related effects, focuses are on understanding the relationship among safety observations, toxicities, drug exposure, Cmax or AUC.
- Objectives are the same for small molecules and biotherapeutics, including identification of 'safe use conditions', target organs of toxicity and characterization of those toxicities, starting doses and dose escalation rationale, clinically translatable means of monitoring identified toxicities(in human subjects or patients). However the specific safety concerns and the way the data is generated and interpreted can be different between small molecules and biotherapeutics.
- After many decades of experience, importance of the following in the safety evaluation of small molecules was acknowledged;
 - Toxicity of parent drug and metabolites
 - Potential DNA interaction leading to genotoxicity and carcinogenicity
 - Off target toxicity
 - Chemotoxicity, effects on metabolizing enzymes
 - Effects on ion channels(hERG)

- Comprehensive and standardized non-clinical safety testing programs have evolved over the years to address these potential safety issues for all small molecules. Many of the aforementioned concerns for the safety of small molecules are not relevant to biotherapeutics. The pharmacology of the biotherapeutic determines the toxicity profile and the required safety assessment design. Therefore, there is need for a 'case-by-case' approach, not a standardized approach. Each safety assessment package determined by the pharmacology will drive the toxicity profile.
- There are guidelines for biotherapeutics safety from ICH(S6, S9, M3) and WHO(draft).
- Small molecules require safety assessment based on both rodent(mouse or rat) and non-rodent(dog or nonhuman primate) for general toxicity studies. Biotherapeutics 'pharmacological relevance' is used to justify species for safety assessment.
- As for genotoxicity assessment, small molecule focuses on in silico structural alerts and bacterial and mammalian cell mutagenicity and clastogenicity assays. However biotherapeutics(proteins, mAbs) do not cross biologic membranes or interact with DNA so these assays are not relevant. These considerations require a 'case-by-case' approach to the design and execution of non-clinical safety assessment studies for biotherapeutics.

2. The Importance of Immunogenicity Assessment of Therapeutic Proteins

- Shalini Gupta, Amgen Inc.



- Assessment program which allows regulators, physicians, and patients to understand the immunogenicity of therapeutic proteins is required.
- Immune response in preclinical studies is not generally predictive of a clinical outcome. Several analytical procedures are available, but none are perfect. Early antibodies are often difficult to detect. Clinical impact of an immune response can vary from "no effect" to complete neutralization of an endogenous counterpart. There are factors to cause therapeutic proteins to be immunogenic which include sequence or glycosylation differences between therapeutic protein and endogenous protein.

- Clinical trials are needed to effectively assess immunogenicity. Immunogenicity is best determined through controlled clinical trials. Most analytical procedures are not well-suited to detect this type of antibody. Initial immune response is typically IgM, low affinity, and low concentration. T cell help is needed for class switching and affinity maturation that is required for a robust immune response. High affinity mature antibodies of the IgG class are more likely to neutralize effects of therapeutic proteins. These antibodies are more likely to be produced at a higher concentration.
- A biological assay can determine if detected antibodies are capable of neutralizing the biological effect of the drug. Historically, many therapeutic proteins have induced antibody formation and effects which range from minimal to significant. Some of these antibodies are associated with serious adverse effects. Both biopharmaceutical industry and regulatory agencies continue to partner for a better approach to antibody testing.
- Many immune responses have no impact on the patients; however, there is the potential for an immune response to affect the safety and/or the efficacy of a therapeutic protein.
- Understanding the immune response requires a systematic and thorough evaluation of immunogenicity during clinical trials using valid, sensitive analytical procedures.

3. Clinical Data Requirements For registration of Biotherapeutics

- Freddy Faccin, Abbvie

- Like conventional medicines, new biotherapeutics must go through a rigorous approval process to ensure they are effective and safe to use. For any medicine, this process can take many years and cost hundreds of millions of dollars. The research, development, and manufacture of biotherapeutics are far more complex than that for small molecule medicines, requiring much greater effort and expense.
- For novel biotherapeutics, the purpose of the clinical development program is to define such biotherapeutics clinical efficacy or benefit, as well as its safety profile



(including immunogenicity). A new set of efficacy and particularly safety issues has been generated by these particular biotechnologies, from evolving processes used in manufacture, process related impurities and the complex structural and biological properties. All clinical trials should be conducted under GCP principles described in the WHO, ICH and/or other pertinent guidelines.

- The ultimate goal of phase I study is to obtain adequate PK data and also assess product's safety for the first time in human subjects to permit the design of valid phase II study. Safety of clinical study participants calls for the paramount consideration in proceeding to FIH studies. Clinical trials should be closely monitored and (generally) conducted with small numbers of healthy volunteers, as dictated by accepted statistical methods. Besides PK, these studies should also be designed to detect common AEs, the tolerated dose range and the potential drug effect.
- FIH safety data are essential components of a CDP. This cannot currently be predicted from analytical or/and animal studies. Initial safety and tolerability studies should preferably be randomized placebo-controlled studies. Drug doses usually start at low levels; study participants are closely monitored as the dose is escalated.
- Phase II data commonly provide the first test of efficacy and safety in patients with the targeted disease. It is designed to determine correct dosage and route(s) of administration, identify common short-term side effects and define the best regimen to be used in phase III.
- Phase III is designed to evaluate the benefit-risk profile of a biotherapeutics in a carefully selected patient population with the disease, confirm efficacy at the chosen dose(s), dosing regimen(s) and route(s) of administration further evaluate safety and monitor side effects and compare the candidate product to commonly used treatments, if any.
- For biosimilar candidates, the purpose of the clinical program is to demonstrate (high) similarity to the reference product, not to show clinical efficacy or benefit per se. The number and extent of clinical studies required to assure any differences in structure do not adversely affect patients depending on extent of residual uncertainty about biosimilarity, and also on the nature of the product.

- The target population of a particular indication should represent a clinical test system that is known to be sensitive enough to detect potential clinically meaningful differences between the biosimilar candidate and the reference biologic.
- Clinical safety and efficacy assessment of any biotherapeutic product is dictated by its complex structural and biological properties, from its manufacturing process through its clinical use. It is critical to characterize as much biotherapeutic's efficacy and safety(including immunogenicity) from high-quality evidence emerging from a step-wise clinical development program as possible. There is no "one size fits all" approach for the development and consequent evaluation and approval of biotherapeutics. For biosimilar candidates, clinical studies should be appropriately designed and sufficient in size and duration and performed in the most sensitive disease condition(and patient population, if pertinent) to detect potential clinically meaningful differences between the biosimilar and the reference product.

» Panel Discussion: Q&A and Roundtable Discussion

1. **Q:** Is it fair to say that biotherapeutics generally have a more favorable safety profile compared to small molecules?

A: Generally true. At least, it is believed that monoclonal antibodies have no safety issues at all. For small molecules, there are multiple potential mechanisms of toxicity. However there are limits with expression of toxicity for biotherapeutics.
(David Hutto)

2. **Q:** Why oncology was excluded in the biotherapeutics testing requirements?

A: The answer is stipulated in the ICH 9 guidance. First reason is the duration of toxicity testing which is the longest required general toxicity study. The second reason is reproducibility of toxicity which is requirement for cancer drugs. However, it does not extend the time period. Expression after birth, therefore, is not considered as requirements. ICH 9 deals with uncommon indication, so related bar can be lowered.(David Hutto)

3. Q: What are the most important factors that need to be considered for the most important assay for immunogenicity testing?

A: An assay is required for detecting binding antibodies which demands sensitive, specific, reliable, binding ADA(anti-drug antibody) assay. There are a lot of choices, even for the binding antibody assays. The Biacore appears to be a better choice for smaller proteins like peptide based products, or growth factor type products. The Biacore is good at detecting low affinity antibodies, which could have a pretty important impact on patient safety. For high risk products, the guidelines from the FDA or the EMA recommend the use of cell based assays, because they reflect the mechanisms of action of the drug in vivo the best. For monoclonal antibody type drugs, which act solely by blocking a soluble ligand, non cell based NAb assays could be used. However, the drug is binding to a membrane bound target, one should carefully consider, whether a cell based or a non cell based assay would be viable. There is a lot of criteria that could be used for selecting an assay. An immunogenicity assay should be sensitive, specific and reliable.(Shalini Gupta)

4. Q: What criteria do you use for a repetition?

A: Biacore is a very complex platform, and assay variability or assay precision is an important point. If any lab or if any analyst is facing that, it appears to be more of a practice issue. Therefore recommendation for them would be to work closely with the Biacore scientists to learn the technology well enough to perform trouble shooting independently.(Shalini Gupta)

5. Q: What is the biggest stumbling block to enhance cooperation in APEC?

A: It depends on economies. What is really important is continuous interaction, early interaction between the sponsor and the regulatory agency. Continuous interaction to validate the clinical development program pursued by the sponsor is also important. Clinical trial references are very finely reflected, at least in the draft stage of the WHO guidance on registration of biotherapeutics. For biosimilars, there is room for growth, of course. For regulation, like in Latin America, Europe, and Asia, there might be a little divergence in certain aspects.(Freddy Faccin)

6. Q: How to handle some of the local clinical data requirements?

A: The situation for every country is slightly different. There are economies like China that require very specific local clinical trials. The same goes for Japan. Local approaches will depend especially upon ethnic differences. (Freddy Faccin)

» Session 4: CMC Considerations – Manufacturing and Quality

(Coordinator: Wassim Nashabeh(Genentech), Chair: Chung Keel Lee(MFDS),
Co-Chair: Wassim Nashabeh(Genentech))

1. ICH Guidelines for Biologics(Q5A to E, Q6B)

- Kowid Ho, Roche



- ICH Q5D provides guidance on the information for market applications with regards to the cell substrate of biotechnological/ biological products as well as preparation and characterization of cell banks.
- Since living organisms can mutate, Q5B focuses on how to control the genetic stability of cell substrates.
- Q5A addresses viral safety in three complementary approaches. First, cell lines and raw materials must be appropriately controlled. Second, test of intermediates at appropriate stage is required. Third, which is very critical, is to have appropriate evaluation of the process capacity to clear infectious viruses.
- In Q6B, specifications are chosen to confirm the quality of the drug substance, drug product or materials at other stages, rather than to establish full characterization. Specifications also should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product. Characterization includes the determination of physicochemical properties, biological activity, immunochemical properties, purity and impurities to allow relevant tests in the specifications to be established. Acceptance criteria should be established and justified based on data from lots used for demonstration of manufacturing consistency, relevant development data, data from stability studies, and data

obtained from lots used in preclinical and/or clinical studies. The assessment of specification could follow a three step approach: 1) identification of relevant Quality Attributes(QA), 2) selection and justification of QA to be included in the specification and 3) setting of acceptance criteria and their justification.

- Q5C addresses the stability for biologics. EMA provides additional complementary guidances on stability for example declaration of storage conditions, in-use stability testing, and maximum shelf-life for sterile products after first opening or following reconstitution. Stability data obtained with batches representative of the final process and justifying the claimed storage conditions are usually requested for the initial MAA. Commitment to place the first three batches is accepted only if the company is able to justify that data covering the claimed storage is representative of the final process. Complete drug product stability produced with final drug substance are usually not available at the time of marketing authorization application, therefore six months data on three batches are usually requested, with the commitment to continue monitoring the post-approval stability, and to report any deviation.
- Q5E is to ensure that pre- and post-change drug product are comparable in terms of quality, safety, and efficacy after manufacturing process change. Demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change products are identical but highly similar, and to ensure that differences in quality attributes(if detected) have no adverse impact upon safety or efficacy of the drug product. In the EU, process changes are categorized in three types: type IA("do and tell"; immediate notification or within 12 months), type IB("tell and do"; approved if no negative opinion received within 30 days), or type II(explicit approval within 60 days, possibility of extension up to 90 days). In practice, the process changes are assessed based on comparability exercise(does the change have any impact on the quality of the product?), process understanding (impact on consistency?), and stability(impact on stability?). Depending on the change, the potential impact, and the difference observe, stability data request to monitor batches through stability program and to provide at least 6 months data on three batches by the end of the procedure. In exceptional cases, complete shelf life could be reconsidered.

2. Review of Recent ICH Quality Guideline focused on Enhanced Process/Product Understanding(ICH Q8-11)

- Mats Welin, Medical Products Agency



- Topics addressed include new paradigm in CMC(Quality by Design). Important considerations include pharmaceutical development(Q8), quality risk management(Q9) pharmaceutical quality system(Q10), development and manufacturing of APIs(Q11).
- It aims to develop a harmonized pharmaceutical quality system applicable across the life-cycle of the product emphasizing an integrated approach to quality risk management and science.
- Basic elements of pharmaceutical development for all products are defining Quality Target Product Profile, identifying critical quality attributes of the drug product, determining(critical) quality attributes of the starting materials(drug substance, excipients), selecting an appropriate manufacturing process and identifying a control strategy.
- An enhanced, quality by design approach to product development would additionally include a systematic evaluation, understanding and refining of the formulation and manufacturing process,
- Depending on the level of development(scientific understanding) achieved and a robust quality system in place, opportunities exist to consider more flexible regulatory approaches. The main driver of pharmaceutical development may be a better understanding of the process and higher predictability of the outcome.
- Q11 Development and Manufacturing of APIs are the same concepts and principles as described in pharmaceutical development(Q8) valid for the active substance and describe how to apply on DS. Influence on CPP and CQA must be controlled and monitored.
- Transparency and clear definition must be ensured in the classification of criticality. Also non-critical factors should not be neglected and their classification should be justified. The criticality of a parameter is linked to the risk of the parameter's effect on a CQA, requiring strategic approaches. If successfully controlled, they should not be treated as risks, becoming quality management.

- CQA monitoring can be affected by scale of manufacturing process, calling for real-time monitoring for not only manufactured goods but also process.
- The new Paradigm to Quality is based on a sound combination of science, use of risk management tools and the establishment of a robust Quality System. It adds nothing new compared to current requirements. However, QbD leads to more structured development, more scientific understanding on interaction of different process parameters and influence on quality attributes, more use of chemometrics, PAT tools etc.
- It is up to the manufacturer to decide on an appropriate development strategy. The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant (strategic decision of a company).

3. Feasibility of Application of ICH Q8-11 to Biotherapeutic Products

- Lynne Krummen, Roche Pharmaceuticals



- QbD Approach to Control Strategy Design goes through questions like "What attributes are important", "What levels", "Does the process control the CQAs within those levels? Are they stable", "What needs to be tested", "Do we have a robust process and testing strategy". A physical, chemical or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. Potential impact on safety, immunogenicity, PK or potency must be assessed. Criticality analysis is basis for justification and for acceptable ranges. CQAs cannot be deemed less critical due to process control.
- CQAs identify CQAs for the product and determine relevant levels for each CQA at each step. Not properly managed and critical characteristics are specially managed. According to ICH Q9, for proper quality management, regulatory requirements should be met. Risk assessment tools should be approved by quality system. Risk assessment to supplement BLA/NDA has to meet GSP.

- QbD dossier contains all traditional NDA/BLA information. It also contains several enhancements; description of Critical Quality Attributes and justification of acceptance criteria based on impact to safety and efficacy as well as manufacturing history, description of design and summary of multi-variate unit operation characterization and unit operation linkage studies and impacts of process variability on all relevant CQAs, justification for process parameter ranges and identification of CPPs based on potential impact to product Quality, justification of Control System Testing & Specifications based on potential impact of the attribute to patient impact and ability of the process to control.
- Risk-Based life-cycle management is a key component of continuous verification. Process knowledge and understanding will grow throughout the commercial lifetime. It is unrealistic to believe that all risks will be known mitigated at the time of licensure. QbD principles offer an opportunity to be transparent about knowledge and uncertainty and how it will be managed.
- The Post Approval Life-cycle Management Plan(PALM) is supported by process/product monitoring.
- Roche submitted marketing applications in most regions. Proposals for Perjeta contained suggested design space only on ICH regions. Gazyva had design space proposal in all of the global filings. QbD, based proposals related to control system design and process parameter ranges, were approved globally with some modifications.
- Health Authorities have encouraged further fine-tuning of the concept to support additional submissions. Pre-submission discussion of CQAs with Health Authorities to facilitate strong Control System and Design Space proposals should be enhanced. PALM has to be clarified and simplified. Illustrations of how parameter criticality and process control "links" to control system to aid reviewer assessments have to be improved.

4. Life Cycle Management for Biotherapeutics: The Complex World of Post Approval Changes

- Richard Lit, Amgen



- Changes in the Chemistry Manufacturing and Controls(CMC) for Biotechnology products(also known as rDNA products, or biologics) are common throughout development and commercialization of marketed therapeutic products. For products that are developed and marketed globally, managing the regulatory approval and notifications requirements of over 100 different economies is complicated, unpredictable and very lengthy. The presentation highlights issues and discusses opportunities for simplification and harmonization of the process of implementing and gaining global approval for post approval changes.
- All changes are not equal. Changes can range from simple to complex changes like new cell line. ICH Q5E gives good guidance on the type of analysis need for these types of changes based on the potential to impact that product.
- Businesses make manufacturing and analytical changes because of commercial process and facility and scale, new manufacturing technology, new testing methodology, regulatory agency requirements. Also it is to learn more about product and process. At times it is to prevent drugs from shortages.
- Different regulators assess the potential impact or the reporting responsibility differently. This can be quite a problem for a manufacture with a single manufacturing site.
- One of hottest topics in the U.S. and Europe is shortage of drugs. Pharmaceuticals and regulators must ensure that important medicines are available to patients. It is critical company management has a commitment to both quality and supply. Relying on robust quality systems can ensure that appropriate actions and reactions occur when changes are needed or desired and that regulators are notified and can approve where necessary.
- In economies with strict regulations, even simple modification of manufacturing processes can be delayed. This can have negative impact on patients. Different economies also have different requirements like the requirements to analyze each and every SKU when proposing a new manufacturing facility. Additionally, having to wait for CPP from first country approvals and then have additional requirements

and lengthy review times, can cause burdens for some companies. One-size-fits all solution cannot be used; making this is very complicated issues.

- A case study was presented for a change in manufacturing site. In 2006, the program was established to address problems, as a result of efforts from many economies. However, it took six years for harmonization among about 100 countries. This calls for stronger actions toward harmonization and recognition. At the moment, even multinationals have difficulties to enter foreign markets without collaboration with local markets. Also there are linguistic barriers.
- All in all, when companies make changes, regulators tend to approve changes. However, sometimes modifications are not approved quickly enough leading to increased complexity, costs and potential for drug shortages. Hence calling for policy changes.

5. GMP Highlights in Biopharmaceuticals

- Chung-Keel Lee, Ministry of Food and Drug Safety



- Bio therapeutic products should be manufactured in compliance with good manufacturing practice(GMP). The major components consist of 4 'M's : Men, Materials, Machinery & Methods. "Men" is about personnel items related to personal hygiene, organizations, duties, qualification, required training, record of training, training programs, name of instructors and evaluation.
- "Machinery" is about proper management, cleaning, building design, manufacturing facilities and tools to prevent cross-contamination. Ventilation and filtering system should be tested. Quality of water should be managed as well. If necessary, pre-treatment and quality have to be controled. Velocity, tense, air flow and particles have to be controled.
- "Materials" are about quality confirmation, name of materials, QC sampling. Cell banking and trust towards sellers must be built.
- "Methods" includes manufacturing, quality control, validation and document control. The philosophy of GMP compliance has been changed since 2002 to risk-based approach and quality systems approach. The new way of the approach enhances significant improvements in manufacturing and reduces regulatory burden for producers and provides solid scientific basis in evaluating the quality of products to regulatory agencies.

» Panel Discussion: Q&A and Roundtable Discussion

- There are differences on regulations for medical products in APEC. Therefore it is very critical to continue to have opportunities to share information and experience. Collaboration among regulators should be highlighted and survey on ICH guideline implementation level of each country would be helpful. Chances to have dialogue and training among regulators are critical for further development of biotherapeutics.
 - This workshop is very meaningful as it raises understanding of differences in biotherapeutic regulations of each country. This kind of opportunities should be encouraged to narrow the gap.
 - It was believed that ethical factors do not apply to biosimilar because originators do not show ethical sensitivity with global market application.
 - Experts believe that extrapolation with different regions is possible for biosimilars.
 - The role of QbD was highlighted because it enables decision-making based on risks for biosimilar.
 - Safety and pharmacovigilance must be part of biosimilar manufacturing because they are critical to secure safety of patients in the long term. All related personnel should explore current tools and database for improvement which are for all new drugs and biosimilars.
1. **Q:** Is it common that the industry applies stability extrapolation in IND for phase I or/and phase II?
- A:** In the EU, it is not about extrapolation but extension of shelf life. There is a protocol that is agreed on, and then from there on you can actually extend following the same rules after approval of clinical trials.(Kowid Ho)
2. **Q:** Is it different from post approval commitment?
- A:** The term post approval commitment can mean different things in different regions, but it is a binding commitment. Reviewers can come and look at our change in management records and see that we lived up to that agreement. (Krumman)

3. Q: What is concept of design space?

A: This is how things will be handled for changes. It is the combination of these parameters, with these input attributes and so forth which will lead to output, and be assessed. It is not much different from how normal process validation is seen to support a certain claims today.(Welin)

4. Q: What is the definition of QAR?

A: The term, design space, is a regulatory term. It is all the non-critical process parameters, all the critical ones, and the unit operations, are equivalent to the design space. With approval, you can treat according to ICH Q8, which means a change within that confine is not a change for regulatory purposes.(Krumman)

5. Q: Is it possible to follow the metricizing method for three lots?

A: The metricizing approach is always possible, albeit not worth all the time. Extreme cases should be concerned which are the most sensitive and worst cases. Other samples should be tested as well.(Kowid Ho)

6. Q: What are the responses to post-approval variations from each country in dealing with life-cycle management?

A: Differences between economies will be reduced with progress in harmonization. There are guidance for regulation from international organizations which can be referred for further harmonization. Regulations show high similarities(about 90 percent). Differences have their root from the objective of regulations.(Lit)

7. Q: Are there any plans to deal with differences between small molecules and biotherapeutics when applying guidance?

A: Safety issues should be concerned based on specific approaches.(Ivana)

8. Q: Is there any plan to develop ICH Guideline for biosimilars?

A: Biosimilar is not in the priority list. QbD should be limited because it is already too broad. In certain extent, it contains biologics.(Welin)

» Plenary Lecture: New Upcoming Biotherapeutics Technology

» Summary of High-level overview of new innovative technologies in biotherapeutics

- James Merson, Pfizer



- Costs to manage chronic diseases are growing exponentially. CVD incidence between 1990 and 2020 is projected to double with 80% of this increase found in developing countries. Options to ensure efficacious, safe and cost-effective healthcare are limited. Therapeutic vaccines may provide a cost effective means for chronic diseases.
- Vaccines are used to improve immunity to prevent disease. Vaccines are no longer simply prophylactic, providing long-term persistence of immunity. Therapeutic vaccines provide an opportunity to direct specific immune responses for therapeutic applications.
- Some 90 percent of lung cancer in the U.S. is attributable to smoking. An anti-nicotine vaccine has a unique mechanism of action for treatment of smoking cessation. When one smokes, nicotine passes through lungs into blood, is taken up in the brain where binds the acetylcholinergic receptors and activates the dopamine pathway that gives the smokers the sensation of pleasure.
- Non-clinical evidence to support MOA: Reduced nicotine in brains of prophylactically or therapeutically vaccinated animals has been reported.
- Clinical evidence to support MOA: Nabi(NicVax) and Cytos(NicQb) provide proof of mechanism in phase II studies where subjects with the highest antibody had enhanced quit rates compared to controls(odds ratio 2:1).
- NIC7 was developed by using functional assays. Both antibody quantity(titer) and antibody quality(avidity) were used to select vaccine.
- Nic7 is a bioconjugate vaccine. As a basic conjugate vaccine structure, it includes a hapten, a linker, a carrier protein and an adjuvant. NIC7(with adjuvant CpG) had better results compared with NicQb. A study is underway to assess the safety and tolerability of different doses of PF-05402536 and PF-06413367 in healthy adult smokers.

- Currently, about 300 million suffer from asthma and the number is expected to rise to 400 million by 2025. A therapeutic vaccine offers the potential to improve existing treatment by providing superior efficacy and safety over oral steroids for mild and non-steroid treatment to severe patients.
- Pfizer is developing a therapeutic vaccine that induces anti-IgE antibodies that bind circulating IgE and block allergic asthma exacerbations. Two IgE peptides were selected for conjugation to a carrier protein that when used as a vaccine to induce anti-IgE antibodies, these antibodies bind specifically to human IgE, preventing it from binding to effector cells such as basophils and mast cells. The magnitude of efficacy of the vaccine in a mouse model broadly aligned with the IgE lowering achievements of Xolair in patients (e.g. 500ng/ml reduces to <50ng/ml for efficacy). Vaccination decreased IgE levels in the "therapeutic" setting.
- ADC development is a complex undertaking, evolving from empiricism to defined parameters for clinical success. Pfizer Oncology is building an extensive ADC toolbox encompassing all ADC components, cell cycle- dependent and independent MOAs. Therapeutic index is a key driver for ADC advancement. Patient selection is critical to support focused, decisive clinical studies.

» Panel Discussion

(Moderator: Teruhide Yamaguchi(PMDA), Panelists: Invited Participants)

Q: What distinguishes cancer vaccine?

A: Cancer vaccines utilize the adaptive immune response for generating immune responses against tumor antigens. As tumor antigens are 'self' proteins, the immune response has to overcome T-cell tolerance to these proteins. From the perspective of regulators, given the status of cancer patients, the balance of risk benefit for generating an immune response against self proteins is justified as the therapy has the potential for high complete and durable responses and they encourage early interactions to review safety and clinical study plans. If the vaccine based therapy is shown to be safe, then it could be envisaged that it could be used not only for treatment but more similar to prevention in early stage disease.

Q: Regulators are more informed about emerging biotherapeutics than those in the industry. Evaluations are made within regulatory frameworks. There are limitations for new technology. Therefore, new regulatory framework is required to deal with new productions. Various departments of MFDS deal with preventive measures and treatments. There is a question to define these materials only as vaccines. Vaccines may have immune reaction but it has to be defined whether it is right to refer to them as "therapeutic vaccine".

A: Clinical and CMC controlled reviews should be viewed differently for prophylactic and therapeutic vaccines. From a CMC perspective, they should be considered as the same as they are biological antigens designed to induce an immune response to the antigen. Therapeutic vaccines should be viewed clinically differently from prophylactic vaccines as they are designed to raise an immune response to a 'self' antigen and this poses an autoimmune risk that is not present for prophylactic vaccines that are made from foreign antigens. From the regulators' perspective, this does pose the need for different considerations when evaluating the risk benefit of treating patients versus preventing disease in healthy subjects. Traditional vaccines are managed by Q16 and Q11. Manufacturing process and implementation of guidance are now on the discussion agenda. However, the scope of implementation is the most critical part, calling for further talks. After consultation with Pfizer, Health Canada conducted research on the risk benefits of conducting clinical trials in patients, which was a good opportunity to understand circulating biomarkers. Still, there is a long way to go with further requirements for system development. Preventive vaccines are well understood. Yet, therapeutic vaccines have not been used in patients enough to determine whether a different set of guidelines are needed.

Q: What is the difference between therapeutic vaccines and monoclonal antibody vaccines?

A: Therapeutic vaccine have relatively long clinical trials, and are evaluated in patients as the elicited immune response, antibody or T cells, has a relatively long half life compared to passively administered monoclonal antibodies. Progress of the immune response has been monitored six months after the last injection to determine the half life of the induced immune response. It has been paid attention to validate the safety of raising immune responses that recognize self proteins. Vaccines enticing

therapeutic antibody should be observed both at the immune response level and the effect on the targeted protein.

Q: Are there big regulatory gaps? What is the level of harmonization?

A: Harmonization is important for patients as this should expedite approval of new medicines or/and vaccines to those with unmet medical need. Still, clinical data on different products are not sufficient for preventing further reviews of different but similar products. Reviews should not be delayed due to lack of regulatory framework for new products. Pre-meetings can be one of the options to solve that problem. MFDS and pharmaceutical companies can also form a consultative body. Consulting should focus on facilitating reviews.

Q: What is adoption level for ADC?

A: Modification of antibody can lead to completely different results. Therefore activities of antibody should be respected while considering all additional treatment effects. There are two ADCs. Due to toxicity, active discussions are now underway. But there is no clear guidance for them. ADC is relatively new, calling for comprehensive approach.

Q: What is the level of "Risk and Benefit" implementation?

A: Therapeutic vaccines may have high risks as compared with prophylactic vaccines. Therefore they should be evaluated for patients who stand to benefit from them. Traditional vaccines are used for healthy subjects, requiring stricter control.

Q: How risk benefit assessment change shift?

A: Prophylactic vaccines tolerate more risks

» Briefing and Conclusion

- Wassin Nashabeh, Genentech



□ Importance of Terms(Biotherapy, biotherapeutics)

* ICH Implementation

► Session 1-2

- There is broader acceptance of the unique scientific and regulatory aspects of Biotherapeutics that are different from small molecule pharmaceuticals. Regulatory harmonization needs to be accomplished and to that end, pharmaceutical companies and regulatory authorities should discuss it more often. As most agree, WHO and ICH guidelines complement each other and they will likely play an essential role in being the basis for APEC harmonization. It is highly recommended that implementation workshops include training sessions with case studies that can be essential in the practical understanding of the guidelines, and thus can greatly contribute to the success of the roadmap. Documentation regarding CMC, non-clinic, clinic should be well prepared to facilitate the review process. True harmonization will take place only after differences have been taken into consideration. Regarding MRCT, it has to be scientifically reviewed whether or not trials conducted in other economies can be applied, also.
- Harmonization for biosimilars may be facilitated if the biosimilar manufacturers have reference cases in other economies which are currently difficult to achieve due to different rules and regulations. Still, there is room for harmonization between economies.
- There are areas that need harmonization. Among requirements, post-authorization modifications of CMC, deadline, due dates and technical requirements are slightly different, thus higher degree of regulatory harmonization is needed. Discussion on how to address differences in regulations, opinions and practices was held and many ideas(for example, WHO survey baseline) were exchanged, some of which may be introduced on the roadmap as part of an action plan.

- Some issues were not addressed due to a time constraint:
GMP inspection for developing countries, work sharing, development of mechanism were not discussed. They may reduce redundancy in inspection.
- Pharmacopoeia was not addressed but it is an important part of the CMC section roadmap.
- Clinical requirements between economies based on scientific information was updated. There are rules and regulations of respective economies, but this also needs to be discussed.
- Due to complex issues to consider, CTD harmonization needs further research.

► Session 3

- Differences on biopharmaceuticals with chemicals in non-clinical setting were presented, and pharmacological properties need to be taken into consideration in toxicity tests. Importance of approaching each biopharmaceutical product on a case by case basis, and selection model that has considered clinical studies was explained.
- There are specific discussions on biopharmaceutical immunogenicity, and most are said to affect efficacy and safety.
- Clinical requirements need to be designed for all I to III phases of clinical studies, but there may not be much of differences. In the meantime, non-clinical models need to reflect unique characteristics of biopharmaceuticals. In the clinical setting, similarity, rather than assessing efficacy is important in endpoint, and demographic sensitiveness needs to be taken into consideration, where regulatory harmonization needs to take place.

► Session 4

- Biopharmaceuticals and chemicals need different approaches. ICH Q5, Q6b have been the foundation of regulations for a long time, with importance on implementation and interpretation, as fundamental rules will not change. Regarding ICH Q8-11, risks need to be controlled strictly, and proper control study may be an option. Conducting analyses between nations is needed, and Q5, Q6b should be

implemented before adopting Q8-11(some areas should be improved). Due to different rules and regulations of economies, it may take some time. In the last case study presentation, importance of biopharmaceutical life cycle and GMP was emphasized.

»» Additional Comments by Jerry Stewart(Pfizer)

- From the initial stage of development to approval, authorities and pharmaceuticals must communicate.

» Closing Remarks

- **Sun-Hee Lee** of MFDS made closing remarks on behalf of AHC Director Jin-Ho Wang. She expressed her gratitude to all speakers and panelists especially for their hardwork to make a meaningful and informative workshop. Her special thanks also went to Mr. Mike Ward who unfortunately could not attend the event. With introduction of the next workshop in Korea on pharmacovigilance, Dr. Lee closed her remarks.

■ Day 3

» Debrief and Discuss

1. Evaluation of Workshop program

- A longer panel discussion and new ways to encourage participation from audience were recommended.
- Including at least one regulator in a panel discussion was proposed.
- Those who would not participate should also be informed about related issues by promoting pre-meeting communication.
- It would be beneficial if workshop preparation begins earlier.
- Participation of all APEC economies is expected.
- Introduction of RHSC biotherapeutics roadmap before the workshop would encourage more participation and raise understanding.
- Upload workshop information as soon as possible was recommended so participants can share information.

2. WHO Survey

- Conducting surveys is very critical. Therefore, tool to decide baseline, subjects and questionnaire should be developed. Survey initiative of WHO was highly recognized. And proposals were made to change from multiple choice tests to short comments.
- Results will be announced no later than October, which will decide modification of RHSC biotherapeutics roadmap.
- Discussion is required whether to conduct a new survey before the result comes out or not. Workshop reports and survey results will demonstrate differences among economies in APEC.

3. Review of Each Session

- Chair for each session was requested to complete a report (about one page) to submit RHSC. Dr. Romi Singh will collect the reports to circulate a final report within month.

4. Proposals for the RHSC's Future Activities

- Meetings to inform more professional knowledge
 - Topics:
 - Non-clinical (including GLP for safety test) or/and Clinical
 - Manufacturing and quality
 - Post-approval
 - Training period: 3 to 5 days
 - Qualification: Middle manager
- Follow-up meeting needs to be held under the implemented topics.
 - Training period will be decided depending on teamwork.
 - Qualification for those who completed first training
 - Meeting venue or other training institute
- Short-term Consulting by inviting experts
 - Duration: three to five days
- ※ Each trainee will be evaluated after the end of the session.
- In 2014, WHO and AHC will have biotherapeutics workshop together. And there will be other workshops connecting RHSC biopharmaceuticals with MRCT and pharmacovigilance.

» Regulators' Meeting

- All APEC economies must have an effective communication. For that, NRAs are required to create single point contacts to facilitate information sharing and provide feedback through secretariat within time frame. RHSC is working to create an online platform for regular communication among members.

- Roles of AHC and RHSC secretariats should be clearly defined. For example, "Who will be in charge of SPOCs among NRA for communication", "Who will circulate and decide time frame for NRA survey for APEC member economies, or "Who will circulate additional questionnaire for NRA?" should be decided.
- Industry and authorities can have different positions.
- Three differences from the position of regulators.
 - Lack of understanding of scientific principles for clinical trials(both small molecules and biotherapeutics)
 - Implementation of internationally approved scientific principles(Evaluation of all sectors including clinical/non-clinical)
 - Differences on requirements for biotherapeutics regulations in APEC. What are the causes of gaps and how these gaps can be narrowed?
- WHO's survey will be completed within 2013. For that AHC or RHSC secretariats need to support the work.
- Additional survey is required to decide baseline of APEC economies. Voluntary NRAs will finalize the process(Korea, Thailand, Indonesia, Malaysia, Chinese Taipei and Singapore).
- Email will be sent to 11 economies which did not participate this workshop to encourage their attendance for the next workshop.
- 2014 WHO workshop hosted by MFDS will be a good opportunity to survey and review our progress. Regulators participating in the workshop are required to actively engage in preparation.
- Tentative topics are
 - key points for regulatory review of clinical data for biotherapeutics approval (for example, conditions for economies with clinical trials: Local clinical data for ethical differences and reasonable explanation based on science)
 - MRCT for biotherapeutics: Immunogenicity evaluation

The 17th AHC Workshop(Pharmacovigilance)

» Opening Ceremony

▣ Opening and Welcoming Remarks

- **Jin-Ho Wang**(AHC) welcomed experts, speakers and participants and extended gratitude to organizers. He briefly introduced the process of AHC's establishment and AHC's activities. He noted safety issues of medical products and increasing importance of pharmacovigilance(PV). He believed that the workshop would help economies to have more interest in pharmacovigilance systems and seek regulatory harmonization.

▣ Congratulatory Remarks 1

- **Byung-Won Jang**(MFDS) also expressed gratitude to all guests to the workshop. He expressed his expectation for stronger international competitiveness of industries through international cooperation in pharmacovigilance. He thought that pharmacovigilance is significant to provide safe medicines to customers. He hoped that the workshop is going to be an opportunity to share experience and knowledge on the topic.

▣ Congratulatory Remarks 2

- **Kyeong-Ho Lee**(KPMA) gave a congratulatory remarks at the workshop. He noted eight RHSC's roadmaps and pharmacovigilance as one of roadmaps. He pointed out that public health has become a huge issue as people are getting exposed to dangers and risks caused by unlawful and undetected medicines and medical products. He hoped to learn emerging knowledge, share experiences on pharmacovigilance.

Keynote Speech: Driving Pharmacovigilance Success

- Moo-Young Yoo, Pharmaceutical Safety Bureau, Ministry of Food and Drug Safety

- As the market of medical products is growing, the population who depend on many different medical products is increasing, leading to bringing unexpected adverse drug reaction(ADR).
- Safety information suggested in the drug approval is very limited and there could be many differences in using drugs in reality. The benefit-risk balance would be changed according to post-marketing evaluation. Therefore, post-marketing evaluation on safety and efficacy (pharmacovigilance) is essential.
- Safety management through PV is considered as an important national policy.
- Approval management should be extended to the whole period of time from R&D to post-marketing study.
- Customized drug development for each patient is increasing. Therefore development and use of new strategies can bring about early detection of risk factors.
- Global trends are to evaluate not only safety but also benefits and such changes are adjusted to global guidelines.
- In Korea, regular report on ADR of new drugs after post-marketing evaluation is mandatory. Such information can be reported through 22 medical product safety centers across the country.
- In Korea, safety related cases and breaking news are offered to doctors and pharmacists through electronic DUR system in real time.
- The workshop would help us to enhance PV of each APEC member country and promote regulatory harmonization in PV.

» Session 1: Harmonization Efforts on Pharmacovigilance

(Co-Chairs: Byung-Joo Park(KIDS), Wimon Suwankesawong(TFDA))

1. APEC Efforts on Pharmacovigilance and Overview of Pharmacovigilance Roadmap

- Jong-Pill Park, Ministry of Food and Drug Safety



- Pharmacovigilance roadmap was presented twice in March and August 2012. The suggested PV roadmap has differences from WHO UMC's PV training course. Medical devices were excluded from the roadmap. Last July Pharmacovigilance roadmap 2020 version 3 was recommended at the APEC SOM III RHSC in Medan.
- The goal of the roadmap is to protect and promote health of the public through pharmacovigilance and streamlined inter-country mutual approval process of member economies.
- We need to improve understanding on current status of PV in each country through questionnaires. Also, reviewing on PV guidelines used globally is necessary as well.
- In addition, collecting and analyzing safety information, developing and providing PV training programs and workshops are critical ways for better PV.
- The steps of pharmacovigilance roadmap are: step 1, overall evaluation (2012-2015), step 2, training program (workshop) (2014-2017) step 3, evaluation of training program (2016-2017) step 4, collecting regulations and recommendation(2017-2020)

2. APEC Efforts on Pharmacovigilance and Overview of Pharmacovigilance Road map

- Shanthi Narayan Pal, World Health Organization



- World Health Assembly Resolution 16.36 was released to invite member states to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use.

- Regardless of economic powers of economies, challenges are the same from the survey of PV systems result. Challenges include lack of political support, resources, competence, PV systems or proper functions, communication and information exchange.
- There are as many as 300 medical products in the pipeline for neglected diseases such as HIV, AIDS, TB and malaria. At least, half of those drugs will be marketed in the coming years with little or no capacity for post approval monitoring.
- Solutions from WHO are: new PV systems, capacity building, technical supports, active surveillance in public health programmes, publishing guidebooks and sharing information
- There are WHO's collaborating centers (UMC, WHO CC Oslo) and some countries (Ghana, Morocco and the Netherlands) work with WHO for PV.
- WHO Advisory Committee on Safety on Medicinal Products (ACSoMP) is composed of 12 members from 6 WHO member countries.
- WHO currently engages in a collaborative project with US FDA on understanding what kind of role pharmacovigilance centers can play in detection and prevention of substandard and falsified medicines.
- The medicines regulatory harmonization is a global concern and it also has been a discussion topic for non-APEC region including Africa.
- economies are also making enormous efforts on counterfeit product issues equipped with rapid detection technology. Reports should be shared among all the community members since these efforts will make best results on how we make sense of the data.

3. ICH Activities on Pharmacovigilance

- Gerald Dal Pan, U.S. Food and Drug Administration



- ICH was created in 1990 in the agreement among the EU, Japan and the US to harmonize technical requirements for registration of pharmaceuticals for human use.
- ICH has Expert Working Groups(EWG) in four main areas. First, safety covers principally non-clinical studies of safety, related to carcinogenicity, genotoxicity and reprotoxicity. Second, efficacy is about many aspects of clinical trial design and reporting as well as pharmacovigilance. Third, quality is related to product quality issues such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice(GMP) risk management. And fourth, multidisciplinary includes cross-cutting topics which do not fit uniquely into one of the other three categories, including the ICH medical terminology(MedDRA), the Common Technical Document(CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI). The ICH Steering Committee oversees and supports EWGs.
- ICH goes through a stepwise process to develop a guideline: step 1, building scientific consensus and developing a draft text, step 2, finalizing the draft text and submitting it for public comment, step 3, review of the comments, and step 4, finalizing the harmonized guideline. A finalized ICH guideline is implemented in each of the ICH regions. Guideline implementation levels are different across ICH regions.
- ICH guidelines related to post-approval drug safety are E2A, E2B/E2BM, E2C and E2C Addendum, E2C, E2D, and E2E.
- Other ICH guidelines specifically related to clinical drug safety are E1A, E2F, E14, E15, M3(R2), M5(the "S"(Safety) series is mainly concerned with non-clinical data). ICH E2A is about expedited reporting safety.

- ICH E2A addresses causality assessment for individual case safety reports, including the "reasonable possibility" standard. FDA published amended safety reporting regulations for investigational new drugs (INDs) on 29 September 2010 and clarified its interpretation of the "reasonable possibility" standard.
- Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.
- ICH E2B is about data elements for transmission of individual case safety reports.
- ICH E2C(R2) elaborates periodic safety update report, Periodic Benefit-Risk Evaluation Report (PBRER). The PBRER is a comprehensive analysis of new or emerging information
- ICH E2D is about definitions and standards for expedited reporting (Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting). ICH E2E tells you about pharmacovigilance planning.

4. Academia's Activities on Pharmacovigilance

- Ian Chi Kei Wong, International Society of Pharmacovigilance

- The International Society of Pharmacovigilance (ISoP) is an international non-profit scientific organization, which aims to foster pharmacovigilance both scientifically and educationally, and enhances all aspects of the safe and proper use of medicines, in all countries.
- ISoP welcomes academics, regulators and representatives from the industry healthcare professionals and patients. ISoP brings together experts from many countries providing a forum for discussion and exchange of information and innovative ideas.
- ISoP works on different academic aspects which include scientific annual conferences, mid-year pharmacovigilance training meetings and development of curriculum of pharmacovigilance to promote training.



- Academia has always played a very important role in PV research, training and education.
- The ISoP held a symposium in Singapore in March 2013 and is going to have ISoP annual meeting in October 2014.

» Session 1 Q&A

Q: When it comes to vaccine safety in Indonesia, we have to fulfill pre-qualification requirements. How about the case of medicines?

A: A pre-qualification process exists also for medicines, and currently for HIV, TB, malaria and some reproductive health medicines as well. It is more about manufactures who would want to manufacture pre-qualified products. So the process exists also for medicines rather than vaccines since there are a lot of private manufacturers for medicines.

Q: There are economies starting PV. It is for them an opportunity to lay the foundation for harmonization. What kind of support WHO is providing to these economies and how could contribute to these WHO action?

A: Every time a new member is brought into the members, they will benefit from our accumulative experience. Therefore, harmonization is not a job for one person, one group, or one country, it has to be collective work, over the years.

Q: What's the big difference of pharmacovigilance regulation between the medical device and medicinal products? And what's the trend for harmonization between those two products groups?

A: A lot of medical device reporting is about medical device failure. We have products that can be characterized as both drugs and devices. We have to determine principal component for regulatory. The device regulations are somewhat different from the drug regulations, especially in the United States.

Q: What about the adverse event from drug eluted stent? Will it be classified in the medicine part or medical device part?

A: The adverse events from drug eluted stent would be reported as devices because they are regulated as devices. And if there's an issue of drug it we can collaborated,

Q: Could you explain more examples of PBRER, or do you have any specific product of PBRER or plan?

A: We are just beginning to get some experience with the PBRER. We've been accepting them since January and we are still working on the best internal practices for review the PBRER. The PBRER is a much more comprehensive document than the PSUR. We are still working on the review procedures. I don't have a specific example for certain product. Our regulations require more than minimum, but a lot of companies are submitting them to us at FDA to fulfill their regulatory requirements because there are preparations for either EU or Japan.

Q: At WHO, we have just gone through some restructuring of our programs. Medicines, vaccines, devices and diagnostics are coming under one category. Therefore, I was I noticed that APEC harmonization is looking to not include devices and possibly not include vaccines. So what is the rationale behind this classification?

A: At pharmacovigilance workshops, we only talked about concerned only medicinal products like human use medicine, but now the AHC is focusing on all medicines and also medical devices. So we are holding the symposium regarding medical devices and vaccines too.

Q: What will be the WHO's plan for collaborating with APEC's PV champion country?

A: We have to have help where closer to the economies. So if there would be economies interested in working with WHO as a collaborating center, we would more than welcoming with an open arms.

» Session 2: Issues and Challenges towards Pharmacovigilance Harmonization

(Co-Chairs: Sun-hee Lee(NIFDS), Antonio Mastroianni(UMC))

1. Global Leadership for the Safer Use of Medicines

- Antonio Mastroianni, WHO Uppsala Monitoring Centre



- It is easy to just collect and store information from different sources. But, analyzing information from different sources is hard, if they are in different structure. Therefore, medical standards such as terminologies and dictionaries are essential.
- Uppsala Monitoring Centre(UMC) was established in 1978. It utilizes ICSRs, WHO Drug Dictionary, WHO-ART and others.
- WHO programs' goal is to identify early signs of previously unknown medicine-related safety problems and information about them.
- Currently, in Vigibase, more than eight million ICSRs are stored. Vigiflow, Vigilyze and Vigibase allow economies to collect, manage, analyse and store ICSR data. UMC provides training and education to build capacity within WHO Programme with the aim to improve patients' health.
- The UMC Value Chain focuses on converting data to wisdom to support improved practice of health care professionals for informed and wise therapeutic decisions that increase patient safety.
- UMC Signal process consists of a selection strategy using a measure of disproportionality between the observed and the expected reporting of a drug-ADR combination and other statistics, which decrease the number of drug-ADR combinations to assess and increase the likelihood of finding to become the most important signals. UMC staff checks Drug-ADR combinations, filtered out by the triage algorithms, in available product information and literature. If there is no record of a reaction or it is not documented well enough the individual case reports are retrieved from Vigibase. These ICSRs undergo a thorough clinical assessment of the individual case reports, either internally by UMC staff or externally by members of the UMC Signal Review Panel. This process occurs routinely on data collected from national PV centers stored in WHO Global ICSR Database, Vigibase.

- In short, new technologies in bioscience will still require PV. Personalized medicine will need even more vigilance. Changing conditions in healthcare mean access and safety are equal concerns. Claims and interests of patients and the public will alter the way safety data is distributed and used. Pressure to reduce cost of healthcare will necessitate a focus on effectiveness. Regional or global adoption of harmonized standards and structured data drastically improves patient safety by providing more effective communication, analysis, and improvement in the use of medicines.

2. Results from Pharmacovigilance Questionnaire of APEC RHSC

- Young-Jin Ahn, Ministry of Food and Drug Safety



- PV is the main priority of the regulatory convergence for medical products by 2020 that APEC RHSC is promoting. Korea has become the Champion of PV sector in September 2011.
- The roadmap for harmonization of pharmacovigilance has been approved at the APEC SOM III RHSC meeting in July 2013, thereby establishing the implementation of the roadmap including current PV activity evaluation and training plans of each APEC economy.
- We conducted a survey from 19 to 30 September 2013 in order to identify current status of pharmacovigilance management system, regulatory gaps in 12 APEC member economies. Feedback from nine economies were received from the China, Indonesia, Japan, Malaysia, Peru, Singapore, Chinese Taipei, Thailand and the United States.
- The survey consisted of questions that could identify the status of PV management such annual budgets, organization, activities, guidelines, spontaneous reporting system and risk management system.
- Based on the result of the survey, we are planning to seek the directionality of training and workshops for regulators from APEC economies and to complement and implement the PV roadmap towards convergence.

3-1. Issues and Challenges

1) Regulatory's Perspective - Indonesia

- Siti Asfijah Abdoellah,
National Agency of Drug and Food Control



- PV in Indonesia is now evolving to respond the changes in regulatory environments. Therefore PV activities in Indonesia is clustered into general PV for HCPs, PV for Industry, AEFI Surveillance and PV for other Public Health Program(PHP).
- Principally, PV system is divided into 2, voluntary system by HCPs, and mandatory system by the Industry.
- Strategic measures for each PV activity are managed, to improve and strengthen PV program in Indonesia. It is done by all relevant stakeholders in the country.
- Data management for PV is important and needed to be improved, especially to meet the global demand on PV harmonization.
- In terms of regulatory harmonization or convergence, NADFC has great challenges both from internal and external sides such as legal framework, system, human resources, processes and communication.
- Advanced economies are more likely to be ready to adjust their PV system, more than developing countries, creating gaps. That should be considered in the implementation of harmonization.
- The strategic approaches need to be defined together with ways to achieve regulatory convergence on PV by 2020.
- It is needed to identify areas where harmonization is required.
- All key players in PV program and activities in the economies will contribute to the success of the regulatory harmonization or convergence on PV by 2020.

3-2. Issues and Challenges

1) Regulatory's Perspective - Thailand

- Wimon Suwankesawong, Thai Food and Drug Administration



- After the inception of PV system, the ADRMC was set up under the authority of the FDA to manage the system in 1983.
- A year later, Thailand became the 26th member of the WHO Program for International Drug Monitoring.
- The name of the Center was changed to the Health Product Vigilance Center(HPVC) in 2008, in recognition of broader responsibilities.
- The HPVC is responsible for monitoring the safety of health products in Thailand, primarily medicines, including herbal and traditional medicines, vaccines and biological products.
- The system is actively implemented. Most of the reports are voluntarily collected nationwide directly from health facilities by several methodologies including spontaneous reporting, intensive hospital monitoring and pharmacoepidemiological research. Only conditional approval of new drugs/biological products and imported investigational drugs are obligated to report by marketing authorization holders and/or investigators.
- Thailand has consistently been in the top ten in the WHO Program's list of economies contributing the highest number of reports to the international database.
- Most recently, the national adverse event database, Thai Vigibase, carries around 500,000 reports, collected since 1984. The increasing number of reports has led to the development of Thai automatic signal detection tool and AE online reporting system.
- Over the years, the system has significantly contributed to the public safety by detecting signals and in a series of regulatory actions to minimize risks.
- Safety issues are disseminated throughout the country by the HPVC as regular information, but sometimes as urgent news.

3-3. Issues and Challenges

1) Current status of Pharmacovigilance and Risk Control in China

- Li Zhang, China Food Drug Administration



- Pharmacovigilance and risk management are playing increasing role in the areas of public health.
- To integrate international medical and ensure safe medication for the patients of the world, it is very significant to establish an internationally standardized procedure to share the experience of post marketing drug surveillance and safety information.
- China's had developed PV system and post marketing surveillance in China has grown rapidly with remarkable achievements.
- A key safety monitoring system strengthens drug safety monitoring and research on new drugs and strong signals.
- China started online ADR reporting in 2004. Network System was put into trial practice in August 2011.
- China's practices of risk management in 2012 include bulletin press release, PV newsletter, revision of the prescribing information/package leaflet, risk communication with manufacturers, restriction on marketing and use, suspension and withdrawal from the market.
- For the better PV system in China, we work to strengthen education, training, and publicity and the roles of pharmaceutical manufacturers as the main body of post-marketing surveillance and risk management. Also, we will integrate recourses, establish drug safety surveillance and investigate the platform of research in APEC and beyond.

3-4. Issues and Challenges

2) Industry's Perspective

- Jean Christophe Delumeau, Bayer



- Efforts have been made for the harmonization of safety reporting requirements and PV systems. Noticeable progresses are being made in some non-ICH Asian countries. However, the current status of harmonization remains sub-optimal from the point of view of the healthcare industry.
- While moving toward harmonization is welcomed by the industry, it may also be beneficial to public health in general, and to patients in each individual country.
- Interested in such a move, the healthcare industry, especially the multinational companies(MNCs), may be keen to support initiatives aiming at widening the harmonization to non-ICH parties.
- Consistently, MNCs would welcome that individual case safety reports(ICSRs), submitted electronically in its standard international E2B format in English.
- MNC's also hopes to see that Health Authorities of non-ICH parties accept to receive 1) periodic benefit risk evaluation reports(PBRER) in their original English version, based upon the product's international birth date 2) risk management documents according to the formats requested by ICH Health Authorities. However the Country-specific aspects may be submitted additionally.
- Harmonizing the current heterogeneity of ICSR submission requirements would simplify ICSR submission process at the industry level. Most importantly, that would improve the global consistency of the safety information forwarded to the WHO safety database.

3-5. Issues and Challenges

3) Academia's Perspective

- Nam-Kyong Choi,
Seoul National University College of Medicine



- The author Jerry Avorn, a professor of Harvard University college medicine, told that the history of medicine is largely the story of medicines, a counting tale of unfolding risks and benefits.
- Brian Strom described that the history of drug regulation in the United States is largely a history of political responses to epidemic of adverse drug reactions.
- The major public interest in the drug safety surveillance surged after the international problems like the thalidomide disasters. So the development of pharmacovigilance emerged without an everlasting strategic plan for government, academia or industry.
- The U.S government was the first to transfer the pharmacovigilance system and develop the sentinel system with an incredible amount of a budget in human resources. They are collecting a healthcare database for surveillance of drug safety involving more than 100 million people.
- Last year new pharmacovigilance legislation came into effect across the European Union. The new legislation strengthens the system for monitoring the safety of medicines. One of the main pillars of new legislation is establishment of a new drug science committee. The committee members will include experts in pharmacovigilance and risk assessment.
- In 2008, the appointment of a qualified person for the pharmacovigilance in pharmaceutical company has become a mandate. In 2012, the Korea Institute of Drug Safety was established. In 2013, the Korea Food and Drug Administration was restructured and elevated to Ministry of Food and Drug Safety. Those changes demonstrate increasing demands for the trained and highly qualified workers for pharmacovigilance.

- Now, all the regulatory agencies, pharmaceutical industries, and academic institutions monitor and evaluate pharmaceutical risks and benefits. Especially academia has unusual independence and autonomy in the generation of fundamental new knowledge to advance scientific understanding and public health.
- The academic programs play pivotal roles in drug safety by promoting education, research, and public service.
- Until now several training programs have been developed. However, these programs are not available for all of the students who are related to drug use. In the United States and Canada, all of the medical school students are educated in safe and effective prescribing practices focusing on medication errors, ADRs and drug interactions. In Japan, some of the graduate school of medicine in public health has department of pharmacoepidemiology.
- In Korea, the new six year education program in pharmacy has taken effect since 2011. The recent published text book of administrative and managerial pharmacy includes pharmacoepidemiology and pharmacovigilance. They are to assess the current plan and the pharmacovigilance activities in low and middle income countries and identify gaps in the most urgent pharmacovigilance priorities.
- In order to meet the recent needs of society, academic institutions should be committed to maintaining a pipeline of qualified practitioners, experts, and leaders in the field of pharmacovigilance.
- This is the time to perform a comprehensive assessment of current educational status of pharmacovigilance in academia among the APEC economies. Secondly, a core content of pharmacovigilance profession should be specified. Thirdly, the academia may have an educational task of training clinicians in pharmacy, medical nursing, and dental schools.

» Session 3: Current Status and Gaps of Pharmacovigilance System in APEC Economies

(Co-Chairs: Gerald Dal Pan(US FDA), Siti Abdoellah(NADFC))

Panelist: Cecilia Beltran(Peru FDA)

Donwoong Choi(MFDS, Korea)

Li Zhang(CFDA, China)

Maria Aldunate(Institute of Public Health, Chile)

Ola Strandberg(UMC)

Rokiah Isahak(Ministry of Health, Malaysia)

Wimon Suwankesawong(TFDA, Thailand)

** alphabetical order*

- Panel Discussion: What are the Current Status and Gaps of Pharmacovigilance?

• China

Q: Level of involvement in WHO Monitoring Program?

A: The gap is found in the format for the transmission to the UMC. China is the 68th country to join UMC. But at present the form used in China is not the same as E2B. But I think it's very difficult for us to change the format right now and it needs a deeper communication and cooperation in the future. Also, another reason why China does not frequently send the reports is that it requires us to translate them into English.

Q: Could you explain a little bit more about what the challenges are in making the reports E2B compatible?

A: Because at the beginning of ADR monitoring and report, we used the same form, which is our own form. Our system also received the form from 1999. We should let people know the significance of using the same form. I have another suggestion. As you addressed at your presentation, I know PCR will be replaced with PBRER. But now in China, we just use PCR according to the new regulation. The PBRER is used in our country. China is thinking of using TCM injection pharmacovigilance. We ask companies to submit the PBRER to the government.

● Korea

Q: Level of involvement in WHO Monitoring Program?

A: Korea's National pharmacovigilance system requested by WHO is well established because of analytic capabilities of adverse event reports in KIDS founded in 2012. Institutions adopted E2B while pharmaceuticals, making reports, show low adoption rates of E2B. Currently, we use WHO-ART for terminology. Therefore we are looking for ways to smoothly change from WHO-ART to MedDRA. Another challenge is a way to report of adverse event of health products and herbal medicines like China.

Q: Could you explain more about challenges regarding MedDRA?

A: MedDRA covers more terminologies than WHO-ART. Also the biggest concern is the burden and pressure to pharmaceuticals as to using MedDRA. As Korean language is used for ADR, to use MedDRA, translation is required. For more efficient work, we are considering to have two different database systems.

● Malaysia

Q: Level of involvement in WHO Monitoring Program?

A: In 1990 we became the WHO member. We established our pharmacovigilance system based on our own database. Unfortunately it was not yet E2B. Our pharmacovigilance system database was in the process of upgrading. We realized that industries should utilize the data. We will incorporate E2B into our new pharmacovigilance system which will take some time. Another challenge in our pharmacovigilance system is the quality of reports. We are able to increase the number of reports from 2004 when we started implementing our clinical pharmacy resource and strengthening the role of clinical pharmacy in the hospital. Another challenge we are facing is the reporting of private institutions and private practitioners. The number of reports from the private sectors especially the general practitioners are still low. We will be backing pharmacovigilance inspections and we hope that it will promote awareness among the company especially the generic company the importance of pharmacovigilance inspections.

Q: So for the report form from pharmaceutical companies, do they have a different format for sending the report to authority?

A: So far we have no problem with the reports. We send reports according to the format. But in terms of the education of information, we still have problems. The reports from the company still are insufficient. I think one of the reasons is the primary report refuses to disclose the information. I think the real cause is to block the department report who have some concern on legal issues that's why they are not willing to give information to the company.

Q: Is there any possibility that pharmaceutical company report in E2B file in the future?

A: At the moment, our E2B is incorporated into our system. Although our pharmacovigilance system will be upgraded, they still have to submit our normal procedures using CIOMS format.

● Thailand

Q: Level of involvement in WHO Monitoring Program?

A: We have involved in WHO Program. We send our reports to UMC by using the old WHO format(INTDIS). It is difficult to start to use E2B format because of limited budget and expertise. In 2009, we started to upgrade our system to electronic. One of the UMC staff recommended to introduce E2B compatible database. We tried, but we were not able to achieve the target because we didn't really understand method.

So far, this issue has been raised again. The UMC has promised to help us to address the problem. We have just received small amount of budget for changing to an E2B compatible database. We have decided to keep a non E2B database and converting them. We hope that it would be achieved in the near future.

As most of economies in APEC are lacking experience in this area, we have to help each other to narrow the gap among us.

● Chile

Q: Level of involvement in WHO Monitoring Program?

A: We will continue to implement the guide of the electronic transmission of safety reports E2B. I have many concerns to implement this type of format because we, at the present, are using the whole ADR software. And I know that it's a very old format but it's the only option that we have. With population of 17 million, Chile is receiving at the moment 8,000 notification a year at the moment. We tried to use VigiFlow, but we have many concerns regarding this software, because we cannot reconcile this software with our existing data. And this is a problem for us because this means that the statistics cannot be obtained with all the data we have. We need a solution to this topic and communication should be more expedited with the UMC to send our reports. We do not have sophisticated database. We need support to implement this type of format(E2B). We need a support in this topic.

● Peru

Q: Level of involvement in WHO Monitoring Program?

A: The Pharmacovigilance Peruvian system was approved in 1999. Since 2002, Peru is an official member of the International Drug Program of the World Health Organization.

The pharmacovigilance Peruvian system has prioritized the development of activities to promote spontaneous reporting, pharmacovigilance in hospitals as well as an active strategic pharmacovigilance medicines used by the Ministry of Health on controlling health interventions and treatment of malaria, tuberculosis and HIV. The Ministry of Health has the responsibility related to risks and evaluates the safety of the drug.

The Pharmacovigilance National Centre receives notification of the members of the pharmacovigilance Peruvian system through those responsibility of pharmacovigilance, the armed forces and police, pharmacies or drugstore, laboratories, drogerias and ESSALUD.

The Pharmacovigilance National Centre is responsible for encoding the reaction of medicines using the WHOART, analyzes reports of suspected Adverse Drug Reaction and deals with the database(Vigiflow). Reports are evaluated individually by Karch & Lasagna algorithm. It is approved in 2000.

• UMC

Q: I also note that there's going to be a transition from E2B version 2 to E2BR3 which will be quite challenging and cumbersome for us to implement. Maybe you could comment on some of the things you've heard.

A: It's the fact that we at the UMC don't duplicate the work of others. There is a significant need for a national and local pharmacovigilance system that takes ethnical, cultural and economical issues into account and establishes processes relevant to particular regions. These are the key success factors for making pharmacovigilance. But when we start thinking about the actual technical requirements they differ very much.

I would like to congratulate APEC on promoting pharmacovigilance as a more important issue, receiving attention for the review and examination. This is also important to gain the attention from political clout and those who can help resource mobilization. I think the increased political support and emphasis on funding will make pharmacovigilance more effective, improve public health systems, and increase patient safety. And that in turn will show decision makers the value of pharmacovigilance. Patient safety is the issue of all as it can affect our families and children. We should keep in mind that ultimately if we don't get the resources needed it would harm us. Effective pharmacovigilance also relies on international standards and harmonization.

The WHO Programme for international Drug Monitoring was created to ensure that early signs of previously unknown medicine-related safety problems are identified and information about them are shared and acted upon. The Uppsala Monitoring Centre was created to maintain the technical and scientific operations of the WHO Programme. When member economies send the data to the UMC and participate in the program information, member economies can see data for their country, neighboring economies and other regions. This is important when analyzing the data. Member economies can analyze all ICSRs submitted to UMC. That is one of the key lessons learned at UMC in the past year - focus on how to bring the value of the data back to the member economies and provide the user friendly and easy-to-use software to analyze the data of all member. As E2B, R2, R3 can be challenging ICH is now crossing the "Ts" and dotting the "Is".

Audience Opinions

- Q:** Even US FDA views to move from M2 to M3 as a quite significant change. The question is about the vigibase level. Through phased adoption based on the current status, all should adopt R3 in the end. That will enable economies to share experience of early adaptors before moving on universal adoption.
- A:** (UMC) From the UMC side and in terms of submitting data to vigibase we will have both of those options and open for them as long as we accept this format.
- A:** (US) We at FDA typically allow companies to transmit case reports using both the current version of ICH 2B which for practical purposes right now is R2 and the preceding version as well because we recognize it takes time for transition.
- Q:** Is there any system for sharing cases that were solved based on adverse event management system?
- A:** (China) Such results will be posted on China FDA in Chinese, but it is hard to share with other economies. If necessary, this will be discussed with relevant departments.
- A:** (Malaysia) We are sharing solved cases in a certain form among ASEAN members thanks to Post Marketing Alert system. I recommend a similar system to APEC.
- Q:** I just wonder whether you see when you upgrade your database if the target is developing countries, like China or Thailand. They will never catch up because it is always one step behind. Which region is being targeted when database or system under development in UMC? What about having two different versions for developing countries and developed countries?
- A:** (UMC) That's a great question. It can vary and it evolves over time. We are very committed to low and middle income countries and in fact the vigilize system was assigned with a very particular persona in mind and through them we try to make up and try to meet this particular users' needs. So the initial vigilize was very specifically targeted to this user and what we are planning to develop is to meet the focus much more on the needs of the low and middle income countries. We are at the stage of sophistication that it meets and exceeds most countries' need so now we are taking a step back and trying to find ways to address the needs for this group. So I think we are trying to focus on our tool development for low

and middle income countries. But at the same time we would like to contribute to more developed world throughout our research team.

A: (US) ICH is willing to work with many more countries outside ICH region.

A: (WHO) If all countries start a race from the same start line, there will be no problem at all. APEC can pursue initiatives by reflecting necessary information and work lists that are given to WHO and UMC.

Q: It would be helpful if the UMC signal document includes scientific aspects of the signal together with policy aspects so that policy makers and decision makers can use the signal documents to assist them in their decision making. The signal document typically publishes data on previously unknown potential adverse drug reactions. Once those signals are confirmed and there is a label change or warning, would it be helpful for signal to publish a couple of year old data on the same adverse drug reaction to see if the pattern of reporting has changed as a measure of the effectiveness of intervention?

A: For example we detect hypothesis activity for one type of global medicine and then we neglect to share the information but we have been criticized that we haven't confirmed yet. We have to conduct some studies. Another problem is medicines that are used in your country which are different from other economies so the signal that is generated by UMC is not relevant to our problem.

A: (audience) In Europe, there are many patients centered health care system more than Asian people. So they have efficient patient information reports widely used for patients. Many patients do not have access to this kind of signal and pharmacovigilance information. So many doctors know about that kind of information and just give their health care service to the patients without informing that kind of signal and pharmacovigilance.

A: (WHO) WHO Pharmaceutical Newsletter and WHO offer all signals and they are open to everyone.

» Session 4: Plenary Lecture – Risk Communication

(Co-Chairs: Jin-Ho Lee(KoPERM), Jean-Christophe Delumeau(Bayer))

1. Risk Communication Introduction and Current Practices

- Gerald Dal Pan, U.S. Food and Drug Administration



- There are many challenges related to risk communication: (1) striking the right balance between warning too much and warning too little, (2) communicating complex information simply through use of plain language, (3) communicating scientific uncertainty, especially new safety when we don't know much about that issue, (4) transparency around FDA actions (5) real world drug usage in the practice of medicine and (6) anticipating and managing questions and/or unintended consequences as a result of the communication.
- The difficulties related to risk communication include: Multiple audiences, scientific uncertainty, the public's tolerance of risk, legal or regulatory constraints, lack of established risk communications methodology for regulators, and difficulty of evaluating effects and outcomes.
- Some of FDA's tools for communicating established and emerging risks are Product Labeling, MedWatch Alerts, and Drug Safety Communications.
- Medication Guides are required for certain medications that "pose a serious and significant public health concern" and are developed by the manufacturer and approved by the FDA. The Medication Guides are required to be given to consumers whenever the medication is dispensed at a pharmacy. Efforts are being made to improve the format and content of Medication Guides in order to increase patient understanding.
- Patients need to receive clear, actionable information in order to use their prescription products safely and effectively.
- FDA is considering new regulation to require all prescription products to have Patient Medication Information(PMI).

- The reasons why FDA issues drug safety communications is to be more transparent about drug risks that emerge in the post-marketing setting, raise public awareness of drug life cycle regulation and oversight, and meet the needs of health care professionals and patients for information to manage healthcare decisions.
- Drug Safety Communications are written in an easy-to-read, interactive format and available online.

» Regulators Only Session

(Co-Chairs: Gerald Dal Pan(US FDA), Donwoong Choi(MFDS))

- PV road map will include vaccines.
- AHC and WHO will have different training modules, developed by the working group in Korea. Korea will collaborate with service team for regulators in WHO.
- Key common items will be selected for regular reporting to WHO and information sharing on safety among economies. If necessary, vaccines will be dealt exceptionally.
- Topics for training programs or workshops of roadmap phase II are: (1) gaps in PV system in each country (2) voluntary report system on ADR (3) ways to build operating system and signal detection (4) establishment of joint PV management system (5) information sharing on safety among APEC members
- Risk Assessment is so important that risks and benefits should be evaluated.
- As CIOMS guidelines are newly pursued, meta-analysis should be included in training sessions. After completing survey for member economies on Vigiflow and Vigibase, the final decision will be made on the inclusion of them in training sessions.

The 18th AHC Workshop(Awareness)

» Session 1 : Introduction of AHC and RHSC

1. Introduction of AHC

- Yeon-Pan Kim, AHC Secretariat



- APEC was founded in 1989 to promote economic cooperation and trade among APEC economies and now it has 21 economies as members. The APEC Harmonization Center(AHC) was established under the authority of APEC LSIF in APEC Committee on Trade and Investment(CTI).
- The necessity of standards and regulatory harmonization in biotherapeutics were mentioned at the third APEC-LSIF meeting in 2005. A year after, it was called upon to harmonize regulations in health and medical products and prepare good manufacturing practices of international best standards of health and medical products. Korea proposed the establishment of the AHC at the 2008 forum. The proposal was approved at the APEC summit held in November 2008.
- The AHC began its operation in June 2009 under KFDA(currently MFDS) to develop and provide training programs and nurture experts in cooperation with ICH and WHO.
- The objectives of the AHC is to enhance international harmonization in production, supply, quality and safety management system of medicines and medical products in APEC economies.
- He introduced the role of the AHC secretariat and AHC's activities, especially results of workshops.
- The KPMA is responsible for operating the AHC secretariat because of (1) entering the global market (2) encouraging Korean pharmaceutical companies to reach out globally (3) utilizing the AHC effectively for the development of pharmaceutical industry.
- He expects a significant role of the AHC in leading regulatory harmonization by exchanging experience and knowledge among international experts.

2. AHC's Role and Operation

- Hye-Soo Kim,
National Institute of Food and Drug Safety Evaluation(NIFDS)



- It was recognized that an educational center for regulatory harmonization in medical products should be established in the APEC region which accounts for around 60% of the global trade. In addition, the AHC aims to stimulate the regional trade of medical products contributing to economic growth in the APEC region.
- Korea became the host country of the AHC after the approval at the APEC summit in November 2008. The AHC has been playing a leading role in establishing a global network among regulators in the APEC region and offering training and education.
- The AHC was founded under the MFDS in June 2009 for fostering professionals to develop health industry in the Asia-Pacific region.
- The AHC's scope of works ranges from research, education, e-publication and international cooperation.
- The AHC has helped to strengthen the international status of Korea in the APEC region and regulators' capacity of economies in Asia and Pacific region. Also, AHC set the foundation for regulatory harmonization in safety management for medical products.
- The AHC organizes workshops three to four times every year.
- He explained the roles and functions of RHSC and LSIF.
- He outlined the AHC development plans
 - Strategies
 - Education: Step up the role of the AHC headquarters for more effective international cooperation and efficiently operate the center for standard work procedures.
 - Research : Conduct survey on approval-related regulation, share the results and increase the number of survey on areas that travel eligible economies of APEC region need.
- The goal of the AHC is to help Korea become a role model for economies as an education institute that mainly focuses on regulatory harmonization in APEC.

- The mission of the AHC is to build educational and research programs to improve competitiveness in the area of medical products in the APEC region.
- The vision of the AHC is to become a hub for regulatory harmonization of medicines and medical products in the APEC region.
- The mid and long-term plan of the AHC is to reinforce fundamental research on regulatory harmonization in medical products and sustain EBI projects which is one of the educational development plans.
- Suggestion and conclusion: (1) Share data of regulatory harmonization network in medical products in the APEC region at the AHC website (2) APEC roadmap for medical products led by the AHC (3) Confirm workshop topics, program and schedule in advance and secure fund in order to smoothly hold workshops and offer quality education to all participants.
- The Korean government will continuously support the AHC activities.

3. Introduction of RHSC and its Activities

- Seo-Ran Choi,
Korea Health Industry Development Institute(KHIDI)



- APEC was established in 1989 and has grown to have 21 member economies. The Republic of Korea joined APEC since its initiation.
- The establishment of LSIF was approved by leaders in 2002. LSIF recognized the importance of regulatory harmonization and aims at encouraging economies to adopt or adapt the existing international guidelines rather than developing new guidelines.
- LSIF serves as a place which brings together representatives from governments, businesses and the academia.
- RHSC and the AHC were established for an effective provision of education. For better cooperation, offering quality training and education programs are significant. That is why LSIF makes efforts in many different areas including combating illicit drugs. Still, the programs have much room for expansion.

- RHSC pursues sustainable strategies for regulatory harmonization, explores areas or sectors with high value and set priority in regulatory harmonization.
 - it mainly focuses on medicines and medical devices
 - RHSC is chaired by Canada with 12 members and business representatives. Russia, the Philippines and Australia announced to join RHSC.
 - The purpose of the Strategic Framework is to promote regulatory harmonization in medicines and medical devices by 2020.
 - The decision regarding when and which technical guidances and best practices should be adopted rests entirely with individual economies.
 - RHSC defined what is regulatory convergence and ministers approved strategic framework in November 2011.
 - Regulatory convergence does not mean that all economies have the regulatory procedures.
 - A General procedure is to select of Priority Work Areas(PWAs), build roadmaps and implement each project.
 - The objective of RHSC is to accomplish regulatory harmonization with a multi-faceted and long-term approach rather than becoming a one-time project.
- PWAs include Multi Regional Clinical Trial(MRCT), Supply Chain, Good Regulation Practices and others. The roadmap for PWAs are being developed or implemented.
 - Korea is a champion economy for pharmacovigilance and biotherapeutics.
 - A new network is being formed in order to attract more members to RHSC.
 - One of the goals is to listen to opinions from APEC economies and other regions and help academia reach to RHSC.
- KHIDI has run RHSC secretariat since 2010. Major tasks are managing documents and members, preparing meetings, planning and supporting projects and facilitating communication.
 - Working groups are organized for a swift discussion on new areas.
 - Acknowledging the independent works of the AHC or RHSC cannot be effective. RHSC has been engaged in cooperative activities with many agencies and initiatives.
 - RHSC's cooperative model is ICH's regulators' forum.

4. Introduction of RHSC Roadmap - Biotherapeutics roadmap

- Byoung-Guk Kim, Ministry of Food and Drug Safety



- The APEC meeting held in September 2011 decided to include biotherapeutics to the PWAs of RHSC. Korea was chosen as a champion economy.
- The roadmap was approved in February 2013 and the first biotherapeutics workshop was held in September 2013. The major goal of the roadmap is regulatory harmonization and convergence in APEC.
- Convergence means the process of breaking down silos between institutions, departments and economies, thereby becoming one. In other words, the goal of the roadmap is to achieve regional regulatory harmonization and cooperation by 2020.
- The roadmap also aims to improve the public health by developing safe, effective and innovative medicines.
- Recombinant DNA, therapeutic vaccines and monoclonal antibody are included in the roadmap. Cell therapy products, gene therapy products and blood components are excluded due to the different status in each country.
- The roadmap has four steps. The first step is consisted of analyses on the current status regarding the roadmap in each country, gap analysis and setting priorities and cooperation agenda.
- The goal of the roadmap is to adjust or adopt existing guidelines to each country according to its situation.
- In the second step, training programs for each country are developed and conducted by 2018. The key is to create networks for information sharing and communication.
 - In the third step from 2018 to 2019, the programs built in the second step will be analyzed, modified and complemented.
 - The final step offers training programs specific to each country. The ultimate goal is for each country to build capacity to provide education in accordance with its needs.

5. Introduction of RHSC Roadmap - Pharmacovigilance(PV) roadmap

- Young-Jin An, Ministry of Food and Drug Safety



- After the approval of RHSC Vision 2020, eight roadmap has been pursued. Korea became a champion economy for PV.
- The draft for the PV roadmap was announced in March 2012. The updated was released in August 2012 with reflection of comments from other economies and medical devices were excluded in the roadmap.
- The draft was revised once again in September 2012 and circulated to member economies. Finally, the roadmap was approved at the meeting in Medan in July.
- The PV workshop was held in November and comments were received on the process of the roadmap from 2014 to 2017.
- From 2012 to 2015, the current status of each country regarding PV will be observed. From 2013 to 2017, training programs and workshops will be conducted. The roadmap will be completed in 2020.
- The goal of PV roadmap is to improve and protect public health, build standards on PV, make coordination for the benefit and risk assessments of drugs and evolve to achieve further confidence from member economies.
- When clinical trials show that a drug has more benefits than risks, the drug is approved. However, PV is needed for detecting and dealing with any unexpected adverse events after the drug is marketed. The awareness on post-marketing adverse event has been raised since Thalidomide tragedy in the late 1960s. Recently, diet pills and arthritis drugs were pulled out of the market because of adverse events.
- Data for drug approval are not enough to secure safety of drugs because the data will be outdated when the drugs are marketed. That is why PV is important to continuously monitor benefits and risks.
- Export and import can be facilitated when products are abided by internationally harmonized regulatory standards. In this sense, global harmonization in PV appeared to be significant.

- The roadmap can be divided into four steps: (1) observing and analyzing current situation (2) providing educational programs (3) evaluation (4) completion.
- The current status of around 10 economies regarding PV is already identified through four rounds of survey. In the third step, it is needed to select priority work areas and identify barriers on regulatory harmonization and the way to implement the roadmap further.
- The model to analyze benefits and risks is very important. economies have used PMS mode, but they are preparing to adopt a new standard, called PBRER. The use of PBRER is not a mandatory in the U.S. and there are no cases of using the standard. Therefore, PBRER can make synergy effects by bringing developing and developed economies together.
- Education on the regional usage of DB and detection of signals are necessary. However, E2B, one of the ICH's template, cannot be adopted since implementation of each country varies. Currently, discussion on the issue is taking place for regulatory harmonization. Also, it is needed to have training programs of standardization of disease classification and PV harmonization.
- The last stage of the roadmap is to propose recommendation on regulatory harmonization after assessment.
- Suggesting a direction for risk management is pivotal to the PV roadmap.

» Session 2 : AHC Mid and Long-Term Work Plans

1. 2014 AHC Plans

- Eun-Hye Park,
National Institute of Food and Drug Safety Evaluation(NIFDS)

- AHC work plan for 2014 was presented according to the scope of work.

- Research: Survey on the current status of implementation of ICH guidelines and demands for training topics



- Education: International workshops will be held four times(two workshops for cell therapy and MRCT in overseas, two workshops in Korea). This plan will be confirmed at the first APEC RHSC meeting.
- Strengthening network: Restructuring of AHC Advisory Board and experts in different sectors in the APEC region
- Website management: Share the outcomes of workshops(presentation materials and videos) and post information of cooperating initiatives(RHSC and ICH)
- Suggesting regulatory harmonization models in cooperation with roadmap champion economies.
- Supporting international cooperation: Lay a foundation for collaborative activities with other initiatives by attending APEC and ICH meetings.

2. AHC Panelists Discussion for AHC Work Plans

- Moderator : Hye-Soo Kim(NIFDS)
- Panelists : Kang-Yong Park(KHIDI)
 Hyon-Soo Kwon(KRPIA)
 Ki-Suk Kim(KoBIA)
 Yong-Hee Choi(KPTA)

[Panelists Discussion]

1) Kang-Yong Park, Korea Health Industry Development Institute

- KHIDI operated AHC and is operating RHSC secretariats.
- The two initiatives were established under the APEC LSIF to discuss medical product regulations. The AHC has a goal of providing training programs of regulations in advanced economies to others. The RHSC was created for discussing regulatory harmonization and regulations themselves.

2) Hyon-Soo Kwon, Korea Research-based Pharma Industry Association

- Expressed gratitude for giving the opportunity of improving awareness on AHC and discussion.

- Requests are:
 - (1) to come up with measures to increase the number of workshops that are held overseas in 2014.
 - (2) to find ways to promote the activities of AHC in relative industries.

3) Ki-Suk Kim, Korea Biomedicine Industry Association

- Achievements in the biotherapeutics industry and requests for AHC's activities.
- Requests are:
 - (1) to provide education programs that are focused on case studies regarding interpretation and implementation of regulations in each country.
 - (2) to conduct survey on regulations of each country such as differences and similarities among regulations.

4) Yong-Hee Choi, Korea Pharmaceutical Traders Association

- Nurturing professionals is critical in developing new drugs and entering into the global market
- The main goal of AHC's training programs is to stimulate regional trade among APEC economies through regulatory harmonization.
- Most of all, pharmaceuticals have to spend enormous amount of money and time to get information. Therefore, from the side of pharmaceutical companies, obtaining necessary information is difficult, thereby facing obstacles in exporting products.

2 2013 Workshop Photos

» Medical products safety and Public Awareness & Establishing of a "Single Point of Contacts System"



[Group Photo]



[Welcoming Remarks:
Mr. Jin-Ho Wang, AHC, Director]



[Congratulatory Remarks:
Dr. Byung-Won Jang, Vice Minister, MFDS]



[Opening Remarks:
Mr. Mark Paxton, US FDA]



[Speaker: Manzatul Azrul Azrie Bin Sulaiman,
Ministry of Health, Malaysia]



[Participants]



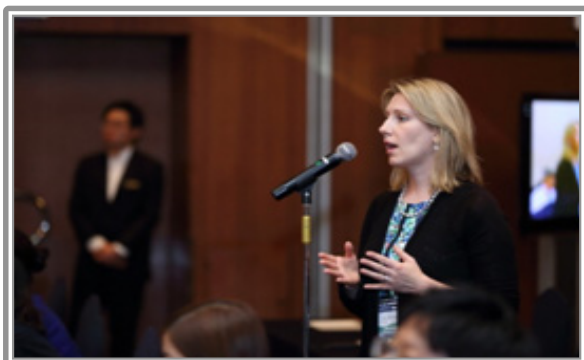
[Panel Discussion 1]



[Panel Discussion 2]



[Question and Answer 1]



[Question and Answer 1]



[Group Discussion 1]



[Group Discussion 2]



[Reporting by Group Discussion]



[Conclusions: Mr. Jeffrey Gren,
U.S. Department of Commerce]



[Gift for Speakers]



[Luncheon]



[Coffee Break]

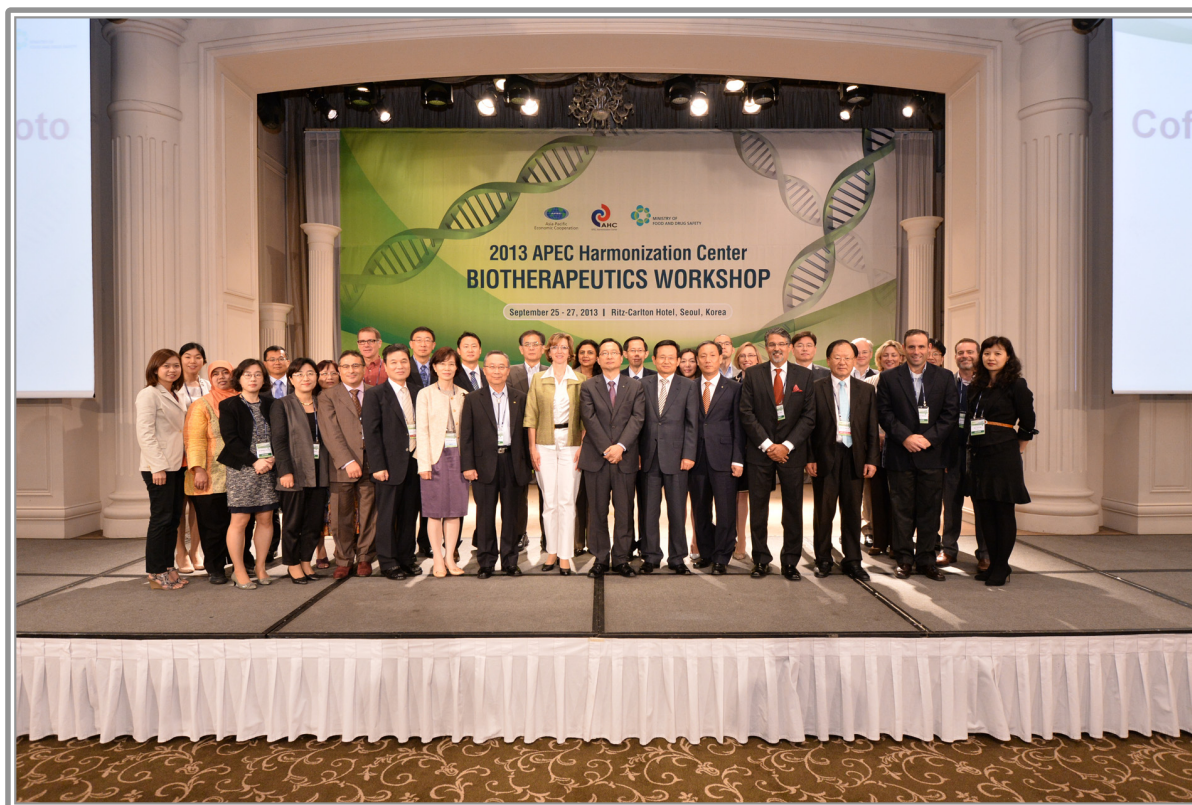


[Welcoming Reception]



[Farewell Dinner]

» Biotherapeutics workshop



[Group Photo]



[Welcoming Remarks:
Mr. Jin-Ho Wang, AHC Director]



[Congratulatory Remarks:
Dr. Byung-Won Jang, Vice Minister, MFDS]



[Congratulatory Remarks:
Mr. Won-Bae Kim, KPMA]



[Welcoming Remarks:
Dr. Byung-Guk Kim, MFDS]



[Keynote Speech:
Dr. Soon-Wook Hong, MFDS]



[Speaker: Ivana Knezevic, WHO]



[Speaker: Shalini Gupta, Amgen]



[Panel Discussion 1]



[Panel Discussion 2]



[Question and Answer]



[Participants]



[Gift for Speakers]



[Closing Remarks:
Dr. Sun-Hee Lee, NIFDS]



[Regulators only Meeting 1]



[Regulators only Meeting 2]



[Coffee Break]



[Welcoming Reception]



[Visit to Hanmi Pharmaceuticals]

» Pharmacovigilance Workshop



[Workshop Attendants Group Photo]



[Opening Remarks:
Mr. Jin-Ho Wang, AHC Director]



[Congratulatory Remarks:
Dr. Byung-Won Jang, Vice Minister, MFDS]



[Welcoming Remarks:
Mr. Kyeong-Ho Lee, KPMA]



[Keynote Speech:
Mr. Moo-Young Yoo, MFDS]



[Introduction of Roadmap:
Mr. Jong-Pill Park, MFDS]



[Speaker: Shanthi Narayan Pal, WHO]



[Panel Discussion]



[Participants]



[Question and Answer 1]



[Question and Answer 2]



[Closing Comments:
Dr. Sun-Hee Lee, NIFDS]



[Gifts for Speakers]



[Regulatory Only Session 1]



[Regulator Only Session 2]



[Coffee Break]



[Welcoming Reception]



[Visit to KIDS]



[Visit to SNU Research Center]

» AHC & RHSC Awareness



[Opening Remarks:
Mr. Jin-Ho Wang, AHC Director]



[Mr. Jin-Ho Wang & Dr. Sun-Hee Lee, NIFDS]



[AHC Introduction:
Mr. Yeon-Pan Kim, Secretary General]



[AHC Plan: Mr. Hye-Soo Kim, NIFDS]



[Biotherapeutics Roadmap:
Dr. Byung-Guk Kim, MFDS]



[Pharmacovigilance Roadmap:
Ms. Young-Jin Ahn, MFDS]



[AHC Plan: Ms. Eun-Hye Park, NIFDS]



[Panel Discussion Moderator, Mr. Hye-Soo Kim, NIFDS]



[Panel Discussion]



[Closing Remarks: Mr. Hye-Soo Kim, NIFDS]



[Question and Answer 1]



[Question and Answer 2]



[Participants]



[Coffee Break]

3 References

»» Websites

- [http://www.nifds.go.kr/apec/\(AHC\)](http://www.nifds.go.kr/apec/(AHC))
- [http://www.apec-rhsc.org/\(RHSC\)](http://www.apec-rhsc.org/(RHSC))
- [http://www.apec.org/\(APEC\)](http://www.apec.org/(APEC))

»» Publication/Reports

- Health in APEC: Creating economic prosperity through strategic health care investments and enabling environments for business by NCAPEC
- Regulatory Harmonization Steering Committee Vision 2020: A strategic Framework
Regulatory Concergence for Medical Products by 2020

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