Preparation of Application Dossier

GRM CoE Pilot Training
Day 2 Sessions A2

Preparation of application dossier

AGENDA

Time	Item	Responsible person
13:00 – 13:10	**1. Introduction** ・ *Learning Objectives*	S. Hatakeyama
13:10 – 13:30	**2. Ice Breaking Game** ・ *QC stands for?*	S. Hatakeyama
13:30 – 16:50	**3. Dossier Preparation**	
13:30 – 14:00	***3-1. Lecture***	S. Hatakeyama
	3-2. Practice	
14:00 – 14:15	・ *Support tools*	M. Toji
14:15 – 14:30	・ *Orientation*	S. Hatakeyama
14:30 – 15:00	・ *Practice-1*	All
(15:00 – 15:20)	*<break>*	
15:20 – 15:50	・ *Practice-2*	All
15:50 – 16:30	・ *Group presentations (5 Gr x 5 min)*	M. Toji
16:30 – 16:50	・ *Examples of support tools (Timeline table, Checklist, Glossary & Template)*	M. Toji
16:50 – 17:00	**4. SOP (Short lecture)**	N. Matsui
17:00 – 17:10	**5. Wrap Up**	S. Hatakeyama

Shinji Hatakeyama Ph.D.

Day 2 Sessions A2

Preparation of Application Dossier

1. INTRODUCTION

LEARNING OBJECTIVES

1. To understand the standard processes for a high-quality submission preparation
2. To improve management of the preparation process for application dossier
3. To improve the QC processes/procedures for future application
4. To understand importance of SOP

Outline of Session A2 Program

STATEMENT OF PURPOSE

- The participants will learn;
  1. A typical case of and process for preparation of an application dossier
  2. How to efficiently prepare a high-quality application document
  3. How to use the support tools to efficiently prepare a high-quality application document
     - ✓ e.g., checklist, template, and glossary
  4. Practical points about QC
  5. Practical points about generating SOPs for proper management of the whole process of submission preparation

Outline of Session A2 Program

Shinji Hatakeyama Ph.D.

Day 2 Sessions A2

Preparation of Application Dossier

2. ICE BREAKING GAME

“QC STANDS FOR?”

Self-introduction

- **From Facilitator to Trainees at each table**
  - **1 minutes**

Then, "QC stands for"

Day 2 Sessions A2

Preparation of Application Dossier

3. DOSSIER PREPARATION

Shinji Hatakeyama Ph.D.

Day 2 Sessions A2

Preparation of Application Dossier

3-1. LECTURE

STANDARD PROCESS OF APPLICATION DOSSIER PREPARATION

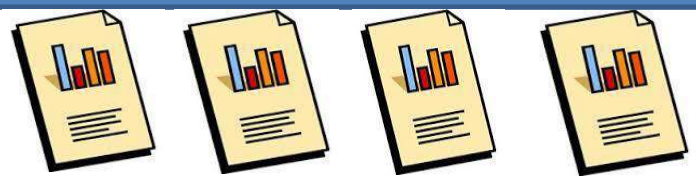
Preparation of Submission Dossier

Preparation of each component

Compilation and assembling of submission dossier

Authors

Experts in each scientific field or medical writers



Submission

APAC
Asia Partnership Conference of Pharmaceutical Associations

Two main steps in preparation of application dossier

① Preparation of each component

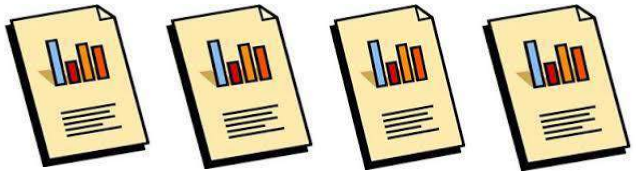
– i.e. writing study reports and summaries, and preparing other required documents

② Compilation and assembling of submission dossier

Two main steps in preparation of application dossier (cont'd)

① Preparation of each component

- **Study Reports**
  - Strong rationale and robust data with scientific evidence
  - Ensure reliability, integrity and traceability of data in the reports
  - Refer to the relevant guidelines on the format and contents of study reports which can be accepted by the review authorities,
    - e.g. ICH M4 and E3

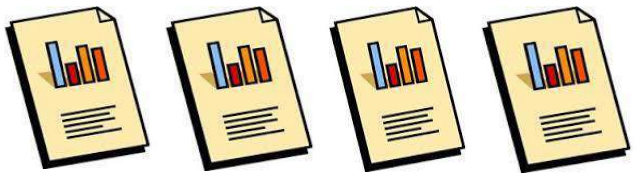


- **Summary documents**
  - Clear rationale with justification based on study reports

Two main steps in preparation of application dossier (cont'd)

① Preparation of each component (cont'd)

- Fundamental of each component
  - Concise
  - Easy to read
  - Validity of scientific contents
  - Accuracy and validity of translation if needed



Two main steps in preparation of application dossier (cont'd)

② Compilation and assembling of submission dossier

- Follow the structure and format of dossier accepted by the authorities
  - e.g. ICH-CTD
- Collect and review of each component document
- Place each component document in the correct location of the format

Submission dossier

Submission of application

- Acceptable format, process and route of application submission
  - All the required information and materials using appropriate format
  - Proper category
  - Electronic dossier or hard copy
  - On-line, mailing or on-site submission

- Sometimes, pre-submission consultation with the review authorities is required to fix the date of submission.

Standard operating procedure (SOP) for submission preparation

4. Short Lecture (16:50 -17:00)

- Standard operating procedure (SOP) for submission preparation

Quality Check (QC)

Purpose of QC

- To ensure information and data in submission dossier have sufficient quality
  - Accuracy, integrity and traceability of scientific data/information
- To check compliance to pre-defined format, template and structure

Types of QC

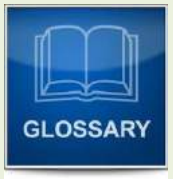
- QC of study reports and summary documents
- QC of submission dossier including electronic dossier

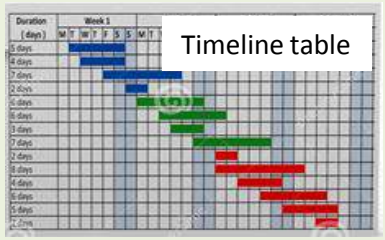
Preparation of Submission Dossier

Preparation of each component

Compilation and assembling of submission dossier

Tools





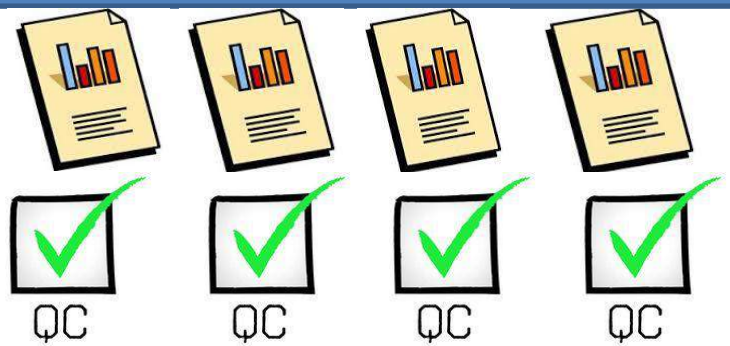
Authors

Experts in each scientific field or medical writers

Regulatory function

Standard Operating Procedures

Standard Operating Procedures



Submission dossier

Standard Operating Procedures

Submission

APAC
Asia Partnership Conference of Pharmaceutical Associations

Mari Toji

Day 2 Sessions A2

Preparation of Application Dossier

3-2. PRACTICE SESSION
HOW TO USE SUPPORT TOOLS

Agenda

Time	Item	Responsible person
	3. Dossier Preparation ***3-2. Practice***	
14:00 – 14:15	・ *Support tools*	M. Toji
14:15 – 14:30	・ *Orientation*	S. Hatakeyama
14:30 – 15:00	・ *Practice-1*	All
(15:00 – 15:20)	*<break>*	
15:20 – 15:50	・ *Practice-2*	All
15:50 – 16: 30	・ *Group presentations (5 Gr x 5 min)*	M. Toji
16:30 – 16:50	・ *Examples of support tools (Timeline table , Checklist, Glossary & Template)*	M. Toji

Introduction

2. PRINCIPLES OF GOOD SUBMISSION

1. *Strong Scientific Rationale and Robust Data with Clarification of Benefit-Risk Profile*
2. *Compliance to Up-to-date Regulatory Requirements*
3. *Well-Structured Submission Dossier with Appropriate Cross-references*
4. *Reliability, Quality, Integrity and Traceability of Submission Documents and Source Data*
5. *Effective and Efficient Communications*

Common Session 3 : An Overview of Good Submission (slide 24)

Introduction

2. PRINCIPLES OF GOOD SUBMISSION

How do you prepare Well-structured **Submission Dossier** and **Submission Documents** with Good Quality?

3. *Well-Structured Submission Dossier with Appropriate Cross-references*
4. *Reliability, Quality, Integrity and Traceability of Submission Documents and Source Data*

You should use **Support tools** effectively.

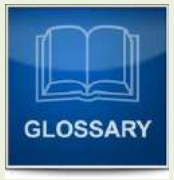
Common Session 3 : An Overview of Good Submission (slide 24)

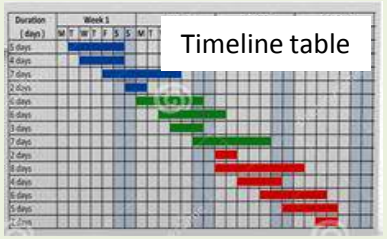
Objective

To learn how to use the following support tools effectively to prepare good quality Submission Dossier and Submission Documents.

- Template
- Glossary
- Checklist
- Timeline table

Tools

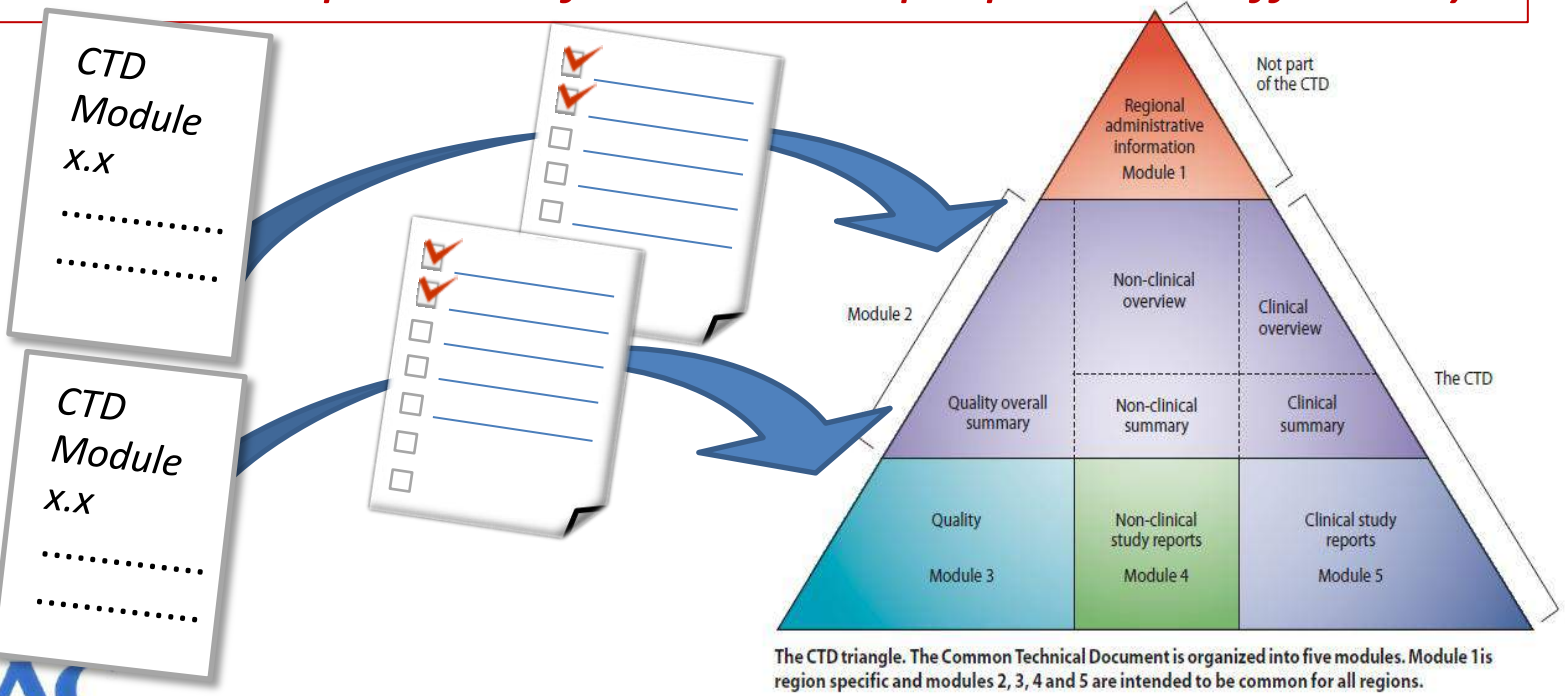




What's tool

Check-list:

……. may include name of each document with information such as responsible person/party, target date and status. Such list will be useful not only to check if there is any missing component but also to manage the whole process of submission preparation efficiently



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

What's tool

Timeline table:

……. is one of the most important tasks in submission planning phase especially when the submission is performed by collaborations among multiple parties of applicants. It is recommended that applicants generate and keep updating a timeline table or a Gantt chart including the role and responsibility of each person/party to manage the whole process of submission preparation efficiently

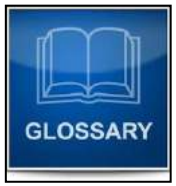
Timeline table for Project F

Timeline				2015/2Q	2015/3Q	2015/4Q	2016/1Q	2016/2Q	2016/3Q	2016/4Q
Preparation of Documents		Responsibility	Done by							
Module 1	Module 1 Table of Contents									NDA Submission
	Application form									
	Letter of Authorization by HQ office									
	Patent Statement									
	Worldwide status									
	CPP with notarization, legalization (original)									
	CPP with notarization, legalization, translation									
	GMP certificate with notarization, legalization (original)									
	GMP certificate with notarization, translation									
	Plant Master File									
	Proposed Package Insert & Patient Information Leaflet									
	Proposed artwork for PTP/aluminium pillow, outer box									
	Risk Management Plan									
	Assesment report									
	Report for HA consultsion									

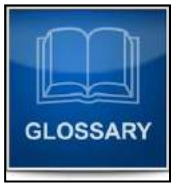
What's tool

Glossary:

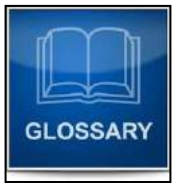
It is important to keep consistency of terminology used throughout a submission dossier. .... recommended to create a list of general glossary before initiating preparation of study reports and summaries.



For abbreviations



For project specific terminology

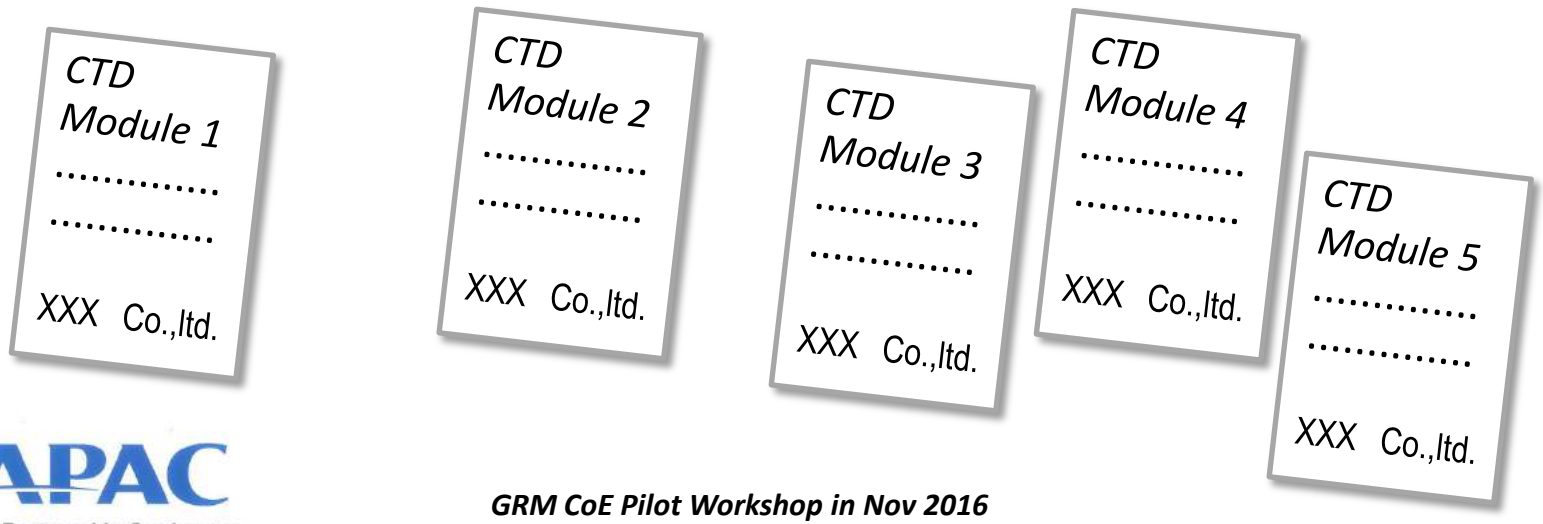


For translation

What's tool

Template:

..... help authors to prepare each component document in structured and consistent manner complying with the required format and contents.... It will also enhance efficiency of preparation. Submission with a unified format of study reports and summaries also enables reviewers to perform review smoothly.



Orientation

Objectives of practice

To experience

- ✓ Preparation of each component
  - ➢ By utilizing Timeline table, Checklist
- ✓ Improvement of documents' quality
  - ➢ By utilizing Glossary and Template
- ✓ Compilation and assembling of submission dossier
  - ✓ By utilizing Checklist

Ms. SAKURA

Nation :

GREEN Country (G country)

Company :

Flower pharm co.

Asia subsidiary
under the Asia region head of multi-national company

Work Experience :

SAKURA graduated from the university two years ago, She joined the company in order to fulfill her dream that patients access innovative drugs early in her county.

She has worked hard and learned the role of regulatory affairs. Now she is appointed regulatory leader of the project(s).

Next project…

Sakuranitive tablets

- ✓ Sakuranitive shows excellent efficacies in Phase 3 studies as life-saving medicine
- ✓ Approvals in Japan, US and EU, are expected in May, June and July, respectively
- ✓ Flower pharam co. are pursuing NDA submission of Sakuranitive tablets in Green country by mid of December
- ✓ Intended commercial sites for Green country
  - Bulk drug product
    - Newpower factory, Flower pharm co. in US
  - Commercial Packaging site
    - Spinach plant, Flower pharm co. in Green country

NDA requirements

Module 1	Application form*	
	1 CPP from reference country (JP, US or EU) with Notarization & Legalization	
	Proposed Package Insert in Green country	
Module 2	2.3.P.1 - 8	
Module 3	3.2.P.1	Description and Composition of the Drug Product
	3.2.P.2	Pharmaceutical Development
	3.2.P.3	Manufacture
	3.2.P.4	Control of Excipients
	3.2.P.5	Control of Drug Product
	3.2.P.6	Reference Standards or Materials
	3.2.P.7	Container Closure System
	3.2.P.8	Stability**

* Need consistency of proposed indications, manufacturers names/addresses among 'Application form', 'Proposed Package Insert' and 'CPP'

** Stability samples need to be manufactured at intended commercial sites including packaging site

SOP in Flower pharm co.

Head Quarter (HQ)

- ✓ Provide the latest NDA dossier in JP, EU, US
- ✓ Arrange CPP preparation
- ✓ Review and approve draft proposed Package Insert based on request by AS

Asia Region Head (ARH)

- ✓ Provide region specific item
  - Conduct additional stability studies and dossier update based on region specific requirements
  - Draft proposed Package Insert based on request by AS

Asia Subsidiary (AS)

- ✓ Manage NDA submission timeline based on corporate milestone
- ✓ Arrange Package Insert preparation
- ✓ Correct and compile NDA dossier
- ✓ Submit NDA dossier to the regulatory authority

Standard period

Application form with HQ signature (11 weeks)	Drafting by affiliate	2 weeks
	Legal review & Sign by HQ	8 weeks
	Return to affiliate	1 week
CPP with Notarization & Legalization (14 weeks)	Request HQ to arrange CPP	1 week
	HQ request authority to issue CPP	8 weeks (JP, US, EU)
	HQ received CPP from authority	1 week
	Notarization & Legalization	4 weeks
Proposed Package Insert (12 weeks)	Request ARH to draft	1 week
	Drafting	8 weeks
	PI Review process in HQ	2 weeks
	Approval	1 week
Compilation & Assembling in November		4 weeks
Final check before submission		1 week

HQ: Head Quarter, ARH: Asia Region Head

Ms. SAKURA's Missions

Practice 1 *(30 min.)*

- ✓ *Decide reference country*
- ✓ *Provide feasible Timeline table and Checklist*
- ✓ *Ask facilitator to review checklist and timeline table*

Practice materials:

1. ***Checklist***
2. ***Timeline table***

Ms. SAKURA's Missions

Practice 2 *(30 min.)*

- ✓ *Do QC of '3.2.P.3.1 Manufacturer(s)' based on glossary, and make annotations*
- ✓ *Fill in application form*
- ✓ *Compile submission dossiers based on checklist*
- ✓ *Ask facilitator to check submission package*

Practice materials:

3. *Glossary*
4. *3.2.P.3.1 Manufacturer(s)*
5. *CPP*
6. *Proposed package insert*
7. *Application form*
8. *2.3.P and 3.2.P cover pages*
1. *Checklist (again)*

Group presentation

Presentation topics

1. Can your group complete all missions?
   - ✓ Reference country, Checklist, Timeline table, QC, Application form, Compilation
2. Which item is most difficult or easy for your group?
3. If there are no supporting tool, what will be happened?
4. Please freely share your group's idea, how you can improve dossier preparation process.

5 minutes/Group

Member's role

Please decide role of each member in your group

- Group head
- Facilitator for discussion
- Time keeper for practice
- Speaker for group presentation
- Dossier manager (SAKURA)
  - Lead and manage all practice items

Practice-1

Ms. SAKURA's Missions

Practice 1 *(30 min.)*

- ✓ *Decide reference country*
- ✓ *Provide feasible Timeline table and Checklist*
- ✓ *Ask facilitator to review checklist and timeline table*

Practice materials:

1. ***Checklist***
2. ***Timeline table***

<break>

Practice-2

Ms. SAKURA's Missions

Practice 2 *(30 min.)*

- ✓ *Do QC of '3.2.P.3.1 Manufacturer(s)' based on glossary, and make annotations*
- ✓ *Fill in application form*
- ✓ *Compile submission dossiers based on checklist*
- ✓ *Ask facilitator to check submission package*

Practice materials:

3. *Glossary*
4. *3.2.P.3.1 Manufacturer(s)*
5. *CPP*
6. *Proposed package insert*
7. *Application form*
8. *2.3.P and 3.2.P cover pages*
1. *Checklist (again)*

Group presentations

Group presentation

Presentation topics

1. Can your group complete all missions?
   - ✓ Reference country, Checklist, Timeline table, QC, Application form, Compilation
2. Which item is most difficult or easy for your group?
3. If there are no supporting tool, what will be happened?
4. Please freely share your group's idea, how you can improve dossier preparation process.

5 minutes/Group

Examples of Support tools

Examples of Timeline table (1)

Timeline table for Project F

Timeline				2016/2Q			2016/3Q			2016/4Q			2017/1Q		
Preparation of Documents		Responsibility	Done by		KoM		Approval in orinal country								
Module 1	Module 1 Table of Contents	Local RA	30/11/2016												
	Application form	Local RA	31/10/2016												
	Application form, review & QC	Tram leader	15/11/2016												
	Letter of Authorization by HQ office	Head office RA	30/09/2016												
	Patent Statement	Head office RA	30/09/2016												
	Worldwide status	Head office RA	30/09/2016												
	CPP with notarization, legalization (original)	Head office RA	30/09/2016												
	CPP with notarization, legalization, translation	Local RA, CRO	31/10/2016												
	GMP certificate with notarization, legalization (original)	Head office RA	30/09/2016												
	GMP certificate with notarization, translation	Local RA, CRO	31/10/2016												
	Plant Master File	Head office RA	31/07/2016												
	Package Insert & Patient Information Leaflet, (original country)	Head office RA	15/08/2016												
	Proposed Package Insert & Patient Information Leaflet for local, prepration	Local RA	15/09/2016												
	Proposed artwork for PTP/aluminium pillow, outer box	Head office RA	15/08/2016												
	Risk Management Plan (original)	Head office RA	15/07/2016												
	Risk Management Plan, preparation	local team	15/09/2016												
	Risk Management Plan, preparation, Review & QC	Tram leader	30/09/2016												
Module 2	Module 2 (2.1~2.5) original	Head office RA	15/07/2016												
	2.1 Overall Common Technical Document Table of Contents, translation	CRO	31/07/2016												
	2.1 Overall Common Technical Document Table of Contents, translation, QC	Local RA	15/08/2016												
	2.2 Introduction, translation	CRO	15/08/2016												
	2.2 Introduction, translation, Review & QC	Local RA	31/08/2016												
	2.3 Quality Overall Summary, translation	CRO	31/08/2016												
	2.3 Quality Overall Summary, translation, Review & QC	Local RA	15/09/2016												
	2.4 Nonclinical Overview, translation	CRO	15/09/2016												
	2.4 Nonclinical Overview, translation, Review & QC	Local RA	30/09/2016												
	2.5 Clinical Summary, translation	CRO	30/09/2016												
	2.5 Clinical Summary, translation, Review & QC	Local RA	15/10/2016												
Module 3	Module 3 original	Head office RA	15/07/2016												
Module 4	Module 4 original	Head office RA	15/07/2016												
Module 5	Module 5 original	Head office RA	15/07/2016												
Publissing	Publissing	Local RA	30/11/2016												
	Pringing and Compiling	Local RA	15/12/2016												
	QC	Local RA	31/12/2016												
	Filing	Local RA	15/01/2017												
submission		Local RA	28/02/2017												

NDA Submission

Examples of Timeline table (2)

- To create at planning session
- To keep the targeted submission date
- To put time for review and QC
- To have minimization of white space
- To share Timeline table in the submission team including multiple parties

Examples of Checklist (1)

Checklist: Module 1 2016/11/17

No.	Items	#	Responsible	Deadline	Meet requirement	Status
1	Original and Copy of Registration Application of Drug Inspection	1	HQ RA	2016/9/30	OK	closed
2	Patent Statement	1	HQ RA	2016/9/30	OK	closed
3	Worldwide status	1	HQ RA	2016/9/30	OK	closed
4	Proposed design of vial label and outer box	2	Local RA	2016/10/30	OK	closed
5	Proposed Package Insert (6 pages) in local language based on translation of EU SmPC	2	Local RA	2016/11/30	OK	QC
6	CPP with notarization, legalization (original)	1	HQ RA	2016/12/30		Request to HA
7	Site Master File	1	HQ RA	2016/9/30	OK	closed
8	Risk Management Plan (original country)	1	HQ RA	2016/10/30	OK	closed
9	Risk Management Plan for local	1	Local RA	2016/12/15		Under preparation

Examples of Checklist (2)

- All items to be submitted are listed based on the latest Regulatory requirement from your authorities
- Submission team members and all related persons including agencies are shared the latest Check list until finalization of dossier
- Check list can also use the quality check

Examples of Glossary (1)

Project-specific terminology

		Note	Inappropriate
Product Name	ABCDE™	All capital letters	Abcd
Generic Name	wxyz	All lower case	Vwxyz
Deveropment No.	AB-1234	Hyphen	AB1234

Item	Unified format
Manufacture Site Name	Flour Phrm Co., Forest Plant
Manufacture Site Address	123-4, Woods Str. Hill Prrf. Green Country

Examples of Glossary (2)

Abbreviations

Abbreviation	Formal name
GSubP	Good Submition Practice

Abbreviation	Formal name	Note	Inappropriate
HER2	human EGFR-related 2	All capital letters	Her3
cDNA	chromosomal DNA	"c" lower case	CNDA,cnda

Examples of Glossary (3)

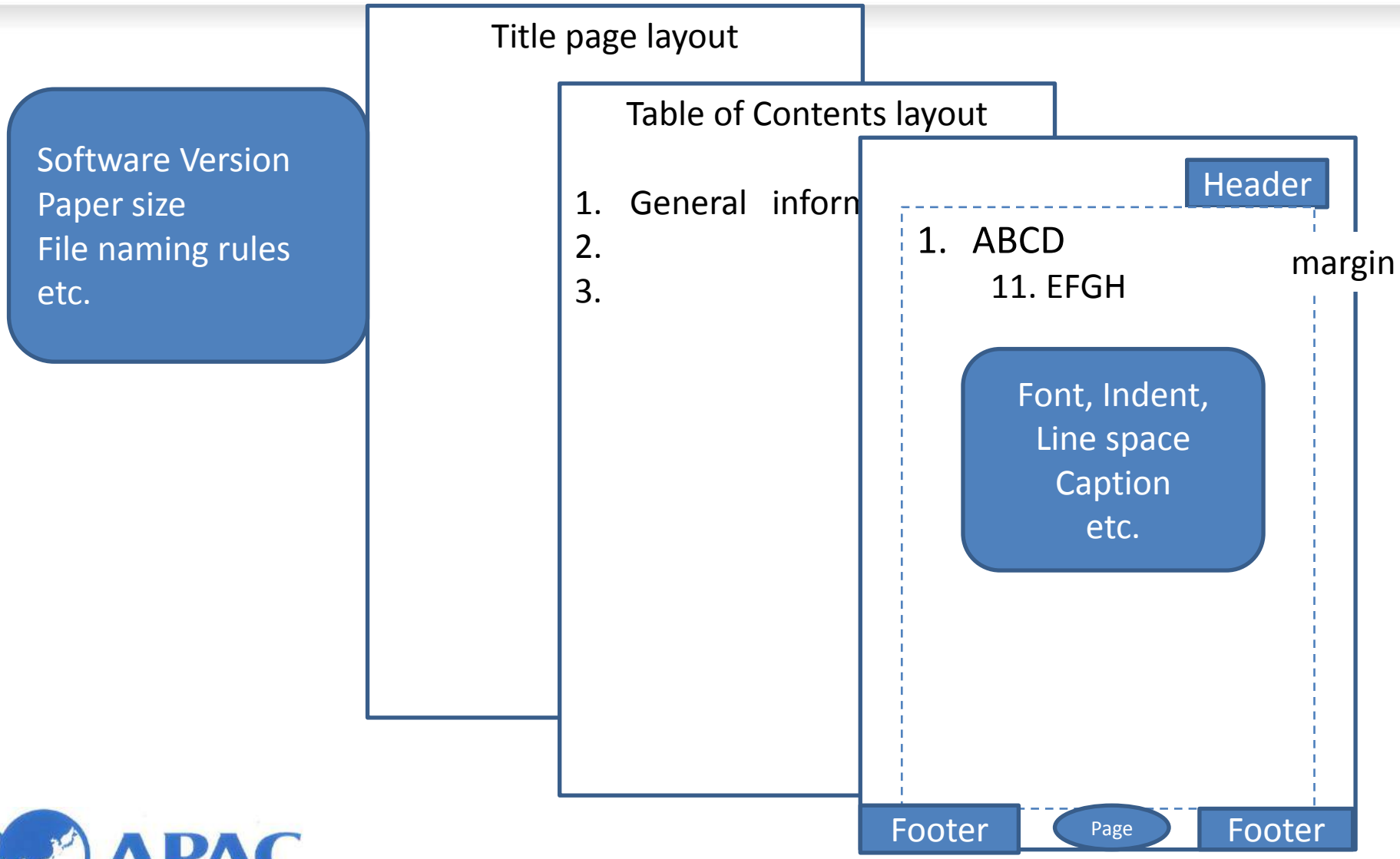
For translation

English	Chinese	Inappropriate
ethyl acetate	醋酸乙酯	乙酸乙酯、醋酸乙基
rat	大鼠	鼠、白鼠

Examples of Glossary (4)

- It is important to decide the word role to prepare submission dossier from initial step.
- Update is acceptable. Inform it to all members.
  - proper name: how to describe
    - Companies' English name and address
  - uppercase letter and Lower case letters
    - Ex. Product name: how to using uppercase letter
  - word list for translation (English vs. local word)
    - In particular, pay attention to use translation agency

Examples of Template (1)



Examples of Template (2)

- Meet the regulatory requirement
  - Items, details and any contents defined by regulation
  - Numbering, font, page's font
  - Adjust e-CTD requirement if have
- Numbering, font, page's font even if no above requirement
- Integration of session title, caption, index, etc.
- File name and draft version rule
- Distribute them to all authors related dossier preparation in the project in advance

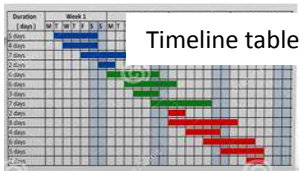
Preparation timing for Support tool

Drug Discovery | Pre-Clinical Development | Phase I | Phase II | Phase III | Application Submission | Review & Approval | Post-Approval

GLOSSARY
Company Name & address

Template
Common in company

GLOSSARY
For project specific terminology


Timeline table

GLOSSARY
For abbreviations

GLOSSARY
For translation

Template
For project

APAC
Asia Partnership Conference of Pharmaceutical Associations

Naoko Matsui

Day 2 Sessions A2

Preparation of Application Dossier

4. SHORT LECTURE

STANDARD OPERATING PROCEDURE (SOP) FOR SUBMISSION PREPARATION

SOPs for submission preparation & management

Application submission is

- Complicated and time-consuming process
- Often requires collaborations among applicants' parties or group of organizations locally and globally

..... It is therefore beneficial for applicants to generate SOPs and share them within the parties or organizations ***for proper management of the whole process of submission preparation.***

- SOP is not a regulatory requirement
- SOP in GSubP Guideline means procedure/operation manual for submission and not subject of strict compliance like SOPs in GCP, GMP

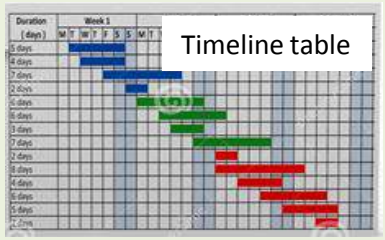
Common Session 3 : An Overview of Good Submission (slide 43)

Preparation of Submission Dossier

Preparation of each component

Compilation and assembling of submission dossier

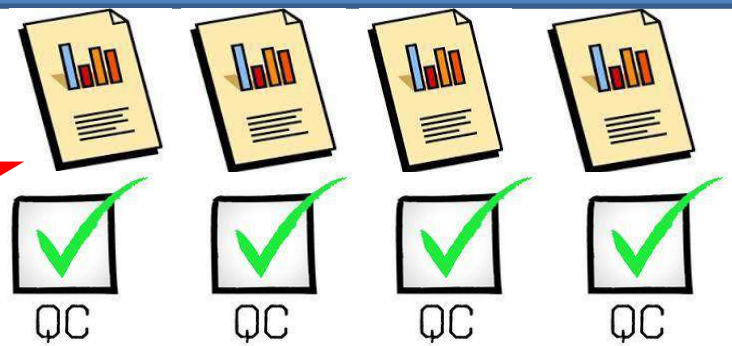
Tools



Authors

Experts in each scientific field or medical writers

Regulatory function



Submission dossier

Submission

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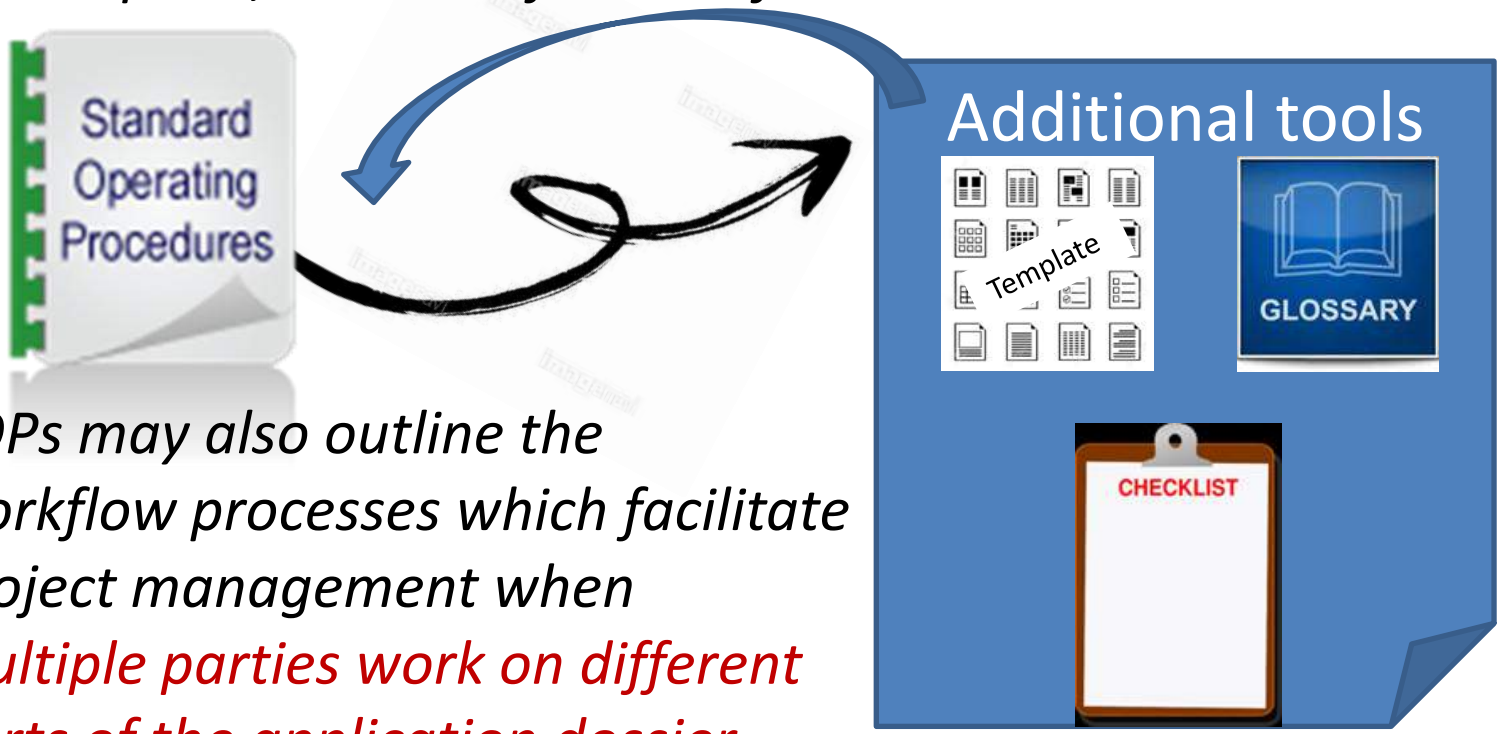
How to write SOP for submission preparation

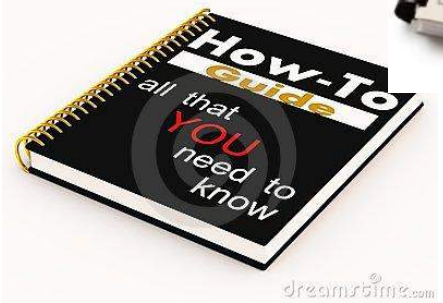
- *SOPs may be structured to contain or refer to additional tools that could assist in performing the procedure for submission, e.g. template, standard format of checklist.*



- *SOPs may also outline the workflow processes which facilitate project management when multiple parties work on different parts of the application dossier.*

Other procedure documents

Additional working procedure documents may also be created to give more detailed instruction and structure in support of SOPs. These documents can describe in detail how a particular process is performed, e.g. procedure for drafting, reviewing and finalization of each study report and summary.



Update for SOP

These SOPs need to be updated depending on the change in applicant's working environment, e.g. change in organization, scheme of work-sharing etc.

Shinji Hatakeyama Ph.D.

Day 2 Sessions A2

Preparation of Application Dossier

5. WRAP UP AND Q&A