Task B
Convergence of NDA Requirements

Proposal Document

APAC RA-EWG

Table of Contents

1 INTRODUCTION

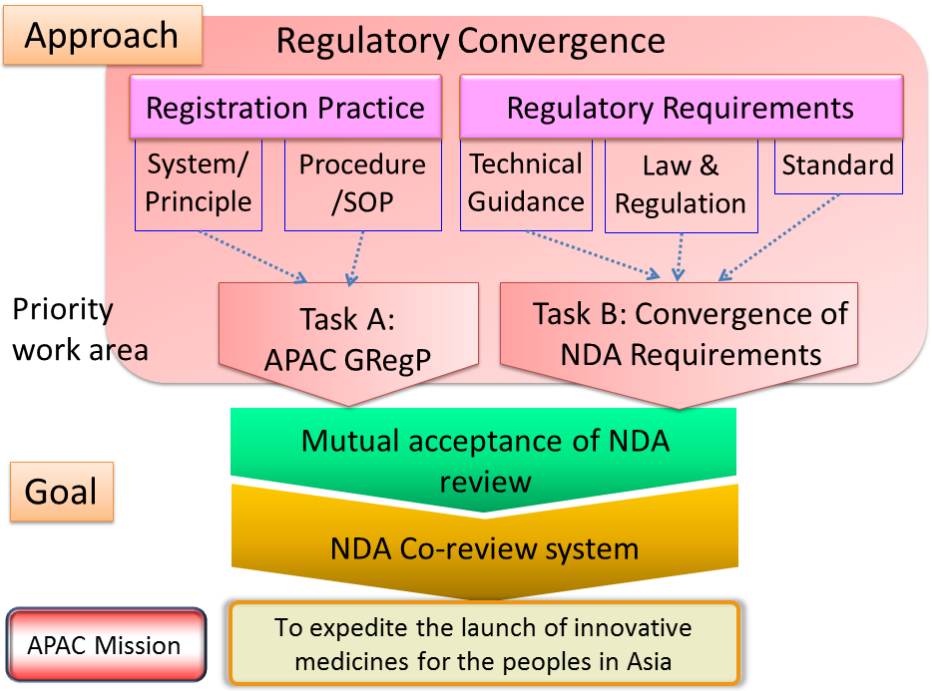
In the 1st Asia Partnership Conference of Pharmaceutical Associations (APAC) meeting in March 2012, the common mission of APAC was confirmed as follows:

" To expedite the launch of innovative medicines for the peoples in Asia. "

Delay in drug approval lag has been recognized as a major issue in Asia, with a large number of drugs having taken for 2 years or more before approval in Asia after first global approval, and that this limits early access to the innovative medicines in the region. In order to improve this condition and resolve the drug approval lag in Asia, it was agreed that APAC member organizations would offer recommendations from the industry viewpoints, to achieve early submission and approval of NDAs for prescription drugs in Asia and to provide a stable supply of quality drugs produced at global standards.

After the 1st APAC meeting, the Regulatory and Approval Expert Working Group (RA-EWG) was established to discuss and resolve these issues in regulatory field.

The working group generated the Concept Paper of APAC RA-EWG activities and set two stepwise goals to realize #1: mutual acceptance of NDA review and #2: NDA co-review system in APAC region. RA-EWG also developed a picture of roadmap describing possible approaches for promotion of regulatory convergence.



To facilitate cooperation between the regulatory authorities in application review and realize aforementioned goals, it is essential to promote convergence of technical guidance, law & regulation and standard in APAC region. RA-EWG decided to establish 'Task B: Convergence of NDA Requirements' to advance regulatory convergence in these areas.

In order to focus on the issues of common interest in APAC region and effectively use available resources for high priority area, RA-EWG drafted list of potential candidate topics and conducted a survey to all associations to prioritize them.

As a result of the survey and voting, the following topics have been selected as high priority topics in APAC. These topics are supposed to be put on the table for discussions in the initial phase of planned activities by RA-EWG.

1. Fast-Track Development/Review Process for Drugs for Serious Diseases with High Frequency or Those Specifically Seen in Asia
2. Acceptance criteria of clinical trial data
3. Establishment of DMF (Drug Master File) system

Followed by

4. Acceptance of USP, EP and JP as internationally harmonized pharmacopeia
5. Clarification of product information (PI) and packaging label requirements

This document provides brief overview of each topic by summarizing background, proposal, expected effect and challenge, and work plan for implementation. More detailed work plan will be developed before starting actions on each topic in the coming year.

2 PROPOSAL OVERVIEW

2.1 Fast-Track Development/Review Process for Drugs for Serious Diseases with High Frequency or Those Specifically Seen in Asia

Background:	• Drug lag has been recognized as a big issue in Asia. It consists of two major parts, i.e. submission lag and review lag. The former is time for submission after first global submission, and the latter is time required for application review before approval. • There is a demand to speed up access to innovative drugs especially for the followings. ➢ Drugs with extremely high clinical usefulness or those for unmet medical needs. ➢ ➢ Drugs for serious or life threatening diseases with high frequency or those specifically seen in Asia It will bring big advantage for patients in APAC region to introduce a new mechanism of fast track drug approval process targeting for specific area of drugs for serious diseases with high frequency or those specifically seen in Asia. Some example of these drugs are for, AIDS, Hepatitis B, Dengue Fever, Malaria, but not limited to them. • There are existing accelerated development and approval mechanisms in the world. Some of these systems are summarized as follows; ➢ ***Fast Track:*** A process designed by US-FDA to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions. A drug that receives *Fast Track* designation is eligible for more frequent meetings/ correspondences with FDA to discuss the drug's development plan, *Accelerated Approval and Priority Review, if relevant criteria are met, and Rolling Review*. ➢ ***Breakthrough Therapy:*** A new process designed by US-FDA to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant

	endpoint(s). ➢ ***Accelerated approval:*** This is also a system by US-FDA. For drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Using a surrogate endpoint enabled the FDA to approve these drugs faster. The drug company is required to conduct phase 4 confirmatory trials. ➢ ***Priority Review:*** Many regulatory authorities including those in Asia introduced this facilitated review process compared to standard review process. Designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications These existing mechanisms will be a good reference for discussions about new fast track approval mechanism. • The fast track drug approval system should not simply shorten the time for application review but keep adequate quality of scientific evaluation process. This can be realized by making use of outcome of scientific and technical evaluation by other review authorities. Also it is necessary to discuss and optimize required risk management measures in post-approval phase.
Proposal:	• Introduction of a fast-track approval system for drugs for specific diseases by referencing or accepting scientific evaluation outcome/report of appropriate reference countries and result of GMP evaluation, e.g. GMP certificates, inspection report, from PIC/S member authorities. • It is critical to ensure adequate quality in efficacy, safety and CMC evaluation by referring to review outcome from reference countries. Also, introduction of appropriate risk management plan should be discussed.
Expected effect & challenge:	• **Effects:** Enable to realize APAC mission "To expedite the delivery of innovative medicines to the peoples of Asia." especially focusing on limited areas of drugs, i.e. those for serious diseases with high frequency or the diseases specifically seen in Asia. • **Challenges:** Develop effective and realistic fast-track approval system to be accepted by all economies. It is necessary to establish a

	clear mechanism for selection of appropriate drug programs that could be eligible for the “fast-track approval system”.
Work plan for implementation:	1. Summarize existing fast track systems in APAC region and conduct analysis by referring to those in ICH countries. 2. Draw a picture of practical procedure and conditions for new fast-track review mechanism. 3. Make proposal to the regulatory authorities in APAC region and discuss for adjustment. 4. Plan for implementation.

2.2 Acceptance criteria of clinical trial data

Background:	• ICH E5 topic describes the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region. • The regulatory authorities in some APAC economies already established and disclosed clear concept on acceptance criteria of foreign clinical trial data as well as bridging concept and its assessment based on ICH E5 (R1). • On the other hand, there exist varieties of regulatory policies and requirements in APAC region concerning acceptability of foreign/global clinical trial data and requirement of local clinical study for drug registration. Typically, the authority of each APAC economy requires any one or two of the following options depending on local regulatory requirements. ➢ Foreign clinical trial data are acceptable (no local registration study required) ➢ Foreign clinical trial data are acceptable with appropriate bridging data (according to ICH E5 (R1)) ➢ Local clinical trial in the economy or participation in MRCT is mandatory for drug registration • There is a demand in APAC region for establishing clear criteria on acceptability of foreign clinical data, required data for bridging, and conditions where local clinical trial data is required. It is necessary to develop rational criteria by considering ICH E5 and the following factors. ➢ Information on ethnic sensitivity & availability of Asian population data ➢ Therapeutic window ➢ Dose response curve & PK/PD profile ➢ Medical practice • Clarification of acceptance criteria of clinical trial data will bring big advantage to applicants as they can create clear clinical development plan and strategy from early stage of drug development phase and therefore can facilitate development process. It is consistent with the need for enhanced access to innovative medicines by the Asian population.

	• There are existing activities for promoting MRCT in Asian region such as APEC MRCT project and China/Korea/Japan Tripartite Cooperation activities. While moving forward this topic, it is necessary to keep eyes on progress of these projects and seek for cooperation as appropriate.
Proposal:	• Prepare a concept paper on basic criteria for acceptance of foreign clinical trial data.
Expected effect & challenge:	• **Effect:** Applicants can prepare clear clinical development plan and strategy in early stage of drug development phase according to the guidance. • **Challenge:** Need to understand existing differences in basic policy, principles and regulatory requirements in each APAC economy
Work plan for implementation:	1. Summarize status of adoption of ICH E5 (R1), experiences and current regulatory requirements in each economy for acceptance of foreign/global clinical trial data and local clinical trial requirements. 2. Discuss and develop scientific rationale for acceptance of foreign clinical trial data. Prepare a concept paper. 3. Discuss with the regulatory authorities and collaborate of with concerned stakeholders

2.3 Establishment of DMF (Drug Master File) system

Background:	• In this topic, Drug master file (DMF) is defined as a confidential, detailed technical and quality document prepared by Active Pharmaceutical Ingredient (API) manufacturers. Typically it consists of open part and closed part, and the latter contains confidential data concerning manufacturing methods of API. It sometimes covers other components and packaging materials and so on. • Generally, DMF is submitted directly to the regulatory authorities by API manufacturers. Registration of DMF is usually voluntarily action, and the registered data is quoted as the necessary information for an NDA review of the drug product in which the API is used. • There has been progress in globalization of supply chain scheme, introduction of marketing authorization approval system and increase in outsourcing of drug substance manufacturing. Under these conditions, there are increased demands for establishment of formal DMF system in APAC region. A few economies in APAC already introduced the system but others do not yet have formal system of DMF. • DMF system is essential for API manufacturers to submit and register confidential data/information directly to the review authorities without disclosing it to NDA applicants.
Proposal:	• Establishment of formal DMF system or equivalent in each APAC economy so that confidential data/information on manufacturing process and conditions can be submitted directly to the review authorities by API manufacturers. • Similar confidential submission pathway should be considered also for submission of GMP documents such as Site Master File.
Expected effect & challenge:	• **Effect:** Enables overseas and domestic API manufacturers to secure confidentiality of manufacturing knowhow by submitting information on API directly to the regulatory authorities without disclosing it to NDA applicant. • **Challenge:** Similar confidential submission pathway should be considered also for submission of GMP documents such as Site Master File.
Work plan for implementation:	1. Prepare summary of existing DMF system in APAC with those in US and EU. 2. Prepare proposal for introduction and/or improvement of DMF

	system for each APAC economy 3. Discuss with the regulatory authorities for implementation

2.4 Acceptance of USP, EP and JP as harmonized pharmacopeia

Background:	• International harmonization of pharmacopeial standards (excipient monographs and selected general chapters) among USP, EP and JP, has been progressed by The Pharmacopeial Discussion Group (PDG) under collaboration with of ICH Q4B topics. The harmonization has brought advantages to reduce manufacturers' burden of performing analytical procedures in different ways using different acceptance criteria. • There is another harmonization activity lead by WHO to harmonize approaches and policies in establishing pharmacopeial standards. This led to the creation of *The International Pharmacopoeia* mainly for essential medicines that are widely used throughout the world. • There are existing differences in understanding and recognition of internationally harmonized Pharmacopeia in APAC region. And there are differences in acceptable pharmacopeia in each APAC country, e.g. EP and USP have been accepted in most APAC economies whereas JP has been accepted only in limited economies.
Proposal:	• Disseminate international harmonization activities on Pharmacopeia in APAC region and facilitate acceptance of JP as one of the internationally harmonized pharmacopeia.
Expected effect & challenge:	• **Effect:** Adoption of harmonized pharmacopeia will bring advantages to reduce manufacturers' burden of performing analytical procedures in different ways using different acceptance criteria. Also it will make applicants able to prepare analytical part of quality dossier for NDA more efficiently. • **Challenge:** For the APAC economy which has its own standard Pharmacopeia, harmonization of the standard Pharmacopeia with ICH Q4B is one of the topics to be addressed.
Work plan for implementation:	1. Summarize status of adoption of internationally harmonized pharmacopeia in APAC region. 2. Discuss with the regulatory authorities in concerned APAC economies to facilitate adoption of internationally harmonized pharmacopeia in APAC region

2.5 Clarification of package insert (PI) and packaging label requirements

Background:	• Package Insert (PI) provides essential information for health professionals on how to use the medicine properly. In many cases, it is a legal document approved by the regulatory authorities as part of NDA, and its information needs to be updated throughout the product life-cycle as new data emerge. It is often provided with another instruction leaflet for patients. • Written guidelines on preparation of PI have been developed in most APAC economies. But sometimes, there are still some issues and/or ambiguity remains e.g. country specific rule and format, short grace period for implementation of PI change, and how to refer safety/efficacy information in PIs of original countries. • For packaging label, progress has been made in harmonization of labeling standard and requirement in ASEAN labeling guideline although country specific requirements remain. • From the view point of efficiency of product supply in Asia, country specific requirements in packaging label as well as difference in language are major hurdles for harmonized PI and packaging label.
Proposal:	• Facilitate establishing and/or improving guideline on PI and packaging label in APAC economies considering the followings; ➢ Creation of patient leaflet or equivalent together with PI ➢ PI contents based on clear scientific rationale ➢ Improvement of administrative process such as grace period for implementation after PI change ➢ Keeping consistency of PI contents between original and generic products ➢ To harmonize packaging requirement and minimize country specific requirement
Expected effect & challenge:	• **Effect:** Harmonized concept of PI contents and its management will bring benefits to both product supplier and health professionals. • **Challenge:** Country specific requirements in packaging label as well as difference in language are major hurdles for efficient product supply in Asia.
Work plan for	1. Summarize current condition and issues on PI and packaging label

implementation:	requirements in APAC region with those in US and EU. 2. Prepare a concept paper for facilitating development or improvement of PI and packaging label management. 3. Discuss with the regulatory authorities for implementation

3 REEFERENCES

1. The 1st APAC meeting minutes, March, 2012
2. Concept Paper for APAC RA EWG Activities, April, 2013
3. RA-EWG Task B: Fact Sheet

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