以下資料 Good Submission Practice (GSubP) Guideline for Applicants 為「藥品優良送審規範指引文件」之參考依據，係亞太經合會(APEC)法規調和推動委員會(Regulatory Harmonization Steering Committee，RHSC)推廣之文件，惟中文版之「藥品優良送審規範指引文件」僅適用於藥品送審，並未涵蓋原文之醫療器材部分，亦無Glossary。

Good Submission Practice (GSubP) Guideline for Applicants

APEC RHSC

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1 INTRODUCTION

1.1 Objective and scope

The objective of this document is to provide general and high level guidance on Good Submission Practice (GSubP, see 1.3 Definition) principles and processes which applicants of medical products should keep in mind. The recommended processes are not intended to provide detailed instructions on how to conduct each submission or to serve as prerequisite for the medical product submissions.

The goal of GSubP is to enhance efficiency and quality of medical product registration process which leads to enhance early access to these products by patients. The GSubP principles and elements described in this document will help applicants to achieve the goal.

Regarding detailed procedures for submission preparation, applicants should consider to generate Standard Operating Procedures (SOPs) in their own organization considering the general guidance provided in this document and specific conditions and requirements in each country.

This document is envisioned as a companion document to Good Review Practice (GRevP, see 1.3 Definition) guidelines, and sufficiently expandable to accommodate additional annexes or ancillary documents in the future.

This document applies to any aspects related to the regulatory submission for medical product registration and its management by applicants. It also covers associated activities by applicants in planning, submission and review stages up to approval.

Although this document was written focusing on application submission for pharmaceutical products and biologicals and higher-risk medical devices for use in humans, the concepts may be applied to other types of medical products. Similarly, the concepts described here may also be applicable to the entire product lifecycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

1.2 Background

In general, registration submission of medical products is made in the final stage following time consuming product development process. It can be regarded as the compilation of all development program and activities of the product. In order to obtain early approval in the registration process, it is important for applicants to prepare and submit application with good quality dossier. It is also essential that applicants keep close communications with the review authorities by taking prompt and appropriate actions in ensuring of smooth registration process. Application submission with poor quality of dossier and management will lead to failure in getting final approval or cause significant delay due to a large number of inquiries

and requests from the review authorities. Applicants should always seek ways to improve their submission in quality and efficiency.

1.3 Definition

Good Submission Practice (GSubP):

An industry practice for any aspect related to the process, format, contents and management of submission for registration of medical products by applicants. It is the practice to enhance the quality and efficiency of the product registration process by improving the quality of submission as well as its management.

To promote continuous improvement, all aspects of GSubP should be evaluated and updated on an ongoing basis.

Applicant (as defined in WHO GRevP guidelines [1])

The person or company who submits an application for marketing authorization of a new medical product, an update to an existing marketing authorization or a variation to an existing marketing authorization.

Good Review Practice (GRevP) (as defined in WHO GRevP guidelines [1])

Documented best practices for any aspect related to the process, format, content and management of a medical product review.

GRevP has been introduced and moved towards step-wise implementation by many regulatory authorities to enhance the timeliness, predictability, consistency, transparency, clarity, efficiency and quality of product review. The GRevP guideline document was endorsed by World Health Organization (WHO).

2 PRINCIPLES OF GOOD SUBMISSION

The objective of GSubP is to help applicants prepare good quality submission leading to successful registration. The 'principles' of a good submission describe the key elements of GSubP which applicants should follow in order to achieve successful product registration. The following five key principles of good submission are provided as a general guide. Applicants should keep them in mind when planning and managing submissions.

Key Principles of Good Submission

Strong Scientific Rationale and Robust Data with Clarification of Benefit-Risk Profile:

A good submission should be based on strong scientific rationale and robust data in terms of integrity, relevance and completeness. The nature of the benefits and types of risks should be clarified with sound evidence.

Compliance to Up-to-date Regulatory Requirements:

A good submission is made in compliance with the up-to-date regulations. In addition, it should keep reasonable consistency with internationally harmonized regulatory standards.

Well-Structured Submission Dossier with Appropriate Cross-references:

A good submission will be made with well-structured dossier complying with the acceptable format by the review authorities. To ease the reviewing process, applicants are encouraged to use appropriate cross-references in the dossier.

Reliability, Quality, Integrity and Traceability of Submission Documents and Source Data:

A good submission is made ensuring the reliability, quality, integrity, and traceability of information and data described in submission documents including their sources.

Effective and Efficient Communications:

A good submission and timely review can only be achieved by keeping effective and efficient communications with the review authorities throughout the product development and registration process. In addition, good communications within the applicants' organization(s) are essential for successful submission as well as its management.

3 MANAGEMENT OF SUBMISSION

The working scheme for applicants to prepare and manage the submission differs by the size of the applicant's organization. Appropriate resource management is also important, considering the submission work is time- and labor-intensive activity.

In case the applicant is a small to medium-sized organization, submission preparation is often managed and handled by a person or a small group of people. Therefore, the applicant may need to plan their submission with sufficient lead time and consult with the review authorities when necessary.

In case of large organization, preparation of an application submission is generally conducted by collaborative work among concerned parties. For example, a submission team consisting of clinical, non-clinical and quality experts, statisticians, medical writers, regulatory staffs, project managers and other relevant stakeholders is formed and work together for a submission. The individual roles and responsibilities should be defined in advance.

Sometimes local and international collaborations among multiple organizations are also required, e.g. local affiliate and headquarters, sponsor and co-development partners, originator and licensee companies.

In any of aforementioned working scheme, applicants should appropriately manage the whole process of product registration including submission.

The principles of project management and quality management are critical for well-organized submission preparation. The submission practices of careful planning, good communications and clearly-defined work instructions can maximize the quality and efficiency of submission process.

3.1 Planning for Submission

Preparation for application submission generally starts with planning phase. Often, submission for product registration takes place in the last stage of lengthy product development process. Even so, applicants need to initiate discussions on submission strategy from an early stage of product development and establish a clear strategy for submission. Clarification of product profile as well as its update according to ongoing development program is a critical part of such strategic discussions. For that purpose, some companies use a document so-called 'Target Product Profile', a summary format of product development program described in terms of labeling concepts.

It is also important for applicants to conduct clinical and non-clinical studies as necessary in compliance with the up-to-date regulatory standards, guidelines and regulations. Applicants shall strive to obtain and understand the regulatory information necessary for product development and registration.

It should be noted that progress has been made in regulatory convergence and harmonization by international cooperation scheme among the regulatory authorities, e.g. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Harmonization of Standards and Technical Requirements in The Association of Southeast Asian Nations (ASEAN) and The International Medical Device Regulators Forum (IMDRF). It is necessary that applicants keep abreast with not only local but also regional and international standards, guidelines and regulations, and update their own submission strategy accordingly.

In order to plan and manage an application submission efficiently, applicants are recommended to prepare and use the following tools.

Checklist:

Applicants are encouraged to make a checklist to plan for every required component of submission dossier. The 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.

Glossary:

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

Template:

Template is a standard file format document containing pre-defined layout, styles, texts and graphics. Templates help authors to prepare each component document in structured and consistent manner complying with the required format and contents, e.g. ICH M4 and E3. It will also enhance efficiency of preparation. Submission with a unified format of study reports and summaries also enables reviewers to perform review smoothly.

Timeline table:

Development and management of timeline 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.

If necessary, applicants shall also plan for pre-submission meeting with review authorities (see section 4.1.1).

These activities in planning stage will enhance quality and efficiency of submission preparation and its management.

3.2 Preparation and Submission of Application Dossier

There are two main steps in preparation of an application dossier. One is preparation of each component, i.e. writing study reports and summaries, and preparing other required documents. The other is compilation and assembling of submission dossier.

In general, authors of reports and summaries are assigned from experts in each scientific field or medical writers, and overall handling of submission is conducted by regulatory function or professionals.

3.2.1 Writing study reports and summaries

Study reports and summaries are key components of technical documents in application dossier. The former corresponds to Module 3, 4 and 5, and the latter constitutes Module 2 in ICH-CTD.

The contents of study reports should be based on strong rationale and robust data with scientific evidence. Needless to say, applicants should ensure reliability, integrity and traceability of data described in the reports. Applicants also need to 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 should be generated based on the contents of study reports to provide clear rationale with justification. It is also necessary to clarify the nature of benefits and risks of the product based on sound scientific evidence.

The contents of these documents shall comply with up-to-date standards and regulations at the time. In addition, it is essential to prepare these documents by taking into account alignment with current international standards and guidelines.

The authors of these documents should strive to write a concise and easy to read document. Sometimes peer review by competent third party or person is effective in order to check the validity of scientific contents before final draft.

Translation of original documents to other language is sometimes required in the process of submission preparation. In such case, applicants should pay careful attention to ensure accuracy and validity of translation.

Besides study reports and summaries, other types of documents are required at application submission by each regulatory authority as regional or country-specific requirements. They include, but are not limited to, application form, proposed labeling, letter of authorization, patent statement, certificates issued by the competent authority etc. Type of required documents differs depending on the type of medical products, category of application and the local regulations. Applicants should review the list of required documents provided by the national regulatory authorities.

3.2.2 Compilation and assembling of dossier

Before compiling and assembling submission dossier, applicants should review the structure and format of dossier accepted by the national regulatory authorities, e.g. ICH-CTD. Collection and review of each component document should be performed in reference to defined table of contents. A checklist will help applicants to manage the collection process

efficiently. In compiling and assembling of submission dossier, applicants need to ensure that every document has been prepared consistently and placed in the correct location of the dossier.

Some regulatory authorities have been accepting application submission with electronic dossier. Applicants should review the local regulatory requirements and follow the relevant instructions when intending to submit their application electronically.

3.2.3 Submission of application

Each review authority has defined acceptable format, process and route of application submission, e.g. hard copy or electronic dossier, on-line, mailing or on-site submission. Sometimes, a pre-submission consultation with the review authorities is required to fix the date of submission.

Applicants are required to submit application dossier following the procedure and instructions provided by each authority. To avoid rejection of filing, applicants should ensure that the submission is made in proper category and contains all the required information and materials using appropriate format.

3.2.4 Standard operating procedure for submission preparation

Preparation of application dossier is a complicated and time-consuming process. It is often performed by collaborations among applicants' parties or group of organizations. 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.

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.

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

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.

3.3 Quality Check

Quality check (QC) of submission dossier and its components is critical and indispensable process in order to achieve a submission of good quality. The purpose of QC is to ensure that information and data described in submission dossier have sufficient quality in accuracy, integrity and traceability of scientific data/information, and to check compliance to pre-

defined format, template and structure. Some regulatory authorities require submission of QC declaration by applicant.

The following types of QC can be conducted depending on the subject, timing and stage of submission preparation.

QC of study reports and summary documents

The main purpose of this QC is to ensure accuracy, integrity and traceability of scientific data and information. This type of QC is usually conducted just before or at finalizing of each report, summary document or any other document which refer to the contents of these documents, e.g. product labeling.

It should also be conducted when making revisions to the contents of these documents.

In case translation of these documents to other language is required, it is useful to review the accuracy and validity of translation. In addition, compliance to pre-defined format and template, e.g. ICH M4, E3, needs to be checked as a part of QC process.

QC of submission dossier

This is the QC process to be conducted at compilation and assembling of submission dossier. The purpose is to check if every required component is ready and placed in the correct section of the dossier.

QC of electronic dossier

This type of QC is required in case of application submission with electronic dossier, e.g. ICH eCTD or NeeS (non-eCTD electronic submissions). The purpose is to confirm if the dossier is compliant with the review authority's electronic dossier requirements, e.g. electronic bookmarks, cross references and hypertext links are correctly functioned.

A record should be created when conducting QC. Also, applicants are highly recommended to have a written SOP for QC procedure.

4 COMMUNICATIONS

Effective communications will help applicants to improve quality and efficiency of the product development as well as registration process, thereby realize timely approval and earlier patient access to new products. Applicants should foster good communications with the review authorities and those within applicants' organization(s).

4.1 Communications with the Review Authorities

Communication with the review authorities can take place in various forms such as meetings, inquiry and response. Applicants should be aware of available communication mechanisms in pre- and post-submission stages and make effective use of them in product development and submission processes. Interactions with the review authorities throughout the processes are greatly facilitated by having a clearly defined contact point in applicants' organization. It is recommended that main communications with the review authorities are conducted consistently through regulatory professionals for all projects.

During post-submission stage, applicants should make prompt and appropriate responses to the inquiries and/or requests from the review authorities. To do so, applicants need to track the progress of review in timely manner and adjust the schedule as well as internal resource accordingly. It is also important to ensure that the review authorities and applicants are able to share information about the timeline and progress of review.

4.1.1 Communications in pre-submission stage

Meeting with review authorities

Meetings with regulatory authorities in product development and pre-submission stages help applicants to fix design of planned clinical/non-clinical studies, clarify requirements and potential concerns of ongoing development program and envisage possible questions in the forthcoming application process. It enables applicants to progress their development program efficiently in compliance with regulatory requirements and prepare a good quality submission dossier by dealing with potential questions and concerns in advance. It will increase the probability of a positive outcome in the forthcoming application submission.

Applicants should proactively use pre-submission communication with the review authorities to make successful submission.

In order to hold effective and productive meeting, applicants should keep the following points in mind.

- Study and follow the defined rules and procedure for the meeting
- Clarify the purpose and discussion points
- Prepare good quality meeting materials
- Discuss based on reasonable scientific rationale
- Prepare and circulate meeting minutes/memo on discussion points and agreements
- Take appropriate follow-up measures on comments and advice received from the authorities

4.1.2 Communications in post-submission stage

Meeting with review authorities

Opportunity of meetings in post-submission review stage is useful not only to track progress of review but also to discuss and solve potential issues, questions and requests raised by reviewers. It also helps applicants to have clear understanding on the background of received inquiries and prepare appropriate response to the point.

Availability of these meetings in post-submission stage depends on the review process adopted by each review authority. Often such meeting is held according to a request from review authorities. Applicants should follow the instructions described in previous section (see section 4.1.1) when having a meeting in post-submission stage.

Inquiry and response

Inquiry and response form the critical communication between reviewers and applicants. In general, inquiries from the review authorities are issued in two separate stages of the course of application review, i.e. in screening phase and in scientific review stage.

Screening or validation for application filing is usually performed by the review authorities at receipt of submission to ensure that the dossier is complete and of suitable quality for scientific review. In case any screening inquiry is received, applicants should correctly understand the contents and make prompt and appropriate action for response.

Once screening phase is finished, official scientific review starts. The review authorities may request additional information based on the outcome of scientific review.

At receipt of an inquiry in scientific review stage, it is important for applicants to clarify and understand the background as well as intention of the reviewer with that inquiry. To make it possible, the review authorities often allow applicants to ask for clarification. Applicants should make the best use of such opportunity.

When applicants received a critical inquiry which would require an additional study (or studies), they should have a consultation meeting with the review authority as much as possible to clarify details of the required study (or studies).

Proper management of the timeline for response preparation is another important element. It is advisable for applicants to confirm the deadline of response, set a reasonable timeline and appropriately manage prompt response preparation.

Preparation of response package needs to be conducted following the procedures and instructions described in section 3 MANAGEMENT OF SUBMISSION.

Depending on the country, the review authorities may request applicants to confirm the contents of draft evaluation report in the last stage of the review process. In such case, applicants should confirm the contents carefully.

4.2 Communication within Applicants' Organization

In many cases, preparation of an application submission is performed by collaborative work among concerned persons or parties in applicants' organization. Sometimes collaborations among multiple organizations are required.

Applicants should understand that a good submission can be achieved only when concerned parties within or among applicants' organizations share a clear strategy and work collaboratively throughout the product registration process up to approval. Good communication within submission team is the key to successful submission.

It is highly recommended that the submission team clarifies and confirms its operation model as well as the role and responsibility of team members when they have a kick-off meeting. Good communications within the team will be facilitated by establishing and sharing standardized working procedure and having a platform of information sharing such as regular meetings.

In case of global product registration, collaboration among multiple regions with time and geographical differences are required for submission in each country. In such case, applicants should make an effort to achieve effective and efficient communications among the regions.

In the case that applicants have outsourced manufacturing, research and development or submission operations, it is applicants' responsibility to keep close communication with the contractor.

5 COMPETENCY AND TRAINING

It is recommended that applicants possess general core competencies to properly manage and prepare submissions. Type of recommended competencies depends on the role and responsibility of each person or party in the submission team.

5.1 Core Competency of Applicants

A core set of recommended general competencies includes the following elements. .

Scientific knowledge and expertise

Applicants should have professional knowledge and expertise that relate to the product safety, efficacy and quality. These knowledge and expertise are especially significant for

the authors and reviewers of technical documents in submission dossier. Writing skills are also essential for the authors.

Logical application of each field of scientific knowledge, understanding on risk-benefit analysis, and critical thinking methodology to ensure compliance with regulatory standards and guidelines are also recommended competencies.

Good understanding of up-to-date regulations

Applicants should always keep abreast with the latest regulatory environment. This can be done by following the regulatory authorities' website and check updated news, notices or highlights. If available, applicants can also subscribe to a mail delivery service provided by the review authorities to allow applicants to receive updated regulatory information from the authorities' website periodically.

Applicants should carefully study published regulations, technical guidelines, notices, Q&A documents etc. Applicants can also attend training programs provided by the regulatory authorities, industry associations or other third parties to help understand the contents and background of these regulations.

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Other hard and soft skills

It is recommended that applicants develop the following hard and soft skills and abilities as a part of their competencies to move forward submission and its management efficiently.

- Planning and project management
- Medical and technical writing
- Technical skills for electronic submission (as necessary)
- Problem-solving
- Communication

Integrity and reliability

Applicants should approach the process with honesty, integrity and reliability and should not jeopardize the confidence of the regulatory authorities and other stakeholders.

5.2 Training and Capacity Building

Training is essential for applicants to acquire sufficient core competencies and strengthen skills and capacity. For that purpose, applicants can make use of various opportunities of

training programs provided by regulatory authorities, industry associations and other third parties.

For example, these parties often hold periodical educational programs, workshops and training sessions for applicants. Sometimes the authorities also provide briefing sessions for applicants when they release a new regulation or guideline, and prepare Q&A documents.

These external training programs are valuable for applicants to deepen their own scientific, technical and regulatory knowledge and expertise. Applicants should strive to participate in these training programs whenever possible.

In addition, it is essential for applicants to acquire necessary skills and competence through their own day-to-day operations. Opportunities of in-house training, self-training and on-the-job training in applicants' organization should be leveraged as a part of capacity building program.

It is also recommended for applicants to establish good documentation practice to document submission requirements and past applications for reference and to allow good practices sharing within their organization(s) so that they can make good use of these valuable experiences and competence for future submissions as well as capacity building. Archival can be in the form of manuals, SOP, database or any other appropriate tools.

6 GLOSSARY

ASEAN	: The Association of Southeast Asian Nations
CTD	: The Common Technical Document
ICH	: The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH-CTD	: Common Technical Document agreed in ICH
ICH eCTD	: Electronic Common Technical Document defined by ICH
IMDRF	: The International Medical Device Regulators Forum
Inquiry	: Questions or information requests made by the review authorities on submitted registration application
NeeS	: Non-eCTD electronic Submissions
Q&A	: Questions and Answers
QC	: Quality Check
RA-EWG	: Regulatory and Approval Expert Working Group established under APAC.
SOP	: Standard Operating Procedure

WHO : World Health Organization

7 REFERENCES

1. Good Review Practices Guidelines for National And Regional Regulatory Authorities, WHO Technical Report Series, No. 992, 2015 Annex9.

   http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex9-TRS992.pdf?ua=1

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