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Roadmap to Promote Multi Regional Clinical Trials and Good Clinical Practice Inspection (GCP Inspection)

Lead Economy: Japan, Thailand

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Goal of Topic:

1. To facilitate MRCTs and acceptance of MRCT results for drug review by regulatory authorities in APEC region.
2. To promote best practice of GCP inspection.

Introductory section on background and challenges:

MRCT:

- It is a common wish that new medicinal products rapidly become available to patients. Multi Regional Clinical Trials (MRCTs) have been increasing as simultaneous global development of drugs and patient's earlier access. Many MRCTs have 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.
- The diseases prevalent in sub-regions of APEC also deserve further attention. For example, gastric cancer is prevalent in Asia. It is therefore important that clinical development include drugs for diseases prevalent to the region. It is also important for APEC to develop a cooperative regulatory approach that would facilitate MRCTs for such diseases, which might be of lesser prevalence to other regions.
- Symposiums and workshops on MRCT have been held to identify the challenge and possibilities of MRCTs under APEC, the China-Korea-Japan Tripartite Cooperation, etc. Several challenges have

been identified, including International Conference on Harmonization (ICH) E5 Guideline 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 guidelines and other relevant internationally harmonized guidelines and promoting harmonization on the regulatory procedures which are conducive to implementing MRCTs, also meet APEC LSIF and RHSC objectives.

GCP Inspection:

- APEC LSIF's strategic plan indicates that the area of clinical trials would help in quick and effective creation of life sciences innovation. The harmonization of regulatory practices in this area, i.e. Good Clinical Practice (GCP), generally following ICH E6 which is an international standard that clinical trials, including MRCTs, need to comply with in order to ensure the human subjects' rights, safety and the credibility of trial's data, is one of the specified best practices to reach our goals. To ensure that trials are conducted in compliance with GCP and appropriate scientific approach, Drug Regulatory Authorities (DRA) need to review and evaluate drug development in clinical trials and to inspect the conduct of trials at their sites.
- During the year 2007-2009, Thailand and 11 co-sponsoring economies initiated and conducted capacity building activities for regulatory authorities on review of clinical trial applications and inspection of clinical trials through 2 APEC supported projects, i.e. "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 1)" and "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)", where facilitators and participants from 13 APEC economies gathered to learn and share best practices and experiences at those practical workshops.
- The projects in 2007-2009 occurred during the early stages of GCP Inspection implementation because at least half of participating economies were at the initial stages of setting up GCP inspection programs in their economies.

MRCT and GCP Inspection:

- Another key issue for the promotion of MRCT is the implementation of Good Clinical Practices (GCP; reference ICH-E6 and WHO-guidelines). There exists related activities in current APEC LSIF, (1) GCP inspection, and (2) MRCT CoE, both are under preparation.
- In response to APEC's RHSC Strategic Framework for achieving regional regulatory convergence for medical products by 2020, MRCT and GCP inspection could be jointly promoted because MRCTs are considered as an important means of promoting innovation and access to important new therapies which reduce regulatory burden within the APEC region. Furthermore, GCP is a standard that widely accepted among clinical trial stakeholders around the world. This is especially important due to the rapid growth of MRCTs, and the capacity building efforts underway related to GCP inspection for regulatory authorities.

- A joint workshop on Multi-regional Clinical Trials (MRCTs) and Good Clinical Practice (GCP) Inspection were held at the Shangri-La Hotel, on 8-10 May, 2014. This event took place at the Second APEC Senior Officials' Meeting (SOM2) in QingDao, China
- The first part of the workshop built upon previous MRCT workshops and the findings of a recent survey in identifying these challenges and how they might be addressed through the convergence of regulatory requirements, training and the application of science based approaches to the review of MRCTs. The second part of the workshop examined the importance of sound, risk-based GCP inspection techniques in ensuring the quality of clinical trials and the protection of patients. The results of a gap analysis were presented, together with the experiences of regulators, industry and the WHO. The workshop included regulators only sessions that included discussions on the best practice for training of inspectors, risk-based approach to inspection and the establishment of information-sharing networks for inspectors.
- A Roadmap is proposed to promote (1) implementation of MRCTs and acceptance of MRCT data in APEC region, and (2) best practice of GCP inspection for MRCT.

Gap Analysis

MRCT:

Gap Analysis had been implemented, and the major results are as follows:

- ICH-GCP has widely been implemented in APEC economies, but some differences were identified in its operation.
- On review of MRCT data, more training opportunities are necessary to facilitate a common understanding which is the basis for further regulatory harmonization.
- Sharing review experiences of MRCT data among APEC economies is important.
 - legislation and regulation
 - GCP inspection
- Establishing an international guideline, such as ICH guideline, will also be necessary to promote a proper enforcement of MRCT so that data from MRCT can be acceptable by multiple regulatory agencies.

GCP Inspection:

Gap Analysis had been implemented, and the major results are as follows:

- Majority of APEC economies have implemented ICH E6 Good Clinical Practice Guideline
- Information from Advanced Workshop on GCP Inspection in the year 2009 in Thailand suggests that all participated economies have adopted ICH E6 Good Clinical Practice Guideline, 10 out of 13 economies (77%) have already performed GCP inspection, and the rest of them (23%) are setting up GCP Inspection. However, the levels of implementation and development are different among economies because of the difference in durations and experiences of implementation of GCP guideline and inspection activity as well as the difference in economies' laws & regulations.

- Differences in current standards of assessment of GCPs between APEC economies result in unnecessary regulatory burdens, compromised patient safety, and can have negative impacts on innovation and access to important new medicines
- Best practice recommendations would be a guide to perform effective GCP inspection.

Specific activities and time frames :

Activities	MRCT	GCP Inspection
Step 1: Assessment	APEC MRCT Workshops (-2013)	Questionnaire to promote GCP inspection (2012)
Step 2: Training	<ul style="list-style-type: none"> ● Joint workshop on Multi-regional Clinical Trials (MRCTs) and Good Clinical Practice (GCP) Inspection (2014) ● MRCT CoE (2014) ● MRCT CoE (2016) 	
Step 3: Assessment of training	Symposiums/ workshops to review the outcomes of Step 2 training (2016)	
Step 4: Training to reach the goal	Recommendations to further regulatory harmonization to be considered by RHSC (2017-2020)	

Step 1: Assessment

MRCT (-2013):

Through APEC MRCT WSs and other meetings/seminars, the situation of conducting MRCT as well as its challenges were 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 were made on the following two aspects:

- Scientific issues to consider for MRCTs - e.g., ethnic factors, nature of new therapies, etc.
- Logistic and regulatory barriers to MRCTs.

GCP Inspection (2012):

The questionnaire covered the following aspects:

- Implementation of GCP
- Progress and implementation of GCP inspection
- Input on next steps for capacity building, networking and information-sharing

The analysis of questionnaire results have identified gaps and recommendations for next steps.

The survey of non-APEC countries, on voluntary basis, had been extended to those harmonization initiatives e.g. ASEAN, EMA, PANDRH, etc.

Step 2: Training

MRCT (2014):

Based on the recommendations from the Step 1 assessment, economy/economies have developed a training curriculum and conducted the training in cooperation with other APEC economies, depending on the situation of the economy/economies. MRCT WG may consider making curricula for training various workers involved, such as medical practitioners, research nurses, CRO employees, etc. Training curricula will seek synergy with the other APEC/RHSC activities, such as MRCT CoE and/or GCP inspection Roadmap. Training will complementarily be conducted through MRCT CoE.

The training can contain the following:

- Relevant ICH guidelines, including ICH E5 key considerations and expectations.
- Experienced HA 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.

GCP Inspection (2014):

Based on assessment's outcome from the Step 1, the 1st training on GCP Inspection was conducted under a joint workshop on MRCTs and GCP Inspection on 10 May 2014 in APEC-SOM 2 in QingDao, China. The training covered major topics, as following;

(1) Open meeting:

- GCP Inspection Roadmap and Gap Analysis:- overview & result
- Regulatory view of practice : (a) small and competent DRAs, (b) industries experience to the GCP issues
- GCP Best Practices and related international cooperation : (a) WHO guideline and related international cooperation, (b) E6 Discussion Group, (c) EMA's GCP Inspection related reflection papers

(2) Closed meeting for Regulator:

- Discussion on Best Practice and Recommendation: (a) Training component for GCP Inspectors, (b) Risk-based approach on GCP inspection
- Discussion on information sharing system and networking with GCP inspectors
- Conclusion from Discussion and further work

Besides APEC economies, experts from other international organizations/initiatives, e.g. WHO, EMA, etc. were invited to participate at the meeting. The format of the meeting included both closed session for regulatory authorities and an open session for all (public + regulator) to increase awareness to promote better quality of clinical trial and subject protection.

Finally, the Training Workshop recommended the next steps of the Roadmap.

Combined MRCT and GCP Inspection (2015):

- MRCT and GCP Inspection Roadmaps combined.

- Three MRCT and GCP Inspection combined (Pilot-) CoE activities [Singapore, China and Japan] were endorsed by RHSC.
- MRCT and GCP Inspection combined Pilot-CoE Workshop to be held in March 2016 at Singapore (Duke-NUS).
- MRCT and GCP Inspection combined Pilot-CoE Workshop to be held in 2016 at China (Peking University).
- MRCT and GCP Inspection combined Pilot-CoE Workshop to be held in 2016 in Japan (PMDA).
- Workshop is targeted for reviewers with experience of clinical review of the MRCT data. The workshop will include sessions on how to review MRCT data and how GCP inspection result be reflected on the reviews. Case studies will also be conducted.

The participants of this Pilot-CoE Workshops (and future CoE regular Workshops) are expected to become the trainers and share the learnings and best practices in their respective economies (adoption of “train the trainers” concept).

Other actions may include drafting of templates to list characteristics of each population from viewpoints of medical practice, demographics, and environmental factors.

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

Step 3: Assessment of training (2016)

The outcomes of the Step 2 training that include the improved implementation of the relevant ICH guidelines (ICH E5, E6) as well as other remaining challenges in conducting MRCTs will be reviewed in symposiums and workshops under the APEC RHSC and by any other organizations. A recommendation to further improve efficiency of MRCTs and GCP inspection in APEC economies will be formulated.

In addition, regular MRCT/GCP CoE Workshop will be prepared and conducted based on the experiences and learnings from the pilot CoE Workshops.

A symposium/workshop to review the outcomes of Step2 training will be held back to back with a MRCT and GCP Inspection combined Pilot-CoE Workshop in Japan.

Step 4: Training to reach the goal (2017-2020) and further recommendations for regulatory harmonization

Based on recommendations from the Step 3 assessment, an economy/economies would revise and conduct own training curricula with assistance from other APEC economies and/or the RHSC, depending on the situation of the economy/economies. Use of case studies should also be considered.

Finally, MRCT and GCP inspection WG should draft recommendations for further regulatory harmonization to be considered by the RHSC based on the experiences and activities conducted.

It is also expected that accumulation of the scientific insights on how MRCTs should be designed and implemented for particular disease group, regarding inter alia, the appropriate patient populations,

appropriate comparators, appropriate endpoints, and methods to address differences in clinical practices across the economies.

Performance Indicators

- Numbers of economy/economies participated for Training
- Numbers of regulators participated for Training
- Numbers of MRCTs (protocols) conducted pre- and post- training in economies participated for Training
- Numbers of economy/economies which has a checklist of GCP inspection

Relevant Guidelines to be provided:

- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A, E2F, E5(R1), E6(R1, R2), E8, E9, E10, E17 etc.