

APEC Biotherapeutic Products Roadmap to reach a high level of regulatory convergence by 2020

(Revised version as of Apr. 25, 2014)

Goals:

- To promote and protect public health through a more harmonized regulatory environment for encourage the development of safe and effective innovative biotherapeutic products within the APEC region, and enhance mutual understanding through trust-building between APEC economies
- To facilitate convergence of approaches to the regulation of biotherapeutic products in APEC economies in an effort to reach a high level of regulatory convergence by 2020
- To identify opportunities to enhance mechanisms within the biotherapeutic products regulatory pathway to improve the quality and establishing clear, science – based, high quality of the regulatory review process
- To enhance mutual understanding of the scientific considerations in demonstrating biosimilarity to a reference biologic product, and advance the implementation of science-based regulatory pathways for biosimilars products that are distinct from traditional regulatory pathways for generic medicines.

Background and Challenges:

Biological products, also known in some countries as biologics, biological medicinal products and biologicals, are defined by the World Health Organization (WHO), as medicines obtained from biological origin, i.e., human and other living organisms which cannot be fully characterized by physicochemical means alone. Moreover, manufacturing procedure of biological products includes the use of living cells or tissues. While the definition and scope are slightly different among regulatory authorities, biological products, in general, cover vaccines, blood, blood components or derivatives, plasma derivatives, recombinant DNA (rDNA) products, monoclonal antibody, therapeutic serum, toxin, antitoxin, cell and gene therapy products involved in the prevention, treatment or cure of a disease or condition of human beings. A biosimilar is a biological product

which is similar to, but not the same as, an already licensed reference biologic product (RBP) in terms of quality, safety and efficacy

We herein use the term biotherapeutic products, which collectively include the originator biological products along with biosimilars with the indication of treating human disease, as defined by WHO.

Among biotherapeutic products, this roadmap will only cover the area of recombinant DNA (rDNA) products, monoclonal antibody, and therapeutic vaccines. Non-recombinant vaccines, blood products and cell/gene therapy products are not within the scope of this roadmap, though they are classified as biotherapeutic products by definition.

Biotherapeutic products have been significantly developed due to scientific and technical advancements and innovation. Since the first rDNA product, insulin, was introduced in the early 1980s, there has been enormous progress in the ability to produce biologically active macromolecules for therapeutic use. However, despite considerable technical advances in analytical techniques, it is still not possible to fully predict biological properties and clinical performance of novel biotherapeutic products from physicochemical characteristics alone. In addition, the production processes of biological systems are very complex and must be tightly controlled to ensure the safety and efficacy of biotherapeutic medicine.

In the last few years, the expiry of patents and exclusivity for the first generation of biotherapeutic products (mainly rDNA products) has led to great interest from manufacturers globally to develop biosimilars, or subsequent versions of innovative biological medicines. Because biosimilars are not innovative biological products, they may be approved on the basis of an abbreviated dossier if it can be demonstrated that the proposed biosimilar is highly similar to the innovative biological product in quality, safety and efficacy. As biosimilar pathways are developed around the world, it is important to balance access to potentially lower cost biosimilars with adequate incentives for innovation that brings new medicines to patients.

It is generally and globally agreed that review and regulation of biological products should be distinct from small molecule drugs, with emphasis on the importance of process control specifications and an understanding of how variations from these specifications relate to the clinical profile of the medicine.

Changes in the biopharmaceutical environment and trends in development and production of innovative biotherapeutic products pose a challenge for each country in APEC region to making efforts such as building appropriate approval review processes and post-market oversight measures for these products, adopting policies for prompt review processes and increasing review personnel. As regulations for biotherapeutic products are being developed and implemented differently by APEC countries, there are regulatory gaps and differences in capacities of responsible regulatory authority. Due to these factors there is also great chance for prospective convergence and harmonization as various parties come together to develop the regulatory guidance and requirements in APEC region.

Under these circumstances, building a roadmap in the APEC region has emerged as a major issue for a consistent means of communication between industry and regulatory authorities. Availability of regulatory expertise and resources, especially in evaluating complex biotechnology product submissions, is an issue for many countries. Increased regulatory cooperation and networking are essential prerequisites for a coordinated and efficient response to these realities. Inter-agency and country level agreements/arrangements in turn serve as key instruments that help govern enhanced regulatory interactions. Bilateral or multilateral forums are designed to support regulators and key stakeholders in their efforts to develop best practices, share knowledge, adopt or contribute to international standards, and develop compatible approaches with international counterparts. These may include sharing knowledge through training and capacity building exercises, undertaking collaborative scientific work, establishing common risk assessment or compliance methods, , and promoting greater regulatory convergence and harmonization through adoption of common international standards.

Therefore it is critical for APEC to devise ways for regulatory convergence that would drive harmonization of biotherapeutic products practice in member nations and promote and protect public health.

Roadmap Overview

- Assess current regulatory preparedness for the authorization of biotherapeutic products. Specifically the regulatory frame works, and related infrastructure in each APEC economy

- Review biotherapeutic products guidelines from competent international regulatory authorities with acceptable regulatory standards (e.g. those of the FDA, EMA, Health Canada and APEC economies) with primary focus on relevant ICH and WHO guidelines.
- Establish common understanding among APEC member nations subject to LSIF regarding key issues including the following¹.
 - Recognition that there is a need for a pathway for an originator biological which is separate and distinct from that of the biosimilar and addressing the unique nature of each of these pathways.
 - Establishment of a stepwise approach in developing evidence to support a demonstration of biosimilarity
 - Development of an appropriate guidance regarding the quality, efficacy and safety expectations for approval of originator biologics products
 - Operational procedures to facilitate effective management and implementation of the roadmap through APEC-wide forums for information sharing and gap assessments..
 - Create opportunities for discussion of collaborative working arrangements and mutual recognition and joint review agreements for CMC, quality, safety, efficacy etc. between APEC regulatory authorities.
- Develop a regional information hub related to medical products that promotes regional cooperation and data utilization/sharing to enable harmonized approaches, standards, and guidelines for medical products regulatory systems.
- Conduct training/workshop for regulatory harmonization involved in biotherapeutic products, in particular regulatory harmonization related to the key issues cited above, biotherapeutic products workshops will be an important facilitator in this process
- Develop regulatory policy approaches to address situations where APEC economies may have already licensed biotherapeutic products prior to the establishment of distinct, science-based regulatory pathways for these medicinal products
- RHSC will support related activities and development of recommendations for the next step

A maximum level of harmonization and convergence of regulatory practices on biotherapeutic products will be achieved through the implementation of the roadmap.

¹ This will be facilitated by a biotherapeutic workshop in 2014.

Specific Actions and Time Frames

Step 1: Assessment (2013-2014)

At APEC biotherapeutic products workshops, meetings and surveys, the current status of biotherapeutic products regulatory practices will be assessed and identified.

The 2013 AHC Biotherapeutics Workshop was held in Seoul, Korea on September 25-27. This workshop brought together representatives from industry (local and global), WHO, and regulatory agencies to discuss challenges and opportunities to advancing regulatory convergence on a global scale.

Two key objectives were a) highlight the differences between biotherapeutics versus small (chemical) pharmaceuticals and provide details of various ICH guidelines that are specific to biotherapeutics, and 2) highlight the importance of science based approval pathway for innovative biologics as well as biosimilars. (Refer to Annex 1. 2013 AHC Biotherapeutics Workshop Report)

The “**2014 AHC Biotherapeutics Workshop-Progress towards Convergence**” will be held for one-and-half days (May 12-13, 2014) as a part of activities of the APEC Regulatory Harmonization Steering Committee (RHSC) *APEC Biotherapeutic Products Roadmap to reach a high level of regulatory convergence by 2020*. This workshop will create facility regulatory convergence of biotherapeutics by holding alignment with the “WHO/MFDS Implementation Workshop: Evaluation of biotherapeutic products” and “WHO/MFDS Implementation Workshop: Evaluation of similar biotherapeutic products with emphasis on monoclonal antibody products” which is held for three-and-half days (May 13-16, 2014). Goals of the 2014 workshop is analyzing the current regulatory status and conditions of the APEC member economies based on regulatory survey results, and coming up with concrete action plans in line with the Biotherapeutic Products Roadmap by providing information on regulations, international guidelines, and details of clinical and non-clinical case studies.

Review of the current status of biotherapeutic products regulation is essential in finding regulatory gaps between APEC member nations. The strategies will take into consideration gaps between “as-is” status and “to-be” goals.

The assessment should be conducted in the following context:

- Collect current status, information and level of quality and safety requirements of the biotherapeutic products in aggregate in each APEC member country through surveys or workshops.
- Analyze and identify gaps between “as-is” status and “to-be” goals of the biotherapeutic products regulatory systems in each APEC economy
- List priorities of requirements and activities for convergence, and major obstacles to biotherapeutic products regulatory harmonization
- Establish broad agreement with the agenda to increase cooperation and facilitate implementation of the roadmap
- These activities in Step 1 will be executed through activities including a survey, programs during AHC workshops, seminars and other events

The assessment and recommendations for the next step will be finalized by the end of 2014.

Step 2: Training/workshop (2015-2016)

Based on the recommendations from Step 1 assessment, identified economy/economies will develop training/workshop curriculum and conduct training/workshop in cooperation with other APEC economies and/or RHSC, depending on circumstances of the economy/economies. Biotherapeutic products workshops may consider creating curricula for training individuals within the regulatory authorities, academia, industry, and research institutes.

<Possible Common Training Subjects>

- Quality (CMC) –
 - Manufacturing process

- Regulatory issues associated with production platform for biotherapeutic products; the new (eg. plant, insects) and the traditional (e.g., mammalian cells, e-coli) production platforms for biotherapeutic products
- Regulatory approaches to dealing with the discovery of adventitious agents in marketed biotechnology products
 - Characterization
 - Specification and test methods
 - Pharmacopeial Standards
 - Stability
 - Manufacturing changes (comparability)
 - Lifecycle risk-based change management for biotherapeutic products (requirements and procedures for post-approval changes)
- Non-clinical study
 - Pharmacological study (*In vivo* and *In vitro*)
 - Toxicological study
- Clinical study
 - Understanding clinical study; clinical trial phases
 - Clinical pharmacology
 - Safety assessment
 - Efficacy assessment
 - Good clinical trial practice
 - Statistical consideration for clinical trial
- Regulation of Biosimilars (Head-to-head comparative exercises for proving biosimilarity, extrapolation, etc)
 - Good Scientific and quality considerations in demonstrating biosimilarity to a reference product.
 - Pre-clinical and clinical requirements for demonstrating biosimilarity
 - Immunogenicity
 - Extrapolation of indications
 - Licensure/regulatory pathway for biological products shown to be biosimilar to a licensed/registered biological reference product.
 - Pharmacovigilance

- Pharmacovigilance and risk management mechanisms
- Orphan biotherapeutic products
- Understanding regulatory oversight of biotherapeutic products in different jurisdictions

Other areas that may require collaboration with APEC economies will be reviewed at workshops.

<Possible area for establishing the collaborative system across the economies>

- Building up the communication channel and establishing information sharing between regulatory authorities. Examples are as follows:
 - Sharing review/approval information and building up the parallel review system in line with applicable confidentiality laws
 - Sharing the findings of GMP inspection and following measures
 - Sharing PMS data and/or following measures
 - Identifying common regulatory issues related to biotherapeutic products and sharing best practices for resolutions
- Develop plans to build Crew Resource Management (CRM) system for transparent biotherapeutic products regulatory system

The curricula developed by the economies and biotherapeutic products workshops will be used in a coordinated program to “train the trainers” which will allow the APEC economies to have the ability to conduct additional training to share best practices. It is expected that by the end of Step 2, highly applicable ideas regarding biotherapeutic products as well as practical visions will be developed.

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

At the completion of the training and workshop activities outlined in Step 2, the resulting impact on regulatory policies will be assessed by APEC and other related organizations. Possible venues for this review include symposia and workshops under RHSC. Possible vehicles for assessment could include surveys.

Recommendations for enhanced efficiencies will be formulated. Recommendations for improving the regulations in economies identified within APEC that have not yet achieved convergence with international best practices will be discussed, and revised training and implementation plans will be developed.

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

- Based on recommendations from Step 3 assessment, economy/economies will revise training/workshop curriculum and conduct additional training/workshop accordingly with the help from other APEC economies and/or RHSC, depending on situations of the economy/economies. And economies should start implementation procedures for convergence, for example revise or upgrade laws, regulations similar to those of well-established organizations such as ICH, WHO and execute follow up training/workshop, and building up infrastructures
- Use of case studies based on actual implementation of biotechnology products roadmap in training should be considered. Collaborative surveillance systems with APEC economies should also be reviewed.
- Build up collaborative system and information sharing (e.g., post-marketing surveillance systems).
- The information shared should be practiced in each APEC members.
- Based on the Step 4 results in terms of degree of convergence achieved by each economy in 2020, further actions and recommendations for the next step collaboration on regulatory process will be discussed.

The biotherapeutic products roadmap, based on experiences and activities generated in the process of roadmap implementation, will be the basis for regulatory harmonization recommendations authorized by RHSC.

Performance Indicators

<Establish highest high level of regulatory harmonization and measure how these activities are used in the APEC region>

- By 2014 complete a detailed assessment and landscape of regulatory status of the region through an AHC workshop – This will serve as a benchmark. and gap assessment From 2014- 2018 conduct a series of workshops and dialogue sessions among regulators and policy makers in order to facilitate increased alignment of biotherapeutic guidelines with ICH and WHO recommendations and to fill the gaps identified from the assessment. 2014 – 2016 for general educational workshops, 2016 – 2018 for experiences sharing and specific workshops for certain topics after gap analysis and assessment at 2016.
- Complete workshop summaries after each workshop and dialogue session and indicate key takeaways and recommendations for implementation
- In 2014-2017 create progress reports of all activities (e.g. dialogue sessions, workshops, surveys etc.) to assess whether the goals of the biotherapeutic products roadmap are being achieved (including a gap analysis and additional recommendations for activities) to promote convergence in the region by 2020
- Complete an assessment of landscape analysis for the regulatory environment in 2020 to measure level of regulatory policy convergence against the 2014 benchmark, and further actions and recommendation for future steps will be discussed.

<Improve mutual understanding about regulatory convergence between APEC members>

- Measure and evaluate the number of established collaborative working relationships between APEC regulatory authorities and resulting Memorandum of Understanding
- Measure the level of satisfaction with activities including workshops and training sessions among regulators and policy makers through surveys
- Conduct surveys and landscape analysis of regulatory guidelines in APEC economies at regulatory intervals (e.g. every 2 years, 2014, 2016, 2018) to evaluate convergence with international guidelines (e.g. WHO, ICH) and measure progress towards achieving the Roadmap objectives.

<Develop next steps for regulatory harmonization of other biotherapeutic products including vaccines, blood and blood components and plasma derivatives >

Convene a working group to review final reports, summaries and lessons learned from convergence activities in order to develop a roadmap for additional biotherapeutics

Relevant Guidelines to be provided:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on Quality of Biotechnological Products : Stability Testing of Biotechnological/Biological Products, and other 11 relevant guidelines
- The World Health Organization (WHO) Guidelines on the Quality, Safety and Efficacy of Biotherapeutic Products Prepared by Recombinant DNA Technology
- US Food and Drug Administration (FDA) Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology, and other 36 relevant guidelines
- European Medicines Agency (EMA) EMEA Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products, and other 9 relevant guidelines
- ICHS6 (R1)- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- ICH-M3(R2)- Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Biosimilar Guidelines
 - ① Guidelines on evaluation of Similar Biotherapeutic Products(SBPs) (WHO)
 - ② Guideline on similar biological medicinal products and other 7 relevant guidelines(EMA)
 - ③ Guidance for industry Biosimilars : Questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009 (FDA)
 - ④ Scientific Considerations in Demonstrating Biosimilarity to a Reference Product(FDA)
 - ⑤ Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product(FDA)
 - ⑥ Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (FDA)
 - ⑦ Guideline for the quality, safety and effectiveness of biosimilar products(PMDA)
 - ⑧ Guidelines on the evaluation of biosimilar products and other 4 relevant guidelines (MFDS)

Annex 1. 2013 AHC Biotherapeutics Workshop Report

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2013/RHSC/AHCREP/xxx/Rxx

2013 AHC Biotherapeutics Workshop Report

Proposed by Workshop Program Committee

The 2013 AHC Biotherapeutics Workshop was sponsored by the APEC Life Sciences Initiation Forum Regulatory Harmonization Steering Committee (RHSC). The Korea Ministry of Food and Drug Safety (MFDS) led the effort to create a roadmap to achieve regulatory regional harmonization of biotherapeutics.

As part of the Biotherapeutic Products Roadmap (Annex 4), this workshop was conducted in Seoul, Korea on September 25-27 that was hosted by the APEC Harmonization Center (AHC). This report summarizes the key highlights of the workshop.

The objective of this workshop is to bring together regulators, industry representatives, and members of academia to facilitate the harmonization and convergence of approaches to the regulations of biotherapeutics products in APEC economies in an effort to reach the highest level of regulatory convergence by 2020. This would facilitate the development of safe, effective and innovative biotherapeutic products in APEC economies by establishing a sound science-based regulatory process. Two key objectives would be to a) highlight the differences between biotherapeutics versus small (chemical) pharmaceuticals and provide details of various ICH guidelines that are specific to biotherapeutics, and 2) highlight the importance of science based approval pathway for innovative biologics as well as biosimilars. Such actions can lead to more efficient use of resources by regulators and industry, and ensure predictable and timely approval to safe and effective biotherapeutics in APEC region. Specifically,

1. This workshop will promote active discussion and participation among participating stakeholders to further promoting the harmonization of regulatory standards for biotherapeutics and to promote trade among APEC economies by ensuring the quality, consistency and timely availability of biotherapeutics to patients in the APEC region.
2. This workshop will provide scientific and technical discussion on how biotherapeutics are different from chemical products and the need for science based regulatory approval of the innovative biologic and biosimilars.
3. This workshop will highlight the various ICH guidelines that are specific to biotherapeutics. Other key biotherapeutic guidelines from USFDA and EMA and relevant WHO guidelines will also be discussed. This will facilitate the convergence on requirements for registration of biotherapeutics throughout the APEC region, which will help provide consistency and certainty with respect to these medicines for patients, health care providers, and biotherapeutics developers.

Further information about the objectives and goals of this workshop can be found in the Workshop Overview document in Annex 2.

I. Overview

This workshop brought together representatives from industry (local and global), World Health Organization (WHO), and national regulatory agencies (NRAs) to discuss challenges and opportunities to advance regulatory harmonization and/or convergence of biotherapeutic regulation on a global scale. This workshop had about 400 participants, 86 regulators from 10 APEC economies (Canada, Chinese Taipei, Indonesia, Japan, Korea, Malaysia, Peru, Philippines, Singapore, and Thailand) + 1 non-APEC country (Sweden) + WHO. There were total number 69 manufacturers from 8 countries (China, Chinese Taipei, Japan, Korea, Singapore, Switzerland, UK, and USA).

The workshop consisted of 5 sessions, and the titles and main contents of each session are as follows (refer to Annex 3):

- **Session 1 – Overview of Biotherapeutics, and a Roadmap Towards Convergence**
Session 1 provided an overview of the Biotherapeutic Roadmap, reviews of at last year’s biosimilars workshop, and discussed of why biologics are different from small molecules and thus should be regulated differently.
- **Session 2 – ICH and WHO role in setting standards for biotherapeutic products**
Session 2 was billed as the anchor session that discussed recently issued WHO guidelines on Biological Medicinal products prepared by recombinant DNA technology. Through presentations and panel discussion, this session conducted a “gap-analysis” of how the ICH guidelines are used in various APEC economies. The presentation in this session was primarily by the regulators.
- **Session 3 – Clinical and Non-Clinical (Case study)**
The Industry provided case studies on non-clinical, clinical and immunogenicity.
- **Session 4 – CMC Considerations: Manufacturing and Quality**
Regulators and industry speakers will focus on the quality attributes of biologics— ICH guidelines, lifecycle management, GMP.

▪ **Session 5 – Plenary Lecture: New Upcoming Biotherapeutics Technology**

Session 5 provided a plenary lecture on emerging technologies with focus on therapeutic vaccines and conjugated antibodies.

A session chair or coordinator was designated to be a rapporteur of each session, and this report is a compilation of the summaries prepared by the session chairs or coordinators with inputs from the program committee members.

II. 2013 APEC Harmonization Center Biotherapeutics Workshop

Day 1: Wednesday, September 25

Session 1:

Overview of Biotherapeutics, and a Roadmap Towards Convergence

- Coordinator / Co-Chair: *Jerry Stewart, JD, Pfizer*
- Chair: *Yeowon Sohn, Ph.D., MFDS*

- *Biologics vs. Small Molecule Pharmaceuticals | Kum Cheun Wong (IFPMA)*
- *Current Development/Regulatory Strategies of Biotherapeutic Products – Key Points to Consider vs. Small Molecules | Jane Bai (IFPMA)*
- *Progress and Update on Biosimilars Development in Korea | Hyuk Jae Lee (Celltrion)*
- *Overview of Biotherapeutic Roadmap | Byoung-guk Kim (MFDS)*
- *AHC 2012 Biosimilars Workshop Output | Jerry Stewart (Pfizer)*
- *Biosimilar Regulatory Frameworks with Room for Convergence- what more is needed? | Judith Macdonald (Pfizer)*
- *Panel Discussion | Session Chairs, Speakers and Invited Participants*

Overview

This workshop brought together representatives from industry (local and global), WHO, and regulatory agencies to discuss challenges and opportunities to advancing regulatory convergence on a global scale.

Session 1 was designed to highlight the unique nature of biologics, current status of developing biotherapeutics, including biosimilars, and their regulatory frameworks.

Moreover, it was to introduce the biotherapeutics roadmap and to pick up where last year's AHC Biosimilar Workshop ended, where the focus was biosimilar development and regulatory pathways. One theme that surfaced last year was the need to better understand the principles of biotherapeutics and how might industry and regulators collaborate to identify the necessary regulatory standards and policies in order to align their direction over time; that is, the pathway toward regulatory convergence.

Session 1 covered the following topics:

- High level summary on the differences between small molecules and biologics, covering quality, non-clinical and clinical development aspects
- Current Development/Regulatory Strategies of Biotherapeutic Products (Key Points to Consider vs. Small Molecules), including the application of harmonized standards and requirements, and the importance of holding scientific advice meetings between sponsor and agency
- Progress and Update on Biosimilars Development in Korea, and overview of the development of Celltrion's first approved biosimilar, Infliximab
- Overview of the recently revised Biotherapeutic Roadmap, and the step-wise approach in conducting workshops in order to achieve regulatory convergence by 2020
- AHC 2012 Biosimilars Workshop Output, emphasizing the areas of convergence and divergence in the Biosimilar space identified last year
- Biosimilar Regulatory Frameworks, and where industry and regulators should focus their efforts to achieve convergence, including the EU experience to date and what challenges and strategies await all parties in the near future

Key messages

Following the presentations, session participants held a panel session to answer questions and raise additional points to consider on the afore-mentioned topics. Here are highlights to the key messages during the panel session:

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- Biotherapeutics represent the next step in revolutionizing modern medicine to treat the world's unmet medical needs such as cancer.
- There exists a strong desire to have dedicated, specific regulations and/or regulatory guidance aimed at biologics development
- In the absence of specific regulations to biotherapeutics, regulators can interpret existing regulations to introduce necessary guidance to define an acceptable and scientific-based regulatory pathway. Furthermore, the expression of technical requirements in the form of guidance documents is desirable and an example of good regulatory review practices.
- There is a strong case to support global biosimilar development, and that one size fits all is not the case. Developmental strategies will vary but be important, depending on the product and its characteristics. Nevertheless, the minimum common standard is that development is rooted in science-based decision making
- Simultaneous global development paradigm should apply; it's efficient, it has worked (products examples marketed globally), and one must recognize that the innovator markets its product globally – i.e., acceptable risk-benefit ratio already exists, which is one key fundamental principle to biosimilar development
- Quality assessment is the foundation to begin the globally accepted “step wise approach comparability exercise” and is an essential element to justifying reduced pre-clinical and clinical studies in biosimilar development. Depending on the product and the sponsor's goal, comparability exercise at the quality level can be extensive, simple or unique; and presenting these data during agency consultation is essential to outlining the product's development course.
- Agency consultation: many speakers and participants emphasized the importance of it, to start early and frequently, ask the right questions, and incorporate their advice
- Risk Management plans and corresponding post marketing or post approval commitments is an area that shows sign of divergence from one agency to the next; what's the right level or how to reach the right balance?
- Specifically, the following areas were identified as areas for opportunities for regulatory convergence (that is, to consider for Roadmap progress)
 - Many areas open for interpretation without common language and principles. Common understanding of globally accepted guidelines would be of value to initiate the regulatory convergence.
 - Further evaluate the “3rd pathway” that has emerged for biosimilar registration in some countries such as Brazil and Colombia, that is inconsistent with WHO guidelines
 - RMP – how to account for different agency requests, and to account for different agency review times and processes

- Biosimilar naming conventions –the impact to traceability of biosimilars for post marketing safety surveillance. Need extensive discussion on WHO’s work and NRA’s effort.
- Additionally, the following table highlights key topics for areas to focus, based on last year’s workshop, and what holds true today, per the panel session:

Opportunities for convergence

- Interchangeability and the methods to achieve it
- Applications of immunogenicity
- Limitations in existing post-marketing surveillance systems and application to biosimilars (e.g., naming)
- Extrapolation of indications; limitations to population characteristics
- Impact of Post-marketing manufacturing changes (“product drift”)

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Session 2:

ICH and WHO role in setting standards for biotherapeutic products

- Coordinator: *Romi Singh (Amgen)*
 - Chair: *Ivana Knezevic (WHO)*
 - Co-Chair: *HongZhang Yin (CFDA)*

 - Development and Implementation of WHO Guidelines for Regulatory Evaluation of Biotherapeutic Products | *Ivana Knezevic (WHO)*
 - Key Issues that Regulators should Consider While Reviewing CT Data | *Jian Wang (Health Canada)*
 - ICH Current Status and APEC Regional Harmonization Efforts | *Mike Ward (Health Canada)*
 - Panel Discussion: Opportunities for regulatory convergence
 - Evaluation of Biologics in Malaysia | *Yvonne Khoo (NPCB, Ministry of Health, Malaysia)*
 - Evaluation of Biologics in Japan | *Yasuhiro Kishioka (PMDA)*
- Agenda: 1. How do Various Economies use WHO and ICH Guidelines?
2. What are the opportunities for regulatory convergence?

Panellists | 1) China (*HongZhang Yin, CFDA*), 2) Chinese Taipei (*Fia (Ya-Ting) Chen, Ministry of Health and Welfare*),

3) Japan (*Yasuhiro Kishioka, PMDA*), 4) Korea (*Jeewon Joung, MFDS*), 5) Malaysia (*Yvonne Khoo, NPCB, Ministry of Health*), 6) Thailand (*Prapassorn Thanaphollert, Ministry of Public Health*)

Overview

One of the objectives of session 2 was to update workshop participants on the developments and availability of standards of the World Health Organization (WHO) for evaluation of biotherapeutic products (BTP). In addition, initiative of the International Conference of Harmonization (ICH) and APEC for promoting regulatory convergence was presented and discussed. Panel discussion with regulators from Canada, Chinese Taipei, Korea, Japan, Malaysia and Thailand, WHO and Industry representatives was intended to explore how countries use WHO and ICH standards and what are the opportunities for regulatory convergence in the area of BTP.

Discussion was focused on the current use of international standards for evaluation of biotherapeutic products, existing regulatory frameworks, diversity of national regulatory requirements for various aspects of quality, safety and efficacy evaluation of these products for the entire regulatory oversight of this important class of biologicals. Speakers and panellists shared valuable information and experience in applying guiding principles on a case-by-case basis to various products including erythropoietin, somatropin, G-CSF and monoclonal antibodies. In terms of product evaluation for the purpose of licensing, the main theme was clinical evaluation of BTP which revealed some differences in regulatory expectations in the countries involved in the panel discussion.

The following topics were covered by the speakers, panellists and participants of the discussion:

- An overview of available WHO written (ie, Guidelines, Recommendations) and measurement standards (reference preparations with defined biological activity in International Units) for biotherapeutic products
- WHO Guidelines for biological medicinal products made by rDNA technology with a special emphasis on principles for clinical evaluation of BTP
- Key issues that regulators should consider while reviewing clinical trial data
- ICH and APEC initiative for regulatory convergence
- National regulatory requirements for BTP and examples of licensed products
- Regulatory pathways for Similar Biotherapeutic Products (SBP) and implementation of internationally agreed guiding principles into regulatory practice

- Preliminary analysis of the survey in 4 APEC countries (Japan, Korea, Chinese Taipei, and Thailand)
- Area of divergence and opportunities for regulatory convergence in APEC economies

Key messages

- WHO Guidelines on BTP were recognized as the key set of scientific principles for regulatory convergence. WHO implementation workshops are helpful in implementing Guidelines but the application of general principles to specific products on a case-by-case basis is quite a challenging task for regulators in some APEC economies. More case studies may help translating principles into practice. With respect to ICH Guidelines, many regulators are familiar with its scope and contents but the level of implementation differs. Some inconsistencies regarding the scope of the documents and applicability of principles to various classes of biological products were identified. It was agreed that further discussion between WHO and ICH in terms of currently available Guidelines and those that are planned in the area of BTP is needed.. Global product specific Guidelines may be needed but there are other ways of elaborating product specific issues that should be explored.
- Clinical evaluation of BTP is an area where many regulatory authorities need technical support in developing expertise for regulatory review of these data. One of the issues in terms of current divergence is national requirement for local clinical data in some countries. In the case of Korea, it was established on the basis of ICH Guideline (E5) in order to address ethnic differences. However, patient number of the trials done in local population may not be sufficient to detect these differences. From this reason, the value of data generated for that purpose was questioned by the multi-national companies. Multi-regional clinical trial initiative which is led by Japan is recognized as an important step towards regulatory convergence in clinical evaluation of medicinal products. It will be good to explore whether similar initiative in the area of BTP may help to align national regulatory requirements for clinical trials. Appropriate application of clinical principles with no harm to patients should be the bottom line of regulatory convergence.
- WHO survey on regulatory requirements in various regions and countries is recognized as an opportunity to start defining baseline in terms of divergence in national regulatory requirements for BTP. Regulators from APEC countries expressed interest to participate in the analysis of the outcomes of the survey and to contribute to further alignment of national regulatory requirements. It was also agreed that more detailed survey to analyze the gap in implementing global guidelines should be conducted and the Working Group was proposed for that purpose.

- Joint activities involving various regulatory networks and industry associations are part of WHO initiative for promoting science based regulation and alignment of regulatory requirements worldwide. In that context, a possibility for organizing joint workshops on BTP and SBP was proposed for further consideration by WHO and APEC secretariat.

Opportunities for convergence

- Analysis of the current national regulatory requirements for BTP needs to be conducted in order to identify differences among countries. Completion of WHO survey is seen as an opportunity to start defining the baseline of the regulatory convergence/divergence
- Scientific basis for establishing/ updating national requirements for clinical data is essential for regulatory convergence
- Criteria for acceptance of foreign clinical data differ among countries. In that context, MRCT as a common approach is recognized as an opportunity for regulators from APEC economies to actively contribute to its development as well as to the subsequent implementation
- Common dossier for CTs
- Better use of CTA mechanism to address key issues regarding the target population
- List of recognized RBPs for development of SBPs
- In the context of SBP, acceptance of foreign RBP with well-defined criteria
- Common approach/principles for evaluation of post-approval changes of BTP
- Training for regulatory evaluation of BTP – review of existing training opportunities and opinion on the suitability of trainings for regulators
- GMP inspections and pharmacopoeia
- Sharing of: Information, Knowledge, Work – joint review, parallel review as examples

Day 2: Thursday, September 26

Session 3:

Clinical / Non-Clinical (Case study)

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

- Non-clinical ICH S6 (Non-clinical evaluation of biotechnology products) | *David Hutto (Eisai)*
- The Importance of Immunogenicity Assessment of Therapeutic Proteins | *Shalini Gupta (Amgen)*
- Clinical data requirements for registration of biotherapeutics | *Freddy Faccin (AbbVie)*

Key messages

- Non Clinical:

The overall objectives for nonclinical safety assessment of small molecules and biotherapeutics are the same: i) identification of ‘safe use conditions’, ii) identification and characterization of potential target organs of toxicity, iii) identification of a clinical starting dose for a first in human study, and a dose escalation rationale, iv) identification of clinically translatable means of monitoring for toxicities in humans, should they occur.

However, there are several important differences in the scientific basis and approaches used in nonclinical safety assessment of small molecules and biotherapeutics. The most important of these differences is that toxicologic effects of biotherapeutics are driven by the pharmacology of the biotherapeutic molecule under study and this circumstance thus requires a ‘case-by-case’ approach to safety assessment, each molecule requiring a customized approach determined by the specific pharmacologic mechanism of action. Specific areas of significant scientific differences in safety assessment of biotherapeutics are:

- Nonclinical species selection-based on pharmacologic relevance
- Genotoxicity assessment-not relevant
- Cardiovascular safety assessment-no expected direct effect on ion channels
- Dose selection for toxicity studies-ideally based on pharmacodynamics effects
- Impact of immunogenicity-effects in animals not predictive of effects in humans
- Dose extrapolation to humans-not converted by allometric methods
- Duration of longest general toxicity studies-6 months is generally sufficient, 3 months for oncology
- Developmental and reproductive toxicity assessment-all endpoints are generally assessed in a single study
- Carcinogenicity assessment-an assessment is required but rodent bioassays are generally not appropriate
- Antibody drug conjugates share many of these special considerations but the toxicity profile is usually predominated by the effects of the conjugates small molecule cytotoxic drug.

- Clinical;
 - 1) Clinical requirements for registering a biotherapeutic, including Phase I, II and III:
 - 2) The program usually consists of a stepwise procedure starting with phase I studies and continuing on to phase II and phase III trials, although some exceptions may apply under specific circumstances
 - 3) Clinical requirements for registration of a biosimilar biotherapeutic:
 - 4) For candidate biosimilars, 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 demonstrate the absence of any clinically meaningful differences depend on several factors that must be carefully assessed, such as extent of residual uncertainty about biosimilarity; nature of the product and patient population to be treated

- Immunogenicity:
 - 1) How to design an immunogenicity program that enables regulators, physicians and patients to understand the immunogenicity of therapeutic proteins
 - 2) Causes of immunogenicity
 - 3) Impact on PK, PD, safety
 - 4) Immunogenicity assessment strategy: methods and technologies
 - 5) Antibody-mediated PRCA: ESA case study

Opportunities for Convergence

Areas of Convergence

| Areas of Convergence | Opportunities for Convergence (Roadmap) |
|--|---|
| <p>Areas of convergence for nonclinical and immunogenicity were not really discussed during the sessions. Both of these sessions were more or less one way flows of information describing current 'state of the practice' approaches to these topics.</p> | <p>Despite the same clinical data presented to each regulatory authority to maximize the consistency, differences in the decision making for marketing authorization have been noticed. Although preliminary, the finding raises questions regarding the consistency of using existing clinical guidance and performing risk/benefit assessment, and underlines the importance of understanding the basis</p> |

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|---|--|
| | <p>of decision made by individual regulatory authorities.</p> |
| <p>Areas of convergence for clinical were addressed during the Q&A session, agreeing that the stepwise, case-by-case approach for the assessment and regulatory decisions on approval are commonly followed in the APEC region.</p> | <p>Country specific studies in local ethnic populations are required by several countries in the APEC region for marketing authorization of (bio) therapeutics in their countries. The scientific rationales for such a requirement need to be understood.</p> |
| | <p>(Lack of clinical expertise for clinical and biostatistical assessment is identified by several regulatory authorities. Training and information sharing in these areas can be helpful for adopting international regulatory guidance and achieving scientific convergence).</p> |
| | <p>The country to country ambiguity around the so called 'third path' towards registration of a biotherapeutic (not an innovator, not a biosimilar) should be further addressed.</p> |
| | <p>There is general agreement regarding immunogenicity testing strategy per se however there is a need to gain a deeper scientific understanding of the assays and technologies as well as around the management of clinical immunogenicity. The recommendation to plan and conduct an immunogenicity workshop in the wrap-up session would be a good mechanism to address the need.</p> <p>The ICH S6 revision is fairly recent and it is not clear what the APEC regulatory take on this is/would be. This could become a potential area of divergence however we do not know that for sure.</p> |

Session 4:

CMC Considerations: Manufacturing and Quality

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

- ICH guidelines for biologics | *Kowid Ho (Roche)*
- Review of recent ICH Quality guideline focused on enhanced process/product understanding (ICH Q8-11) | *Mats Welin (Medical Products Agency)*
- Feasibility of application of ICH Q8-11 to Biotherapeutic products | *Lynne Krummen (Genentech)*
- LifeCycle Management for Biotherapeutics: The Complex world of post-approval changes | *Richard Lit (Amgen)*
- GMP highlights in Biopharmaceuticals | *Chung Keel Lee (MFDS)*

Overview

Session 4 was designed to focus on the unique CMC and GMP aspects of Biotherapeutics by providing an overview of the basic global regulatory guidelines that are applicable and often unique to Biotherapeutics. A specific focus was placed on the core ICH Q5 series and Q6B principles and their appropriate interpretation as a baseline for regulatory convergence within the APEC economies. In addition, a discussion regarding the aim and evolving concepts of the ICH Q8-11 series was presented highlighting the concepts of quality risk management, quality by design elements including an example of practical applicability of these concepts to a Biotherapeutic development program. Beyond the ICH documents, the topic of Life Cycle Management of Biotherapeutics (especially in regard to post-approval changes) was also discussed including current issues with the complexity of global change management and opportunities for simplification and harmonization of the process of implementing and gaining global approval for post approval changes. Lastly, the unique aspects of cGMP requirements for Biotherapeutics were also presented with reference to ICH Q7 and specific considerations associated with sterile production and control.

Specifically Session 4 covered the following topics:

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- High-level overview of the ICH Quality documents that are applicable to Biotherapeutics. These documents cover the key aspects of Biotherapeutics manufacturing process and associated control strategy including genetic development, cell bank characterization and testing, drug substance production. .
- An in-depth discussion of the core principles of the ICH Q5/Q6 series with focus on Q5C (Stability), Q5E (Comparability) and Q6B (Specification). These three documents are essential guidelines to establish appropriate control strategy for Biotherapeutics and enable scientific based assessment and review of changes to the manufacturing process.
- An overview of the recent ICH guidelines (Q8-11) that relate to enhanced process and product understanding (i.e., Quality by Design and Quality Risk Management). These principles reflect a new paradigm focused on the development of a harmonized pharmaceutical quality system across the lifecycle of the product emphasizing integrated quality risk management based on product and process understanding.
- The practical aspect of use of risk assessments to analyze process performance and product quality attributes to determine critical process parameters and critical quality attributes for Biotherapeutics.
- A detailed Monoclonal antibody case study developed using ICH Q8-11 principles, illustrating the development of a risk-based integrated control strategy that forms the basis for ongoing process verification.
- The necessity for post-approval changes to Biotherapeutics manufacturing process to ensure prevention of drug shortage and enable introduction of improved testing and manufacturing technologies. The complexity associated with efficient implementation of such changes due to differing regulatory requirements across APEC economies and globally was discussed.
- GMP highlights in Biopharmaceutical production with focus on the key elements referred to as the 4 “M”s: Men, Materials, Machinery and Methods

Key Messages

Following the presentations, session participants held a panel session to answer questions and raise additional points to consider on the afore-mentioned topics. Here are highlights to the key messages during the panel session:

- In regard to Quality (CMC) aspects, there are significant differences between Biotherapeutics and small molecule pharmaceuticals, especially in regard to complexity of molecule characterization, production techniques and appropriate control strategies. These differences are the basis for the development of a

significant number of ICH Quality guidelines that are specific to Biotherapeutics, most notably ICH Q5 series and Q6B.

- The ICH guidelines are further complemented by the (draft) WHO guidance on recombinant products and they are as such considered the core essential guidances for adoption and convergence within the APEC economies.
- There is a need for a clear definition of “Biotherapeutics” and an understanding of the scope of the ICH/WHO quality guidelines. For instance, ICH stability guidelines may not be readily applicable to vaccines. In general, the ICH guidelines are focused on products deemed “Well-Characterized” and the broader applicability of such guidances to other biologics such as traditional vaccines should be carefully assessed on a case by case basis. The scope definition and rationale should be well articulated in the APEC Biotherapeutic Roadmap.
- For Biotherapeutics, ICH Q5E on Comparability is a fundamental document that provides the principles for studies required to support changes for approved products.
- Quality cannot be tested into products but should be assured by the process’ design. The Quality by Design principles in ICH Q8-11 are broadly applicable to all pharmaceuticals including Biotherapeutics. The use of QbD in Biotherapeutics development is still at early stages globally, but the frequency of adoption is expected to continue to increase as it offers a better understanding of the product and the manufacturing process.
- The use of the enhanced approach and associated tools (extensive risk assessment, design of experiment studies, critical quality and process attribute definition...) will require additional capability building and implementation workshops for regulators in the APEC economies. It is essential to establish a solid core capability and common interpretation of the basic ICH documents (Q5 series, Q6B) to enable further adoption of the recent enhanced approach (Q8-11).
- There is a broad acknowledgment of the global complexity of implementing post-approval manufacturing changes for a Biotherapeutic, largely driven by differing regulatory and procedural requirements (stability requirements, different classification of changes, Certificate of Pharmaceutical Product pre-submission...). The panel discussed various opportunities to bridge the gap:
 - There is a need of increased awareness among the APEC economies of the various diverging local/regional requirements and procedures and their impact. The use of implementation workshop and case studies is very helpful in that regard.
 - There is currently no ICH or WHO guidance that addresses the principles for assessing post-approval changes for Biotherapeutics that can be used as a basis for convergence.

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- It is worthwhile to explore the possibility of inclusion of recombinant products within the current draft WHO guideline on post-approval variations for vaccines, given significant overlap in principles.
- Other avenues such as ICH and expansion of ASEAN variation guidelines to Biologics can be further explored as additional secondary options.
- The growing trend of APEC economies joining PIC/S (8 of 21 economies are members with 4 more under consideration) should provide a basis for greater work-sharing on GMP inspections, and ultimately reduction in repetitive inspections.

Opportunities for convergence

- Common definition of “Biotherapeutics” and associated scope of products, and better link between scope of products covered by ICH and WHO guidelines (vaccines/recombinant products)
- Common adoption and future implementation of WHO guidelines, which are in line with ICH core quality guidelines for Biotherapeutics (ICH Q5 series and Q6B). Use of implementation workshops with case studies to converge to a common understanding of the available guidances.
- Common approach for Life cycle management with focus on post-approval changes: gaps identified relate to change classification categorization, data submission requirements including stability, and procedural elements (timelines...)
- Explore opportunities for inclusion of Biotherapeutics within WHO draft guidelines on variations for vaccines

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Session 5: Plenary Lecture

New Upcoming Biotherapeutics Technology

- Speaker: *Dr. James Merson (Pfizer)*
- Moderator: *Teruhide Yamaguchi (PMDA)*
- High-level overview of new innovative technologies in biotherapeutics | *Dr. James Merson (Pfizer)*
- Review of the day and wrap up / Conclusion and read-out from Day 1 and 2 | *Wassim Nashabeh (Genentech)*

Key message from plenary lecture:

High-level overview of new innovative technologies in biotherapeutics

- Ever-increasing health costs need to be addressed. CVD-related incidents doubled between 1990 and 2020, of which 80% occurred in developing countries. This illustrates a stark reality where health policies conducive for a better access to safe, efficacious and affordable medicines are lacking. Prevention along with production of generic drugs should be promoted to resolve this issue. In particular, vaccines that cure chronic diseases are placed an added importance.
- Vaccines are used to increase immunity which helps prevent contracting diseases. However, preventing diseases for life with immunity acquired from vaccines is impossible. Thus, special immune treatment vaccines should be developed.
- At present, 90% of lung cancer develops from smoking. Anti-nicotine vaccine with unique mechanism of action that will help stop smoking has been developed (smoking-induced pleasure will not be felt because the vaccine stops nicotine from reaching the brain's reward center).
- Non-clinical example: in animal study, a mouse that was vaccinated showed less nicotine going into the brain. It needs to be reviewed whether this has preventive or curative properties.
- Clinical example: Nabi NicVax and Cytos NicQb are on the 2nd phase clinical study and they displayed high anti-smoking rate (2:1)
- Pfizer's NIC7 is being developed after conducting functional analyses, and antibody titer and avidity were used to determine the type of vaccine.
- NIC7 is a bioconjugate vaccine and is made up of hapten, linker, carrier protein and immune-controlling adjuvant. NIC7 vaccine that contains adjuvant CpG demonstrated better efficacy than NicQb vaccine in non-primal placebo study. For healthy smokers, different doses of PF-05402536 and PF-06413367 are being administered to test for safety and tolerance.
- Roughly 300 million people worldwide are suffering from asthma and the number is estimated to reach 400 million by 2025. Thus, improvement in efficacy and safety of oral asthma treatments for severe asthma and as well as enhancement in non-steroidal prescription and existing treatments need to be made.

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- Pfizer developed IgE antibody that treats allergic asthma by addressing what triggers asthma attacks and related symptoms inflammatory cascades asthma attacks. Tests of IgE peptide on IgE C ϵ 3 domain that is combined with QbYLP on mice and nonhuman primates displayed special IgE antibody reaction. IgE Qb vaccine blocked antigen that increases circulating IgE while lowering current IgE levels (IgE level: went down from 500ng/ml to 50ng/ml). Antigens that produce specific IgE were lowered, also.
- Antibody Drug Conjugates will be the future of protein-based cancer treatments. Thus, Pfizer oncology is creating a comprehensive ADC toolbox that is the collection of all ADC components. Therapeutic index will be the essence of ADC development. Selection of patients is critical in conducting more proactive and integrated clinical studies.

Key messages on panel discussion:

- Regulators generally agreed that a separate registration pathway is unnecessary; the application of existing regulatory frameworks cover it, though case-by-case assessments apply.
- Panelists commented that the risk-benefit assessment would shift due to the differences between a prophylactic vaccine compared to a therapeutic vaccine (e.g., administering the product to healthy volunteers vs. patients with active disease), where more risk might be acceptable with a therapeutic vaccine.
- When considering applicable Quality/CMC regulations, most agreed that internationally recognized vaccine manufacturing and quality requirements would best apply, even though a therapeutic vaccine is aimed at treatment, like a drug.

III. Summary and Comment for Sessions

| *Wassim Nashabeh (Genentech)*

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 countries can be applied, also.

- Harmonization for biosimilars may be facilitated if the biosimilar manufacturers have reference cases in other countries which are currently difficult to achieve due to different rules and regulations. Still, there is room for harmonization between countries.
- 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 (e.g., 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 in developing countries as a whole: areas that can be accepted or whose areas can be work-shared and if so, such mechanism can be established. If succeeded, redundant inspection sessions will be minimized.
- Pharmacopoeia was not addressed but an important part of the CMC section roadmap.
- Updating of clinical requirements between countries based on scientific information. There are rules and regulations of respective countries, but this also needs to be discussed.
- Due to complex issues to consider, CTD harmonization needs further research.

Session 3

- Differences of 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 1-3 phases of clinical studies, but there may not be much that is different. 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, which where regulatory harmonization needs to take place.

Session 4

- Biopharmaceuticals and chemicals need a different approach. ICH Q5, Q6b have been the foundation of regulations for a long time, thus implementation and interpretation are more important, 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 countries, it may take some time. In the last case study presentation, importance of biopharmaceutical life cycle and GMP was emphasized.

Day 3: Thursday, September 27

Debriefing and Discussion

Discussion on the content of the “White Paper” or the meeting report | *Session for session chairs, speakers, regulators*

Summary

1. Assessment of workshop composition and contents

- Participation by audience with longer panel discussion time and different means of participation encouragement should be promoted

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- At least one regulatory official should join each panel discussion
- Information should be passed on to unattended speakers by having more engaged pre-meeting communication
- Workshop preparation time should have been longer.
- All APEC members should be encouraged to take part.
- For higher participation and better understanding, RHSC biopharmaceutical roadmap should be passed on to speakers and audience.
- Workshop results and contents should be put up on official website for more people to share sooner than later.

2. WHO Survey

- Surveys are important and a tool should be established in which how a baseline will be measured and who will create survey questions will be determined. WHO's survey initiatives are very positive. Questions that choose from multiple choices as well as subjective questions should be included in the survey.
- WHO survey results will be announced before the end of October and the RHSC biotherapeutics roadmap will be modified accordingly.
- Whether or not we should wait for WHO survey results to come out or new round of survey should be conducted needs to be discussed. APEC workshop result report and WHO survey results will help find discrepancies among APEC member countries.

3. Summary of each session

- Each session chair will send session summary (0.5-1 page long) to Dr. Romi Singh to help Dr. Kim create a final version of RHSC report which will be submitted within several months.

4. Suggestions for future RHSC activities:

- Meetings discussing training and education with a focus on detailed knowledge should be held
 - Meeting agenda
 - Clinical/Non-clinical (including GLP regulations for safety testing)
 - Manufacturing and quality
 - Post-marketing authorization
 - Training duration: 3—5 days
 - Trainee qualification: middle manager
- Follow-up meetings will be hosted by different agenda groups

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- Training duration will be different depending on team work properties
 - Trainee requirements: must complete first round of training
 - Training venue: meeting venue or established training organization
 - Chance for advice/recommendation by inviting experts (at the training facility)
 - Duration: 3-5 days
- * Each trainee and overall training programs need to be evaluated after training
- WHO and AHC will hold WHO biopharmaceuticals workshop in 2014 and holding a workshop around RHSC biopharmaceuticals roadmap in coordination with other RHSC roadmaps including those of multiregional clinical trials or pharmacovigilance.

Regulator only session

Discussion on the results of the WHO Survey and evaluate opportunities for regulatory convergence amongst DRAs

- Chair: *Ivana Knezevic (WHO)*
- Co-Chair: *Yeowon Sohn (MFDS)*

Key Messages

- Efficient communication between APEC countries is essential. To this end, single communication network between NRAs should be established and this network should be in charge of information exchanges and providing feedback to the secretariat in time. RHSC is developing an online platform with which regular communication between network members will happen.
- Roles of AHC secretariat and RHSC secretariat should be clearly defined. Who will determine single contact network for efficient communication between NRAs and who will circulate survey papers to APEC NRAs for how long, and if there is an additional survey papers, who will circulate them are some of the questions that should be clearly answered.
- Gap analyses results may be different depending on points of views (Industry or NRAs perspectives).
- Three gaps confirmed from the perspectives of NRAs:
 - Understanding on scientific theories required in conducting clinical evaluation for both chemicals and

biopharmaceuticals is lacking

- Means with which internationally-verified scientific theories will be applied (evaluations for both clinical and non-clinical areas)
- Requirements mandated by APEC countries in regulating biopharmaceuticals are different. What are rational explanations for the differences and will they be ironed out in the future?
- WHO survey will be finalized before the end of 2013. AHC secretariat or RHSC secretariat should please cooperate in getting feedback from NRAs.
- Additional surveys should be conducted to determine APEC members baseline. The NRAs volunteered to participate will complete the survey (Korea, Thailand, Indonesia, Malaysia, Taiwan, Singapore)
- Until all 11 countries that are not part of the current network have participated, all the workshop participants will be shared information via email.
- Biopharmaceutical/chemical WHO workshop due to be held by the MFDS in May, 2014 will offer a great chance to not only conduct WHO survey, but to review APEC survey progress. The national regulatory authorities that participated in the 2013 AHC workshop are encouraged to get involved in the preparation of the May, 2014 workshop including suggesting workshop agendas. Agenda topics for the 2014 May workshop for now are as follows:
 - Major considerations when reviewing regulations for clinical data in support of issuing biopharmaceutical product license
- National requirements for clinical data: local clinical data in discussing ethical differences and rational explanations regarding science-base conditions
 - Multi-regional clinical studies with a focus on biopharmaceuticals
- Assessment of immunogenicity

Major issues for discussion

- Adoption of biopharmaceutical guidelines by ICH and WHO that will be cited in realizing biotherapeutics harmonization in the APEC region
- Need to conduct regulatory gap analyses between APEC members and need to implement biotherapeutics guidelines by international organizations
- Discuss holding the WHO biopharmaceutical workshop (due to be hosted by MFDS in 2014) in connection with APEC biotherapeutics roadmap as well as APEC RHSC roadmap.
- Discuss establishing an online platform to emphasize more efficient communication and realize regular communication between all APEC members

- Conduct additional round of survey to define APEC region baseline
(Survey to be completed by volunteered NRAs: Korea, Thailand, Indonesia, Malaysia, Taiwan, Japan, and Singapore)

Visit a local Korean Biotec (Hanmi Pharmaceutical Co., Ltd.)

- 15 Regulators visited the Korean Biotech

IV. Conclusion: Areas of Regulatory Convergence

- The desired outcome of AHC and the Workshop Planning Committee was achieved in that a number of topics were identified to further advance via the AHC Biotherapeutics Roadmap, which is aimed to outline the major steps toward regulatory convergence. The following summarizes common themes (areas of convergence) and potential gaps (opportunities for convergence). Specifically, the following areas were identified as areas for opportunities for regulatory convergence (that is, to consider for Roadmap progress)
 - Many areas open for interpretation without common language and principles. Common understanding of globally accepted guidelines would be of value to initiate the regulatory convergence.
 - Further evaluate the “3rd pathway” that has emerged for biosimilar registration in some countries (e.g., Brazil and Colombia), that is inconsistent with WHO guideline
 - Despite the same clinical data presented to each regulatory authority to maximize the consistency, differences in the decision making for marketing authorization. This can be addressed through common adoption and future implementation of WHO guidelines, which are in line with ICH core guidelines for Biotherapeutics (e.g., ICH, S6, E5, Q5 series and Q6B)
 - Understanding the basis of decision made by individual regulatory authorities
 - Scientific basis for establishing/ updating national requirements for clinical data is essential for regulatory convergence which includes criteria for acceptance of foreign clinical data. In that context, MRCT as a common approach is recognized as an opportunity for regulators from APEC economies to actively contribute to its development as well as to the subsequent implementation
 - Biosimilar naming conventions –the impact to traceability of biosimilars for post marketing safety surveillance

- Common approach for Life cycle management with focus on post-approval changes: gaps identified relate to change classification categorization, data submission requirements including stability, immunogenicity, pharmacovigilance requirements

V. Recommendations to RHSC

1. Continue the analysis of the current national regulatory requirements for BTP needs to be conducted in order to identify differences among countries. Completion of WHO survey is seen as an opportunity to start defining the baseline of the regulatory convergence/divergence
2. Training for regulatory evaluation of BTP – review of existing training opportunities and opinion on the suitability of trainings for regulators
3. Explore opportunities for inclusion of Biotherapeutics within WHO draft guidelines on variations for vaccines
4. Continue the sharing of information, knowledge through joint workshops with the regulators from the APEC economies, WHO and the biopharmaceutical industry as outlined in the AHC biotherapeutics roadmap

VI. Next Steps

1. Revise the Biotherapeutics Roadmap based on the outcome and recommendations of this report
2. Consider the possibility of inclusion AHC Biotherapeutics component/session in the upcoming WHO meeting in Seoul in May 2014
3. Consider conducting next workshop in 2014 China with CFDA co-sponsorship (note China is the APEC Host Economy in 2014)

Annex 1: Program Committee Members

APEC LIFE SCIENCES INNOVATION FORUM REGULATORY HARMONIZATION STEERING COMMITTEE

| Name | Organization | Affiliation |
|-----------------------------|--|---|
| Dr. Byoung-Guk Kim CHAIR | MFDS | Senior Scientific Officer Biopharmaceutical Policy Division |
| Mike Ward | RHSC | Health Canada |
| Dr. Teruhide Yamaguchi | PMDA | Technical Expert Office of Cellular and Tissue-based Products |
| Dr. Yasuhiro Kishioka | PMDA | Reviewer Office of Cellular and Tissue-based Products |
| Dr. Jo-Feng Chi | TFDA | |
| Ivana Knezevic | WHO | Scientist Quality, Safety and Standards Team |
| Dr. Chung Keel Lee | MFDS | Special Advisor |
| Dr. Yeowon Sohn | MFDS | Director General Biopharmaceuticals and Herbal medicine Evaluation Department National Institute of Food and Drug Safety Evaluation |
| Dr. Seunghoon Lee | MFDS | Director Biopharmaceutical Policy Division |
| Dr. Youngju Choi | MFDS | Director Recombinant Protein Products Division |
| Dr. Sun-Young Baek | MFDS | Director Advanced Therapy Product Research Division |
| Dr. Jeewon Joung | MFDS | Deputy Director Recombinant Protein Products Division |
| Jisang Yoon | MFDS | Assistant Deputy Director, Pharmacist Biopharmaceutical Policy Division |
| Dr. Romi Singh Co-Chair | Amgen Inc. | Executive Director Global Regulatory Affairs & Safety |
| Dr. Wassim Nashabeh | Genentech (A Member of the Roche Group) | Global Head Technical Regulatory Policy & Strategy |
| Jerry Stewart | Pfizer | Asia Regional Lead and Emerging Markets Policy Lead International Regulatory |
| Douglas Hunt | Baxter Bioscience | Vice President Regulatory Affairs |
| Ziqun Han | AbbVie (Abbott) | Regulatory Policy and Intelligence Regulatory Affairs |
| Dr. Wen Chang | Bristol-Myers Squibb (BMS) | Vice President N. Asia Strategy and China Regulatory Sciences |
| Moo-Young Song | Yuhan Corporation | Bioinnovation unit Senior Principal Scientist |
| Dong Ho Ahn | Green Cross Corporation | Vaccine Process Development Unit Vice President |
| Chang-nam An | Il-Yang Pharm.Co.,Ltd. | Vaccine Production Division Division Manager |

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| | | |
|----------------------|--|--|
| Younghoon Kim | Hanmi Pharmaceutical Co.,Ltd. | Hanmi Innovation Research Center Research Director |
| Seungwon Lee | LG Life Sciences | Institute of Biopharmaceuticals Director |
| Hyuk Jae Lee | CELLTRION, INC. | Department Head |
| Ike Kim | Hanwha Chemical Corp. | Manager |
| Ji-Young HONG | Samsung Bioepis | Senior manager |
| Dr. Lindsay Tao | Johnson & Johnson | Corporate Director Global Health Policy |
| Lila Feisee | BIO (Biotechnology Industry Organization) | Vice President International Affairs Biotechnology Industry Organization |
| Jocelyn Ulrich | PhRMA | DIRECTOR SCIENTIFIC & REGULATORY AFFAIRS |
| Toshihiko Tsunenari | JPMA | Director Global Regulatory Affairs Dept |
| Dr. Hye-Soo Kim | MFDS | Director Drug Review Management Division |
| Dr. Jeong-Mi Kim | MFDS | Deputy Director Drug Review Management Division |
| Eun Hye(Grace) Park | MFDS | Director Drug Review Management Division |
| Hana Kim | KPMA | International Meeting Specialist |
| Esther Min Jeong Kim | KPMA | Researcher |
| Dahye Kim | KPMA | International Meeting Coordinator |
| Seoyoung Park | KPMA | International Meeting Coordinator |

Annex 2: Overview document

[Overview]

**2013 APEC Biotherapeutics Workshop
25-26 September 2013, Seoul, Korea**

The workshop will take place 25-26 September 2013. Registration begins the evening of September 24.

Workshop objectives:

The objective of this workshop is to bring together regulators, industry representatives, and members of academia to facilitate the harmonization and convergence of approaches to the regulations of biotherapeutics products in APEC economies in an effort to reach the highest level of regulatory convergence by 2020. This would facilitate the development of safe, effective and innovative biotherapeutic products in APEC economies by establishing a sound science-based regulatory process. Two key objectives would be to a) highlight the differences between biotherapeutics versus small (chemical) pharmaceuticals and provide details of various ICH guidelines that are specific to biotherapeutics, and 2) highlight the importance of science based approval pathway for innovative biologics as well as biosimilars. Such actions can lead to more efficient use of resources by regulators and industry, and ensure predictable and timely approval to safe and effective biotherapeutics in APEC region. Specifically,

1. This workshop will promote active discussion and participation among participating stakeholders to further promoting the harmonization of regulatory standards for biotherapeutics and to promote trade among APEC economies by ensuring the quality, consistency and timely availability of biotherapeutics to patients in the APEC region.
2. This workshop will provide scientific and technical discussion on how biotherapeutics are different from chemical products and the need for science based regulatory approval of the innovative biologic and biosimilars.
3. This workshop will highlight the various ICH guidelines that are specific to biotherapeutics. Other key biotherapeutic guidelines from USFDA and EMA and relevant WHO guidelines will also be discussed. This will facilitate the convergence on requirements for registration of biotherapeutics throughout the APEC region, which will help provide consistency and certainty with respect to these medicines for patients, health care providers, and biotherapeutics developers.

Target audience:

Officials from regulatory authorities involved in the review and authorization of biologics, including biosimilars. Industry representatives and members of academia will also be invited.

Expected outputs:

As part of the goals of Roadmap to Promote Harmonization and Convergence of Regulatory Pathways for Biotherapeutic Products, participants in 2012 AHC Biosimilar Workshop (held in Seoul in April 2012) shared information on the biosimilar regulations/guidelines developed in a few economies and the expected issues on regulating biosimilars. A Workshop Report was generated by the organizing committee that provided recommendations that were submitted to the RHSC of APEC LISF.

During the discussion was the outcome and recommendation of the aforementioned workshop, it was decided to expand the scope of Roadmap to all biotherapeutics, which include biosimilars. At the RHSC meeting in March 2012 it was agreed to use the term biotherapeutic products, which collectively include the biological products along with biosimilars with the indication of treating human disease, as defined by WHO. Among biological products, this roadmap will only cover the area of recombinant DNA products, monoclonal antibody, and therapeutic vaccines. Vaccines, blood products and cell/gene therapy products are not within the scope of this roadmap, though they are classified as biotherapeutic products by definition.

This workshop is meant to be a “catch-up” workshop to the previously held biosimilars workshop in 2012. After this workshop, future training and workshops (as outlines in the Roadmap) will include all biotherapeutics, including biosimilars.

A summary of discussions, ideas and recommendations from each of the sessions will be used to guide the development of future workshop and a project report and series of recommendations to be considered for follow up action. The report will be published as an important contribution to promoting a common understanding of review and approval of biosimilars based on their quality, efficacy and safety. This would help understand the principles to ensure biotherapeutics are safe and effective for patients and create an effective regulatory pathway for biotherapeutics. Workshop materials and summary reports will also be made publicly available, including on the website of the APEC Harmonization Center following review by presenters and chairs. The outcome will be submitted to RHSC of APEC LSIF.

Background and overview:

This workshop was endorsed by the RHSC at the APEC SOM1 & related meetings, in March 2013 in Jakarta, Indonesia and is expected to contribute to regulatory harmonization of biopharmaceuticals in the APEC region.

This follow-up workshop is meant to cover through series of interactive discussions, framed by brief introductory presentations and a series of Q&A and discussions. The workshop will provide series of recommendations to be considered for follow up action.

This workshop will also build upon recent and the ICH and other regional harmonization efforts, for example,

- AHC Biosimilars Workshop (Seoul, April 2012)
- MRCT, PV, Supply Chain Roadmaps

Speakers from the above conferences will be invited to this workshop.

As a follow-up of 2012 biosimilars AHC workshop, the 2013 AHC Biosimilar workshop aims to deliver the global trends for biotherapeutics development and the latest therapeutics regulations and guidelines of major economies, including ICH; to discuss specific issues and challenges in the development and approval of biotherapeutics compared to small molecules; and to develop the necessary tasks for future regulatory harmonization.

The specific organization of each session varies according to specific objectives, as described below. Instructions for chairs have also been developed to provide further detail and clarity on the organization of sessions. A number of sessions include “facilitated discussion components, wherein participants, led by chair(s) will be encouraged to express their views and ideas on a topic without challenging or debating the views of other participants. In the panel discussion, chair(s) and speaker can answer the participants’ questions and exchange (or share) their viewpoints on the raised issues. All ideas will be captured and subsequently assessed by session chairs and volunteers to develop summary reports, to be presented later in the workshop.

Session Objectives and Methods

Introduction: In experts and welcome participants from various APEC Economies, to present the workshop objectives and deliverables. The workshop will start with a welcome ceremony from the AHC. A keynote lecture by Ministry of Food and Drug Safety (MFDS), Korea, will include summary on the 2012 Biosimilar Workshop by AHC and the introduction and outline of the 2013 workshop.

Method: A keynote speech

Session 1 – The Basics: will discuss **Biologics vs. Chemical Pharmaceutical: How Are They Different?**

Will introduce the Roadmap. Presenters will provide overarching scientific principles that distinguish biologics from chemical products. Why certain elements of the current small molecules regulations may not be applicable to biologics/biotherapeutics. The workshop will encourage the development and consensus-building toward best practices for regulation of biologics.

Method: Overview presentation

Session 2 – Discuss ICH Framework: **ICH Guideline Relevant to Biologics/ Biotherapeutics**. This session will also include guidelines from USFDA and EMA as well as WHO and how they relate to ICH guidelines. The workshop will encourage the development and consensus-building toward best practices for regulation of biotherapeutics innovative biologics as well as biosimilars.

Method: Presentation and roundtable discussion ICH guidelines and future directions. Presenters will include ICH Steering Committee members.

Session 3 –**Non-Clinical and Clinical Considerations for Development of Biologics**: Specific ICH guidelines that have been developed for biologics will be discussed. .

Method: Presentation, facilitated discussion and case studies.

Session 4— CMC Considerations. **Manufacturing, Quality and Supply Chain**: This session will discuss application of relevant ICH guidelines used for development of biologics. The workshop will discuss both traditional and enhanced approaches (ICH Q8-11) as they apply to the development and commercialization of Biotherapeutics. This section will also focus on the aspects of "Lifecycle Management for Biotech Products", given the varying degrees of requirements (especially on comparability requirements including stability) and timelines globally where a manufacturing site change for a biotech product can take up to 4 years to be registered globally. The convergence on the scientific and procedural requirements to support post-approval changes for Biotherapeutic products is essential to ensure continuous supply of safe and effective products. This topic is also being considered by the ICH Quality Brainstorming Group to as a potential future ICH topic and would thus provide an opportunity for RHSC to play a significant role in its formative stages.

Method: Presentation followed by a moderated panel discussion that will include representatives from regulatory agencies and from industry. Panelists will share their views on best practices.

Roles of active participants:

Chair: Two Session Chairs will be nominated—one from the industry and the other from the HA. The Session Chair(s) will be responsible for the overall organization and objectives of the session and confirming, or assist in confirming, speakers and subject and order of plenary presentations. At the actual event, the Chair would introduce speakers, monitor time and moderate/facilitate discussions or Q/As that follow. The Industry Co-Chair will provide concluding remarks as the Rapporteur.

Rapporteur: The Rapporteur will be from the industry, and serve as the session co-chair responsible for reporting on outcomes of the session. They will also be responsible for taking notes on discussions and capturing ideas and recommendations generated by the group.

Session Coordinator: The Session Coordinator will reach out to industry and HA speakers for their participation on topics that were agreed by the Organizing Committee. The Session Coordinator will ensure coordination of topics with other sessions. The Session Coordinator can be nominated to be the Session Chair. There could be multiple Session Coordinators.

Program Coordinator: Ensures copies of materials are available for session participants. AHC and MFDS officials have kindly volunteered for this activity.

Annex 3. The workshop program

APEC Harmonization Center Biotherapeutics Workshop

September 25-27, 2013, Seoul Korea

| Time | Speakers / Description | Sessions |
|--|---------------------------------------|---|
| <i>Day 1: Wednesday, September 25</i> | | |
| 8:00 - 9:00 | Registration | |
| Opening Ceremony | | |
| 9:00 - 9:05 | Byoung-guk Kim (MFDS) | Welcome Remarks by Program Chair |
| 9:05 - 9:10 | Jin-Ho Wang (Director, AHC) | Opening Address |
| 9:10 - 9:15 | Byung-Won Jang (Vice President, MFDS) | Words of Encouragement |
| 9:15 - 9:20 | Won-Bae Kim (Chairman, KPMA) | Congratulatory Remarks |
| 9:20 - 9:35 | Romi Singh (Amgen) | <ul style="list-style-type: none"> • Special Remarks (Program Co-Chair) • Introduction and Outline of the 2013 Biotherapeutics Workshop |
| 9:35 - 9:50 | Soon-wook Hong (MFDS) | Keynote Speech |
| 9:50 - 10:05 | Coffee Break & Group Photo | |
| Session 1: Overview of Biotherapeutics, and a Roadmap Towards Convergence · Coordinator: Jerry Stewart (Pfizer) · Chair: Yeowon Sohn (MFDS) · Co-Chair: Jerry Stewart (Pfizer) | | |
| 10:05 – 10:30 | Kum Cheun Wong (IFPMA) | Biologics vs. Small Molecule Pharmaceuticals |
| 10:30 – 10:55 | Jane Bai (IFPMA) | Current Development/Regulatory Strategies of Biotherapeutic Products – Key Points to Consider vs. Small Molecules |
| 10:55 – 11:10 | Hyuk Jae Lee (Celltrion) | Progress and Update on Biosimilars Development in Korea |
| 11:10 – 11:30 | Byoung-guk Kim (MFDS) | Overview of Biotherapeutic Roadmap |
| 11:30 – 11:50 | Jerry Stewart (Pfizer) | AHC 2012 Biosimilars Workshop Output |

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|--------------------------|--|---|
| 11:50 – 12:10 | Judith Macdonald (Pfizer) | Biosimilar Regulatory Frameworks with Room for Convergence- what more is needed? |
| 12:10 – 12:40 | Panellists: Session Chairs, Speakers, Invited Participants | Conclusion and Q&A, Round Table Discussion |
| 12:40 – 14:00 | Luncheon | |
| | Session 2: ICH and WHO Biotherapeutic Considerations for Development of Biologics · Coordinator: Romi Singh (Amgen) · Chair: Ivana Knezevic (WHO) · Co-Chair: HongZhang Yin(CFDA) | |
| 14:00 - 14:35 | Ivana Knezevic (WHO) | Development and Implementation of WHO Guidelines for Regulatory Evaluation of Biotherapeutic Products |
| 14:35 - 14:55 | Jian Wang (Health Canada) | Key Issues that Regulators should Consider While Reviewing CT Data |
| 14:55 - 15:15 | Panelists: Invited Participants | Discussion |
| 15:15 - 15:45 | Mike Ward (Health Canada) | ICH Current Status and APEC Regional Harmonization Efforts |
| 15:45 - 16:00 | Coffee Break | |
| | Panel Discussion - Opportunities for regulatory convergence | |
| | Yvonne Khoo (NPCB, Ministry of Health, Malaysia) | Evaluation of Biologics in Malaysia |
| | Yasuhiro Kishioka (PMDA) | Evaluation of Biologics in Japan |
| 16:00 - 17:20 | Panellists: 1) China (HongZhang Yin, CFDA) 2) Chinese Taipei (Fia (Ya-Ting) Chen, Ministry of Health and Welfare) 3) Japan (Yasuhiro Kishioka, PMDA) 4) Korea (Jeewon Joung, MFDS) 5) Malaysia | Discussion: 1. How do Various Economies use WHO and ICH Guidelines? 2. What are the opportunities for regulatory convergence? |

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|--------------------------|---|---|
| | (Yvonne Khoo, NPCB, Ministry of Health) 6) Thailand (Prapassorn Thanaphollert, Ministry of Public Health) | |
| 17:20 - 17:50 | Ivana Knezevic (WHO) | <ul style="list-style-type: none"> • Review of the day and wrap up • Conclusion and read-out from Day 1 |
| 18:00 - | Reception (Hosted by AHC & MFDS) | |

| <i>Day 2: Thursday, September 26</i> | | |
|--|--|--|
| Session 3: Clinical / Non-Clinical (Case study) · Coordinator: Lila Feisee (BIO) · Chair: Jian Wang (Health Canada) · Co-Chair: David Hutto (Eisai) | | |
| 9:00 - 9:45 | David Hutto (Eisai) | Non-clinical ICH S6 (Non-clinical evaluation of biotechnology products) |
| 9:45 - 10:15 | Shalini Gupta (Amgen) | The Importance of Immunogenicity Assessment of Therapeutic Proteins |
| 10:15 - 10:30 | Coffee Break | |
| 10:30 - 11:00 | Freddy Faccin (AbbVie) | Clinical data requirements for registration of biotherapeutics |
| 11:00 - 11:35 | Panellists: Session Chairs, Speakers, Invited Participants | Q&A and Roundtable Discussion |
| Session 4: CMC Considerations: Manufacturing and Quality · Coordinator: Wassim Nashabeh (Genentech) · Chair: Chung Keel Lee (MFDS) · Co-Chair: Wassim Nashabeh (Genentech) | | |
| 11:35 – 12:15 | Kowid Ho (Roche) | ICH guidelines for biologics |
| 12:15 – 13:15 | Luncheon | |
| 13:15 – 13:45 | Mats Welin (Medical Products Agency) | Review of recent ICH Quality guideline focused on enhanced process/product understanding (ICH Q8-11) |
| 13:45 – 14:05 | Lynne Krummen (Genentech) | Feasibility of application of ICH Q8-11 to Biotherapeutic products |
| 14:05 – 14:25 | Richard Lit (Amgen) | LifeCycle Management for Biotherapeutics: The Complex world of post-approval changes |

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| | | |
|---|---|---|
| 14:25 - 14:45 | Chung Keel Lee (MFDS) | GMP highlights in Biopharmaceuticals |
| 14:45 - 15:15 | Panellists: Session Chairs Speakers, Invited Participants | Q&A and Roundtable Discussion |
| 15:15 - 15:30 | Coffee Break | |
| Plenary Lecture: New Upcoming Biotherapeutics Technology | | |
| 15:30 – 16:15 | James Merson (Pfizer) | High-level overview of new innovative technologies in biotherapeutics |
| 16:15 – 16:45 | Moderator: Teruhide Yamaguchi (PMDA) Panelist: Invited Participants | Q&A and Roundtable Discussion |
| 16:45 - 17:15 | Wassim Nashabeh (Genentech) | <ul style="list-style-type: none"> • Review of the day and wrap up • Conclusion and read-out from Day 1 & 2 |
| 17:15 – 17:20 | SunHee Lee (MFDS) | Closing Remarks by MFDS |
| | | |

| | | |
|------------------------------------|---|--|
| Day 3: Friday, September 27 | | |
| | Debrief and Discuss | |
| 9:00 - 10:00 | Session Chairs, Speakers, Regulators only Session | Discuss the content of the “White paper” or the meeting report |
| 10:00 - 11:00 | Regulators only Session · Chair: Ivana Knezevic (WHO) · Co-Chair: Yeowon Sohn (MFDS) | Discuss the results of the WHO Survey and evaluate opportunities for regulatory convergence amongst DRAs |
| 11:00 - afternoon | Visit a local Korean Biotec (Hanmi Pharmaceutical Co., Ltd.) | |
| | | |

Annex. 4. Biotherapeutic Products Roadmap (as of September 27, 2013)

Proposed APEC Activities for a Roadmap to Promote Harmonization and Convergence of Regulatory Pathways for Biotherapeutic Products

Goals:

- To facilitate the harmonization and convergence of approaches to the regulation of biotherapeutic products in APEC economies in an effort to reach the highest level of regulatory convergence by 2020
- To facilitate and encourage the development of safe, effective and innovative biotherapeutic products in APEC economies by establishing sound science - based regulatory processes
- To identify opportunities to enhance mechanisms on the biotherapeutic products regulatory pathway to improve public health
- To promote and protect public health through a more harmonized regulatory environment for biotherapeutic products within the APEC region.
- To enhance mutual understanding through trust-building between APEC economies

Background and Challenges:

Biological products, also known in some countries as biologics, biological medicinal products and biologicals, are defined by the World Health Organization (WHO), as medicines obtained from biological origin, i.e., human and other living organisms which cannot be fully characterized by physicochemical means alone, and which therefore require the use of some form of bioassay. Moreover, manufacturing procedure of biological products may include one or more of the following elements: growth of strains of microorganism and eukaryotic cell, extraction of substances from biological tissues, recombinant DNA (rDNA) techniques, hybridoma techniques, propagation of microorganisms in embryos or animals. While the definition and scope are slightly different among regulatory authorities, biological products, in general, cover vaccines, blood, blood components or derivatives, plasma derivatives, recombinant DNA products, monoclonal antibody, therapeutic serum, toxin, antitoxin, cell and gene therapy products involved in the prevention, treatment or cure of a disease or condition of human beings. Biosimilars (similar biotherapeutic products) are included in the term biological products, also. A

biosimilar is a biological product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

We herein use the term biotherapeutic products, which collectively include the biological products along with biosimilars with the indication of treating human disease, as defined by WHO.

Among biological products, this roadmap will only cover the area of recombinant DNA products, monoclonal antibody, and therapeutic vaccines in line with the RHSC decision made in the last meeting (Mar 28-30, Singapore). Vaccines, blood products and cell/gene therapy products are not within the scope of this roadmap, though they are classified as biotherapeutic products by definition.

After traditional biological products were released in the 1800s, biological products have been significantly developed thanks to technological improvement. Since the first rDNA product, insulin, was introduced in the early 1980s, there has been enormous progress in the ability to purify and characterize biologically active macromolecules. Separation and analytical technologies have improved significantly and many biological macromolecules can now be characterized in considerable detail making them much better defined than traditional biologicals. Nevertheless, it is still not possible to fully predict biological properties and clinical performance of these products from physicochemical characteristics alone. In addition, the production processes are biological systems which are known to be inherently variable, a feature which has important consequences for the safety and efficacy of the resulting product.

In the last few years, the expiry of patents for the first generation of biotherapeutic products (mainly rDNA products) has led to great interest from manufacturers globally to increase investment in biotherapeutic products. Biosimilars are expected to be more affordable than the originals and contribute to increased access to much needed products. This is due to the fact that it is expected they will be licensed subsequent to an approved originator product but on the basis of a reduced data package relying partly on originator data.

Along with the expansion of biological products, it is generally and globally agreed that review and regulation of biological products require regulatory needs distinct from chemical drugs, with emphasis on production process controls, standardization and stability. Potential safety concerns arise from the novel processes used in manufacture and from the complex structural and biological properties of the products themselves. Of particular concern in manufacturing are the needs to minimize product variability and prevent contamination. Adequate control measures are essential for these products.

Changes in the biopharmaceutical environment and trends in development and production of innovative biotherapeutic products pose a challenge for each country in APEC region to making efforts such as building appropriate approval review processes and post-market oversight measures for these products, adopting policies for prompt review processes and increasing review personnel. As regulations for biotherapeutic products are being developed and implemented differently by APEC countries, there are regulatory gaps and differences in capacities of responsible regulatory authority. So, it can be viewed as a new area, there is also great chance for prospective convergence and harmonization as various parties come together to develop the regulatory guidance and requirements in APEC region.

Under these circumstances, building a roadmap in the APEC region has emerged as a major issue for a consistent communication network 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. There is a growing realization that no single regulatory authority has a monopoly on good science/approaches nor can go it alone. Available regulatory expertise and resources, especially in evaluating complex biotechnology product submissions, are an issue for many countries. Closer regulatory cooperation and networking are essential prerequisites for a natural response to these realities. Inter-agency and country level agreements/arrangements in turn serve as key instruments that help govern enhanced regulatory interactions. Bilateral or multilateral forums will be supportive to develop best practice, share knowledge, adopt or contribute to international standards, and develop compatible approaches with international counterparts that may include sharing information, undertaking collaborative scientific work, common data collection, risk assessment or compliance methods, and joint review, developing common or international standards, equivalency or mutual recognition to promote greater regulatory convergence and harmonization.

Therefore it is critical for the APEC to devise ways for regulatory convergence that would drive harmonization of biotherapeutic products practice in member nations. This will, in turn, enable the APEC to respond to calls from the international community for enhanced regulatory harmonization in biotherapeutic products. The APEC - an eco-geographical community - needs an integrated system where information on all available pharmaceuticals has been compiled sufficiently and expertly reviewed/evaluated fairly and safety information will be made accessible with participation of all the APEC economies guaranteed.

Roadmap Overview

- Assess current regulatory preparedness for the authorization of biotherapeutic products. Specifically the regulatory frame works, and related infrastructure in each APEC economy

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- Review biotherapeutic products guidelines from competent international regulatory authorities with acceptable regulatory standards (e.g. those of the ICH, WHO, FDA, EMA, Health Canada and APEC economies)
- Establish common understanding among APEC member nations subject to LSIF regarding key issues including the following. This will be facilitated by biotherapeutic products workshop.
- Development of an appropriate quality, efficacy and safety level for approval of biotherapeutic products
- Understanding and description of current status of biotherapeutic products, stages of biologics development including product characterization, nonclinical safety, clinical pharmacology, and clinical development
- Stepwise approach in developing evidence to support a demonstration of biosimilarity
- Operational/regulatory procedures to facilitate effective implementation of the roadmap through cross-talk and information sharing between APEC members
- APEC-wide risk management, equivalency or mutual recognition and joint review for CMC, quality, safety, efficacy, etc
- Develop new ways of collecting, analyzing and sharing biotherapeutic products information including regulatory pathway information
- Conduct training/workshop for regulatory harmonization involved in biotherapeutic products, in particular regulatory harmonization related to the key issues cited above, biotherapeutic products workshops will be an important facilitator in this process
- Make possibility to develop regulatory framework for approval of biotherapeutic products
- Recommend agenda for biotherapeutic products regulatory harmonization
- RHSC will support related activities and development of recommendations for the next step
- Develop approaches to addressing situations where APEC economies may have already licensed biotherapeutic products without due attention to the regulatory needs for these medicinal products

A maximum level of harmonization and convergence of regulatory practices on biotherapeutic products will be achieved through the implementation of the roadmap.

Specific Actions and Time Frames

Step 1: Assessment (2013-2014)

At APEC biotherapeutic products workshops, meetings and surveys, the current status of biotherapeutic products regulatory practices will be assessed and identified. Common strategies for biotherapeutic products

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progress in the APEC region should be devised. Review of the current status of biotherapeutic products

regulation is essential in finding regulatory gaps between APEC member nations. The strategies will take into consideration gaps between “as-is” status and “to-be” goals. The strategies will factor in other relevant roadmaps and frameworks including APEC LSIF. Other related regulations will be discussed in symposia and workshops under APEC and other organizations.

The assessment should be conducted in the following context:

- Collect current status, information and level of quality, safety of the biotherapeutic products in each APEC members through survey or workshops.
- Analyze and identify gaps between “as-is” status and “to-be” goals of the biotherapeutic products regulatory systems in each APEC economy
- List priorities of requirements and activities for convergence, and major obstacles to biotherapeutic products regulatory harmonization
- Lists should reflect the characteristics of each biotherapeutic products, subscribe in this roadmap
- Identify and share main agenda for cooperation towards and implementation of the roadmap
- These activities in Step 1 will execute through some programs like survey, during AHC workshop, seminar and other events

RHSC will help facilitate the process. The assessment will include recommendations for the next step.

Step 2: Training/workshop (2014-2018)

Based on the recommendations from Step 1 assessment, economy/economies will develop training/workshop curriculum and conduct training/workshop in cooperation with other APEC economies and/or RHSC, depending on circumstances of the economy/economies. Biotherapeutic products workshops may consider creating curricula for training those in the regulatory authorities, academia, industry, and research institutes. Training and workshop will be created to reflect the common subject and the characteristics of biosimilars.

<Possible Common Training Subjects>

- Quality (CMC) –
 - Manufacturing process

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- Regulatory issues associated with production platform for biotherapeutic products; the new(eg. plant, insects) and the traditional(mammalian cells) production platforms for biotherapeutic products
- Regulatory approaches to dealing with the discovery of adventitious agents in marketed biotechnology products
- Characterization
- Specification and test methods
- Pharmacopeial Standards
- Role of reference materials and their establishment
- Stability
- Manufacturing changes(comparability)

- Non-clinical study
 - Pharmacological study (*In vivo* and *In vitro*)
 - Toxicological study

- Clinical study
 - Understanding clinical study; clinical trial phases
 - Clinical pharmacology
 - Safety assessment
 - Efficacy assessment
 - Good clinical trial practice
 - Statistical consideration for clinical trial

- Regulation of Biosimilars (Comparability exercise for proving biosimilarity, extrapolation, etc)
(This can be incorporated into sections of CMC, Non-clinical study and clinical study mentioned above.)
 - Good Scientific and quality considerations in demonstrating biosimilarity to a reference product.
 - Licensure/regulatory pathway for biological products shown to be biosimilar to a licensed/registered biological reference product.

- Pharmacovigilance and risk management mechanisms

- Orphan biotherapeutic products

- Understanding regulatory oversight of biotherapeutic products in different jurisdictions

Other areas that may require collaboration with APEC countries will be reviewed at workshops.

<Possible area for establishing the collaborative system across the economies>

- Building up the communication channel and establish information sharing system between economies. Examples are as follows:
 - Sharing review/approval information and building up the parallel review system
 - Sharing the findings of GMP inspection and following measures
 - Sharing PMS data and/or following measures
 - Communicating the recent regulatory issues related to biotherapeutic products
- Develop plans to build Crew Resource Management (CRM) system for transparent biotherapeutic products regulatory system

The curricula developed by the member countries and biotherapeutic products workshops will be used in a coordinated program to “train the trainers” which will allow the APEC economies to have the ability to conduct additional training to share best practices. It is expected that by the end of Step 2, highly applicable ideas regarding biotherapeutic products as well as practical visions will be developed.

Step 3: Assessment for following up of training/workshop (2018-2019)

Results of Step2 training/workshop, post-implementation of international guidelines and other attempts will be reviewed by the APEC and other related organizations. If necessary, they will be reviewed at symposia and workshops under RHSC. Biotherapeutic products recommendations for enhanced efficiency at the APEC nations will be formulated. Depending on the results of Step2 training/workshop, to raise the regulatory and/or guideline level of rated low APEC countries, build convergence regulatory and/or guideline of biotherapeutic products can be considered.

Step 4: Training/workshop to reach goals (2019-20) and recommendations for regulatory convergence to RHSC

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- Based on recommendations from Step 3 assessment, economy/economies will revise training/workshop curriculum and conduct training/workshop accordingly with the help from other APEC members and/or RHSC, depending on situations of the economy/economies.
- All APEC member countries will have their upgraded regulatory systems that are in line with best international regulatory practices.
- Use of case studies based on actual implementation of biotechnology products roadmap in training should be considered. Collaborative surveillance systems with APEC countries should also be reviewed.
- Build up collaborative system and information sharing (e.g., post-marketing surveillance systems).
- The information shared should be practiced in each APEC members.
- Based on the Step 4 results, economy/economies should upgrade level of regulatory, guideline like well established organization such as ICH, WHO and execute following up training/workshop.

The biotherapeutic products roadmap, based on experiences and activities generated in the process of roadmap implementation, will be the basis for regulatory harmonization recommendations authorized by RHSC.

Performance Indicators

<Establish of the highest level of regulatory harmonization and how these activities used in APEC region>

- Assessment and analyses of regulatory status by 2014 through AHC workshop
- Conduct training and introduce biotherapeutic products guidelines by 2018 and educate regulatory specialist
- Reflect results generated from assessment in training sessions and workshops by 2018 and raise up regulatory levels of each APEC members
- Progressive reports in line with goals of biotherapeutic products roadmap by 2020
- Follow-up meetings and additional recommendations for regulatory harmonization by 2020 and reach high level of regulatory convergence. It may be contain develop common regulatory of biotherapeutic products roadmap in APEC region

<Enhance mutual understanding about regulatory convergence through network between APEC member>

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- The number of APEC economies who have adopted regulatory measures in line with international guideline and the status of implementation to regulate biotherapeutic products by 2020
- Prepare for number of MOUs between agencies by 2020, which possibly include the activities of data format, sharing, communication, etc

<Give another opportunities about develop next step of regulatory harmonization for another biologics>

- Reports to be provided at each RHSC meeting
- Final report summaries
- Lessons learned(regulatory specialist development through training/workshop, To identify demand for education, possible training hopes survey during AHC workshop, will be considered

Relevant Guidelines to be provided:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on Quality of Biotechnological Products : Stability Testing of Biotechnological/Biological Products, and other 11 relevant guidelines
- The World Health Organization (WHO) Guidelines on the Quality, Safety and Efficacy of Biotherapeutic Products Prepared by Recombinant DNA Technology
- US Food and Drug Administration (FDA) Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology, and other 36 relevant guidelines
- European Medicines Agency (EMA) EMEA Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products, and other 9 relevant guidelines
- ICHS6 (R1)- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- ICH-M3(R2)- Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Biosimilar Guidelines
 - ① Guidelines on evaluation of Similar Biotherapeutic Products(SBPs) (WHO)
 - ② Guideline on similar biological medicinal products and other 7 relevant guidelines(EMA)
 - ③ Guidance for industry Biosimilars : Questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009 (FDA)
 - ④ Scientific Considerations in Demonstrating Biosimilarity to a Reference Product(FDA)

- ⑤ Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product(FDA)
- ⑥ Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (FDA)
- ⑦ Guideline for the quality, safety and effectiveness of biosimilar products(PMDA)
- ⑧ Guidelines on the evaluation of biosimilar products and other 4 relevant guidelines (MFDS)