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Regulatory Harmonization Steering Committee Vision 2020: A Strategic Framework - Regulatory Convergence for Medical Products by 2020

Purpose: Consideration
Submitted by: CTI

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Regulatory Harmonization Steering Committee
VISION 2020:
A Strategic Framework
Regulatory Convergence for Medical Products by 2020

Executive Summary

The strategic plan adopted in 2010 by APEC's Regulatory Harmonization Steering Committee (RHSC) and the Life Sciences Innovation Forum in Sendai, Japan provided the basic proposal and rationale for achieving regional regulatory convergence for medical products by 2020. The purpose of the strategic framework is to outline a strategic multi-year approach for meeting this objective in support of the broader objectives of improved public health and economic development. Each economy would determine the level of convergence it desired, would develop specific strategies to promote regulatory convergence and would set its timetable in the context of its own regulatory system and socio-cultural objectives. While each economy may adopt each phase on its own timeframe, the ultimate aim would be for APEC economies to achieve the maximum level of regulatory convergence feasible by 2020.

What does "regulatory convergence" mean in the context of this framework and APEC principles of voluntary action?

- Regulatory convergence represents a *voluntary process* whereby the regulatory requirements across economies become more similar or "aligned" over time as a result of the gradual adoption of internationally recognized technical guidance documents, standards and scientific principles (harmonization) and common or similar practices and procedures.[1]
- It *does not* represent the harmonization of laws and regulations, which is not necessary to allow for the alignment of technical requirements and for greater regulatory cooperation.

This initiative does not seek to develop new guidances; rather, it will rely upon existing guidances already developed by international harmonization organizations. The decision regarding when and which technical guidances and best practices should be adopted, or adapted, rests entirely with individual economies. Such voluntary action in no way creates expectations of, nor obligations upon, participating economies. Economies engaged in regulatory convergence in the area of medical products will do so because they believe it will allow for more science- and risk-based approaches, greater regulatory cooperation and efficiencies, reduced regulatory burden and ultimately, more timely access to medical products and advances in public health.

Capacity building is a fundamental element of this initiative and will be critical to its success. Rather than proposing single projects for APEC funding, member economies will propose areas of work and will develop strategic roadmaps to ensure that APEC's capacity building activities support one another and contribute to the success of the overall initiative. Training activities will focus on increasing awareness of regulators and industry of regulatory best practices to promote use of harmonized regulatory guidances, focusing initially on pharmaceuticals (with ICH as the primary source of guidance) and medical devices (with GHTF as the primary source of guidance). Examples of projects currently underway include Multi-Regional Clinical Trials and Good Review Practices.

The Strategic Approach

The proposed strategic approach for Regulatory Convergence in the Medical Products Sector is a multi-phase program representing a continuum of activities leading to 2020.

[1] For the purposes of RHSC activities and this Framework, the concept of "harmonization" represents the development and adoption of the same standard or requirements. Harmonization may also be applied to procedures and practices so these are the same across economies. Harmonization represents an important means of achieving regulatory convergence over time, as does the adoption of common procedures and practices.

Phase One - Setting the Foundation – Building Capacity in Procedures for Developing and Implementing Regulatory Best Practices (2011-12): Understanding of the elements of a basic regulatory system for medical devices and for pharmaceuticals is a critical part of setting the foundation for convergence. During 2011, the RHSC will draw up a list of key areas of focus for two medical product sectors: pharmaceuticals and medical devices. Member economies would nominate and act as a champion for a topic that their regulatory authority believes is important and would benefit from regulatory convergence. The champion would draft a specifically tailored roadmap for the topic it selects. These roadmaps would define the issue and its importance; identify gaps learned from diagnostic workshops, issue analysis, or economy-compiled checklists; prioritize the needs based on risk assessment and other relevant criteria; and develop a strategic program to close gaps that include training activities tied to these needs.

Phase Two - Advancing the Process (2013-15): Once the key areas of focus are determined and initial gaps identified, the RHSC will determine the expertise and resources needed to make progress in each area as well as the sources of the resources – e.g., government only or including the private sector. The areas of focus and the roadmaps would guide this process, and projects would flow from the work plans laid out in the roadmaps.

Phase Three – Assessing Convergence (2015-20): As 2020 approaches, participating economies should be encouraged to voluntarily complete a readiness assessment on their individual progress toward the goals they have set for themselves in developing a regulatory system that converges with international best practices. The RHSC will develop a regulatory evaluation template that economies can use to generate self-diagnosis on their degree of implementation of best regulatory practices; a process to use these reports to identify gaps; and a procedure for developing targeted capacity building to close these gaps. During this period, periodic reports would be made to APEC Senior Officials on the overall progress toward the goal of the maximum level of regulatory convergence feasible by 2020.

Introduction

Proposal

The strategic plan adopted in 2010 by APEC's Regulatory Harmonization Steering Committee (RHSC) and the Life Sciences Innovation Forum in Sendai, Japan provided the basic proposal and rationale for achieving regional regulatory convergence for medical products by 2020. The purpose of this document is to outline a strategic multi-year approach for meeting this objective in support of the broader objectives of improved public health and economic development. While each economy may adopt each phase on its own timeframe, the ultimate aim would be for APEC economies to achieve as much regulatory convergence as possible by 2020.

APEC agreement to achieve the maximum level of regulatory convergence feasible by 2020 will invigorate economies' work in this area and produce meaningful results for regulators and industry. Greater convergence among APEC members' regulatory systems for medical products will have important benefits in improving public safety and patient access to life enhancing medical products. A new focus on implementation of harmonized regulatory guidances and standards and the adoption of best practices will guide APEC capacity building activities towards concrete outcomes, which will require concerted efforts at all levels of government and within APEC. The LSIF Regulatory Harmonization Steering Committee will develop specific strategies to promote and enhance understanding of regulatory convergence in consultation with other APEC groups such as the Standards and Conformance Sub-Committee (SCSC) and the APEC Harmonization Center.

Member economies – working in concert with industry, academia and others as appropriate – are encouraged to develop specific strategies to promote regulatory convergence. Each economy would determine the level of convergence it desires and would set the timetable that makes the most sense in the context of its own regulatory system and socio-cultural context. The ultimate goal would be to achieve greater uniformity among APEC members' medical product regulatory systems by 2020 with a view to facilitating exchange of information among regulators to improve safety and efficacy of medical products and creating more efficient regulatory processes and aligned regulatory requirements to promote public health and innovation, as well as reduce market access hurdles for companies active in the APEC region. While APEC would be seeking convergence at the regional level in the evolution of regulatory systems for medical products, the right of participating economies to address the protection of public health by the regulatory means considered to be most suitable is acknowledged and would be preserved.

Regulatory Convergence Seeks…

- To achieve by 2020 greater uniformity among APEC member's medical product regulatory systems in terms of technical requirements and regulatory best practices
- To facilitate exchange of information among regulators to improve safety and efficacy of medical products
- To create more efficient regulatory processes to promote innovation and reduce market access burdens for companies
- To focus on guidance, standards and regulatory practices
- To preserve the right of participating economies to address the protection of public health by the regulatory means considered to be most suitable
- To preserve regulators' right to independent action
- To preserve existing (legal) frameworks

Regulatory Convergence Will Allow Each Economy…

- To adopt each phase in its own timeframe
- To define its own goals and what is feasible by 2020
- To benefit from targeted APEC capacity building to achieve these goals
- To decide not to harmonize every element of its regulatory system
- To determine its own criteria for success and judge its own level of convergence in 2020

Regulatory Convergence Does NOT…

- Seek to establish new or change existing (legal) frameworks
- Involve the harmonization or convergence of laws and regulations
- Require regulators to be subject to any outside authority
- Constrain regulatory authority to protect and protect public health

Achieving greater alignment over time of regulatory requirements based on recognized international guidances, standards and best practices will require understanding of the regulatory best practices already being undertaken, an assessment of ways to improve convergence, and a capacity building program to fill gaps through education and regulatory revision as defined above. Critical to success will be an ongoing training program to increase awareness of regulators and industry of regulatory best practices to promote compliance with the underlying harmonized regulatory guidances. APEC projects for training programs should be explicitly designed to show how each would enhance economies' progress toward the maximum level of regulatory convergence feasible by 2020.

This document describes a strategic framework for achieving the maximum level of regulatory convergence for medical products feasible by 2020. It focuses on a model based on long term goals and emphasizes a focused and disciplined approach in discerning divergent regulatory approaches and working towards established international best practices. The results would be a movement away from ad hoc individual proposals to defined priority work areas. Needs assessments from diagnostic workshops, self –assessment by individual

economies and a "roadmap" for promoting best practices will help define individual projects to promote discussion and consensus by regional technical experts on the use of recognized international best practices in the regulatory frameworks of APEC economies. (See Figure 1).

FIGURE 1

Building on APEC Regulatory Convergence Work

APEC has a long record of supporting the concept of regulatory convergence. Life sciences officials in APEC economies have affirmed that achievement of public health goals requires an appropriate health care infrastructure, including an appropriate regulatory system. In launching the Life Sciences Innovation Strategic Plan in 2004, they agreed on the following points:

- To harmonize quality standards for life science products and services according to international best practices;
- To recognize the APEC principle that where there are existing international standards these will be the basis for harmonization in APEC and - where appropriate international organizations exist for developing international standards - APEC economies will focus their coordinated efforts on promoting the development of international standards through these bodies; and
- To base its work on international standards and best practices such as those of the Global Harmonization Task Force (GHTF)[2] for medical devices, including *in vitro* diagnostic medical devices and the

[2] Four of the five founding members of the Global Harmonization Task Force (GHTF) are members of APEC (Australia, Canada, Japan, and United States). The fifth founding member is the European Union.

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)[3] for pharmaceuticals.

In 2010, the LSIF Regulatory Harmonization Steering Committee adopted the following guiding principles as it works to achieve its mandate of increasing the level of convergence of regulatory requirements for medical products throughout the APEC region:

- Regulatory harmonization proposals and activities should respect APEC principles on harmonization, specifically that:
  - Harmonized international standards and guidances should form the basis for harmonization;
  - Where appropriate organizations exist for developing harmonized international standards and guidances, APEC economies should focus their coordinated efforts on promoting the development of international standards and guidances through these bodies;
  - Participation in harmonization activities is open to all APEC member economies on a voluntary basis and decisions consensus-based; and
  - Actions may be undertaken at collective and individual levels.
- Take advantage of APEC LSIF's unique role as an 'enabler of harmonization' in promoting the use of existing international standards, guidances and best practices across a number of medical product lines while at the same time serving as a vehicle to promote prospective harmonization dialogue in the area of advanced therapies.
- Adopt a strategic, coordinated approach to harmonization
- Strive to complement rather than duplicate the work of other parties, thereby leveraging respective resources and efforts.

For several years, APEC Ministers and Leaders have declared that harmonization of standards for life sciences products according to international best practices will promote improved public health and give the APEC region a competitive edge, facilitate trade, and expand opportunities for the rapid development of innovation. In 2010, APEC Ministers called for advancing regulatory harmonization with specific goals and target dates for concluding this work.

As work proceeds on regulatory convergence for medical products, the Regulatory Harmonization Steering Committee will draw on and take note of relevant documents already agreed in APEC[4] as well as the activities of multilateral organizations[5] so as not to duplicate effort. The initial areas of focus would be medical devices and pharmaceuticals, based on the importance of these sectors to member economies as well as the existence of a comprehensive set of best regulatory practices developed primarily through the GHTF and ICH.

The Strategic Approach

Strategy Overview: Individual and Collective Actions

[3] Two of the three founding members of the ICH are members of APEC (Japan and the United States) and Canada also participates in the ICH process

[4] Including the Life Sciences Innovation Strategic Plan; the Life Sciences Innovation Checklist; and the APEC-OECD Integrated Checklist on Regulatory Reform, among others.

[5] Including ICH, GHTF, Asian Harmonization Working Party (AHWP), Latin American Harmonization Working Party (LAHWP), Association of Southeast Asian Nations (ASEAN), International Standards Organization (ISO), Organization for Economic Cooperation and Development (OECD), and World Health Organization (WHO), among others.

The proposed strategic approach for regulatory convergence in the medical products sector is a multi-phase program. As is the usual practice in APEC, regulatory convergence goals would be achieved through individual and collective actions by APEC Economies. It is anticipated that each APEC Economy will proceed at its own pace with the objective of achieving as much regulatory convergence for medical products as possible by 2020. The desired outcome would be greater uniformity of regulatory principles and requirements in accordance with agreed-upon harmonized guidance and best practices. Efforts would be made to standardize the form in which evidence of conformity with those requirements is presented. Importantly, economies would always retain the right, authority, and responsibility to make their own decisions in the context of their public health systems.

Multi-phase Approach

The phases described below are intended as guides for economies to use to progress toward regulatory convergence. Each phase is not meant to be a discrete element but a series of steps on the continuum of activities leading to 2020. For example, some economies may have reached their desired level of development for most aspects in one phase but not in another and may wish to continue working on completing that initial phase while also moving on to the next. The time periods suggested are intended to provide guideposts for economies to evaluate progress on implementing their strategy for regulatory convergence. It should also be noted that this plan refers to the overall methodology, not the individual topic roadmaps (see below), which may have more or fewer phases in their work plan.

Phase One - Setting the Foundation – Building Capacity in Procedures for Developing and Implementing Regulatory Best Practices(2011-12): Understanding of the elements of a basic regulatory system for medical devices and for pharmaceuticals is a critical part of setting the foundation for convergence. During 2011, the RHSC would draw up a list of key areas of focus for two medical product sectors: pharmaceuticals and medical devices. These would be the first areas of effort and could be expanded as the program advances, as decided by the RHSC.

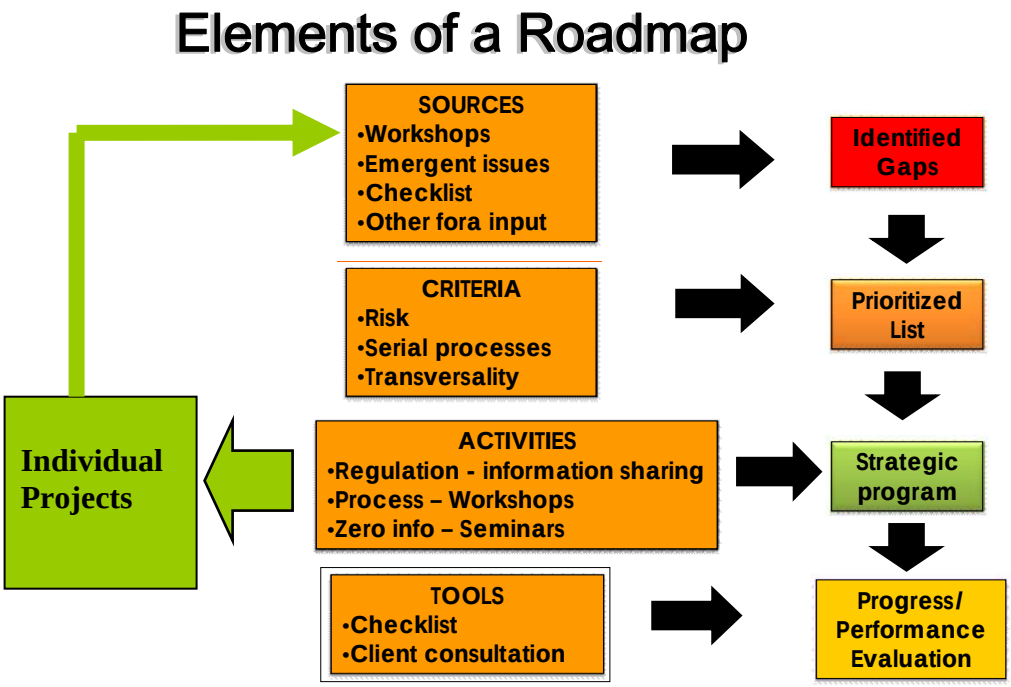
Through discussions at the RHSC, APEC Economies would determine the key areas of focus for medical devices, which could include quality management systems, post-market surveillance, good review practices and clinical evidence. Initial areas of focus for pharmaceuticals could include drug product quality, multi-regional clinical trials, supply chain integrity, good review practices and pharmacovigilance. GHTF guidance documents would be the core reference materials guiding best practices for medical device regulations, while ICH documents would be the core reference materials for pharmaceutical regulations. As part of this process, APEC could refer to other agreed international best practices to determine common goals. Examples include common definitions, a harmonized risk-based device classification system, and standardized submission formats.

In setting the foundation for a robust regulatory system that is science-based, transparent, effective and predictable, the RHSC could draw on broader APEC efforts, including APEC's Transparency Principles as well as the APEC-OECD Integrated Checklist on Regulatory Reform, which provides a list of areas that form the basis of a sound regulatory system.

At the direction of the RHSC, the APEC Harmonization Center would support these efforts through targeted training programs, research and other measures. Member economies would choose the areas of focus by nominating a topic that their regulatory authority believes is important and would benefit from a harmonized approach. That economy would then become that topic's "champion" from among the member economies. This champion would take the lead within the RHSC for organizing activities to promote convergence and would be the primary author of a specifically tailored roadmap for the issue being championed. These

roadmaps would define the issue and its importance; identify gaps learned from diagnostic workshops, issue analysis, or economy-compiled checklists; prioritize the needs based on risk assessment and other relevant criteria; and develop a strategic program to close gaps that include training activities tied to these needs. As the roadmap is implemented, the champion would also be involved in leading the effort to evaluate progress and alter the work plan as necessary. Once a champion has come forward, their efforts can be supplemented by other interested economies that join in advancing the program. An example is the Roadmap for Multi-Regional Clinical Trials, currently being championed by Japan. [See Figure 2 and Annex 3A]

FIGURE 2:



Phase Two - Advancing the Process (2013-15): Once the key areas of focus are determined and initial gaps identified, the RHSC would determine the expertise and resources needed to make progress in each area as well as the sources of the resources described – e.g., government only or also private sector. The areas of focus and the roadmaps would guide this process, and projects would flow from the work plans laid out in the roadmaps. For example, a roadmap on good review practices may advocate the principle that an adequately functioning healthcare infrastructure should include a science-based regulatory system. Specifically, the roadmap could declare that evaluation staff should possess the regulatory review capacity to interpret detailed technical dossiers compiled in accordance with GHTF and ICH guidance and standardized dossier formats. The APEC Harmonization Center could then organize training programs designed to teach these skills. Overall, the RHSC would evaluate proposed training programs on the basis of how they would improve participants' ability to implement the recommended best regulatory practices for key areas in each sector. Identified gaps would inform the RHSC on additional capacity building needs for individual regulatory authorities. Economies would determine the level of convergence they seek and inform the RHSC of gaps they would like to address through APEC capacity building.

Phase Three – Assessing Convergence (2015-20): As 2020 approaches, participating economies should be encouraged to voluntarily complete a readiness assessment on their individual progress toward the goals they have set for themselves in developing a regulatory system that converges with international best practices. The RHSC would develop a regulatory evaluation template that economies can use to generate self-diagnosis on their degree of implementation of best regulatory practices; a process to use these reports to identify gaps; and a procedure for developing targeted capacity building to close these gaps. During this period, periodic reports would be made to APEC Senior Officials on the overall (collective) progress toward the goal of the maximum level of regulatory convergence feasible by 2020.

Principles and Objectives

Building on the RHSC's Guiding Principles for Harmonization, APEC's regulatory convergence for medical products would be governed by the following principles and objectives and would include the following types of activities:

Principles of Operation

- Activities should be under the umbrella of the APEC LSIF Regulatory Harmonization Steering Committee (RHSC)
- Training activities should make use of existing resources, particularly the APEC Harmonization Center, and leverage other international fora
- Activities should be open to all APEC member economies
- Participation should be open to regulators (government), industry and academia
- Any activities/agreements will be flexible and should take account of societal or cultural needs (but aimed toward regulatory convergence)
- Participation and activities will be voluntary and contingent on resources
- Economies can propose to the RHSC an area for focused convergence efforts by drafting a roadmap for RHSC approval, thus becoming the issue's champion, leading efforts for mapping best practices and arranging training programs
- Member economies should encourage the establishment and/or continued activities of local industry associations to involve local manufacturers and importers in the process and to promote industry wide capacity-building and compliance.

Key Regulatory Objectives

- Focusing efforts on convergence towards international guidances and standards developed through bodies such as the Global Harmonization Task Force (GHTF), International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), international standardization organizations (ISO and IEC) and regional harmonization efforts (ASEAN and AHWP)
- A regulatory framework that allows for efficient introduction of new and innovative safe and effective medical products into the market
- A regulatory framework that is science-based, transparent, predictable, least-burdensome, and non-discriminatory
- An efficient clinical investigation regime based on GHTF and ICH guidance focused on safety, efficacy, protection of human subjects, and ethical standards
- Adequate number and level of ongoing training programs for regulatory personnel

- A regulatory framework providing for stakeholder consultation and input during the drafting and review process and sufficient transition times to allow regulatory authorities, conformity assessment bodies, and industry to prepare and come into compliance with new requirements.

Concrete Activities

- A common understanding of regulatory best practices, including from GHTF and ICH.
- Evaluation of current practice relative to international best practices according to GHTF, ICH, APEC and OECD principles
- Gap Analysis: Facilitated identification of capabilities and/or needs
- Setting priorities within APEC and within individual economies
- Creation of economy-specific implementation task forces including stakeholders
- Training and education activity through the APEC Harmonization Center and other venues
- Coordinated program for "training the trainers" (regulatory agencies) within APEC, including a common curriculum developed by the APEC Harmonization Center:
    - APEC economies share best practices
    - Develop training programs in each economy responding to self-identified gaps
- Formation of Working Groups to advance objectives faster
- Creative use of technology to progress work program (e.g., videoconferences, web casts)
- Possible groupings within APEC based on similar standards, needs, and current level of development of regulatory systems

ANNEX 1. Regulatory Convergence for the Medical Device Sector

International Best Practices

Currently, the most relevant organization for medical device regulators and manufacturers is the Global Harmonization Task Force, which was launched in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems. GHTF has two goals: enhancing patient safety and increasing access to safe, effective and clinically beneficial medical technologies around the world. GHTF guidance documents cover almost every area of regulatory harmonization, including premarket evaluation (study group 1), post-market surveillance/vigilance (study group 2), quality management systems (study group 3), auditing (study group 4), and clinical safety/performance (study group 5). *Ad hoc* working groups are addressing other emerging regulatory issues, including combination products, unique device identifiers and nomenclature and members are involved in training and other activities to promote awareness of GHTF principles and guidance. Detailed documentation can be found at www.ghtf.org.

Many APEC members are members of the Asian Harmonization Working Party (AHWP, www.ahwp.info)[6], which was founded in order to promote harmonization in accordance with GHTF guidance within the Asia-Pacific region. In addition, the Association of Southeast Asian Nations (ASEAN)[7], which also includes many APEC members, has committed to a harmonized regulatory approach, based on GHTF guidance, for medical devices by 2015.

The Medical Device Regulatory System

The key stages of medical device regulatory development have been defined as follows: (1) import controls; (2) device listing and establishment (manufacturers and importers) registration controls; (3) implant registration distribution records; (4) recall procedure problem reporting, complaint handling; (5) quality management system requirements, and, (6) pre-market evaluation.[8] As part of the proposed strategy, APEC Economies would refer to GHTF guidance documents, or other agreed international best practices, necessary for each stage. Examples include a common definition of medical devices, a harmonized risk-based device classification system, and labeling requirements. Initial areas of focus could be: quality management systems, post-market surveillance, good review practices and clinical evidence.

As champions are identified and roadmaps drafted, economies may wish to identify specific standards as best practices; for example, reviewers of quality management systems should be able to interpret inspection reports conducted in accordance with any one of the following internationally-recognized standards: ISO 13485 (2003), China YY/T0287-2003, US QSR (21 CFR § 820, 1996), and EC Directives 93/42/EEC (1993), 90/385/EEC, and 2007/47/EC. Successful convergence work should increase economies' ability to accept assessment results from other recognized authorities and conformity assessment bodies.

[6] AHWP includes the following APEC members: Brunei Darussalam, Chile, Chinese Taipei Hong Kong, Indonesia, Korea, Malaysia, China, Philippines, Singapore, Thailand, Vietnam and the following non-APEC members: Abu Dhabi, Cambodia, India, Jordan, Kingdom of Saudi Arabia, Laos, Myanmar, Pakistan, South Africa, Yemen.

[7] ASEAN includes the following APEC members: Brunei Darussalam, Indonesia, Malaysia, Philippines, Singapore, Thailand, Vietnam and the following non-APEC members Cambodia, Laos, Myanmar.

[8] Drawn from World Health Organization, Medical Device Regulations: Global Overview and Guiding Principles, 2003. The original document also stressed the importance of promotion and advertising controls, which currently are not covered by GHTF guidance but could be included in APEC's work once an acceptable international consensus on best practices has been established.

Potential Indicators of Success (Milestones)

- Adoption of common definition of the terms "medical device," "manufacturer," "authorized representative," "distributor," "importer" and other terms as defined in GHTF guidance
- Medical device classification system based on GHTF Principles of Medical Devices Classification
- Regulatory requirements and processes based on manufacturer quality management systems (based on GHTF guidance and international standard ISO 13485, among others)
- Incorporation in the regulatory system of the GHTF essential principles of safety and performance of medical devices
- Adoption of the GHTF Principles of Conformity Assessment for Medical Devices
- Use of standards as guidance in the assessment of medical devices, not mandatory measures, as flexibility is necessary to provide for product improvements and innovation
- Adoption of the GHTF Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices *or* ASEAN/AHWP) Common Submission Dossier Template for medical devices
- Common understanding of STED/CSDT requirements
- Standardized labeling requirements, including use of symbols, for medical devices according to GHTF guidance and international standards
- Adoption of GHTF guidance for adverse event reporting for medical devices
- Participation in the GHTF national competent authority report exchange program for post-market surveillance (NCAR) and/or AHWP Safety Alert Dissemination System (SADS)
- Common format for field safety corrective action notices

ANNEX 2: Regulatory Convergence for the Pharmaceutical Sector

International Best Practices

Currently, the predominant initiative for creating technical guidelines for registration of pharmaceuticals is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Created in 1990, ICH has promulgated over 70 guidances that are then implemented by the US Food and Drug Administration, Japan's Ministry of Health, Labour and Welfare, Pharmaceuticals and Medical Devices Agency, the European Medicines Agency, Health Canada and Swissmedic, the Swiss Agency for Therapeutic Products according to national/regional procedures. These guidelines are categorized into four broad areas: Safety, Efficacy, Quality, and Multidisciplinary, and are widely used by pharmaceutical companies in the United States, Europe, and Japan, Canada and Switzerland to guide them in meeting regulatory submission requirements ICH Guidelines are widely recognized across the globe and the complete set of ICH Guidelines as well as a description of the harmonization process may be found at www.ich.org.

In 2003, as a result of increasing openness of ICH proceedings and in recognition of the need to actively engage with other harmonization initiatives, a number of Regional Harmonization Initiatives (RHIs) were invited to become involved in ICH. Among these RHIs were 3 associated with the APEC Region-- the ASEAN Pharmaceutical Product Working Group (PPWG), the Pan-American Network for Drug Regulatory Harmonization (PANDRH), and the APEC/LSIF Regulatory Harmonization Steering Committee (RHSC).

The Pharmaceutical Regulatory System

The key components of a robust effective regulatory system require that industry develop documented evidence to support the safety, efficacy and quality of products proposed for marketing. As a general rule this data should be reviewed by the drug regulatory authority in the target market prior to marketing, verified by inspection prior to commercial launch, and periodic reinspection to assure continuing compliance.

As part of the proposed strategy for regulatory convergence, APEC Economies would refer to ICH guidances addressing these areas, or other agreed international best practices necessary for each stage. Examples include guidances addressing the safety, efficacy, and quality aspects of the drug development process and technical documentation for marketing registration. Further, the integrity of the supply chain should be assured to promote safe and effective pharmaceuticals. As part of regulatory convergence, and to reduce the burden of repetitive assessments, Member Economies should generally work towards the acceptance of assessment results from other recognized regulatory authorities.

Potential Indicators of Success (Milestones)

Safety and Efficacy

- Identification of differing requirements for proof of safety and efficacy across Member Economies and progress towards regulatory convergence
- Developing, understanding and disseminating information regarding the appropriate role of PK/PD studies in clinical trials conducted in the APEC region

Quality

- Adoption of uniform quality guidelines for marketing registration
- Acceptance and approval of registrations based on Quality-by-Design (QbD) principles
- Increased collaboration among APEC drug regulatory authorities in obtaining inspection information and cGMPs

Integrity of the Supply Chain

- Adoption of quality systems designed to secure active pharmaceutical ingredients and finished product throughout the product life cycle
- Evaluation of the similarities and dissimilarities of distribution channels across APEC Member Economies
- Design and implementation of an appropriate scheme to authenticate product using an e-pedigree system that is harmonized with international standards

ANNEX 3 – ROADMAP TEMPLATE

2011/RHSC/XXXXX

ROADMAP TEMPLATE

Version August 2, 2011

The APEC Strategic Framework describes a more coordinated approach for achieving the maximum level of regulatory convergence for medical products feasible by 2020. It focuses on a model based on long term goals and emphasizes a focused and disciplined approach in discerning divergent regulatory approaches and working towards established international best practices. To promote efficiency and conserve resources, individual projects proposed by APEC Member Economies should be part of an overall strategy and contribute to the overall goals of the Regulatory Harmonization Steering Committee (RHSC). Therefore, there is a need to move away from ad hoc/individual proposals and to focus on priority work areas based on diagnostic workshops and roadmaps for promoting best practices. This document will provide details on the drafting of a roadmap and will serve as a template for submitting roadmaps for review and approval by the RHSC.

An abbreviated or modified version of the template may be used when proposing a new priority work area to the RHSC for consideration. The resulting document could serve as a concept note for that priority work area to promote discussion with other APEC economies. Using a standardized format will enable the building of a strategic plan from preliminary and background information as more details becomes available and a champion of the project is determined.

Essential Elements of a Roadmap

A roadmap should cover key elements of the chosen topic. First, a process to identify gaps in the regulatory frameworks of APEC Economies must be established. This could be accomplished through the analysis of the needs raised at technical workshops, determined from emerging issues of public health concern, input from other international fora and/or results from surveys or specific checklists.

Once the gaps are identified, they need to be prioritized according to agreed criteria such as the level of risk to public health. If the gap is part of a serial process, i.e. issues must be addressed in a sequential manner, this should be described. If correction of the gap would allow the solution of several others, this should also be described, especially if it involves multiple medical product areas.

The prioritized list of gaps or work areas is then translated into a strategic program which contains the specific activities needed to tackle the issues. These activities would depend on the outcome needed and the information available. For example, if there is a need to address differences in regulation, then it would suffice to share information and discuss it in a bilateral manner. However, if there is a need to discern best practices or implement a more efficient process, workshops or specific training could be designed and proposed as individual projects.

Finally it is of utmost importance that all efforts be evaluated to determine that they have contributed to regulatory convergence in the APEC Region. Therefore, each roadmap should have progress/performance indicators that allow for evaluation at each stage of the strategic program. This will also facilitate accountability of those assigned specific tasks or projects.

TEMPLATE

Title:

Roadmap to Promote (Topic)

Goal of Topic: Should be focused and succinct

Introductory section on background and challenges:

- This section should describe the overall goal, prevalence of the perceived problems preventing reaching that goal, the current state and identified gaps.
- Explain the proposed topic's links to the RHSC Strategic Framework and the LSIF strategic plan.
- Describe the current degree of harmonization/disharmonization along with the recommended harmonizat ion vehicle
- Describe activities on this topic held to date and their results (e.g. diagnostic workshops)
- Describe possible synergies with other APEC roadmaps or initiatives.
- Identify major challenges

Gap Analysis

- Describe in detail current practices within the APEC region relative to international best practices
- Provide details on the status of the topic proposed within the APEC region including the following:
  - The current state of implementation of relevant guidelines
  - Operational/regulatory procedures necessary to facilitate the topic under consideration
  - Possible cooperative regulatory approaches and enablers to facilitate implementation
  - Proposed training to promote best practices between APEC economies.
  - Issues each economy should consider in developing training curricula.

Specific activities and time frames :

Step 1: Assessment (specify timeframe)

The assessment should cover the following aspects:

- Scientific issues to be considered
- Perceived logistic and regulatory barriers
- Readiness assessment
    - Identification of capabilities
    - Identification of needs

The need for a points-to-consider document or suggestions to harmonization initiatives for new guidances or revisions to existing guidances should also considered. The assessment should also include recommendations for next steps such as training methods (meeting, seminars, research, symposiums, workshops, etc) and possible curricula to be used in Step 2.

Step 2: Training (specify timeframes)

Based on the recommendations from the Step 1 assessment, present a training curriculum and describe how the training will be conducted in cooperation with other APEC economies. Provide details on the level of training and those to receive the training (industry, drug regulatory authorities, medical practitioners, research nurses, CRO employees, etc.), along with expected results of the training.

The training curriculum should contain the following:

- Relevant ICH or GHTF guidelines (or other guidance as appropriate),
- Experiences of regulatory authorities and industry in the region
- Relevant data
- A “train the trainers” component to provide APEC economies with the ability to conduct additional t raining and to share best practices.

Step 3: Assessment of training (specify timeframe)

The outcomes of the Step 2 training should be described. This should include the status of implementing relevant harmonization guidances and the need to consider remaining challenges in symposiums and workshops under the APEC RHSC and by other organizations, if necessary.

Step 4: Training to reach the goal (specify timeframe) and further recommendations for regulatory convergence

Based on recommendations from the Step 3 assessment, training would be updated/ revised and conducted with assistance from other APEC economies and/or the RHSC. Use of case studies based on actual implementation of the topic under consideration should be considered.

Finally, recommendations for further regulatory convergence on the experiences and activities conducted during all phases of the roadmap should be considered by the RHSC

Performance Indicators

- Include time intervals to or activities/participation to be measured
- Reports to be provided at each RHSC meeting
- Final report summaries
- Lessons learned

Relevant Guidelines to be provided:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutic als for Human Use, (ICH)
- Global Harmonization Task Force (GHTF)
- The Pharmaceutical Inspection Cooperation Scheme, (PIC/S),
- The World Health Organization, (WHO) and
- The World Trade Organization, (WTO)
- Other relevant documents

ANNEX 3A

Proposal for APEC Activities to Promote Multi Regional Clinical Trials
- Roadmap to Promote MRCT -

Background and Challenge：

- It is a common wish that new good medicinal products rapidly become available to patients. Recently Multi Regional Clinical trials (MRCTs) have been increasing remarkably as simultaneous global development of drugs is becoming a norm. Many MRCTs have also been conducted in APEC economies.
- Another conspicuous recent trend is the emergence of specifically targeted agents. Many of these agents act on specific genetic processes or genes that may not necessarily be common across ethnicities. It therefore becomes even more important for the Asian economies to participate in MRCTs in order to generate information about the effects of these drugs in their patient populations in the context of a broad general population to permit comparison.
- Symposiums and workshops on MRCT have been held to identify the challenge and possibilities of MRCTs, under APEC, China-Korea-Japan Tripartite Cooperation, etc. Several challenges have been identified, including *International Conference on Harmonisation* (ICH) E5 guidance implementation and adequate design of MRCTs. The former is particularly important for facilitating evaluation of ethnic factors among populations and acceptance of the data obtained from MRCTs by regulatory authorities. The latter necessitates careful statistical consideration. Another major challenge for MRCTs lies in the clinical trial operations/procedures, which can help or hinder starting clinical trials simultaneously in the economies participating in MRCTs.
- Implementation of the ICH guidances and other relevant international harmonized guidances and promoting convergence of regulatory procedures, which are conducive to implementing MRCTs, also meet APEC RHSC objectives.
- We are proposing a Roadmap to promote MRCT in APEC region to encourage the mode of trials in a concerted fashion. Also, MRCT data should be accepted by every economy where the MRCT is conducted. This approach is recommended in the LSIF strategic plan. The plan suggests to “consider the development of roadmaps to achieve desired objectives” for the purpose to promote a strategic, effective and sustainable approach to training and capacity building activities within the APEC region.
- Another key issue for promotion of MRCT is GCP implementation（ICH-E6 guidance and WHO guidance）. APEC LSIF has a road map for implementation of GCP guidance and the related activities have been being made according to the plan among the APEC economies. A synergy effect can be expected if a roadmap for MRCT is developed and related activities are conducted in parallel with the activities to promote GCP implementation.
- The diseases prevalent in sub-regions of APEC deserve further attention. For example, gastric cancer is prevalent in Asia, and it is highly advisable to implement clinical development of drugs for the disease in the region. It is important for APEC to develop a cooperative regulatory approach that would facilitate MRCTs for such diseases, which might not interest the industry and regulators in other regions.

Goal：

To facilitate MRCTs and acceptance of MRCT results for drug review by regulatory authorities in APEC region.

Roadmap Overview

- Evaluate current practices relative to international best practices (regarding ICH E5 implementation, study design on MRCT, operations at trial sites, etc.).
- Establish a common understanding regarding the key issues including the following within APEC region under the auspices of LSIF. MRCT Workshops (MRCTWSs) shall facilitate the process.
    - Implementation of ICH E5 guidance
    - Study design of MRCT
    - Operational/Regulatory procedures to facilitate MRCT efficiently
    - Cooperative regulatory approach to facilitate MRCTs on diseases prevalent in sub-regions of APEC.
- Implement training for those involved in MRCT, especially regarding the key issues cited above. MRCTWS will be one of the main vehicles for that.
- Develop necessary items for Training/Workshop to promote MRCT
    - APEC economies share best practices
    - MRCTWS as well as each economy considers developing training curricula
- Issue recommendation on regulatory convergence regarding MRCT
- RHSC will support the activities and development of recommendation for next step.

Activities

Step 1: Assessment (2011, 2012)

Through APEC MRCTWSs and other meetings/seminars, the situation of conducting MRCT as well as its challenges will be identified. China-Korea-Japan Tripartite the research group has been studying ethnic factors in East Asian populations. The research results should also be taken into account. Assessment of the relevant factors in MRCTs and discussion on their significance will be made in symposiums and workshops under APEC and other organizations.

The assessment should be made on the following two aspects:
- Scientific issues to consider for MRCTs - e.g., ethnic factors, nature of new therapies, etc.
- Logistic & administrative barriers to facilitated MRCTs.

RHSC may help this process. The assessment will include recommendations for next step.

Step２：Training/workshop (2013-2015)

Based on the recommendation from Step 1 assessment, an economy/economies will develop a training/workshop curriculum and conduct training/workshop in cooperation with other APEC economies and/or RHSC, depending on the situation of the economy/economies. MRCTWS may consider making curricula for training various workers involved, such as medical practitioners, research nurses, CRO employees, etc.

The training can contain the following:

- ICH E5 key considerations and expectation
- Experienced regulatory authorities and industry members in the region share the past experiences, and considerations from past data.
- Researcher's training regarding implementation of early phase trials
- Each economy conducts training programs for the investigators/researchers to encourage early phase trials in the economy. The practice of implementing trials for regional diseases should be emphasized in the training because they are especially beneficial to the patents in the region.
- Quality of Clinical Data
- Observance of GCP is the key element in conducting MRCTs, or any clinical trial. Other rules such as those on safety reporting during clinical trials (e.g. those based on ICH E2A guidance) should also be abided by. Those involved in MRCTs should be trained to enhance the observance and improve the data quality. RHSC Roadmap "A Best Practices Roadmap for Interested Economies for Clinical Trials: The Necessary Elements and Steps" should also be considered.
- Researcher's training regarding implementation of early phase trials.

The curricula established in the economies and MRCTWS will be used in the coordinated program to "train the trainers" so that APEC economies will have the ability to conduct additional training, to share best practices. Also, depending on the recommendation made at the end of Step 1 period, other actions should be taken. They may include drafting of templates to list characteristics of each population from viewpoints of medical practice, demographics, environmental factors, etc.

It is expected that by the end of Step 2 period, highly applicable insights regarding the design of MRCTs as well as trial site operations will be developed.

Step３：Assessment for training /workshop(2016)

The outcomes of the Step2 training/workshop that include the status of implementing ICH E5 guidance as well as those of other challenges in conducting MRCTs will be reviewed in symposiums and workshops under APEC and other organizations, including RHSC, if necessary. A recommendation to further improve efficiency of MRCTs in APEC economies will be formulated.

Step４：Training/workshop to reach the goal (2017-2020) and recommendations for regulatory convergence

Based on recommendation from Step 3 assessment, an economy/economies will revise a training/workshop curriculum and conduct training/workshop with assistance from other APEC economies and/or RHSC, depending on the situation of the economy/economies. Use of case studies based on actual implementation of MRCTs in the training should be considered.

Finally, MRCTWS should draft recommendations for regulatory convergence to be authorized at RHSC based on the experiences and activities during the period of the Roadmap.

Also expected is accumulation of the scientific insights on how MRCTs should be designed and implemented for particular disease group, regarding *inter alia*, the appropriate patient population, appropriate comparators, appropriate endpoints, and methods to control difference in clinical practices across the economies.